Chapter 1

General Features of the Gastrointestinal Tract and Evaluation of Specimens Derived from It

General Comments

In many ways the gastrointestinal (GI) tract is a remarkable organ. The embryonic endoderm will give rise to the future GI tract. The GI tract will acquire multiple cell types that will be dispersed into two planes: A vertical plane that allows one to recognize different layers of the bowel wall and a horizontal plane that develops into the esophagus, stomach, small intestine, colon, and anus. Although these cell types will resemble one another, important histologic differences allow specific physiologic functions to be carried out in each anatomic region. Interactions between cell populations regulate subsequent patterns of gene expression and organ development (1).

The physiology of the GI tract is also impressive. It serves as the digestive organ of the body, taking in everything that is swallowed and turning it into useful nutrients or discarding what is left over as waste. These processes begin in the mouth and terminate at the anus. While digesting everything to which it is exposed and breaking it down into smaller, absorbable, chemical substances, the gut is itself able to withstand these processes and avoid autodigestion. Complex neuromuscular interactions allow the GI tract to move food and liquids from one section of the gut to the next while at the same time controlling the passage of food in such a way that maximum digestion and absorption occurs in each of the appropriate spots. Even in a single organ, such as the small intestine, a differentiation gradient exists such that different substances are preferentially absorbed at different intestinal sites and through different parts of the cell. Not everything taken into the mouth and swallowed is healthy for the patient. Therefore, the GI tract serves as a major interface between the outside world and the rest of the body. The gut is continuously exposed to toxins and infectious organisms, yet it is often capable of eliminating these agents without causing any harm to itself. Not surprisingly, breakdown in these defense processes often results in disease. This generally occurs when the integrity of the bowel wall becomes compromised. The gut also serves as a major immune organ. It is the major site of the generation of mucosal immunity, hence the utility of oral vaccines. These immunologic processes largely take place in the small bowel. Finally, the GI tract is a major endocrine organ. In humans, the gut is divided into four major organs: Esophagus, stomach, small intestine, and large intestine. These are separated by sphincters that control the passage of contents from one organ to the next. The junctions between organs are identifiable by an abrupt change in the mucosal nature and by the presence of the sphincters.

Embryology

Multiple interactions occur during development between and within the three germ layers (endoderm, mesoderm, and ectoderm). Each of these layers may reciprocally induce development of other layers. The endoderm induces the mesoderm (2). It also confers a dorsal-ventral pattern on it (2). The endoderm and ectoderm contact one another in the 2- to 4-week embryo. The endoderm, which forms the roof of the yolk sac, gives rise to the future gut, creating the majority of the epithelial lining of the GI tract, biliary passages, liver, and pancreas. The primitive gut temporarily consists of foregut, midgut, and hindgut. The splanchnic mesoderm surrounding the primitive gut forms the muscular and connective tissue layers. Embryologic development takes place with a large number of inducers that share overlapping expression patterns and redundant functions. The core of this system consists of a set of structurally similar genes known as homeobox genes. The embryology of each region is discussed in detail in the relevant chapters. Multipotent neural progenitors give rise to various derivatives, including neurons, glia, and ganglia, as the result of local environmental signals. These progenitors differentiate based on specific molecules they encounter either during their migration or within the organ in which they terminally differentiate as discussed in detail in Chapter 10. Abundant endocrine cells are present by 8 weeks’ gestation. The diversity of the GI endocrine cell component is established early. There is a higher density of endocrine cells in both the proximal duodenum and distal colon/rectum compared with other areas. Endocrine cell numbers increase with age, roughly paralleling the growth of the gut. The full adult profile is attained by the second trimester. The endocrine system is discussed in detail in Chapter 17.
Peripheral lymph nodes develop by the second month of gestation. Mononuclear cell aggregates are also identified in the fetal intestine in proximity to the endodermal epithelium.

**Cell Proliferation**

The GI tract undergoes continuous development and proliferation. Its mucosa varies from the esophagus to the colon and it contains multiple cell types. New cells form from stem cells within the basal layers of the anal and esophageal squamous epithelium, in the mucous neck region of the stomach, or from the bases of the crypts in the intestines (Fig. 1.1). Cells then migrate out of the proliferative zone and differentiate into multiple cell lineages. The differentiation pattern of the gut epithelium is influenced by other cells in its environment (3). Eventually the cells are shed into the lumen or undergo apoptosis. Cellular life span is 5 to 7 days in the duodenum and jejunum, 4 to 5 days in the ileum, and 4 to 6 days in the large intestine. Specific details of cell proliferation in the esophagus, stomach, small intestine, and colon are discussed in the relevant chapters. The intestine alters its rates of cellular renewal and adapts to surgical, nutritional, and other toxic stimuli, as well as to physiologic and disease states. Stem cells show three general features: (a) the capacity to undergo asymmetric division, producing one daughter that remains a stem cell and another that undergoes a seemingly irreversible commitment to enter a differentiation pathway; (b) proliferative potential; and (c) the ability to retain a position in a particular environmental niche (4,5). Some stem cells are unipotential, giving rise to a single differentiated phenotype, whereas others are multipotential, giving rise to multiple cell types.

**FIG. 1.1.** Diagrammatic representation of the proliferative zones (green) in the various regions of the gastrointestinal tract. **A:** The proliferative zone of the esophagus is restricted to the basal cell layer of the stratified squamous epithelium. **B:** In the stomach, proliferation occurs in the neck region of the glands, and cells migrate in two directions to populate the pits and the bases of the glands. **C:** Proliferation in the small intestine occurs in the basal one third of the crypts. **D:** In the colon, proliferation is restricted to the basal one third to one half of the crypt. **E:** Like the esophagus, proliferation in the anus occurs in the basal zone of the epithelium.
Of interest is the fact that not all stem cells that give rise to gastrointestinal epithelia are gastrointestinal stem cells. It now appears that bone marrow stem cells may be recruited to sites of injury and give rise to a host of cell lineages, including cells with mixed gastrointestinal phenotypes. This phenomenon is best exemplified in the development of gastric cancer following *Helicobacter pylori* infections as discussed in Chapter 5.

**Gastrointestinal Structure**

In general, the gut consists of four concentric layers as one progresses outward from the lumen: The mucosa, submucosa, muscularis propria, and serosa or adventitia (Fig. 1.2). These layers are easily visualized histologically and can also be imaged using ultrasound. The high correlation that exists between the ultrasound image and the histologic features allows one to use ultrasound to provide diagnostic information about the status of the GI tract.

**FIG. 1.2.** Although the basic architecture is similar in all regions of the gastrointestinal tract, functional and histologic differences do exist. The four quadrants of the diagram compare the *(A)* esophagus, *(B)* stomach, *(C)* small intestine, and *(D)* large intestine.

**Mucosa**
The mucosa consists of an epithelial lining, a lamina propria that contains loose connective tissue rich in immunocompetent cells, and the muscularis mucosae. The lamina propria is most visible in the stomach, large and small intestines, and appendix, and is least visible in the esophagus and anus. The smooth muscle cells in the muscularis mucosae are predominantly arranged in a circular orientation, although some longitudinal muscle fibers are also present. The epithelium may invaginate to form glands that extend into the (a) lamina propria (i.e., mucosal glands in the stomach) (Fig. 1.2), (b) submucosa (i.e., submucosal glands in the esophagus [Fig. 1.2] or Brunner glands in the duodenum), or (c) ducts that extend to organs outside the gut, such as to the pancreas or the liver. The mucosa and submucosa may also project into the GI lumen as folds (plicae or rugae) (Fig. 1.2). Additionally, villi may be present (Fig. 1.2).

GI epithelium differs substantially in various organs. Squamous epithelium lines the mucosa of the esophagus and anus (Fig. 1.3). In the stomach, the epithelium is divided into surface epithelium, pits, and glands (Fig. 1.3). In the small intestine, the mucosa consists of crypts and villi containing a population of intestinal epithelial cells. The colon contains similar cells but it lacks villi. The squamous lining of the esophagus protects it from the passage of undigested food over its surface. Likewise, in the anus, the squamous epithelium protects the mucosa from the damaging effects of the passage of solid waste. In the stomach, the mucosa facilitates digestion by secreting acid. The epithelial lining of the small intestine is uniquely suited to the further digestion and absorption of nutrients along a gradient from the duodenum to the ileum. The colon predominantly resorbs water. The specific features of the various portions of the gut are discussed in their appropriate chapters.

The lamina propria forms the mucosal interglandular tissues. It appears as a delicate, loose, connective tissue containing lymphocytes, plasma cells, eosinophils, rare neutrophils, and mast cells. The majority of the cells are plasma cells and lymphocytes, with the majority of plasma cells secreting IgA; however, IgM-, IgG-, and IgE-secreting cells are also present. The lamina propria also contains large numbers of macrophages, which play important roles in mucosal immunity, antigen presentation, elimination of exogenous pathologic antigens or organisms, immunoglobulin production, and immunoregulation.

The gut-associated lymphoid tissue (GALT) primarily lies within the lamina propria. It is distributed diffusely or appears as solitary (Fig. 1.5) or aggregated nodules, which in the ileum and appendix are called Peyer patches. Larger aggregates contain germinal centers. Peyer patches are present on the antimesenteric border of the intestine. These lymphoid nodules often span the muscularis mucosae (Fig. 1.5), breaking through into the superficial submucosa and creating gaps in the muscularis mucosae. Solitary nodules occur in the esophagus, in the gastric pylorus, and along the small and large intestines. Both blood and lymphatic capillaries form a plexus around the lymphoid follicles. The majority of the cells within the follicles are lymphocytes, macrophages, and plasma cells. The basement membrane overlying the Peyer patches is more porous than that of the adjacent epithelial areas, facilitating the bidirectional passage of lymphocytes during antigenic stimulation (8). The lamina propria also contains vessels and unmyelinated nerve fibers.

Mast cells comprise an important, but heterogeneous, component of the lamina propria and submucosa. Specialized contacts exist between mast cells and other cell types; these contacts facilitate intercellular communication. Mast cells often lie adjacent to blood vessels or lymphatics, near or within nerves, and beneath epithelial surfaces, particularly those of the GI tract where they are exposed to environmental antigens. Numerous cells respond to mast cell mediators, as exemplified by the presence of histamine receptors on their surfaces. Cells with surface histamine receptors include lymphocytes, macrophages, neutrophils, basophils, eosinophils, smooth muscle cells, and parietal cells. Neuropeptides and hormones influence mast cells, inducing them to release their mediators. Mast cells initiate acute inflammation and propagate chronic inflammatory changes. These cells may also be antigen-presenting cells. In some IgE-dependent inflammatory responses, mast cells are the sole or primary initiator of the reaction, and in others they may influence pre-existing inflammation. By virtue of their location and number, mast cells participate in a wide variety of GI diseases. The most important include food allergies, eosinophilia, immunodeficiency syndromes, immediate hypersensitivity reactions, host responses to parasites and neoplasms, immunologically nonspecific
inflammatory and fibrotic conditions, and tissue remodeling. Mast cells are also important in angiogenesis, wound healing, peptic ulcer disease, and other chronic inflammatory conditions, including graft versus host disease and inflammatory bowel disease.

**FIG. 1.3.** Gastrointestinal epithelia. *A:* The esophagus is lined by nonkeratinizing stratified squamous epithelium. *B:* The epithelium of the stomach is arranged into pits and glands. The pits are lined by foveolar cells and have a similar appearance in all regions of the stomach. The glands contain numerous cell types that differ from one region of the stomach to another. *C:* The small intestinal mucosa consists of crypts and villi. *D:* The colon lacks villi and consists of rows of parallel crypts lined by columnar absorptive cells, goblet cells, and endocrine cells.
Chapter 1

**FIG. 1.4.** Thick section from a portion of small bowel showing the lamina propria that contains large numbers of lymphocytes, plasma cells, and macrophages.

**FIG. 1.5.** The colonic mucosa is separated from the submucosa by the muscularis mucosae, which is punctuated only by the lymphoid follicle. Collagen bundles and large vessels are prominent in the submucosa.

Eosinophils might also be present within the lamina propria. Eosinophils are most abundant in tissues with an epithelial interface, such as the GI tract. Their intracellular granules cause their tinctorial features. Eosinophils express receptors for
IgG, IgE, and IgA on their external membranes (11). Eosinophils also have receptors for complement components and cytokines. They themselves produce and release numerous mediators in response to activation (11). Eosinophils have both beneficial and detrimental roles in the host. They function in host defense, including the phagocytosis and killing of bacteria and other microbes, but they also mediate allergic reactions, and the oxidative products of eosinophils can damage cells. The eosinophilic products that are most damaging are the cationic proteins (11).

**Submucosa**

The submucosa is a more densely collagenous, less cellular layer than the mucosa. However, in some areas it may have a loose organization. Major blood vessels, lymphatics, nerves, ganglia, and occasionally lymphoid collections are located here. It also contains fat.

**Muscularis Propria**

The muscularis propria is a continuous structure composed of two smooth muscle layers that extend from the upper esophagus to the anal canal (Fig. 1.6). The only exception to this occurs in the stomach, where three layers are present. At the junctions between adjacent organs, the muscular coat rearranges to form sphincters including the pharyngoesophageal, esophagogastric, pyloric, ileocecal, and anal sphincters. The function of these sphincters is based on physiologic and pharmacologic characteristics of the musculature and on their innervation. The muscle fibers are usually arranged in a concentric circular fashion in the inner muscular layer (the circular layer), whereas the outer muscle fibers are arranged longitudinally (the longitudinal layer). In the cecum and in parts of the colon, the longitudinal muscle is extremely attenuated except in the regions where it forms thick cords (i.e., the taeniae coli).

**FIG. 1.6.** Hematoxylin and eosin–stained section demonstrating the circular and longitudinal smooth muscle layers of the muscularis propria.

Circular muscle, from the esophagus to the internal anal sphincter, behaves as an electrical syncytium. The syncytial properties result from nexuses between the plasma membranes of contiguous muscle fibers. These nexuses function as intracellular pathways for conduction of excitation between adjacent cells. Even in the absence of neural influences, these syncytial properties allow for three-dimensional spread of excitation (12). Smooth muscle cells also contain gap junctions or nexuses that electrically couple adjacent cells (12).

The musculature also contains the interstitial cells of Cajal (ICCs). ICCs have three major functions: (a) they act as pacemakers for the GI muscle (13), (b) they facilitate active propagation of electrical events, and (c) they mediate neurotransmission. They may also act as mechanoreceptors (13). These cells may be abnormal in motility disorders as
Chapter 1

discussed in Chapter 10 and they give rise to the group of tumors known as GI stromal tumors (GISTs) as discussed in
Chapter 19.

The cells of the muscularis propria contain numerous receptors, allowing them to respond to neural signals as well as other
stimulatory and inhibitory signals during the digestive process. Contraction of the circular layer constricts the lumen;
contraction of the longitudinal layer shortens the digestive tube. When the bowel becomes obstructed or the intestinal lumen
distends on a persistent basis, the muscle increases in volume through both hypertrophy and hyperplasia. Smooth muscle
hyperplasia also follows myenteric ablation. Obstruction results in a number of changes to both the muscular and neural layers.

**Adventitia or Serosa**

The adventitia consists of loose connective tissue containing fat, collagen, and elastic tissues (Fig. 1.7). If it is covered by
mesothelium, it is called a serosa. A serosa is present on the stomach, those parts of the small intestine that are not
retroperitoneal, the appendix, and the large intestine above the peritoneal reflection.

**Blood Vessels**

Both blood vessels and lymphatics enter the gut from the surrounding tissues. The largest arteries pass through the GI wall
and are arranged longitudinally in a submucosal plexus.

P.6

The submucosal plexus sends arterioles and capillaries into the mucosa, muscularis, and adventitia or serosa. The mucosa
contains an irregular capillary plexus, often with its most terminal branches underlying the luminal surface epithelium (Fig. 1.8).
Within the muscular layer the vessels lie parallel to the muscle fibers. Veins arising in the mucosa anastomose in the
submucosa and course with the arteries out of the intestine. Valves are present in veins in the adventitia or serosa. The
vascular anatomy of each region of the GI tract is described in the relevant chapters.

**FIG. 1.7.** Well-delineated serosal surface of the intestine (A) covered with mesothelium contrasts sharply with the irregular loose tissue of the adventitia of the esophagus (B).
FIG. 1.8. Blood-filled capillary penetrates to the surface epithelium, where a rich capillary network is located (arrow).

The intestinal mucosa receives the highest vascular perfusion of any peripheral organ (14), a feature critical to the absorption of nutrients from this site. Vascular contractility is controlled by submucosal neurons whose excitation leads to vasodilation of the submucosal arterioles. This increases mucosal blood flow (15). Intestinal blood flow is determined by three mechanisms: intrinsic (myogenic and local metabolic), extrinsic (sympathetic nervous), and circulating vasoactive agents (14).

Nitric oxide (NO) is continuously released from the arterial and arteriolar endothelium (Fig. 1.9) (16). Vessels, particularly arteries, also contain large amounts of superoxide dismutase (SOD). This enzyme modulates NO activity. NO acts as an important intracellular signal causing smooth muscle relaxation, including the smooth muscle of the vascular system (17). NO also contributes to thromboresistance of vessel walls.

Lymphatics

The gut is richly supplied with lymphatics, but their distribution, particularly in the mucosa, varies with the location in the gut. The richest lymphatic distribution occurs in the small intestine, where the lymphatics are intimately involved in nutrient absorption. Larger submucosal lymphatics branch freely and contain numerous valves. Smaller mucosal and submucosal
lymphatics may be difficult to detect because they are often collapsed and blend in with the surrounding connective tissue. They are also sometimes difficult to distinguish from small blood capillaries. However, each vessel type has distinctive features. The lymphatics from the submucosa pass through the gastrointestinal wall and eventually drain into the regional lymph nodes.

**Innervation**

The enteric nervous system (ENS) is the most complex portion of the peripheral nervous system. It is discussed in detail in Chapter 10.
Nitric oxide (NO) mediates vascular relaxation. NO is produced in endothelial cells by the action of calcium-dependent nitric oxide synthase (NOS). Mediators such as acetylcholine and bradykinin stimulate its production. NO acts on smooth muscle cells through a process involving conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (GMP), affecting relaxation. NO released into the interstitium may produce damaging free radicals after interacting with superoxide molecules. This process is inhibited by the action of superoxide dismutase (SOD) on superoxide.

**Endocrine Cells**

The gastrointestinal tract is the largest endocrine "organ" in the body and contains a large number and type of endocrine/paracrine cells. It is the second richest source of regulatory peptides outside of the brain. Some endocrine cell types found in the gut also occur in the pancreas, and thus the entire population is also sometimes referred to as the gastroenteropancreatic system. This system is discussed in detail in Chapter 17.

**Types of Gastrointestinal Specimens**

GI pathology specimens fall into three major categories: Biopsy specimens, resection specimens, and cytology specimens. GI specimen interpretation is facilitated by a familiarity by the pathologist of clinical gastroenterology and the nature of the procedures used to obtain the specimens. Endoscopy, diagnostic imaging, and therapeutic instrumentation are currently generating biopsy or small resection specimens from sites that were previously inaccessible without a major resection. As a result, gastroenterologists, surgeons, endoscopists, and radiologists currently provide specimens to the pathology laboratory. It is important that these individuals understand the information different types of specimens can provide and what the limitations of different types of specimens are.

Biopsies are taken to establish a specific diagnosis or to follow the evolution of a particular lesion or disease. They are also taken to determine disease extent as in inflammatory bowel disease or to judge its severity, to determine response to therapy, and to detect cancers or their premalignant stages. Biopsies may also be taken to acquire tissues for other specific purposes, including microbial culture, biochemical examination, ultrastructural examination, or evaluation by molecular markers. Specimen interpretation is always enhanced by an effective dialogue between the pathologist and the clinician, usually via pertinent information provided on the requisition form or through routine clinical-pathologic correlation conferences.

It is important that the clinician indicate the exact site of origin of a biopsy since this provides critical information for specimens from some locations. For example, the presence of gastritis in the proximal stomach versus the antrum has different clinical implications and etiologies. The significance of intestinal metaplasia in the esophagus differs from that in the stomach. Inflammation in the distal colon may have different implications than inflammation in the proximal colon. Thus, it is important that the clinician not submit samples from multiple locations in the stomach or colon in the same specimen bottle, as critical information can be lost when this occurs. This is especially true in the colon, where the distribution of a colitis provides important diagnostic information. It is also helpful to know whether the areas biopsied appeared endoscopically normal or abnormal.

Incisional biopsies (such as biopsies of cancer) represent only part of a lesion, and these are purely diagnostic biopsies. In contrast, excisional biopsies (such as a polypectomy) can be therapeutic as well as diagnostic. The decision of the clinician to perform an incisional or an excisional biopsy depends on the size of the lesion and, in some cases, its growth pattern. Ideally, once biopsies are obtained, they should be oriented to avoid tangentially cutting when the specimen is processed and to facilitate the assessment of certain measurements such as a crypt:villus ratio in the small bowel or an evaluation of the length of the papillae in the esophagus. However, even if the specimens are received unoriented, the presence of multiple biopsies examined at several levels usually provides sufficient information that one can interpret the biopsies without special care having been taken to the orientation.

Some GI lesions will be sampled cytologically, although in the United States exfoliative cytology does not play the same role that gastrointestinal biopsy interpretation does, except possibly in the diagnosis of esophageal infections. However, cytologic
examination can be an important adjunctive technology in the diagnosis of malignancies. Cytologic samples are particularly helpful in portions of the GI tract that are stenotic and therefore difficult to biopsy. Cytologic preparations can also be used in areas where a gross lesion is present because large areas of the surface can be sampled with a cytology brush. Cytologic examination can help confirm the presence of neoplasia. This approach has been used much more extensively for screening for cancer of the esophagus or stomach in places such as China and Japan. It is much less commonly used to diagnose colonic and rectal lesions.

Resections are performed to surgically treat cancer or precancerous lesions, life-threatening ischemia, severe ulcerating diseases, obstructions, and pseudo-obstructions, as well as various other conditions. Resection specimens received in the fresh state should be examined as soon as possible to determine whether or not the specimen requires special handling for procedures such as microbial cultures, ultrastructural examination, histochemical stains requiring frozen sections or special fixatives, biochemical analysis, imprints, cytogenetic studies, or molecular studies prior to fixation. The pathologist should be able to examine the entire specimen. It is a common practice to remove a fresh piece of tumor (or other disease) and normal mucosa for future research if this does not interfere with the pathology assessment. This should be done under the supervision of a pathologist and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. Removal of any tissue before a pathologist has examined the specimen often results in loss of critical material that is needed to properly interpret the specimen.

**Specimen Fixation**

Biopsies should be placed in an adequate amount of fixative, which for biopsies should be at least five times the volume of the specimens. Ten percent buffered formalin is the most commonly used fixative in histology laboratories because it is stable and allows staining with most currently used histochemical and immunohistochemical stains. It does, however, induce substantial tissue shrinkage. In some circumstances where a more accurate rendering of the cytologic features is required, additional fixatives can be used that contain heavy metals, such as Bouin, B5, or Hollende solution. These fixatives cause less tissue shrinkage and permit analysis of nuclei that appear less distorted. However, the latter fixatives interfere with the ability to isolate high-quality nucleic acids from the biopsy specimens should this be intended later. Additionally, these fixatives are often not routinely available.

In some cases it is important that the samples be presented in an unfixed state so that they can be handled in a special way. For example, in suspected lymphomas, fresh tissue should be obtained for flow cytometry, freezing, and other special studies. In patients with motility disorders such as Hirschsprung disease, submission of fresh tissue allows the use of enzyme histochemistry to evaluate the neural structures. Fresh tissue is also required to demonstrate fat within the tissues as in some lipid storage diseases. Finally, rapidly acquired fresh tissue may be necessary for some genetic or chromosomal studies. There should be a duplicate sample that is fixed in formalin if all of the fresh tissue is to be used for special studies.

Glutaraldehyde is the fixative of choice for specimens that may require ultrastructural examinations. Situations where this might be necessary may include a search for microsporidia, an evaluation of storage diseases, or a mitochondrial myopathy. Ultrastructural examination may also be useful in the identification of certain tumors, although this is becoming less common with the wide array of immunohistochemical and more recently genetic markers that is available. A duplicate formalin-fixed specimen should also be submitted in these situations.

**Handling Resection Specimens**

Resection specimens should be opened longitudinally and cleansed to remove blood, stool, and other substances that may interfere with obtaining information from the specimen. The prosector should describe all lesions, including tumors, ulcers, or other abnormal areas. Attention should be given to documenting the size, appearance, and anatomic relationship of any lesions. The distance of a tumor from the proximal, distal, and radial margins should be measured. The depth of invasion should be estimated and extension beyond the organ should be documented, if present. Specimen palpation helps delineate full tumor extent. Painting the margins with India ink can be useful in making these determinations. A comment should be as to
whether or not the nodes appear to be grossly involved. If the resection specimen is a resection for ischemia, a search for thrombi should be made in the mesenteric vessels.

The specimen should be photographed if it contains an obvious lesion. These photographs are invaluable for presentations at tumor boards and other clinical care conferences. They also serve as invaluable teaching resources. They allow physicians to recognize the gross aspects of the diseases that are encountered on a daily basis. They also facilitate correlation with endoscopic and/or radiologic appearances. Carcinomas should be photographed from both the surface and the cut section to show the extent of tumor invasion. Vascular lesions can be enhanced by intravascular ingestion of ink or other compounds. When the specimen is photographed, it should be properly oriented and should include some normal tissue for orientation. The photographic table should be clean.

The resection specimen should be placed in 10% neutral buffered formalin with a fixative volume that is at least ten times that of the tissue. Bowel specimens should be pinned out to optimize flat, well-oriented lesions. If a specimen is pinned to a corkboard, gauze or paper towels can be placed beneath the specimen to serve as a wick for the fixative. Tissues should be adequately fixed prior to sectioning. Blocks should be obtained to evaluate the nature and extent of all lesions. If the patient has received preoperative radiation and/or chemotherapy, residual cancer may not be obvious and one may need to block an entire suspicious area in order to find remnants of tumor. This is especially true in esophageal, gastric and rectal resection specimens from patients undergoing neoadjuvant therapies. It is important that when sections are submitted, the origins of each section be noted in the gross description.

Sometimes vital staining is used in the evaluation of gross specimens, although this is most commonly done in research settings. Examples include Lugol staining of esophagectomy specimens with squamous cell lesions, alkaline phosphatase staining of gastric resections to map areas of intestinal metaplasia (see Chapter 4), or vital staining to identify aberrant crypt foci.

Endoscopic mucosal resection (EMR) specimens require special handling in order to determine whether the resection margins are microscopically complete (18). The specimen should be stretched and pinned to a block. Deep and lateral margins should be marked with India ink. The specimen should be sectioned longitudinally at 2-mm intervals after fixation for 24 hours in formaldehyde. A resection may be classified as complete for neoplasia if the deep and lateral margins are negative and complete for Barrett esophagus if the margins are composed of nonmetaplastic mucosa.

Patients with invasive duodenal adenocarcinomas are often treated with a pancreaticoduodenectomy (i.e., Whipple resection: A resection of the distal stomach, duodenum, distal biliary tree, and head of pancreas), and they require special handling. The stomach and duodenum should first be placed in a fixative, preferably formalin, to allow for deep fixation. Inserting a probe from the cut surface of the common bile duct through the biliary tree and into the duodenal lumen is not recommended. Metal probes damage and distort the lining cells of these ducts and subsequent sections will often show complete loss of the epithelial lining. Neoplasms involving the ampulla and distal bile ducts should be blocked in their entirety. Sections should be taken parallel to the long axis of the bile duct and pancreatic ducts as they enter the ampullary area. In this manner, the entire ductal system can be followed and reconstructed, as the ducts will appear on more than one slide. In addition, the entire mucosal surface surrounding the ampulla should be examined. In many cases, residual adenomatous epithelium can be found involving the adjacent duodenal mucosa, the ampulla, or the biliary and/or pancreatic ducts.

If, on gross examination, a tumor grossly involves the serosal surface or the adjacent pancreas, sections should be taken in these areas to document the extent of local invasion. Sections should be taken of the pancreas, including the surgical line of resection, to examine the pancreatic ductal system. Carcinomas arising in the duodenum and ampulla will infrequently be associated with atypical changes within pancreatic ducts away from the ampulla, and usually not at the line of resection. Similarly, one should examine the resected end of the common bile duct to look for atypia of the lining cells. Again, as for the pancreatic ducts, one usually will not find dysplastic or neoplastic changes in the lining cells of the common bile duct at the line of resection when the tumor originates in the duodenum. However, an invasive carcinoma that has extended from a primary site may be found in the wall of the bile duct. The connective tissue between the duodenum and pancreas should be
Chapter 1

examined carefully for lymph nodes. Adenocarcinomas arising in the duodenum or ampulla metastasize first to these pancreaticoduodenal nodes and then more distantly. Invasive carcinomas arising in longstanding Crohn disease or ulcerative colitis may produce grossly apparent lesions that resemble other small bowel carcinomas. However, the carcinomas may also produce stenotic areas or diffuse thickening of the bowel wall, mimicking the gross appearance of the underlying inflammatory bowel disease. Since these carcinomas may be difficult to identify by gross examination, we recommend that many sections be obtained of the resection specimen. Ideally, sections should be taken along the entire length of the grossly abnormal bowel, but this may not be practical, especially when long segments of bowel are involved. At least one section should be taken for every 5 cm of inflamed bowel.

Section Orientation

Sections, whether from biopsy or resection specimens, should be taken with the proper orientation, which usually involves a section perpendicular to the mucosa. This allows one to evaluate mucosal height and its component parts. In some circumstances, however, one may wish to produce an en face section. Unicryptal adenomas or aberrant crypt foci are identified in this way because it allows for evaluation of a greater number of crypts per slide. Sections should not be taken until the specimen is well fixed. Specimens submitted for histology should not be more than 3 mm thick because they do not fit appropriately into the cassettes and they fail to become adequately infiltrated.

Lymph Node Dissection

Although all pathologists agree that pathologic stage and grade are among the most important tumor prognosticators, sufficient care is often not taken to carefully dissect the lymph nodes. Optimally in the GI tract, the fatty tissue should be dissected from the muscularis propria while the specimen is fresh. Most lymph nodes lie closely apposed to the muscularis propria, so that the dissection should be done in such a way that the fat is cleaned off the muscle completely and then dissected to find the lymph nodes. It is often helpful to follow vasculature because many of the lymph nodes lie along the vessels. Examination of the fat at a distance from the specimen is usually not very productive and examination of the omentum is useless because lymph nodes are not present here. Fixation of the removed fatty tissues in Bouin, a clearing solution, or Carnoy solution helps highlight the lymph nodes.

If an entire colectomy is performed in a patient with multiple cancers or with dysplasia in ulcerative colitis, it is helpful to divide the bowel and its lymph nodes into four sections extending from the proximal to the distal bowel, keeping the lymph nodes from each section separate. This allows accurate staging of each cancer, should multiple cancers be present. It is also important to obtain as many lymph nodes as possible since the staging system for some tumors is based on the number of positive nodes that are present, as in gastric cancer (see Chapter 5). If insufficient lymph nodes are removed, understaging of a tumor may occur.

Detailed guidelines for handling and reporting gastrointestinal specimens are provided by the Collage of American Pathology in its guidelines (19,20,21).

References

17. Vanhoutte PM, Boulanger CM, Mombouli JV: Endothelium-derived relaxing factors and converting enzyme inhibition. Am J Cardiol 1995;76:3E.
Chapter 10
Motility Disorders
Introductory Comments

Normal gastrointestinal (GI) motility depends on intact neuromuscular functions that consist of both intrinsic and extrinsic innervation. Extrinsic control includes the enteric nervous system (ENS), smooth muscle cells, and interstitial cells of Cajal (ICCs), with the latter serving as both pacemaker cells and as intermediaries of enteric innervation (1,2). Motility disturbances constitute a complex array of clinical and pathologic disorders that result from neural, muscular, or ICC abnormalities (Tables 10.1, 10.2, 10.3, and 10.4). Intestinal neuropathies appear to be more common than intestinal myopathies. Motility disorders occur at any age and may be primary or may complicate systemic diseases. Primary motility diseases more typically affect children than adults. Conversely, secondary conditions, such as scleroderma-associated myopathy, diabetic neuropathy, drug-induced damage, or viral infections, more frequently affect adults. Primary motility disorders may be familial or sporadic. They may remain limited to the gut, as in Hirschsprung disease (HD), or they may be part of a generalized peripheral autonomic neuropathy, as in familial visceral neuropathy. Familial disorders are inherited as both autosomal recessive and autosomal dominant diseases.

The clinical and/or pathologic findings of gastrointestinal motility disorders may be subtle or dramatic. They can present as dysphagia, nausea, vomiting, diffuse esophageal spasm, gastroparesis, intestinal pseudo-obstruction, constipation, or intestinal diverticulosis. Intestinal pseudo-obstruction is defined as a rare, severe disabling disorder characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic documentation of a dilated bowel with an-air–fluid levels in the absence of a fixed, lumen-occluding lesion (3). In contrast, Ogilvie syndrome is a term used synonymously with acute colonic pseudo-obstruction. The terms megasigmoidus, megaduodenum, megajejenum, megacolon, and megarectum describe visceral enlargement of each of these anatomic sites. There is no agreement on the criteria for the minimum diameters of the dilated gastrointestinal segments.

Small intestinal pseudo-obstruction leads to diarrhea, malabsorption, and steatorrhea secondary to bacterial overgrowth. Some patients become malnourished with extreme weight loss. Extraintestinal manifestations depend on the nature of the underlying disease; some help define specific syndromes. Features suggesting autonomic dysfunction include postural dizziness, difficulties in visual accommodation to bright light, and sweating abnormalities. Recurrent urinary infections and difficulty emptying the urinary bladder suggest a general visceral neuro-myopathic disorder. Patients should also be questioned about drug use. Bedridden patients, such as those with dementia, stroke, and spinal cord injuries, are particularly prone to developing megacolon and a chronic pseudo-obstruction. Motility disorders are clinically diagnosed using specific physiologic measurements of gastrointestinal motor function, including scintigraphy, gastroduodeninojejunal manometry, and surface electrogastrography. The clinician will also often seek the pathologist’s assistance to rule out the presence of infiltrative lesions, such as amyloidosis or connective tissue diseases, or to document the presence of neuromuscular abnormalities.

Even though the clinical or gross findings may be dramatic, the histologic features are often inconspicuous, and they may also overlap with nonspecific neural and/or muscular histologic abnormalities accompanying other conditions, such as carcinoma or previous surgery. Additionally, some patients with clinically evident motility disorders may have histologic abnormalities that have not been well described or placed into specific syndromes. In other patients, there may be neurotransmitter alteration that may or may not associate with morphologic abnormalities. These most commonly involve alterations in the nitricergic neural system or changes in vasoactive intestinal polypeptide (VIP) or substance P (SP)-containing nerves. Changes may also be present in the muscle cells or ICCs.

Clinically evident motility disorders may have histologic abnormalities that have not been well described or placed into specific syndromes. These are often inconspicuous, and they may be part of a generalized peripheral autonomic neuropathy, as in familial visceral neuropathy. Familial disorders are inherited as both autosomal recessive and autosomal dominant diseases.

Even though the clinical or gross findings may be dramatic, the histologic features are often inconspicuous, and they may also overlap with nonspecific neural and/or muscular histologic abnormalities accompanying other conditions, such as carcinoma or previous surgery. Additionally, some patients with clinically evident motility disorders may have histologic abnormalities that have not been well described or placed into specific syndromes. In other patients, there may be neurotransmitter alteration that may or may not associate with morphologic abnormalities. These most commonly involve alterations in the nitricergic neural system or changes in vasoactive intestinal polypeptide (VIP) or substance P (SP) containing nerves. Changes may also be present in the muscle cells or ICCs.

Histologic examination using conventional hematoxylin and eosin (H&E) stains is usually augmented with the use of special stains or ultrastructural examination (Table 10.5). Some histologic changes are so subtle that they require precise neuronal counting to document their presence. However, this is fraught with problems, since the number of neurons and ganglia vary with age, location, other disease processes, and section thickness. A method for rapidly counting enteric nerve cell bodies using antibodies to c-kit and NF 68. The procedure takes approximately an hour to perform (4). It remains to be seen whether it will be widely adopted.

<table>
<thead>
<tr>
<th>TABLE 10.1 Gastrointestinal Neural Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Developmental abnormalities</strong></td>
</tr>
<tr>
<td>Hirschsprung disease and its variants</td>
</tr>
<tr>
<td>Hypanganglionosis (intestinal neuronal dysplasia [IND] type A)</td>
</tr>
<tr>
<td>Hyperanganglionosis (IND type B)</td>
</tr>
<tr>
<td>Hyperanganglionosis associated with ganglioneuromatosis</td>
</tr>
<tr>
<td>Neuronal immaturity</td>
</tr>
<tr>
<td>Absent enteric nervous system</td>
</tr>
<tr>
<td>Neuropathies currently difficult to classify</td>
</tr>
<tr>
<td>Familial visceral neuropathies (see Table 10.12)</td>
</tr>
<tr>
<td><strong>Sporadic visceral neuropathies</strong></td>
</tr>
<tr>
<td>Type I</td>
</tr>
<tr>
<td>Type II</td>
</tr>
<tr>
<td><strong>Paraneoplastic pseudo-obstruction</strong></td>
</tr>
<tr>
<td>Isolated ganglioneuromatosis</td>
</tr>
<tr>
<td>Eosinophilic ganglionitis</td>
</tr>
<tr>
<td>Granulomatous visceral neuropathy</td>
</tr>
<tr>
<td>Megacystis—microcolon and intestinal hyperperistalsis</td>
</tr>
<tr>
<td>Severe idiopathic constipation</td>
</tr>
<tr>
<td>Acquired hyperanganglionosis</td>
</tr>
<tr>
<td>Neurotransmitter disorders</td>
</tr>
<tr>
<td>Chronic slow transit constipation</td>
</tr>
<tr>
<td>Internal anal sphincter achalasia</td>
</tr>
<tr>
<td>Achalasia</td>
</tr>
<tr>
<td>Allgrove syndrome</td>
</tr>
<tr>
<td>Infantile hypertrophic pyloric stenosis</td>
</tr>
<tr>
<td>Associated with systemic neurological diseases</td>
</tr>
<tr>
<td>Polio</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
</tr>
<tr>
<td>Parkinson disease</td>
</tr>
<tr>
<td>Wallenberg syndrome</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Shy-Drager syndrome</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td>Herpes zoster</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
</tr>
</tbody>
</table>
TABLE 10.2 Gastrointestinal Muscular Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megacystis–microcolon and intestinal hypoperistalsis</td>
<td>Developmental defects in the intestinal musculature</td>
</tr>
<tr>
<td>Familial visceral myopathies</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Autosomal recessive with total gastrointestinal dilatation</td>
<td>Autosomal recessive with ptosis and external ophthalmoplegia</td>
</tr>
<tr>
<td>Sporadic visceral myopathies</td>
<td>Autosomal recessive with ptosis and external ophthalmoplegia</td>
</tr>
<tr>
<td>Mitochondrial myopathies</td>
<td>Autosomal recessive with ptosis and external ophthalmoplegia</td>
</tr>
<tr>
<td>Autoimmune enteral leiomyositis</td>
<td>Hereditary internal anal sphincter myopathy</td>
</tr>
<tr>
<td>Disorders affecting the skeletal muscles</td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Progressive muscular dystrophy</td>
</tr>
</tbody>
</table>

Treatment of motility disorders ranges from dietary changes or pharmacologic treatment to surgery or intestinal transplantation. Prokinetic drugs such as cisapride, metoclopramide, and octreotide benefit some patients. Patients with acute colonic pseudo-obstruction may benefit from neostigmine treatment. Bowel decompression through gastrostomy and jejunostomy may help some patients. Small bowel transplantation is the only definitive cure for patients with chronic pseudo-obstruction. Candidates for transplantation include those receiving total parenteral nutrition with frequent episodes of sepsis, limited intravenous access to nutritional support, or impending liver failure. However, small bowel transplantation tends to be challenging in this clinical setting.

Normal Neuromuscular Structure

Muscles

The muscularis propria is a continuous structure composed of two smooth muscle layers that extend from the upper esophagus to the anal canal (Fig. 10.1). The only exception to this occurs in the stomach, where three muscle layers are present. At the junctions between adjacent organs, the muscular coat rearranges to form sphincters including the pharyngoesophageal, esophagogastric, pyloric, ileocecal, and anal sphincters. The function of these sphincters is based on physiologic and pharmacologic characteristics of the musculature and on their innervation. The muscle fibers are usually arranged in a concentric circular fashion in the inner muscular layer (the circular layer), whereas the outer muscle fibers are arranged longitudinally (the longitudinal layer). In the cecum and in parts of the colon, the longitudinal muscle is extremely attenuated except in the regions where it forms thick cords (i.e., the taeniae coli).

TABLE 10.3 Disorders Involving the Interstitial Cells of Cajal

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirschsprung disease</td>
<td>Intestinal neuronal dysplasia type A</td>
</tr>
<tr>
<td>Intestinal neuronal dysplasia type B</td>
<td>Congenital hyperplasia of interstitial cells of Cajal</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>Internal anal sphincter achalasia</td>
</tr>
<tr>
<td>Achalasia</td>
<td>Infantile hypertrophic pyloric stenosis</td>
</tr>
<tr>
<td>Visceral myopathies</td>
<td>Diabetic gastroparesis</td>
</tr>
</tbody>
</table>

TABLE 10.4 Secondary Neuromuscular Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
</table>
Circular muscle, from the esophagus to the internal anal sphincter, behaves as an electrical syncytium resulting from nexuses between the plasma membranes of contiguous muscle fibers. These nexuses function as intracellular pathways for excitation conduction between adjacent cells. Even in the absence of neural influences, these syncytial properties allow three-dimensional spread of excitation (6). Smooth muscle cells also contain gap junctions or nexuses that electrically couple adjacent cells (6). The musculature also contains the ICCs, which act as pacemakers for the GI muscle (see below) and facilitate active propagation of electrical events.

**TABLE 10.5 Markers Useful in Evaluating Intestinal Motility Disorders**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Stains</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGP 9.5</td>
<td>nerves</td>
</tr>
<tr>
<td>NSE</td>
<td>nerves, ganglia</td>
</tr>
<tr>
<td>MAP-2</td>
<td>nerves</td>
</tr>
<tr>
<td>NCAM</td>
<td>nerves</td>
</tr>
<tr>
<td>Nerve growth factor</td>
<td>nerves</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>nerves</td>
</tr>
<tr>
<td>Neurofilament protein</td>
<td>nerves</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>nerves</td>
</tr>
<tr>
<td>Ret</td>
<td>ganglia</td>
</tr>
<tr>
<td>Acetylcholinesterase activity</td>
<td>cholinergic nerves</td>
</tr>
<tr>
<td>c-kit</td>
<td>interstitial cells of Cajal</td>
</tr>
<tr>
<td>VIP</td>
<td>VIP-containing nerves</td>
</tr>
<tr>
<td>Substance P</td>
<td>substance P-containing nerves</td>
</tr>
<tr>
<td>S100</td>
<td>Schwann cells and glia</td>
</tr>
<tr>
<td>GFAP</td>
<td>glia</td>
</tr>
<tr>
<td>actin</td>
<td>smooth muscle cells</td>
</tr>
</tbody>
</table>

**FIG. 10.1.** Hematoxylin and eosin–stained section demonstrating the circular and longitudinal smooth muscle layers of the muscularis propria. This layer is present throughout the gastrointestinal tract.

The cells of the muscularis contain numerous receptors, allowing them to respond to neural signals, as well as other stimulatory and inhibitory signals during the digestive process. Contraction of the circular layer constricts the lumen; contraction of the longitudinal layer shortens the digestive tube. When the bowel becomes obstructed or the intestinal lumen distends on a persistent basis, the muscle increases in volume through both hypertrophy and hyperplasia. Smooth muscle hyperplasia also follows myenteric ablation. Obstruction results in a number of changes to both the muscular and neural layers.

**Innervation**

The ENS is the most complex portion of the peripheral nervous system. Three divisions of the nervous system (sympathetic, parasympathetic, and enteric) contribute to the neural control of at least four physiologic effector systems: The visceral smooth muscle responsible for motility and sphincteric functions, the mucosa responsible for gastric acid secretion and intestinal fluid and electrolyte homeostasis, the immune cells responsible for mucosal immunity, and the vasculature. Complex reflex activities involving GI motility, ion transport, and mucosal blood flow all occur in the absence of extrinsic autonomc and sensory input.

Functionally, neurons of the ENS fall into five types: (a) motor neurons, efferent or effector neurons acting to control smooth muscle tone in the wall of the gut; (b) vasomotor neurons, which control vascular muscle tone; (c) secretory neurons, other effector neurons regulating exocrine and endocrine secretion; (d) sensory neurons, which carry sensory information to the central nervous system; and (e) interneurons, which provide communication between neurons and the gut wall (Fig. 10.2). These intermingle in the myenteric and submucosal ganglia.
The ENS consists of three ganglionated plexuses in the gut wall: The myenteric (Auerbach) plexus located between the longitudinal and circular muscle layers of the muscularis propria and the submucosal (Meissner) plexus found in the submucosa. A third plexus, which derives from extrinsic nerves, occurs in the inner quarter of the circular muscle coat adjacent to the submucosa and is rich in ICCs (7). These plexuses extend uninterrupted from the esophagus to the anus, innervating the mucosa, muscle layers, and blood vessels. Interconnections between submucosal and myenteric plexuses coordinate motility and ion transport. Intramural ganglia contain nerve cells, glia (Fig. 10.3), and a neuropil formed by neuronal processes (some of extrinsic origin and others issued by intrinsic neurons) and glial processes. Since neural fibers from many different origins exist within the neuropil, the neuronal organization is extremely complex with controls coming from both the intramural and extramural ganglia.

Generally, the longitudinal musculature is poorly innervated (6). The innervation of the musculature is particularly dense at the level of the sphincters. The anal sphincter has the densest adrenergic innervation found in the GI tract. Most of its fibers originate from the superior mesenteric ganglion, but some derive from ganglionic neurons of the sacral sympathetic chain. Adrenergic fibers are also plentiful in the sphincter of Oddi. Nerve fibers containing VIP are numerous in the musculature of the gastroesophageal junction, the pylorus, and the sphincter of Oddi.

It is estimated that there are more neurons in the GI tract than there are in the spinal cord (8). Neurons of the ENS may be classified by their transmitters. Utilizing this classification, there are at least five types of neurons: (a) cholinergic (acetylcholine containing); (b) adrenergic (norepinephrine containing); (c) GABAergic (γ-aminobutyric acid containing); (d) peptidergic (peptide containing); and (e) nitrergic. The intrinsic nerve fibers are nonadrenergic noncholinergic (NANC) peptidergic nerves. The myenteric plexus neurons may also be viewed as argyrophilic and argyrophobic cells based on their silver staining characteristics. Argyrophilic cells are often multiaxonal. The argyrophobic cells are cholinergic nerve fibers that may directly contact the muscle cells; argyrophobic neurons do not commonly contact muscle cells. Myenteric nerve trunks consist of both extrinsic (sympathetic and parasympathetic) and intrinsic nerve fibers. In most GI regions, the ENS independently regulates many gut functions including motility, vascular tone, secretion, and release of hormones, although the central nervous system modulates the reflexes (9,10).

Normal bolus propagation depends on both cephalic excitation of gut segments producing propulsive pressure and on caudal relaxation and reduction in flow resistance.

Further, active relaxation of the sphincters is critical to prevent functional obstruction of these regions. Motor neurons of the myenteric plexus, which can be excitatory or inhibitory in nature, are responsible for the immediate neural control of gut tone. The major excitatory motor pathway involves acetylcholine, enkephalin, and tachykinins such as substance P and neurokinin A, whereas the main inhibitory transmitters are nitric oxide (NO), VIP, and adenosine triphosphate. Neural NO is produced by neural nitric oxide synthase (nNOS) (11). VIP and NO are cotransmitters in the NANC nerve–mediated smooth muscle relaxation, and part of VIP actions may be mediated by NO (Fig. 10.4) (12). The nitrergic neurons lie within the myenteric plexus. NO is also produced by the smooth muscle cells (13). The pyloric sphincter has the highest nNOS levels (13). The internal anal sphincter also contains high levels of the enzyme (13).
Most patients with congenital myenteric plexus abnormalities fall into one of five categories: (a) aganglionosis, (b) hypoganglionosis, (c) hyperganglionosis, (d) ganglionic immaturity, and (e) poorly classified abnormalities. The pathogenesis of developmental disorders of the ENS results from genetic factors, environmental influences, and cell-cell interactions.

**Development of the Enteric Nervous System**

The ENS develops from vagal and sacral regions of the neural crest. The process begins with the migration of neural crest cells (10). These cells give rise to the enteric ganglia, which are clusters of ganglion cells that develop in the myenteric plexus of the gut. The myenteric plexus is a network of nerve cells that control the smooth muscle of the gastrointestinal tract.

**Intestinal Cells of Cajal**

ICCs act as the pacemaker cells controlling smooth muscle contractions (14). They also act as spatial coordinators (15) and intermediaries in the neural control of gut muscular activity (16). ICCs are present in the esophagus, stomach, small and large intestine, and anorectum (17,18). There are distinct subpopulations of ICCs including intramucosal ICCs, myenteric plexus ICCs, and submucosal ICCs (19). In the esophagus, gastric cardia, and fundus, they are present in the muscularis propria but not in the myenteric plexus or submucosa. In the gastric nonfundic corpus and pylorus and in the intestines, they are present in the myenteric plexus. Submucosal ICCs are seen in the small and large intestines. ICCs express the proto-oncogene c-kit (1), making them easy to visualize with immunohistochemical stains. ICCs have long cell processes and show bipolar or multipolar configurations.

**TABLE 10.6: Genes Involved in Enteric Nervous System (ENS) Development**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Intestinal Phenotype after Genetic Manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ednrb (endothelin receptor B) Growth factor receptor</td>
<td>Neural crest cells in Ednrb knockouts fail to colonize the hindgut</td>
</tr>
<tr>
<td>Hox-4</td>
<td>Transgenic animals show abnormal ganglia in the colon and short segment hypoganglionosis in the distal colon</td>
</tr>
<tr>
<td>Mash-1</td>
<td>Knockout leads to aganglionosis of the esophagus and gastric cardia; absence of early lineage of enteric neurons in the rest of the bowel</td>
</tr>
<tr>
<td>NCX1</td>
<td>Homozygous-targeted disruption animals show neural hyperplasia and hyperganglionosis</td>
</tr>
<tr>
<td>Phox2P</td>
<td>Phox2 knockout mice die in utero. There is an absence of foregut and midgut ENS</td>
</tr>
<tr>
<td>Sox 10</td>
<td>Sox transgenics develop distal intestinal aganglionosis and die shortly after birth</td>
</tr>
</tbody>
</table>

At birth, normal enteric ganglia contain both mature and immature neurons. Premature infants have more immature neurons than term infants. Mature neurons are larger than immature neurons and they have a distinct cell membrane, a vesicular nucleus, and a large amount of basophilic cytoplasm. Immature neurons are small cells with dark nuclei, clumped chromatin, and scant cytoplasm (Fig. 10.6). Neural stains highlight immature neurons. The normal mature colon contains 7 ganglion cells/mm of myenteric plexus, 3.6/mm in the jejunum, and 4.3/mm in the ileum in 3 micron sections (31). Ganglion cells lie approximately 1 mm apart; they may occur in clusters of from one to five cells in normal adults (32). Normal neonates often have plentiful, prominent ganglion cells, but they appear small when they are immature (30).

Most patients with congenital myenteric plexus abnormalities fall into one of five categories: (a) aganglionosis, (b) hypoganglionosis, (c) hyperganglionosis, (d) ganglionic immaturity, and (e) poorly classified abnormalities. The pathogenesis of developmental disorders of the ENS results from genetic factors, environmental influences, and cell-cell interactions.
defects, failed neural crest migration or differentiation, anoxia, or inflammation. Developmental neural diseases occur alone or coexist with systemic disorders such as neurofibromatosis.

**Hirschsprung Disease**

Synonyms for Hirschsprung disease include aganglionic megacolon, congenital megacolon, and aganglionosis.

HD is a congenital disorder characterized by intestinal megacolon, neural hyperplasia, and aganglionosis. Several forms of the disease are recognized.

- **Classic form:** The aganglionic segment begins in the distal colorectum and extends proximally for variable distances into the adjoining proximally dilated bowel (Fig. 10.7).
- **Short segment form:** The aganglionic segment involves several centimeters of the rectum and rectosigmoid. The aganglionic segment may be as short as 3 cm, so that this variant may be missed if the biopsy is taken too high above the pectinate line. This form affects 67% to 90% of patients.
- **Long segment form:** The aganglionic segment extends beyond the sigmoid and involves a variable length of colon but does not extend beyond the cecum. This form affects <10% of patients (33).
- **Total colonic aganglionosis:** The entire colon is involved along with variable lengths of ileum, jejunum, and even the stomach. This form affects 2.6% to 14.9% of cases. This form almost always presents in the first weeks of life.
- **Zonal colonic aganglionosis** (synonym: Skip segment HD): A short bowel segment is involved in this form of HD (Fig. 10.8). Ganglion cells are present, both proximal and distal to the aganglionic segment. (This form of the disease may in fact not be HD, but the result of intrauterine injury.)

HD affects 1 in every 5,000 to 30,000 live births; 80% of patients are male (34). Approximately 4% to 6% of cases are familial (34), especially when the megacolon extends to the cecum. Five percent of patients have an affected sibling (35).

---

**FIG. 10.5.** Fetal plexus stained with an antibody to neurofilament protein. **A:** A 13-week fetus with only rare cells immunoreactive for neurofilament protein. Note the lack of dendritic processes. **B:** A 15-week fetus showing further development of the neuroblastic cells and the beginning of the appearance of dendritic processes. **C:** A 17-week fetus with better developed processes and the beginning appearance of submucosal plexuses with fibers having neuronal extensions.

---

**FIG. 10.6.** Fetal gut stained with hematoxylin and eosin. Note the presence of immature neuroblastic cells without clearly identifiable ganglia (arrows).

---

**Etiology and Pathophysiology of the Disease**

---
HD is a heterogeneous genetic disorder with autosomal dominant, autosomal recessive, and polygenic forms of inheritance. Current etiologic hypotheses revolve around two major schools of thought: Arrested neuroblast migration and intestinal microenvironmental abnormalities that cause failed neuronal differentiation. Specific genetic mutations are present in about 50% of cases. Much of the phenotypic variability of the disease relates to the biologic complexity underlying the normal development of the ENS and the diversity of the molecular alterations that have been identified. Thus, no single genetic abnormality accounts for the development of the disease.

There are several susceptibility genes for HD (Table 10.7) (36,37,38,39,40,41,42,43,44). Other genes that may be abnormal include endothelin-converting enzyme and the transcription factor Sox10 (40,41). Several genes may modify the severity of the HD phenotype in patients with or without coexisting intestinal neuronal dysplasia. These may lie near 21q22 (43) and may account for the prevalence of HD among patients with trisomy 21 (43). The nerves in HD also fail to express the trkC tyrosine receptor and its ligand neurotrophin, suggesting that neurotrophic factors that are critical for cellular survival and differentiation may play a role in the pathogenesis of HD (45).

The RET protein is a tyrosine kinase receptor with extracellular cadherin-like and cysteine-rich domains, a transmembrane domain, and an intracellular tyrosine kinase domain (46). Point mutations in the RET gene give rise to HD, multiple endocrine neoplasia (MEN) types IIA and IIB, and familial medullary thyroid carcinoma (47). In the case of MEN-II, the RET mutations are activating, enhancing the function of the encoded protein, whereas in HD, the mutations are inactivating, leading to loss of its function (48). A ret codon 618 ser mutation could predispose patients with MEN-IIA to HD (49).

More than 50 RET mutations, including missense, nonsense, deletion, and insertion mutations, have been described in HD. These mutations occur throughout the gene, without any mutational hot spots (50). They fall loosely into two groups: Frame shift or missense mutations that disrupt the structure of the intracellular tyrosine kinase domains and missense mutations in exons 2, 3, 5, or 6 of the extracellular domain (51). Patients with mutations of the intracellular domain have either short segment or long segment HD, whereas those with mutations in the extracellular domain all have long segment HD. RET mutations are more common among familial cases (50%) than among sporadic cases (15% to 33%) (50). Immunohistochemically, the bowels of patients with HD show reduced ret protein expression.
Chapter 10

Mutated Gene | Function | Disease
---|---|---
ret (intracellular tyrosine kinase domain) | Tyrosine kinase receptor | Short segment HD
ret (extracellular domain) | Tyrosine kinase receptor | Long segment HD
Endothelin B receptor (EDNRB) | Growth factor receptor | Short segment HD
EDN3 | Ligand for EDNRB | Shah-Waardenburg syndrome
Gial cell line–derived neurotropic factor (GDNF) | Ligand for ret | Serves as HD modifier
Neurturin | Ligand for ret | Serves as HD modifier
SMADIP1 | Transcription factor | Syndromic HD with microcephaly, facial dysmorphism, and mental retardation

In addition to the presence of specific RET mutations that may lead to the development of HD, there are also RET intragenic polymorphisms that lead to various clinical phenotypes (52). The c135G/A polymorphism or sequence variations in linkage disequilibrium with this polymorphism modulate the phenotypic influences of RET germline mutations. The c135A variant associates more commonly with short segment disease when it is on the same chromosome with the germline mutation (52).

Alterations in the intrinsic gastrointestinal innervation contribute to the clinical and pathologic features of HD. VIP and NO, components of the NANC system that relax smooth muscle and form part of the inhibitory component of the peristaltic reflex, are absent (53,54,55). However, extrinsic parasympathetic, cholinergic, and sympathetic adrenergic innervation persist. As a result, the distal aganglionic bowel is under constant, unopposed extramural stimulation so that it becomes narrowed, spastic, and unable to support peristalsis. There are also conflicting reports on the ICCs in HD. Some authors find normal numbers of ICCs, whereas others suggest that they are decreased in number.

The pathogenesis of the enterocolitis, which affects some patients, is not well understood. It is likely to result from the toxemia due to bacterial stasis in the dilated colonic lumen. Risk factors for enterocolitis include a delayed diagnosis of HD, long segment disease, family history for HD, female gender, and trisomy 21 (56).

**Clinical Features**

HD is the most common form of congenital intestinal obstruction, often presenting within the first 24 to 48 hours of life. Up to 80% of cases are diagnosed during the first year of life; 10% first present in adults. Typically, the lack of propulsive movements and inhibitory reflexes in an intestinal segment leads to abdominal distension, vomiting, severe constipation, and marked dilation of the proximal ganglionic segment. Infants with obstruction but without meconium should be suspected of having HD involving the entire colon. Reduced food intake and malabsorption result in failure to thrive. As the nutritional status deteriorates, infections may worsen the underlying motility problem. Some patients develop mucosal prolapse at the juncture of the ganglionic and aganglionic bowel due to differential luminal pressures in these bowel segments. Mucosal prolapse is more prominent in older patients and correlates with disease duration. HD patients may also present in the neonatal period with perforation due to a coexisting necrotizing enterocolitis. The enterocolitis has an ischemic basis and is characterized by mucosal ulceration, colonic bleeding, perforation, sepsis, and toxemia. Patients with trisomy 21 exhibit an increased incidence of HD-associated enterocolitis (56).

Ten to fifteen percent of patients have associated congenital anomalies or other diseases (Table 10.8). Ten percent of patients have Down syndrome; 5% have other serious neurologic abnormalities (57).

**Pathologic Findings**

The widely dilated, fluid-filled, hypertrophic colon empties into a funnel-shaped transitional zone extending to the anus (Fig. 10.7). Plain abdominal films may show air-fluid levels. The anal canal and rectum are small and empty, and the anal sphincter is tight. In adults, an abrupt, smooth rectal transition zone with proximal colonic dilation, in the setting of an appropriate clinical history, suggests the diagnosis. A diagnosis of HD is usually made on a suction rectal biopsy containing both the mucosa and submucosa since the aganglionosis coincides closely in both the submucosal and myenteric plexuses. Biopsies are usually taken 2 cm from the pectinate line and at about a 5-cm distance. In very small neonates, the biopsy is taken just above the pectinate line and as high as can be taken safely without risking perforation. Two biopsies, one to overcome the possibility of a hypoganglionic segment, and to provide guidance as to the length of the aganglionic segment. Full-thickness rectal biopsy is reserved for patients in whom the diagnosis cannot be made with a more superficial biopsy.

**Table 10.8 Other Abnormalities Affecting Patients with Hirschsprung Disease**

<table>
<thead>
<tr>
<th>Genetic abnormalities</th>
<th>Congenital abnormalities</th>
<th>Tumors</th>
<th>Other syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>Deafness</td>
<td>Neuroblastoma</td>
<td>Pallister-Hall syndrome</td>
</tr>
<tr>
<td>Tetrasomy 9p</td>
<td>Intestinal malrotation</td>
<td>Neurofibromatosis</td>
<td>Jaw winking syndrome</td>
</tr>
<tr>
<td>Tetrasomy 9q</td>
<td>Esophageal and intestinal atresia</td>
<td>Medullary carcinoma of the thyroid</td>
<td>Haddad syndrome</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>Hypothalamic hamartoblastoma</td>
<td>Pheochromocytoma</td>
<td>Goldberg-Shprintzen syndrome</td>
</tr>
<tr>
<td>Deafness</td>
<td>Cartilage–hair hypoplasia</td>
<td>Other syndromes</td>
<td>Achalasia</td>
</tr>
<tr>
<td>Intestinal malrotation</td>
<td>Dandy–Walker cysts</td>
<td>Pallister-Hall syndrome</td>
<td>Multiple endocrine neoplasia type IIIB</td>
</tr>
<tr>
<td>Esophageal and intestinal atresia</td>
<td>Brachydactyly and polydactyly</td>
<td>Jaw winking syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Typical features of HD include aganglionosis (Fig. 10.9) and increased numbers of hypertrophic, nonmyelinated, submucosal, and myenteric plexus cholinergic nerves (part of the extrinsic parasympathetic innervation) (Fig. 10.10). While neural hyperplasia is characteristic of HD, it should be noted that neural hyperplasia is present in other disorders (Table 10.9). Ganglion cells are absent from both plexuses in the distal narrowed bowel and are decreased in number in the first few centimeters of the transitional zone. An increase in the number of ganglion cells occurs as one progresses proximally into the funnel-shaped transitional zone and into the normally innervated bowel. The transitional zone usually occurs over a short distance with ganglia appearing almost simultaneously in both the myenteric and submucosal plexuses. Some patients have longer transitional zones than others; prominent nerve trunks may be present for several centimeters. The transitional zone may contain abnormally shaped ganglia. Some transition zones show features of colonic neuronal dysplasia (see below).
FIG. 10.10. Hypertrophic nerve in Hirschsprung disease stained with an antibody to S100.

In premature infants it may be difficult to recognize the immature ganglion cells due to their small size and inconspicuous nuclei (Fig. 10.6). They form rosettelike structures arranged around a central neuropil-type matrix producing a horseshoelike structure. The immature ganglia may mimic macrophages, smooth muscle cells, and Schwann cells. The ganglia may be highlighted with special stains. However, it should be kept in mind that immature ganglia may fail to stain with ganglionic markers. These patients also have decreased numbers of synaptophysin-positive synapses in the circular and longitudinal muscle layers in the transitional segments and in aganglionic segments (58) and the adrenergic and peptidergic innervation of aganglionic gut is abnormal. Patients also have a relative loss of ICCs (59), although this finding is not present in all studies (60). Increased numbers of mast cells, often in direct contact with the hypertrophic nerves, are present. These produce nerve growth factor, which stimulates neural growth.

### TABLE 10.9 Conditions Associated with Hyperplasia of the Myenteric Plexus

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirschsprung disease</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type IIB</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Neuronal dysplasia</td>
</tr>
<tr>
<td>Hyperganglionosis with ganglioneuromatosis</td>
</tr>
<tr>
<td>Hyperplastic response to many forms of injury</td>
</tr>
</tbody>
</table>

Frequently, the bowel wall proximal to the aganglionic segment is biopsied at the time of surgery to ensure that the proximal resection margin is normal. Submucosal nerve trunks >40 µm in diameter or abnormal-appearing ganglia strongly correlate with abnormal innervation and aganglionosis (Fig. 10.11) (81). If hypertrophic nerve trunks or abnormal ganglion cells are present in frozen sections, the surgeon should extend the resection proximally and monitor it with additional frozen sections to identify a region that contains completely normal neural structures in order to prevent recurrent disease. Once resection specimens are received, the extent of the aganglionosis should be determined and the status of the proximal margin should be ascertained, if this was not done intraoperatively. Patients who develop postoperative symptoms may have either a retained portion of the transitional zone with neuronal dysplasia or an aganglionic segment or they may have developed an acquired disorder secondary to postoperative ischemia or infection.

If enterocolitis develops, the histology may include crypt dilation with mucin depletion, cryptitis, crypt abscesses, mucosal ulcers, transmural necrosis, and perforation. Enterocolitis affects both ganglionic and aganglionic intestinal segments, and resembles other forms of enterocolitis. Pneumatosis intestinalis may be present. One occasionally sees abnormal submucosal blood vessels in HD. The abnormal arteries are most conspicuous in the transitional zone, where they appear thickened and may show bizarre microscopic changes. Adventitial fibromuscular dysplasia, as evidenced by increased collagen around the internal elastic lamina, marked hypertrophy of the media, and obliterator endarteritis, also develops (62). The vascular changes predispose to ischemic injury.

### Histologic Variants

There are several histologic variants of HD. One associates with intestinal neuronal dysplasia. Generally, there is a hypoganglionic transitional zone at the cranial end of the aganglionic segment, but hyperganglionic segments can also be found. Total colonic aganglionosis can be divided into two groups based on the histologic findings. Some cases are histologically similar to short segment and long segment disease, whereas in others, the bowel is aganglionic but there is little or no neural hyperplasia. The latter finding can lead to a false-negative diagnosis.

In HD with coexisting intestinal neuronal dysplasia (IND), the IND lies within, or just proximal to, the aganglionic transitional zone. Patients have also been described with aganglionosis involving the entire colon and terminal ileum and coexisting jejunal and gastric IND. The IND accounts for residual symptoms in HD patients following pullthrough operations (63).
FIG. 10.11. Hirschsprung disease. A: Full-thickness section through the wall demonstrates the usual layers, but no ganglion cells. B: High-power magnification of the myenteric plexus shows abnormal small ganglion cell in the transitional area. C: A higher power magnification of another abnormal-appearing ganglion cell. D: Abnormal ganglion compared to a normal ganglion (E).

Zonal aganglionosis, or skip segment HD, may affect some patients with total colonic aganglionosis (64). In this setting, one sees variable lengths of hypoganglionic or normoganglionic transverse or ascending colon resulting in a segmental aganglionic colon. Normal distal innervation or a skip area containing some ganglia is present within an area of aganglionosis (64). Such cases are thought to have an ischemic origin. If biopsies are performed on the unaffected segments, the diagnosis will be missed.

Special Techniques for Evaluating Hirschsprung Disease Specimens

Acetylcholinesterase (ACE) enzymatic staining (Fig. 10.12) demonstrates an increased network of coarse, thickened, irregular, cholinergic nerve fibers within the muscularis mucosae and lower mucosa. The lamina propria fibers travel in a plane parallel to the mucosal surface. Numerous submucosal small nerve fibers and smaller and larger nerve trunks may also be present. This pattern is evident even in the most distal biopsies, including those from the mucocutaneous junction. Increased ACE nerve fibers are consistently present in short and long segment HD, but they may be absent in total colonic aganglionosis. ACE staining patterns are also less dramatic in neonates than in older individuals, possibly leading to false-negative diagnoses.
FIG. 10.12. Acetylcholinesterase staining reactions. The positive reaction is shown by the blackish brown color. A: Normal bowel characterized by the presence of thin, wispy, acetylcholinesterase-positive nerve fibers within the muscularis mucosa. None is present in the overlying lamina propria of the mucosa. B: Patient with Hirschsprung disease demonstrating thick, irregular fibers both within the muscularis mucosae and extending up into the lamina propria and around the glands. (Pictures courtesy of Dr. Kevin Bove, Cincinnati Children's Hospital.)

The common procedure for the ACE staining is as follows: Two mucosal suction biopsies are obtained 3 to 4 cm above the pectinate line. One is snap-frozen at the bedside. The other is placed in formalin for paraffin embedding. Delayed freezing after specimen delivery may cause false-negative results due to enzyme degradation. The frozen sample is cut in a plane perpendicular to the mucosal surface. Several paraffin sections are used to complement the evaluation of acetylcholinesterase activity. The special stains listed in Table 10.5 help delineate specific structures.

Treatment and Prognosis

Surgery is invariably necessary to treat symptomatic HD and the HD-associated enteroocolitis. Persistent constipation is the most important long-term problem in patients operated on for HD. Inadequate resection, anastomotic strictures, coexisting IND, or achalasia of the internal anal sphincter may also cause these sequelae.

Intestinal Neuronal Dysplasia

IND, another developmental abnormality involving the ENS, occurs in two forms: Type A is characterized by decreased or immature gastrointestinal sympathetic innervation, and type B is characterized by increased numbers of ganglion cells, a dysplastic submucosal plexus, and defective neuronal nerve fiber differentiation (65,66). IND type A is also known as hypoganglionosis. IND type B is also known as hyperganglionosis. The entity known as oligoneural disease, which is sometimes called the hypogenetic type of dysganglionosis (67), may also be a form of intestinal neuronal dysplasia type A. These diseases are poorly understood and widely used consensus definitions for each entity are not available.

**Intestinal Neuronal Dysplasia Type A**

IND type A is very rare, and the symptoms caused by hypoganglionosis resemble those seen in HD. In newborns, there may be delayed meconium discharge; affected infants and small children have rare bowel evacuations that respond to enemas. With increasing age, fecal masses can be palpated through the abdominal wall. The colon becomes dilated and contains fecalomas. Distension causes intermittent colicky pain, often relieved by massive flatulence. Some children experience overflow discharge of sometimes bloody stool.

The diagnosis of hypoganglionosis is usually difficult to establish. X-ray studies, determination of transit times, and anorectal manometry are unreliable indicators of the disease. The disorder is characterized by an immaturity or hypoplasia of the extrinsic sympathetic nerves supplying the gut (68). Hypoganglionosis occurs in three forms: (a) an isolated form occurring as a segmental or even disseminated disease, (b) hypoganglionosis of variable length adjacent to an aganglionic HD, and (c) hypoganglionosis in combination with IND type B of a proximal segment. Hypoganglionosis may result from a developmental hypoplasia of the myenteric plexus (65), possibly due to the absence or abnormal expression of neurotrophic factors.

Patients with IND type A have reduced numbers of myenteric ganglia and myenteric plexus neurons, no or low colonic mucosal ACE levels, and secondary hypertrophy of the muscularis mucosae and the circular muscle of the muscularis propria. Absent or small submucosal and myenteric ganglia containing only one or two ganglia and immature neuroblastlike cells extend throughout the affected parts of the gut. Some patients have irreversible neuronal degeneration. Patients with IND type A may also have reduced numbers of ICCs, perhaps contributing to the dysmotility (69).

There is no consensus of how few ganglion cells there should be to make a diagnosis of hypoganglionosis. Meier-Ruge suggests that a 50-fold decrease in the number of ganglion cells per centimeter of bowel as compared to normal bowel is diagnostic (66). The distance between the ganglia in hypoganglionosis is nearly double that of the normal bowel. The treatment of hypoganglionosis (IND type A) is resection of the affected bowel and a pullthrough operation.

**Intestinal Neuronal Dysplasia Type B**

In contrast to IND type A, the incidence of IND type B varies from 0.3% to 40% of rectal suction biopsies (65,66). The mean age at diagnosis is 1.5 years. It occurs as an isolated disorder or it complicates many disorders (Table 10.10) (68,70). Patients with MEN-IIB and IND type B have RET mutations. In some cases, IND and neurofibromatosis are familial and associate with a tandem duplication in the NFI gene and a reciprocal translocation (115;16) (q26.3;q12.1) (71). IND may also be one component of a complex malformation pattern.

IND type B clinically both mimics and complicates HD, as discussed in an earlier section. Patients present with nausea/vomiting, diarrhea, constipation, intestinal obstruction, intussusception, and volvulus. Symptoms develop insidiously, with progressive development of severe constipation that results in overflow incontinence (66). Many patients eventually spontaneously develop normal colonic motility (66). A significant number of patients develop severe intra-abdominal complications during the perinatal period, including necrotizing enterocolitis (NIEC), meconium ileus, or bowel perforations. Such complications are especially common in premature neonates.

<table>
<thead>
<tr>
<th>TABLE 10.10 Conditions That May Be Associated with Intestinal Neuronal Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
In mucosal, submucosal, and arterial adventitial nerves, neuronal dysplasia can be diffuse, involving both the small and large intestine, and may remain confined to a single intestinal segment. Extensive disease may involve the stomach and esophagus. The bowel grossly appears either normal or variably dilated.

Controversy exists over the diagnostic criteria of IND type B. The diagnostic controversy is best exemplified by a study in which three pathologists agreed on the diagnosis in only 14% of children without aganglionosis (72). Smith also found that according to the criteria described by Borchard, only 11% of patients with megacolon had the obligatory criteria (hyperplasia of the submucosal plexus, an increase in ACE-positive nerve fibers around submucosal blood vessels, and ACE activity in the lamina propria) (73). The diagnosis of IND type B is also complicated by the fact that the density of ganglion cells in the myenteric plexus decreases significantly with age during the first 3 to 4 years of life and estimates of nerve cell density are influenced by section thickness (74). The diagnostic criteria of IND type B have included prominent hyperplasia of the parasympathetic myenteric and submucosal plexuses characterized by increased numbers of neurons and ganglia (Fig. 10.13); giant submucosal ganglia containing 7 to 15 ganglion cells; hypertrophic nerve bundles containing increased numbers of thickened, beaded, and disorganized axons (Fig. 10.13); increased ACE activity; increased NCAM and nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase activity (75).

Neuronal dysplasia can be diffuse, involving both the small and large intestine, or it may remain confined to a single intestinal segment. Extensive disease may involve the stomach and esophagus. The bowel grossly appears either normal or variably dilated.

Controversy exists over the diagnostic criteria of IND type B. The diagnostic controversy is best exemplified by a study in which three pathologists agreed on the diagnosis in only 14% of children without aganglionosis (72). Smith also found that according to the criteria described by Borchard, only 11% of patients with megacolon had the obligatory criteria (hyperplasia of the submucosal plexus, an increase in ACE-positive nerve fibers around submucosal blood vessels, and ACE activity in the lamina propria) (73). The diagnosis of IND type B is also complicated by the fact that the density of ganglion cells in the myenteric plexus decreases significantly with age during the first 3 to 4 years of life and estimates of nerve cell density are influenced by section thickness (74).

The diagnostic criteria of IND type B have included prominent hyperplasia of the parasympathetic myenteric and submucosal plexuses characterized by increased numbers of neurons and ganglia (Fig. 10.13); giant submucosal ganglia containing 7 to 15 ganglion cells; hypertrophic nerve bundles containing increased numbers of thickened, beaded, and disorganized axons (Fig. 10.13); increased ACE activity; increased NCAM and nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase activity (75).

**FIG. 10.13.** Four-month-old infant with intestinal neuronal dysplasia type B. The hypertrophic nerves are accentuated by an S100 immunostain.
Patients with IND may also exhibit ICC hyperplasia (77). When it is marked, it can be visible grossly as a thick, white, fibrous band between the inner circular and outer longitudinal muscle layers throughout the full length of the resected bowel, especially in children with neurofibromatosis type 1 (NF-1). Microscopically, this bandlike layer consists of haphazardly arranged spindle to oval-shaped cells. The nuclei are long and oval in shape with slightly tapered ends and possess hyperchromatic or clumped chromatin and occasional small nucleoli. The cells have a moderate amount of eosinophilic cytoplasm; mitotic figures are rare. The muscle layers are partially replaced by these hyperplastic spindle cells and focally the full thickness of the inner muscular layer can be involved. Residual myenteric plexus can be identified in the midst of the hyperplastic cells. The hyperplastic cells are c-kit positive. Patients with IND often have large numbers of most cells in the bowel wall compared to the normal colon. Mast cells produce nerve growth factors that support the development and functional maturation of the sympathetic and cholinergic neurons, and they may be important in the neuronal hyperplasia seen in this condition (78). We have also seen enteroendocrine cell hyperplasia associated with hyperganglionosis in the neonate.

Individuals with IND also often have secondary changes in the muscularis propria. There may be areas of significant muscle atrophy in one or another layer of the muscularis propria. Alternatively, there may be hyperplasia of either the circular or longitudinal layer of the muscularis propria or these two changes may both be present. These changes may be focal or diffuse in nature and they may be present in the circular layer in some parts of the gut and in the longitudinal layer in others. These secondary changes undoubtedly reflect abnormal innervation of the muscle layers and the neuromuscular junction.

Overall, it would be desirable to have better quantitative diagnostic criteria of IND to distinguish normal variants from pathologic conditions, particularly in very young children. Moore et al introduced a morphologic scoring system based on the finding of hyperganglionosis, giant ganglia, neural maturation, heterotopic neuronal cells, and ACE activity in the lamina propria, muscularis mucosae, or adventitia of submucosal blood vessels. Hyperganglionosis and increased ACE activity of nerve fibers in the lamina propria had major importance in this scoring system (79). The best diagnostic indicator of IND in adults may be the detection of six to ten giant ganglia with more than seven nerve cells in 15 biopsy sections (80).

Some patients, especially those with IND type B, outgrow their disease as the ENS matures. Patients with persistent symptoms are managed with prokinetic agents, colonic irrigations, and cathartics. If bowel symptoms persist after 6 months of conservative treatment, surgery is often considered.

Resection and pullthrough operations may be indicated in extensive IND.

Hyperganglionosis and Ganglioneuromatosis

Patients with hyperganglionosis and diffuse ganglioneuromatosis (Fig. 10.15) almost always have MEN-IIb and a mutation in the RET gene. The changes may associate with or be a form of IND type B.

Neuronal Immaturity

Neuronal immaturity, also known as neuronal maturational arrest syndrome, is characterized by the failure of neural elements to mature properly so that the ganglia appear immature and the patients present with clinical features resembling HD and IND. There may be overlap with IND. The underlying cause of failed neuronal maturation is unknown. Pathogenetic mechanisms may include (a) failure of normal numbers of neural crest cells to migrate into the gut, (b) inadequate neural proliferation in the gut, or (c) lack of growth or death of neuroblasts once they arrive in the gut due to the failure of the local microenvironment to support normal neuronal development during fetal life. There may also be a lack of neurotrophins since the latter are known to be important in neuronal development, differentiation, maturation, survival, and maintenance. There may also be absence or delayed maturation of the ICCs, contributing to pseudo-obstruction in neonates.

The histologic features differ depending on the stage at which myenteric plexus development ceased. Patients exhibit several major histologic abnormalities: (a) no myenteric plexus seen on either H&E or specially stained sections, (b) small numbers of neuronal structures (ganglia and nerve trunks), or (c) an apparently normal myenteric plexus seen on H&E-stained sections but a neural deficiency shown by silver or immunohistochemical staining. The immature neurons lack neurofilaments. The ganglion cells may also line up at the periphery of the ganglia (ring-shaped ganglia) as occurs in premature infants (Figs. 10.16 and 10.17). There is no inflammation or neural degeneration. These findings contrast with those seen in patients with HD or IND type B in that there is no neural hyperplasia, but as noted there may be overlap with IND.

Neuronal immaturity often spontaneously improves with conservative therapy and the normal development of the child unless it occurs as part of IND. In other patients the changes persist.

Congenital Hyperplasia of Interstitial Cells of Cajal

As noted earlier, ICCs are the pacemaker cells of the GI tract that initiate peristalsis in the stomach and the intestines.

![Image](https://example.com/image.png)
Chapter 10

FIG. 10.15. Patient with pseudo-obstruction, intestinal neuronal dysplasia, and ganglioneuromatosis. A: Gross appearance of the bowel lumen demonstrates numerous polyps. B: Histologic examination shows a cellular proliferation that obliterates the normal mucosal–submucosal junction. C: Section through the base of the polyp showing a ganglioneuroma. D: Higher power magnification shows the neural tissue and ganglion cells. E: Submucosal ganglion demonstrating peripheral fibrosis and abnormal architecture. F: The architecture of the myenteric plexus is abnormal and there are numerous inflammatory cells within the myenteric plexus. (Case courtesy of Dr. E. Foucar, Albuquerque, NM.)

FIG. 10.16. Infant with pseudo-obstruction and neuronal immaturity. The submucosa contains ring-shaped ganglia.

Absent Enteric Nervous System

The absence of nerves and ganglia from the stomach to the colon characterizes the absent enteric nervous system. This very rare disorder presents as severe perinatal pseudo-obstruction. No nerves or ganglia are present in either the submucosal or myenteric plexus, or in the muscularis propria. S100 and ACE staining confirm the absence of enteric neural structures. Sparse PGP 9.5–positive extrinsic nerve fibers are present in the submucosa. Prominent ICCs are present in the area between the circular and longitudinal muscle layers in a normal distribution in some parts of the gut. In other parts they are absent or in various stages of destruction. The overall prognosis is poor (81).
Pediatric Motility Disorders not Fitting Specific Diagnostic Criteria

Damage to the ENS results in enteric neuropathies, the best characterized of which is HD. However, a number of children present clinically with pseudo-obstruction syndromes in the first few weeks, months, or years of life who lack the classic features of either HD or IND (type A or B). These cases are challenging for clinicians to manage and they often look to the pathologist for help in establishing a diagnosis that will guide them into the appropriate therapy for the affected children. Pathologic features are not readily associated with clinical findings and vice versa.

The cases that we see in consultation are challenging in this regard since they often lack features that allow them to be easily categorized (Fig. 10.18). We have seen examples of neuronal immaturity with variable numbers of ganglia and with or without obvious neural disorganization in the bowel wall. Increased, thickened nerve fibers with or without giant ganglia or aganglionosis cases are also encountered. There may be cases with neural degeneration, variable inflammation, and increased apoptosis. We have also seen some cases associated with myenteric plexus loss and cases of hypo- or aganglionosis with shrunken ganglia and dense submucosal fibrosis that may be the equivalent of what has been described as zonal HD. Often in these cases there is a history of intestinal atresia, and we have interpreted such cases as representing prenatal neural injury rather than HD. This injury is likely to be ischemic in nature, complicating the complex series of intestinal twists and turns that associate with fetal intestinal development. Ischemia secondary to malrotation or other events may damage the neuromuscular structures of the gut, especially in the intestines.

The development of the gastrointestinal tract is in some ways more complex than other organ systems with marked lengthenings, rotations, and a cranial-caudal differentiation gradient. Additionally, as noted in earlier sections of this chapter, ENS development is a complex process that is governed by the interactions of numerous proteins that are responsible for neural migration, growth, differentiation, and survival. Alterations in any of these proteins can presumably result in disorders that present clinically like HD but fail to meet the diagnostic criteria for that disease. Lastly, the developing ENS may be negatively influenced by other fetal events such as intrauterine infections that may lead to ganglionic loss or other neural abnormalities.

A specific patient with a motility disorder may show one or more of the following abnormalities: Aganglionosis, hypoganglionosis, intestinal neuronal dysplasia, neural hyperplasia including ganglineuromas, neural intraneuronal inclusions, inflammatory changes, neural degeneration or apoptosis, or alterations in the ICC. Hypoganglionosis occurring in the pediatric population may represent one of several entities. It may be a finding in the transitional zone of patients with HD or represent IND type A, or it could be a finding associated with neuronal immaturity. It may also be unrelated to any of these diseases and represent a failure of the cells to migrate or grow in the gut or represent the loss of cells once neuroblastic migration has occurred.

Given the confusion surrounding the diagnosis of pediatric motility disorders, the question arises how to best diagnose the changes present. Our current practice is to diagnose HD, IND, or neuronal immaturity if classic features of these diseases are present. In cases in which the pathologic findings do not fit a specific diagnostic entity we tend to be descriptive, listing the major findings that are present and stating whether these findings could account for the clinical findings. Perhaps a standardized template approach to reporting these cases could lead to a better understanding of pediatric motility disorders in general. Once such approach is shown in Table 10.11. If one does not have tissue for ACE staining, the abnormal neural proliferations can be highlighted by silver stains or antibodies to synaptophysin, S100, neuron-specific enolase (NSE), PGP 9.5, NPY, or neurofilament protein.

These makers will only identify the neural hyperplasia and will not allow one to determine whether or not the nerves are cholinergic.

### TABLE 10.11 Possible Template for Reporting Pediatric Motility Disorders That Fail to Meet the Diagnostic Criteria of Hirschsprung Disease or Intestinal Neuronal Dysplasia

---

FIG. 10.17. Infant with pseudo-obstruction and neuronal immaturity. This picture of the myenteric plexus is from the same case that is shown in Figure 10.16. A number of immature ganglion cells line up at the periphery of the myenteric plexus.

FIG. 10.18. Example of a neuropathy in a 1-month-old with pseudo-obstruction that is difficult to classify into currently recognized disorders. Ganglia are present in both the submucosal (A) and myenteric plexus (B). They are neither increased nor decreased in number but they appear small and shrunken. There is no neural hyperplasia.
Ganglia
Present
Absent
Reduced in number

Giant ganglia present (highest number of ganglion cells in a single ganglion)
No giant ganglia present

Inflammation: Present or not
Mature or immature

Ectopic ganglion cells in the muscularis mucosae or lower mucosa: Present or absent

Histologically normal or shriveled

Staining characteristics with special stains: State the stains that are positive and negative

Neural hyperplasia (present or absent)

Seen on hematoxylin and eosin

Acetylcholinesterase stains

Interstitial cells of Cajal

Normal numbers
Hyperplasia
Reduced in number

Familial Visceral Neuropathies

Hereditary familial visceral neuropathies are a rare group of genetic diseases characterized by pseudo-obstruction (Fig. 10.19) and by myenteric plexus abnormalities with variable inheritance patterns and characteristic clinical and extraintestinal manifestations (Table 10.12). The nerves often appear vacuolated (Fig. 10.20). Silver stains or immunostains highlight both the number and the shape of the myenteric plexus neurons and nerve fibers.

Neuronal Intranuclear Inclusion Disease

This disease presents with symptoms of intestinal pseudo-obstruction, diffuse neurologic abnormalities, evidence of mild autonomic insufficiency, and denervation hypersensitivity of the smooth muscles (82,83). Patients characteristically pass less than one stool per week despite the use of laxatives and enemas (82), and they exhibit abnormal esophageal, small intestinal, and colonic motility. Patients also develop gastroparesis, neurogenic bladder, and atrophy in other organs. The abnormalities are restricted to the myenteric plexus with a significant reduction in the number of neurons, a third of which contain a round, eosinophilic intranuclear inclusion (82). Most remaining neurons are misshapen with reduced numbers of nerve fibers in the nerve tracts. Ultrastructural examination in this autosomal recessive visceral neuropathy shows intranuclear neuronal inclusions consisting of a random array of straight or slightly curving filaments. They have a characteristic beaded pattern with a periodicity of 15 to 30 nm and measure 17 to 27 nm in diameter.

Autosomal Recessive Disease with Mental Retardation and Calcification of Basal Ganglia

Some mentally retarded individuals present with episodes of pseudo-obstruction and malabsorption. The intestinal smooth muscle layers appear normal or reduced in thickness. The variably sized neurons are decreased in the colon but normal in the esophagus, stomach, and small intestine and they appear degenerated with misshapen pyknotic nuclei. The brain shows extensive foci of calcification within the subcortical white matter and a striking reduction of neurons in the basal ganglia (83).

Autosomal Dominant Visceral Neuropathies

Some patients have intestinal pseudo-obstruction predominantly affecting the small intestine, without evidence of central, autonomic, or peripheral nervous system involvement. Special stains show decreased numbers of degenerated neurons and axons and many ganglia contain only one or two neurons with decreased argyrophilia. These appear swollen, distorted, and vacuolated and they lack inclusions. Nerve fibers appear hypertrophic with swellings or beading. Inflammation is absent but muscular hyperplasia may be present (83).

Sporadic Visceral Neuropathies

Sporadic visceral neuropathies include at least two distinct morphologic diseases affecting the myenteric plexus of any part of the GI tract. The changes are not familial and do not affect extragastrointestinal structures. The disorders typically affect adults.

Type I Sporadic Visceral Neuropathy

In type I sporadic visceral neuropathy, the number of myenteric plexus neurons is reduced and they are swollen and fragmented with neuronal dropout. Neurons appear irregular and have slightly concave shapes. Their cell boundaries are sharply defined and have a number of distinct tapering processes...
neuronal processes may appear thickened and haphazardly arranged. Some neurons swell two to three times their normal size, causing their cell boundaries to become rounded and indistinct with fewer processes than normal. Gliosis replaces the plexus. These areas are devoid of neurons and only a few axons remain within the glial scar. The changes are difficult to appreciate without the use of silver or immunohistochemical stains. The disorder differs from neuronal intranuclear inclusion disease by the absence of intranuclear inclusions and clubbed dendrites, the presence of swollen neurons with degenerated cytoplasm, and the presence of gliosis (83).

<table>
<thead>
<tr>
<th>Disease and Genetic Transmission</th>
<th>Clinical Findings</th>
<th>Gastrointestinal Lesions</th>
<th>Microscopic Lesions</th>
<th>Silver Stains</th>
<th>Extraintestinal Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Forms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal recessive with mental retardation and basal ganglia calcification</td>
<td>CIP</td>
<td>Megaduodenum</td>
<td>Atrophy of smooth muscle in all gastrointestinal tissues</td>
<td>Argyrophilic neurons decrease in number; remaining neurons appear misshapen and pyknotic</td>
<td>Extensive focal calcification of basal ganglia and subcortical white matter</td>
</tr>
<tr>
<td>Neuronal intranuclear inclusion disease (autosomal recessive)</td>
<td>CIP</td>
<td>Dilation and nonperistaltic hypoactivity involving the esophagus, stomach, and small intestine Extensive colonic diverticulosis</td>
<td>Reduction and degeneration of myenteric plexus neurons Eosinophilic neurofilament containing intranuclear inclusions in myenteric and submucosal plexus neurons</td>
<td>Neurons in myenteric plexus; remaining argyrophilic neurons are misshapen with only a few processes</td>
<td>Neural inclusions in central and peripheral nervous systems</td>
</tr>
<tr>
<td>Autosomal dominant visceral neuropathy type I</td>
<td>Patients present at any age with intestinal pseudo-obstruction Symptom onset at any age Postprandial abdominal pain Distension Diarrhea Gastroparesis Constipation</td>
<td>Abnormal gastric emptying Dominant segmental dilation of jejunum and ileum Small intestinal diverticulosis Proximal small intestine always involved</td>
<td>Hypertrophy of smooth muscle Reduction and degeneration of myenteric plexus neurons</td>
<td>Decreased number of degenerated neurons with poorly defined cell borders and decreased silver staining; some neurons appear vacuolated or beaded</td>
<td>None</td>
</tr>
<tr>
<td>Autosomal recessive visceral neuropathy type II</td>
<td>Symptoms start in infancy</td>
<td>Hypertrophic pyloric stenosis Short dilated small intestine Intestinal malrotation</td>
<td>Neural abnormalities Neuroblasts present Hypertrophy of muscularis propria No muscle degeneration</td>
<td>Deficiency of argyrophilic cells No visible intrinsic neurons or processes</td>
<td>CNS malformations with heterotopia and absence of operculum temporale Patent ductus arteriosus</td>
</tr>
<tr>
<td>Sporadic Visceral Neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I sporadic</td>
<td>Similar to other forms of CIP</td>
<td>Reduced myenteric neurons No inflammation Neuronal swelling Gilosis No inclusions</td>
<td>Neuronal swelling, fragmentation, and dropout Eventually neurons disappear</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Type II Sporadic Visceral Neuropathy

Type II sporadic visceral neuropathy affects both the small and large intestines, and is characterized by neural degeneration. Neurons within individual ganglia vary in a continuum from near-normal to having a central loss of staining when stained with silver stains. Only a peripheral rim of cytoplasm remains, providing a pattern somewhat resembling signet ring cells. Axonal disorganization and degeneration are also present, but no dendritic swelling or glial cell proliferation is noted. Nuclear inclusions and inflammatory cells are absent. Some ganglia show neuronal dropout, producing intercellular spaces containing only traces of neuronal cytoplasm.

FIG. 10.20. Sporadic visceral neuropathy. Note the extensive vacuolization of the neural elements in the myenteric plexus with the cells simulating signet ring cells.

Slow Transit Chronic Constipation

Slow transit constipation, also referred to as chronic severe idiopathic constipation or colonic inertia, is a distinctive clinical syndrome affecting adults. This poorly understood disease has many potential causes. Most often the changes are thought to result from a visceral motor neuropathy. A complicating feature is the fact that many adults use antidepressants and narcotics for abdominal pain and related disorders, making it unclear whether the disease is a primary myenteric plexus disorder or the result of long-term cathartic, antidepressant, or narcotic use (abuse). If there is any history of use of these drugs, the cases should be classified as drug-induced motility disorders and not an idiopathic disorder. Some postulate that the abnormalities are developmental in origin, rather than an acquired destructive lesion, since frank axonal degeneration, Schwann cell hyperplasia, and inflammation are absent. This disease typically affects two major groups of patients: Adult women with severe chronic constipation or children with a similar presentation. Patients present with chronic constipation. Symptoms vary in their severity. Adults with severe disease may have no more than one bowel movement per week, despite laxative use. Patients may also develop abdominal pain, bloating, and nausea, and may require manual disimpaction. Rarely, marked ileus and large intestinal pseudo-obstruction develop. Complications include stercoral ulceration, intestinal ischemia, GI bleeding, bowel perforation, and peritonitis. Patients may also exhibit abnormal gastric emptying and gastroparesis. Despite the fact that patients experience severe constipation, the degree of intestinal dilation is seldom sufficient to warrant a diagnosis of megacolon or megarectum. If the bowel is resected, the intestinal wall may appear contracted, thickened, and markedly stenotic. Alternatively, the bowel may appear dilated and thinned (Fig. 10.21). Diverticula, prolapsing mucosal folds, and/or stercoral ulcers (Fig. 10.22) may be present. Pathologists typically encounter specimens from these patients if the patient develops pseudo-obstruction or stercoral ulcers severe enough to warrant a resection. Some surgeons will also resect the bowel in patients with severe, recurrent stool impactions. At this time, any of the abnormalities listed in Table 10.13 may be present. These include decreased, small, irregular neurons; decreased neuronal processes; and clusters of variably sized intraganglionic nuclei, which represent glia, Schwann cells, or immature neurons. There is also a notable decrease in ganglionic density and size. In other patients, there may be an increase in neuronal supporting tissues demonstrable by S100 staining. There are also increased numbers of PGP 9.5-immunoreactive nerve fibers in the muscularis propria. Melanosis coli is frequently present.
FIG. 10.21. Idiopathic constipation. Note the shrunken, contracted distal anorectum and the massively dilated megarectum.

FIG. 10.22. Stercoral ulcer in a patient with severe constipation.

TABLE 10.13 Changes That May Be Present in Slow Transit Constipation
Chapter 10

Decreased numbers of ganglia, neurons, and/or axons
Abnormal-appearing neurons or ganglia
Decreased nerve density in the myenteric plexus
Gliosis of the myenteric plexus
Decreased or increased VIPergic nerves
Decreased or increased substance P nerves
Increased nitricergic nerves
Increased galanin
Increased neuropeptide Y
Decreased enkephalin
Decreased neuronal filament staining in the myenteric plexus
Decreased numbers of interstitial cells of Cajal
VIP, vasoactive intestinal peptide.

Paraneoplastic Pseudo-Obstruction

Paraneoplastic pseudo-obstruction develops in patients with neuroendocrine or neural neoplasms (small cell carcinoma of the lung [97], carcinoid tumors, medulliformas, oligodendrogliomas, and ganglioneuroblastoma [97–99]) due to the production of autoantibodies that cross-react with neural tissues, destroying them (100,101). Patients develop distinctive antineuronal autoantibodies (Table 10.14) (97,98,99,100,101). The most common antineuronal antibody is anti-Hu, which recognizes a group of nervous system–specific RNA-binding proteins with molecular weights in the range of 35 to 40 kilodaltons expressed by both neurons and neoplastic cells. The antibodies induce neuronal apoptosis, contributing to the enteric neural disorder (102).

Patients present with GI dysmotility and autonomic dysfunction, often before the diagnosis of the underlying malignancy. They experience weight loss; pseudo-obstruction affecting the stomach, small intestine, and colon; constipation; gastroparesis; gastroesophageal reflux; esophageal spasm or achalasia; intractable dysphagia; postprandial fullness; nausea; vomiting; diarrhea; incontinence; and/or bloating (97,100). They also develop associated peripheral, sensory, and motor neuropathies; neurogenic bladders; ataxia; encephalopathy; orthostatic hypotension; and decreased deep tendon reflexes (97), giving a clue to the likely etiology of this motility disorder.

Myenteric neurons, from the esophagus to the colon, are reduced in number and the myenteric plexus is infiltrated with plasma cells, lymphocytes, and eosinophils (Fig. 10.23). Remaining neurons appear vacuolated and display cytoplasmic irregularities and decreased cellular processes. Axons swell, become fragmented, and drop out. The damage leads to gliosis, sometimes completely replacing the neural tissues. Only a few normal-appearing neurons remain. The key finding that should alert one to the possibility of this diagnosis is the presence of numerous lymphoid cells and plasma cells within the myenteric plexus. Serologic testing for the Hu antibody offers a simple means of identifying the majority of patients with paraneoplastic gut dysmotility syndromes (101).

<table>
<thead>
<tr>
<th>Antibody Target</th>
<th>Antibody Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I Anti-Hu</td>
<td>Neurons</td>
</tr>
<tr>
<td>Type II anti-Ri</td>
<td>Neurons</td>
</tr>
<tr>
<td>Anti-Yo</td>
<td>Anti–Purkinje cell cytoplasmic antibodies</td>
</tr>
<tr>
<td>N-type voltage-gated calcium channel antibodies</td>
<td>N-type voltage-gated calcium channels</td>
</tr>
<tr>
<td>P/Q-type calcium channel antibodies</td>
<td>P/Q-type calcium channel</td>
</tr>
<tr>
<td>Ganglionic and muscle-type nicotinic acetylcholine receptor antibodies</td>
<td>Nicotinic acetylcholine receptors</td>
</tr>
</tbody>
</table>

The differential diagnosis includes toxic neural damage from drugs, infection, an autoimmune neuropathy, or aganglionosis in the absence of a tumor. Treatment of the underlying tumor does not necessarily reverse the intestinal manifestations, which require symptomatic and supportive therapy.

Idiopathic Ganglionitis

Ganglionitis can be primary or secondary to a wide array of disorders. When it is primary, it is referred to as idiopathic ganglionitis. This motility disorder is associated with chronic inflammation of the gastrointestinal ganglia in the absence of a known cause for the inflammation. Idiopathic ganglionitis often affects young women with an average age of 25 years. Its etiology is poorly understood. Potential mechanisms of injury include viral antigen expression in the enteric neural environment, molecular mimicry of onconeural antigens, and cellular and humoral autoimmunity (103). The disease may result from circulating autoantibodies directed against the ENS in the absence of cancer. Some patients have antineuronal autoantibodies, especially anti-Hu and -Yo proteins; antibodies against neurotransmitter receptors; and ion channels (103). The clinical symptoms reflect the involved gastrointestinal segment (achalasia, gastroparesis, pseudo-obstruction, and megacolon). Patients present with severe constipation and abdominal pain late in childhood. Some may have associated mental retardation or psychiatric disorders. Initially, the motility disorder remains limited to the colon. Later it involves the entire gut. Other patients present with abdominal pain, nausea, vomiting, malnutrition, diarrhea, weight loss, and hypergammaglobulinemia (104). The rectum tends to be full of stool; fecal impaction is not unusual. A rectal diameter ≥6.5 cm at the pelvic brim on lateral radiograph view is common, as is a cecal diameter in excess of 12 cm.
FIG. 10.23. Pseudo-obstruction in a patient with a carcinoid tumor of the ovary. Note the inflammation of the myenteric plexus.

The gastrointestinal tract may show extensive inflammation of the ganglia (ganglionitis) with neuronal vacuolization and destruction. The diffuse lymphoplasmacytic infiltrate may affect all layers of the intestinal wall, but it tends to center around the neural microenvironment, extensively damaging the submucosal and myenteric nerve plexuses and resulting in a marked reduction in the number of myenteric nerve fibers. The nerves may show increased apoptosis. CD3+ and CD4+ T lymphocytes surround the altered ganglia and nerves. However, it should be noted that neural degeneration does not occur in all patients. There may also be a reduction in a specific subset of nerves, most commonly substance P-containing nerves (88). The histology of the muscularature varies, appearing hypertrophic or atrophic, probably secondary to the neural abnormalities (104). The differential diagnosis includes paraneoplastic ganglionitis, drug injury, and infectious injury to the ganglia most commonly from viruses or Chagas disease.

Eosinophilic Ganglionitis

Eosinophilic ganglionitis is a very rare form of ganglionitis, and it is characterized by an eosinophilic infiltrate in the myenteric plexus in the absence of neural degeneration. It affects both children and adults who present with pseudo-obstruction (68,105).

Granulomatous Visceral Neuropathy

Granulomatous visceral neuropathy affects the intestines and complicates non-small cell carcinoma of the lung (106).

Acquired Hypoganglionosis in Adults

Hypoganglionosis is both a congenital and an acquired disease (Table 10.15). It may be part of both HD and IND. Hypoganglionosis also develops secondary to the inflammation as seen in patients with inflammatory bowel disease, Chagas disease, HIV, or cytomegalovirus infections and paraneoplastic syndromes.

Internal Anal Sphincter Achalasia

Internal anal sphincter achalasia is a disorder characterized by the failure of the internal anal sphincter to relax in the presence of ganglion cells in rectal suction biopsies (107). This disorder used to be referred to as the ultrashort form of HD but is now recognized as a separate and distinct entity. It results from abnormal innervation of the internal anal sphincter. Normal relaxation of the internal anal sphincter occurs secondary to activation of the intramural NANC nerves (108) via NO, the transmitter involved in NANC signaling (109). In anal sphincter achalasia, there is loss of NANC function in the anal sphincter due to abnormalities in NOS and NADPH-diaphorase. There is also a reduction in ICCs (110). The diagnosis is established by anorectal manometry, which shows the absence of the rectosphincteric reflex. Patients are treated by internal sphincter myotomy or botulinum toxin injections.

<table>
<thead>
<tr>
<th>TABLE 10.15 Causes of Hypoganglionosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Failed migration</td>
</tr>
<tr>
<td>Failed differentiation</td>
</tr>
<tr>
<td>Loss from inadequate microenvironment</td>
</tr>
<tr>
<td>Acquired</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Status postsurgery</td>
</tr>
<tr>
<td>Status postradiotherapy</td>
</tr>
<tr>
<td>Prenatal ischemia</td>
</tr>
</tbody>
</table>

Achalasia

Achalasia is a rare disorder that results in neural degeneration and esophageal aperistalsis, impaired esophageal motility, and failed relaxation of the lower esophageal sphincter. It is sometimes referred to as cardiospasm or megaesophagus. The disorder affects about 7 to 13 per 100,000 population in Europe and the United States. Patients are usually adults between the ages of 21 and 60, affecting both sexes equally (111). Approximately one third of patients are newly diagnosed after age 60. Some cases are sporadic; others are familial (112,113,114).

Achalasia probably results from a combination of genetic, autoimmune, and infectious factors. Familial achalasia may result from a common exposure to an infection or environmental toxin or it may represent a genetically transmitted disease. Implicated environmental factors include bacteria, viruses (115,116), esophageal trauma, and fetal ischemic esophageal damage resulting from gastrointestinal malrotations (117,118,119).

An autoimmune etiology is suspected because of achalasia's association with the class II human leukocyte antigen (HLA) antigen DQw1 and evidence of circulating antibodies against the myenteric plexus. A significant association exists between idiopathic achalasia and the DQB1*0602 allele and the DRB1*15 allele in whites. In blacks, there is no association between these two alleles and achalasia but a trend is present with DRB1*12, suggesting that idiopathic achalasia associates with HLA alleles in a race-specific manner (113). The expression of HLA antigens on ganglion cells could initiate their autoimmune destruction by T lymphocytes (113). An unknown factor may trigger the expression of the DQw1 class II HLA antigen on myenteric ganglia. This antigen is then recognized as foreign by T lymphocytes, which initiate an autoimmune attack, destroying neurons and ganglion cells. The degenerative process preferentially affects NO producing inhibitory neurons that affect the relaxation in the esophageal smooth muscle. There is also loss of inhibitory VIP-containing nerve fibers that results in a hypertonic lower esophageal sphincter (LES).

FIG. 10.25. Achalasia with esophagitis and squamous hyperplasia. The distal esophagus shows prominent whitish patchy squamous hyperplasia and two ulcers. This patient had had a sphincterotomy for the treatment of the achalasia and developed subsequent reflux esophagitis.

Since the esophagus never completely empties, it dilates (Fig. 10.24) and a column of swallowed food builds up within it (120), presenting clinically as recurrent, progressive dysphagia; pain; regurgitation; dyspepsia; retrosternal fullness; aspiration; and weight loss (121). As the esophagus dilates, it may compress the bronchi. Erosive esophagitis (Fig. 10.25) complicates achalasia when acid reflux develops, but it may also occur secondary to bacterial fermentation in a stagnant esophageal pool. Manometry is the most sensitive test for the disease (122). Some patients have an increased incidence of constipation and abnormal anorectal function, suggesting that there may be a variant esophageal syndrome (123).
The characteristic gross features of achalasia consist of an enormously dilated, lengthened esophagus that tapers into a shortened narrowed tube at the esophagogastric junction (Fig. 10.24). The changes may also extend into the proximal stomach. In advanced disease, diverticula form, sometimes attaining a diameter of 10 cm or more. Some patients develop esophagobronchial fistulas.

Histologic abnormalities affect the esophageal myenteric plexus, dorsal vagal nucleus, and vagal trunks. The earliest changes consist of myenteric inflammation with injury to, and subsequent loss of, neurons and ganglia and subsequent fibrosis of the myenteric plexus (124). Lewy bodies identical to those seen in Parkinson disease may be found in the ganglion cells in the myenteric plexus. Ganglionitis consisting of a mixture of lymphocytes and eosinophils with a less conspicuous population of plasma cells and mast cells develops. The lymphocytic infiltrate is also present along nerve fascicles (125). The majority of the myenteric lymphocytes are CD3+, CD8+ T cells (125). They also express TIA-1, indicating that these cells are cytotoxic T cells. The TIA-1 cells appear to decrease in number as the disease progresses (126).

In late-stage disease, the infiltrate becomes more patchy and located in and around myenteric nerves (Fig. 10.26). Occasionally, one sees marked eosinophilia of the muscularis propria. Presumably, the eosinophils contribute to neuronal loss by activation and/or liberation of toxic proteins. The Auerbach plexus widens as scar tissue and small infiltrating inflammatory cells replace dying neurons (Fig. 10.26) (124,126). Satellite cells increase in number and may be difficult to distinguish from the lymphocytes. Sometimes the muscularis propria becomes markedly thickened as a result of a combination of smooth muscle fiber hypertrophy and fibrosis. Small leiomyomas may develop (Fig. 10.27). Patients with disease severe enough to necessitate esophageal resection may completely lack myenteric ganglia, especially in the distal segment (122,124). Some patients have residual ganglion cells in the proximal esophagus and a few randomly distributed ganglion cells in the mid- and distal esophagus. There may also be reduced numbers of ganglion cells in the proximal stomach. In the most severe cases, there is an almost total loss of the myenteric ganglion cells in the distal third of the esophagus. The remaining ganglion cells appear degenerated. There may also be a reduced number of contacts between the ICCs and the nerves (127). The muscularis propria appears atrophic, hypertrophic, or normal depending on disease severity; the changes preferentially involve the inner circular layer, especially distally (124,128). The muscle fibers may be infiltrated with eosinophils. There may also be degeneration and vacuolation of the muscle fibers. These changes are secondary to the neuronal and ganglionic alterations. Occasionally there is dystrophic calcification. Neural fibers in the vagal trunk degenerate and become fragmented. The esophageal vagal branches demonstrate myelin sheath abnormalities, disruption of axonal membranes, and changes typical of wallerian degeneration.

Achalasia of the Cardia in Allgrove Syndrome

Allgrove syndrome (achalasia, Addison disease, and alacrima syndrome [AAAS]) is a rare autosomal recessive disorder seen in children. It associates with mutations in the AAAS gene on chromosome 12q13. The gene encodes the protein known as aladin or adracalin. AAAS develops in the first 6 months of life and differs from achalasia in adults in that the achalasia is part of a multisystemic disorder. Children often present with vomiting undigested food, failure to thrive, and recurrent chest infections. They also develop chest pain, progressive dysphagia, nocturnal
regurgitation, chest infections, and weight loss. Other abnormalities include an autonomic and motor neuapathy, short stature, microophthalmia, nerve deafness, and prominent ophthalmic symptoms (131). All patients with AAAS show a striking fibrosis of the myenteric plexus. Myenteric ganglia and ICCs are absent or markedly decreased. Numerous CD3+ lymphocytes surround the myenteric ganglia. The nerves fail to stain for nNOS, a finding that may be related to the failure of the lower esophageal sphincter to relax (132).

Secondary Achalasia
Secondary achalasia, also known as pseudoachalasia, causes 2% to 4% of esophageal motor abnormalities. The symptoms result from neoplasms or benign disorders that interfere with its innervation (133). The most frequent cause is an adenocarcinoma involving the gastric cardia. Secondary achalasia also complicates vagal involvement by tumor. Megasophasus also follows stenosis induced by acid or alkali burns and it complicates amyloid deposition. Achalasia may also complicate inflammatory disorders including Chagas disease. Some suggest that achalasia complicates neurologic and psychiatric diseases, including Parkinson disease, depression, hereditary cerebellar ataxia, and neurofibromatosis.

Infantile Hypertrophic Pyloric Stenosis (Congenital Pyloric Stenosis)
Infantile hypertrophic pyloric stenosis (IHPS) ranges in incidence from 0.28% to 0.4% of all live births (134), commonly affects Anglo-Saxons, and rarely develops in Latin Americans or blacks (135). The disorder typically affects the first-born child, with a male-female ratio of approximately 4:1. The incidence of this disorder is decreasing in some countries such as Denmark and Canada and increasing in others such as Great Britain (136). Other anomalies occur with IHPS in 6% to 12% of infants (137). Some children manifest the Brachman-de Lange syndrome. Pyloric stenosis also associates with chromosome 9q duplications (138).

The etiology of this disorder is unclear and genetic and environmental causes have been postulated including the use of prenatal antibiotics (139). Pylorospasm has also been a postulated etiology, although this may reflect underlying neuromuscular abnormalities. Excessive gastrin production (140) abnormalities in somatostatin (140) ENS immaturity (141), lack of ICCs (142), inherent submucosal peptidergic nerve fiber abnormalities, or a lack of nitric oxide (NO) synthetase (143) may all play a role in its development. Indeed, transgenic mice carrying an inactivating gene for NOS develop pyloric hypertrophy (144),

Intestinal Muscle Diseases occur either as a primary disorder or secondary to muscular dystrophy or a variety of collagen vascular disorders. Adults commonly have intestinal muscular motility disorders as part of the manifestations of an underlying systemic disease, whereas children typically have a primary intestinal myopathy that usually presents clinically as pseudo-obstruction.

Megacystis–Microcolon and Intestinal Hypoperistalsis Syndrome (MMIHS)
Megacystis–microcolon and intestinal hypoperistalsis syndrome (MMIHS), a rare (<100 reported cases), generally fatal, congenital disorder affecting newborns, is characterized by intestinal and urinary bladder distension; an atomic, short, dilated small intestine; a displaced or matted microcolon; and widespread gastrointestinal hypoperistalsis, hydroureter, and hydronephrosis (144). It is also referred to as neonatal small left colon syndrome, adynamic bowel disease, non-Hirschsprung megacolon, and neonatal hollow visceral myopathy. It predominantly affects girls (female:male ratio 4:1) (145). Prune belly syndrome may be the male equivalent of the disease. An autosomal recessive mode of inheritance is present (146). More than 50% of affected infants are born to diabetic mothers. Recent evidence suggests that the disorder results from the absence of the α3 nicotinic acetylcholine receptor subunit (146).
TABLE 10.16 Megacystis–Microcolon–associated Gastrointestinal Conditions

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal atresia</td>
</tr>
<tr>
<td>Colonic atresia</td>
</tr>
<tr>
<td>Esophageal atresia</td>
</tr>
<tr>
<td>Imperforate anus</td>
</tr>
<tr>
<td>Intestinal malrotation</td>
</tr>
<tr>
<td>Intestinal stenosis</td>
</tr>
<tr>
<td>Mesenteric anomalies</td>
</tr>
<tr>
<td>Omphalocele</td>
</tr>
<tr>
<td>Pyloric hypertrophy</td>
</tr>
</tbody>
</table>

MMHS invariably presents during the first week of infancy. All patients develop intestinal and urinary bladder pseudo-obstruction. The most common gross abnormalities include megacystis, bilateral hydronephrosis, megaureters, short bowel, microileum, microcolon, and intestinal malrotation. A megaesophagus resembling achalasia may develop. Uterine ganglioneuromas may be present. Other associated gastrointestinal changes are listed in Table 10.16 (146).

The major pathologic abnormalities involve the intestinal musculature. The longitudinal muscle coat is thinned, with abundant connective tissue lying between the muscle fibers. The smooth muscle cells of the bowel and bladder appear vacuolated and degenerated (146). Ultrastructurally, the smooth muscle cells show myofilament disorganization, cytoplasmic central core degeneration, and abundant intracellular connective tissue proliferation. Excessive intracytoplasmic glycogen displaces contractile fibers to the cell periphery, suggesting defective glycogen energy utilization (147). Neural abnormalities are absent.

Patient prognosis is generally poor. Most patients die in the first few days of life from intestinal pseudo-obstruction and sepsis (146). Some patients live up to 4 years, but they usually need to be maintained on total parenteral nutrition and they may also require renal transplantation for renal failure.

Developmental Defects of the Intestinal Musculature

Some patients completely lack a muscularis propria (Fig. 10.29), making the affected areas vulnerable to spontaneous rupture. In other patients, developmental abnormalities in the arrangement of the muscle coats occur, and patients may present with chronic constipation and intestinal pseudo-obstruction (148). Deficiencies in α-smooth muscle actin in the circular muscle coat suggest that contractile protein abnormalities may contribute to the motility disorder. No other significant morphologic changes are identified histologically or ultrastructurally (148).

FIG. 10.29. Congenital absence of muscularis propria. The small intestinal wall is markedly thinned. A muscularis mucosae is present, as well as a submucosa and serosa.

Hollow Visceral Myopathies

Hollow visceral myopathies are muscle disorders that affect the gastrointestinal tract or they may affect all the hollow viscera, including the entire gastrointestinal tract, urinary tract, and gallbladder. They are characterized by degeneration, thinning, and fibrous replacement of the gastrointestinal smooth muscle. They affect both children and adults, and 75% of symptomatic patients are females (83,149,150,151,152,153,154,155,156,157,158). Some cases are sporadic; others are familial in nature. Among the familial cases, the genetic mode of transmission differs (Table 10.17). Other cases may have a relationship with glycosogenosis type IV (154), polysaccharidosis (142), or the dysplastic nevus syndrome (143).

TABLE 10.17 Classification of Familial Visceral Myopathies

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic transmission</td>
<td>Autosomal dominant</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive?</td>
</tr>
<tr>
<td>Age at onset</td>
<td>After the 1st decade of life</td>
<td>Teenagers</td>
<td>Middle age</td>
</tr>
<tr>
<td>Percentage of symptomatic cases</td>
<td>&lt;50%</td>
<td>&gt;75%</td>
<td>100%</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Varies from dysphagia and constipation to intestinal pseudo-obstruction</td>
<td>Severe abdominal pain; intestinal pseudo-obstruction</td>
<td>Intestinal pseudo-obstruction</td>
</tr>
<tr>
<td>Extragastrintestinal manifestation</td>
<td>Megacystis; uterine inertia; mydriasis</td>
<td>Ptosis and external ophthalmoplegia; mild degeneration of striated muscle</td>
<td>None</td>
</tr>
<tr>
<td>Gross findings</td>
<td>Esophageal dilation, megaduodenum, redundant colon, and megalocystis</td>
<td>Gastric dilation, slight dilation of the entire small intestine; small intestinal diverticulosis</td>
<td>Marked dilation of the entire digestive tract from the esophagus to the rectum</td>
</tr>
<tr>
<td>Histologic features</td>
<td>Degeneration and fibrosis of both muscle layers of digestive tract</td>
<td>Resembles type I</td>
<td>Resembles type I</td>
</tr>
</tbody>
</table>

The morphologic abnormalities are identical in all families, but the pattern of gut and bladder involvement and the mode of genetic transmission differ, and include autosomal dominant, autosomal recessive, and possibly X-linked dominant forms (83). Type I familial visceral myopathy is transmitted as an autosomal dominant trait (156). It is characterized by esophageal dilation, megaduodenum, redundant colon, and megacystis. The stomach and distal small intestine are usually normal, although the jejunum may appear distended.

Type II familial visceral myopathy is transmitted as an autosomal recessive trait and is characterized by gastric and small intestinal dilation and small intestinal diverticulosis of the entire small intestine. Patients have ptosis and external ophthalmoplegia, but they do not have a megacystis or megaduodenum.

Type III familial visceral myopathy was reported in a family with marked dilation of the entire GI tract from the esophagus to the rectum (83). No extraintestinal manifestations were observed and an autosomal recessive inheritance was probable.
Type IV familial visceral myopathy was described in two siblings with gastroparesis, a tubular narrow small intestine without diverticula, and a normal esophagus and colon. Severe vacuolar degeneration and atrophy of the longitudinal muscle of the small intestine was associated with a striking hypertrophy of the circular muscle in both cases. The hypertrophy probably caused the small intestinal tubular narrowing and it was likely that the disorder was transmitted as an autosomal recessive trait.

Clinical Features of Visceral Myopathies

Symptoms usually develop after menarche and persist with recurrences of varying intensity and chronicity (83,149). Other forms only become evident in middle age. Symptoms include dysphagia, heartburn, bloating, pain, distension, nausea, vomiting, constipation, and alternating diarrhea and constipation. Patients are usually short, underweight, and malnourished with postprandial abdominal pain, leading to decreased food intake. Sigmoid or cecal volvulus results from a redundant colon. Patients with bacterial overgrowth in a dilated duodenum develop malabsorption and diarrhea, which often improve when treated with antibiotics. Severe constipation may occur during pregnancy. In some women, spontaneous labor does not occur and may need to be induced. Intestinal pseudo-obstruction characterized by gastric and small intestinal dilatation and diffuse small intestinal diverticulosis complicates most symptomatic cases (149,150). Small intestinal diverticula may perforate leading to perforitis and intra-abdominal abscesses (83). Extragastrintestinal manifestations, if present, include megacystis and microscopic hematuria. The clinical differential diagnosis includes other causes of megacolon, including metabolic causes such as hypothyroidism, hypercalcemia, and systemic disorders such as amyloidosis, progressive systemic sclerosis, and diabetes.

Pathologic Findings

Typically, patients develop an atonic dilated esophagus, megaduodenum, small intestinal diverticulosis, redundant colon, and megacystis. The stomach and distal small intestine usually appear normal, although the jejunum may become distended. Areas of dilatation vary considerably in length (153). The morphologic abnormalities in all of the familial myopathies resemble one another and are easily recognizable by routine light microscopy. The changes that are present predominantly affect the muscularis propria (153,154), but some patients also have abnormalities in smooth muscle cells of the muscularis mucosae and/or the blood vessels. In the muscularis propria the changes may preferentially affect the inner circular or outer longitudinal layer or both layers may be equally affected. The smooth muscle fibers show various changes (Table 10.18). The may appear smudgy with indistinct boundaries (Fig. 10.30). Other muscle fibers appear densely eosinophilic or fragmented and have a threadlike appearance. Myocyte degeneration and dropout lead to fibrosis of the muscularis propria (Fig. 10.31). The muscularis propria may also show muscular hyperplasia and hypertrophy, especially in early stages of the disease. This may represent a compensatory response to muscularis propria degeneration. The muscle cells of the muscularis propria and muscularis mucosae contain numerous ovoid, translucent gray, cytoplasmic inclusions, which may be easily visualized in routine H&E-stained sections, but are enhanced by their strong periodic acid–Schiff (PAS) positivity. Ultrastructurally, the muscle cells appear very abnormal. The inclusions stain with antibodies to muscle-specific actin and appear to result from progressive myofibrillar degeneration (Fig. 10.32). In late-stage disease, a severe reduction in cell numbers is accompanied by extensive patchy fibrosis, a change easily highlighted with trichrome stains. Collagen sometimes deposits around degenerating muscle cells producing a honeycombed appearance. In the most advanced stages, the muscle layers are completely replaced by collagen with extreme thinning of the intestinal wall (158). Neurons, nerve processes, nerve terminals, and the myenteric plexus all appear normal. However, ICCs may be absent (159). There is no inflammation or vasculitis. Patients with a malabsorption syndrome due to luminal stasis develop a patchy chronic mucosal inflammatory cell infiltrate in the superficial lamina propria. A myopathy may be suspected when the bowel appears polypoid due to mucosal prolapse (Fig. 10.33). In late-stage disease, the muscle lesions mimic those seen in scleroderma or diabetes, but these two disorders can be distinguished clinically.

Nonfamilial Myopathies

Pathologically, sporadic visceral myopathies are heterogeneous, although the clinical features resemble one another. Unlike the familial forms, which show segmental GI dilatation, the nonfamilial form shows more extensive involvement, usually involving both the GI tract and urinary bladder with concomitant megacystis and megaloureter. As a result, patients are often very ill and there is little that surgery or medical therapy can do to alleviate the disease. Patients present at all ages. Infants present within the first few months of life with pseudo-obstruction and involvement of the entire GI system. Adults experience recurrent or persistent bowel obstruction as well as dysphagia, nausea, vomiting, postprandial abdominal pain, and bloating. Bowel habits are erratic and alternate between constipation and diarrhea. Severe bowel dysfunction may occur with impaction, stercoral ulcerations, or colonic perforation. The perforation usually results from ischemia secondary to vascular obstruction during volvulus, torsion, or intussusception.

### TABLE 10.18 Muscle Changes in Intestinal Familial Myopathies

<table>
<thead>
<tr>
<th>Muscle Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smudgy appearance</td>
</tr>
<tr>
<td>Loss of staining intensity</td>
</tr>
<tr>
<td>Cellular eosinophilia</td>
</tr>
<tr>
<td>Indistinct cell boundaries</td>
</tr>
<tr>
<td>Fragmentation</td>
</tr>
<tr>
<td>Vacular degeneration</td>
</tr>
<tr>
<td>Cellular dropout and apoptosis</td>
</tr>
<tr>
<td>Fibrosis of the muscularis propria</td>
</tr>
<tr>
<td>Cytoplasmic inclusions</td>
</tr>
</tbody>
</table>

In late-stage disease, a severe reduction in cell numbers is accompanied by extensive patchy fibrosis, a change easily highlighted with trichrome stains. Collagen sometimes deposits around degenerating muscle cells producing a honeycombed appearance. In the most advanced stages, the muscle layers are completely replaced by collagen with extreme thinning of the intestinal wall (158). Neurons, nerve processes, nerve terminals, and the myenteric plexus all appear normal. However, ICCs may be absent (159). There is no inflammation or vasculitis. Patients with a malabsorption syndrome due to luminal stasis develop a patchy chronic mucosal inflammatory cell infiltrate in the superficial lamina propria. A myopathy may be suspected when the bowel appears polypoid due to mucosal prolapse (Fig. 10.33). In late-stage disease, the muscle lesions mimic those seen in scleroderma or diabetes, but these two disorders can be distinguished clinically.
FIG. 10.30. Primary visceral myopathy in a patient presenting with intestinal pseudo-obstruction. A: The muscularis propria appears distinctly abnormal. The muscle fibers in both the circular and longitudinal layers are disorderly and edematous. B: Higher power magnification of the junction of the circular and longitudinal layers demonstrates prominent contraction bands. The entire muscular layer has acquired a smudgy appearance. (Courtesy of Dr. Michael Schuffler, University of Washington, Seattle, WA.)

FIG. 10.31. Intestinal myopathy. A: Hematoxylin and eosin–stained section showing the smudgy, almost syncytial-like appearance of the smooth muscle cells in the lamina propria. B: Trichrome-stained section of a different area of the same bowel showing the fibrosis of the muscularis propria.
FIG. 10.32. Intestinal myopathy stained with anti–smooth muscle actin antibody. A: The immunostain serves to highlight the atrophy and vacuolar degeneration of the smooth muscle cells. B: In some patients the distribution of actin filaments in the cells is abnormal with clearing of the cytoplasm and a peripheral localization of the actin filaments.

FIG. 10.33. Some patients with motility disorders show mucosal prolapse as recognized by the presence of multiple mucosal polypoidlike extensions containing a core of submucosal tissue. The gross features resemble other forms of chronic intestinal pseudo-obstruction. The histologic abnormalities involve the smooth muscle cells and include edema, fragmentation and degeneration, marked nuclear enlargement and irregularity, interstitial fibrosis, and perinuclear cytoplasmic vacuolization (Fig. 10.34). Smooth muscle hypertrophy with hyperplasia develops. Unlike the familial form of visceral myopathy, which lacks inflammation, nonfamilial visceral myopathies often have a moderate increase of polymorphonuclear leukocytes and mononuclear cells scattered throughout both muscle layers. These changes are most severe in the muscularis propria, but similar changes develop in the muscularis mucosae and blood vessels. In its most advanced stages, fibrosis replaces the muscularis propria, causing extreme thinning of the intestinal wall. The mucosa sometimes exhibits polypoid projections typical of the redundant mucosal folds that can be present in any motility disorder. These folds consist of upward submucosal extensions covered by an essentially normal mucosa.

Diffuse Lymphoid Infiltration without Neuronal Damage

Patients with this disorder present with diarrhea, malabsorption, and intestinal pseudo-obstruction. Grossly, the bowel appears dilated and thickened. Diffuse lymphocytic infiltrates involve the lamina propria, submucosa, serosa, and muscularis propria. The muscle cells appear hyperplastic and hypertrophic along with muscle cell dropout and there is fibrosis of the muscularis propria. There are no neuronal or axonal morphologic abnormalities. The loss of muscle cells in the vicinity of the lymphoid infiltrates may account for the pseudo-obstruction. Alternatively, the lymphocytes may secrete cytokines that inhibit smooth muscle contractility.
Mitochondrial Neurogastrointestinal Encephalomyopathies

Mitochondrial encephalomyopathies are a heterogeneous group of diseases characterized by the presence of defective mitochondrial DNA and various neuromuscular abnormalities (Table 10.19) (160,161). These disorders result from structural, biochemical, or genetic mitochondrial derangements and they are usually maternally inherited.

Mitochondria contain DNA known as mitochondrial DNA, or mtDNA (162), which differs from nuclear DNA in that it is maternally inherited, demonstrates DNA heteroplasmy and mitotic segregation, and is more susceptible to mutation than nuclear DNA (163). (Heteroplasmy refers to the fact that cells harbor both wild-type and mutant mtDNA.) Point mutations in mitochondrial structural genes result in impaired mitochondrial protein synthesis (163), disruption of oxidative phosphorylation and the respiratory chain, and decreased mitochondrial protein synthesis (164). There is no relationship between the site of mutation and the clinical phenotype (163). The presence of heteroplasmy allows different tissues harboring the same mtDNA mutation to be affected to different degrees, resulting in tremendous symptom variation.

<table>
<thead>
<tr>
<th>TABLE 10.19 Mitochondrial Myopathies Affecting the Gastrointestinal Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns-Sayre syndrome</td>
</tr>
<tr>
<td>OGIMD (oculogastrointestinal muscular dystrophy) syndrome</td>
</tr>
<tr>
<td>MINGE (mitochondrial neurogastrointestinal encephalomyopathy) syndrome</td>
</tr>
<tr>
<td>MEPOPL (mitochondrial encephalopathy, sensorimotor polyneuropathy, ophthalmoplegia, pseudo-obstruction) syndrome</td>
</tr>
<tr>
<td>POLIP (polyneuropathy, ophthalmoplegia, leuko-encephalopathy, intestinal pseudo-obstruction) syndrome</td>
</tr>
</tbody>
</table>

Mitochondrial neurogastroencephalomyopathy (MINGE) is an autosomal recessive disease caused by mutations in the thymidine phosphorylase (TP) gene. This results in markedly increased concentrations of thymine and deoxyuridine (160), which in turn causes mtDNA defects (depletion, multiple deletions, and point mutations) (165). Patients with MINGE show multiple deletions and site-specific point mutations in mtDNA (166). Kearns-Sayre syndrome (KSS) is a sporadic condition that almost invariably associates with large-scale mtDNA rearrangements (deletions and more rarely duplications) (167). A deletion flanked by a 13-bp direct repeat is the most common molecular defect (164).

Mitochondrial disorders should always be considered when patients exhibit unexplained neuromuscular, gastrointestinal, and nonneuromuscular symptoms. These multifluid mitochondrial diseases are characterized by gastrointestinal dysmotility with pseudo-obstruction, abdominal pain and persistent vomiting, gastric and duodenal dilation, and duodenal diverticulosis, ophthalmoplegia, and peripheral neuropathy. The gastrointestinal manifestations of mitochondrial myopathies may present at any age: In the neonate with hepatomegaly or hepatic failure, in infancy with failure to thrive and diarrhea, and in childhood and early adulthood with hepatic failure and chronic intestinal pseudo-obstruction. Patients may appear chronically malnourished and exhibit severe growth failure. Muscle biopsies show a mitochondrial myopathy usually with ragged red fibers (166). Patients with some of the mitochondrial myopathies, particularly those with oculogastrointestinal muscular dystrophy (OGIMD), are sometimes included under the familial visceral myopathies type II (chronic intestinal pseudo-obstruction with ophthalmoplegia). Mitochondrial myopathies can be diagnosed based on biochemical respiratory chain analysis or by mitochondrial DNA analysis.

The external layer of the muscularis propria becomes atrophic, and increased numbers of abnormal-appearing mitochondria are present in ganglia and smooth muscle cells, especially in the small intestine (165). Megamitochondria manifest as round, brightly eosinophilic, refractile, cytoplasmic inclusions in submucosal ganglion cells (165). The smooth muscle cells show a marked depletion of mtDNA (165). Microvesicular steatosis affects the liver, skeletal, and gastrointestinal smooth muscle and Schwann cells of the peripheral nerves. Other changes that occur include increased numbers of mitochondria within endothelial and vascular smooth muscle cells (163).

Therapy is largely supportive, including total parenteral nutrition and treatment of complications, such as perforated diverticula and bacterial overgrowth. The prognosis of MINGE is poor and prior to the availability of long-term parenteral nutrition, the average patient died around age 30 (166). Therapy with coenzyme Q, riboflavin, and other vitamins, cofactors, and oxygen scavengers may be useful (161,162). These therapies are used with the aim of mitigating, postponing, or preventing damage to the respiratory chain (163).

Autoimmune Enteric Myositis

This rare motility disorder combines intestinal pseudo-obstruction with a diffuse transmural lymphoid infiltrate in the absence of neural damage (168). It may follow an attack of acute gastroentritis (168) or chronic active hepatitis. The latter is of interest because immune responses to hepatitis viruses may result in the production of smooth muscle antibodies through molecular mimicry (169). Hepatitis B virus shows sequence homology with myosin and caldesmon and hepatitis C virus shares sequence homologies with vimentin and myosin.

Several autoantibodies can be found in these patients, including antineutrophil cytoplasmic antibody (ANCA) antinuclear antibodies, anti-DNA antibodies, and anti-smooth muscle antibodies, supporting an autoimmune etiology. Patients present in the same way as other patients with chronic gastrointestinal pseudo-obstruction, with intractable diarrhea and vomiting.
Lymphocytes infiltrate the lamina propria, submucosa, muscularis propria, and serosa of the ileum and colon. This infiltrate, which largely consists of CD3+ and CD68+ positive cells with some CD3- and CD45 cells and occasional B cells, is especially dense in the muscularis propria around blood vessels. The infiltration of the muscularis propria can be intense enough to obscure the circular muscle coat. There is loss of smooth muscle actin immunoreactivity in the inner circular muscle. As the disease progresses, myonecrosis occurs in the circular muscle layer. Although there are scattered lymphocytes in the myenteric plexus, there are no neural abnormalities. Both layers of the muscularis propria become thickened secondary to muscular hyperplasia, hypertrophy, and collagen deposition (168).

Treatment with immunosuppressive drugs may alleviate the pseudo-obstruction. Following treatment with immunosuppressive drugs, the infiltrates decrease, although some lymphocytic infiltrates may remain. Some patients require parenteral nutrition (168).

**Hereditary Internal Sphincter Myopathy**

Patients with hereditary internal sphincter myopathy present with proctalgia fugax usually in the 3rd to 5th decades of life. Proctalgia fugax is characterized by sudden episodes of severe pain in the anorectum that lasts for several seconds or a few minutes and then spontaneously resolves, leaving the patient asymptomatic until the next episode. Patients experience severe pain intermittently during the day and hourly during the night. They also experience constipation and difficulty with rectal evacuation (64). The disease is inherited in an autosomal dominant fashion (170). The internal anal sphincter appears thickened and has decreased compliance. Histologically, the hypertrophic muscle demonstrates unique myopathic changes consisting of vacuolar damage and PAS-positive polyglycosan bodies in the smooth muscle fibers (170), as well as an increased endomyosial fibrosis.

**Infectious Causes of Motility Disorders**

Secondary gastrointestinal neuropathies and pseudo-obstruction can result from infections that damage the nerves, muscles, or both. Infections with neurotrophic viruses may damage the myenteric plexus. These viruses include herpes zoster (172), Epstein-Barr virus (EBV) (173), and cytomegalovirus (CMV) (174). Other infections result in autoimmune attacks on neural structures due to the presence of cross-reacting antigens, such as those present in some Campylobacter infections. Transient delayed gastric emptying occurs as a consequence of acute viral gastroenteritis, due to CMV (174), rotaviruses (175), or Norwalk or Hawaii virus infections (176). Motility returns to normal after the patient recovers from the viral infection. However, patients have been described in whom pseudo-obstruction and abdominal pain persist following treatment. Patients with Lyme disease may develop pseudo-obstruction (177). Chagas disease is discussed on p. 580.

**Muscular Dystrophy**

Esophageal motor dysfunction complicates several types of muscular dystrophy (myotonic, oculopharyngeal, ophthalmoplegic, and Duchenne). Myotonic dystrophy is a slowly progressive illness, inherited as an autosomal dominant disorder that affects smooth muscles in any part of the gut (171). Duchenne muscular dystrophy is a fatal X-linked recessive disease. Patients complain of dysphagia (171). The dysphagia may become so severe that the patients starve themselves. Patients also frequently aspirate. The most severe changes affect the upper esophageal sphincter, which demonstrates weak pharyngeal contractions and diminished sphincter pressure. Grossly, the esophageal musculature appears pale. Histologically, the abnormalities remain restricted to the skeletal muscle cells and they vary in their severity from cell to cell. The caliber of the striated muscle fibers varies due to the presence of necrosis and regeneration, and the fibers contain internalized pyknotic nuclei. The muscle fibers contain excessive amounts of lipofuscin and multineurited fibers are present. Myosin immunostains highlight the variability of the muscle fibers. Fatty infiltrates separate the muscle fibers (Fig. 10.35). There is usually little or no inflammation and the neural structures are normal in appearance.

Acute gastric dilation and intestinal pseudo-obstruction can be fatal in patients with a history of dysphagia in the smooth muscle cells. Significant motor abnormalities (hypomotility with delayed transit) affect the esophagus, stomach, small intestine, large bowel, and anal sphincters. The changes are most prominent in the esophagus, stomach, and colon. Occasionally, intestinal symptoms dominate the clinical picture and these may appear before the typical muscular/skeletal features become apparent. Megacolon may also develop. Generally, the nerves appear normal. Smooth muscle atrophy and fibrosis all develop, with the histologic changes being most marked in the esophagus and stomach and less apparent in the smaller and large intestines (171). Some smooth muscle cells appear swollen, partially destroyed, and replaced by fat (Fig 10.35). The muscle fibers are thinned and disorganized in the circular and longitudinal layer of the muscularis propria. These changes are most prominent in the small and large intestines (171). Some smooth muscle cells appear swollen, partially destroyed, and replaced by fat (Fig 10.35).

**Gastrointestinal CMV neuropathy** is rare. Viral inclusions may be identifiable in the myenteric plexus neurons or in the muscle fibers (Fig. 10.36). These may be accompanied by inflammation and gliosis. Axons degenerate, resulting in extensive axonal dropout. The remaining axons appear hypertrophic and disorganized, with evidence of sprouting. Neuronal injury and dropout also occur. The process is patchy in nature; not all ganglia are affected. In patients without obvious inclusions, the enteric nerves may harbor either latent virus or residual inflammation without significant mucosal alterations. Ultrastructural examination, immunohistochemistry, or in situ hybridization can demonstrate the presence of the virus in cases that are not obvious in H&E-stained sections.

**Chagas Disease**

Chagas disease affects approximately 12 to 20 million people in Central and South America. Moreover, 25% of the populations living in these areas are under a high transmission risk (178). The disease is caused by the parasite Trypanosoma cruzi, which is transmitted to humans by blood-sucking triatomine bugs and by blood transfusions. The organism can also be acquired by accidental contamination with infected blood or cultures in laboratories, and congenially by transplacental passage of parasites (178). An alternative view postulates that the damage results from the failure of the host to clear the infection, resulting in infection-induced immune damage (180).
FIG. 10.36. Cytomegalovirus immunoreactivity in the muscularis propria. One of the muscle fibers (arrow) shows this reactivity. The surrounding tissues appear inflamed.

FIG. 10.37. Life cycle of Chagas disease.

The disease has two successive phases, acute and chronic. The acute phase lasts 6 to 8 weeks. After several years of starting the chronic phase, 20% to 30% of infected individuals develop irreversible lesions in the heart and gastrointestinal system (181). The infection leads to GI motility disorders, including pseudo-obstruction. Patients present with cardiac manifestations and a dilated esophagus and colon (182). The esophageal changes resemble those seen in achalasia. Intestinal involvement manifests as a motility disorder and pseudo-obstruction. Chagasic megacolon may evolve into toxic megacolon and enterocolitis, often resulting in death (182).

The histologic features reflect the stage of the disease. In the acute infection, the organism is found in and around the myenteric plexus (Fig. 10.38). However, the acute disease is rarely seen. More commonly, patients present with complications of the myenteric plexus involvement. Early on, there is marked degeneration of the muscularis propria and the myenteric plexus, with decreased nerves in Auerbach plexus. Motor functions and aperistalsis develop when >90% of ganglion cells are lost (183). The autonomic innervation becomes destroyed, probably via the combined action of the parasitic toxins and the production of various cytokines and other inflammatory mediators and ischemia secondary to changes induced in the cardiovascular system. ICCs are severely reduced in numbers (184). Because of the severe neural changes, the smooth muscle becomes hypertrophic.

Eventually, the infected sites become fibrotic (Fig. 10.39). At the time that tissues involved by chronic disease are examined, the parasites are usually no longer evident. However, the organisms are detectable by more sensitive techniques such as polymerase chain reaction (PCR) (180). In cases where the diagnosis is in doubt, tissue can be analyzed by a PCR test for the organism.
Patients with chagasic achalasia have an up to 20% possibility of developing esophageal squamous cell carcinoma. Of interest is the finding that the achalasic esophagus without cancer shows evidence of multiple chromosomal aneuploidies and loss of the p53 gene in up to 60% of specimens. The tumors arising in these esophagi show multiple chromosomal aneuploidies and p53 deletions in 100% of the tumors (185).

Motility Disorders Accompanying Systemic Diseases

Scleroderma

Scleroderma is a generalized autoimmune connective tissue disorder characterized by fibrosis and degenerative changes of the skin and multiple internal organs including the gastrointestinal tract. By definition, esophageal scleroderma is part of the CREST syndrome (calcinosis cutis, Raynaud, esophageal, sclerodactyly, and telangiectasia). It is the most common connective tissue disease causing generalized GI dysmotility. Scleroderma has a worldwide distribution and is more common in women than in men, usually affecting them in their 3rd to 5th decades. Ethnic origin plays a role in disease susceptibility. The disease is significantly more likely in black than white women. There are also differences in genetic backgrounds for the various HLA types in various ethnic groups.

Scleroderma is associated with an increased frequency of class I and class II major histocompatibility complex (MHC) alleles. Autoantibody associations divide patients into two groups: Those with anticentromere antibodies (ACAs) that are associated with limited scleroderma, and those with antitopoisomerase-1 (SCL-70) with the diffuse form. In some patients, antibodies specifically inhibiting M3-muscarinic receptor-mediated enteric cholinergic neurotransmission may account for the gastrointestinal dysfunction seen in patients with scleroderma.

Pathogenesis

The pathogenesis of scleroderma involves vascular, immunologic, and fibrosing processes. Progressive fibrosis of various organs, including the gastrointestinal tract, is the pathologic hallmark of scleroderma. The fibrosis disrupts the normal architecture of the affected organs, ultimately leading to their dysfunction and failure; the extent and rate of progression of the fibrosis determine the patients' clinical course and prognosis. Fibrosis of the walls of medium- and small-sized arteries also plays a critical role in many manifestations of the disease.

The microvascular system is one of the first targets to be involved in the disease (186). Vascular changes affect small arteries and consist of arteritis and myointimal proliferation with luminal narrowing and irregularity, intimal fibrosis, and disruption of the internal elastic lamina. Capillary basement membranes thicken. Vessels of vessels (vasa vasora) and of nerves (vasa nervosa) are altered early in the disease. Vasoconstriction occurs secondary to increased levels of the vasoconstrictor endothelin-1 and decreased NO resulting in ischemia and neural and muscular dysfunction (186). Neural atrophy and collagen deposition occur before smooth muscle contractility is impaired (187). Complete denervation releases the intestinal smooth muscle from its customary inhibitory factors, resulting in loss of normal peristalsis.
Clinical Features

Scleroderma presents either as a localized disease or as a systemic disorder. The localized form remains confined to the skin; GI involvement complicates systemic disease. The esophagus, small intestine, colon, and stomach are affected in a decreasing order of frequency (188). The clinical features differ depending on the site of involvement. Up to 90% of patients show esophageal disease with ineffective peristalsis resulting in delayed esophageal emptying. LES pressure progressively diminishes until no high-pressure zone lies between the esophagus and stomach, and gastroesophageal reflux (GER) develops. Peptic esophagitis, with all of its complications, ensues. GER results from three major physiologic defects: Decreased LES pressure; failure to clear acid in the esophagus, due to poor peristalsis; and delayed gastric emptying. All of the complications of GER as discussed in Chapter 2 develop. The patients also develop lower mucosal rings at the esophagogastric junction (189). Some patients with Raynaud phenomenon have cold-induced vasospasm of the esophageal vessels (esophageal Raynaud).

Gastric dysmotility and gastroparesis affect more than 50% of patients (190) causing dyspepsia. Gastric involvement may also present with bleeding secondary to the development of vascular abnormalities, including gastric antral vascular ectasia (191). Forty percent of patients with generalized scleroderma develop intestinal symptoms in their 4th to 6th decades of life (188). Patients with small intestinal involvement present with anorexia, early satiety, nausea, vomiting, intestinal pseudo-obstruction, abdominal pain, weight loss, impaired motility, malabsorption, steatorrhea, diarrhea, constipation, and intestinal perforation. Patients also develop multiple diverticula or megaduodenum (192). Colonic involvement affects 10% to 50% of patients. Patients with large intestinal disease develop colonic or rectal diverticula, pseudo-obstruction, constipation, diarrhea, fecal incontinence, rectal prolapse, spontaneous perforation, and infarction. They also develop wide-mouthed diverticula. Anorectal involvement is almost as common as esophageal involvement. It leads to fecal incontinence or rectal prolapse (182).

Specific serologic tests help identify the exact collagen vascular disease that is present. Antinuclear antibody (ANA) profiles are particularly helpful. ANAs are usually positive in scleroderma patients. Nuclear ribonucleoprotein (RNP) and centromere antibodies are more specific but not very sensitive. Patients with CREST have ANA restricted to the centromeric DNA. ANA with anti-SS-A/Ro specificity associates with vasculitis and nephritis and ANA with anti-SS-dLa and anti-nRNP specificity associated with milder clinical disease (193).

Pathologic Findings

The early changes of well-developed scleroderma are seldom seen because tissue is not removed until complications develop. A mild inflammatory infiltrate may affect the neural plexuses, but the myenteric plexus generally appears histologically normal unless it has become entrapped by fibrous tissue. Smooth muscle atrophy follows the neural damage (Fig. 10.40) and progressive fibrosis develops (Fig. 10.41). The changes affect the circular layer of the muscularis propria more than the longitudinal layer. At this stage the muscle fibers appear atrophic, fragmented, and fibrotic, often completely disappearing. Initially, the damage appears patchy, but with time it becomes more extensive. These changes are superimposed on neural damage. The submucosa and muscularis propria become progressively atrophic and replaced by fibrous tissue. The fibrosis may mimic amyloidosis. Ceroid pigment granules may deposit in degenerating muscle cells. Intimal fibrosis and elastosis affects smaller arteries and blood vessels may be markedly thickened with perivascular collagen deposition. Degranulating mast cells, macrophages, and activated lymphocytes infiltrate the perivascular tissue.

In uncomplicated cases, the mucosa appears normal. At most, there may be edema and mild chronic inflammation in the lamina propria. Mucosal erosions and ulcerations may occur, especially in patients with reflux esophagitis. Gastric alterations may include gastric mucosal atrophy. Duodenal Brunner glands may develop periglandular fibrosis (194). The intestinal mucosa may also show a nonspecific increase in the mononuclear cells in the lamina propria. This is often a manifestation of the decreased motility and a change in the bacterial flora. Patients with scleroderma may also develop eosinophilic gastroenteritis. The eosinophilic infiltrate often localizes in the basaI mucosa and the muscularis propria, resulting in myonecrosis (Fig. 10.42).

Pathologists may receive GI biopsies to rule out the diagnosis of scleroderma. Unfortunately, this is usually not possible because the biopsies are generally too superficial; sampling mainly the mucosa and rarely sampling the submucosa. The muscularis propria is virtually never biopsied. The biopsied tissues either appear normal or may show evidence of mild nonspecific mucosal inflammation or fibrosis. Patients with malabsorption may show evidence of mild atrophy or inflammation secondary to bacterial overgrowth.

Differential Diagnosis

Early scleroderma can usually be differentiated from a visceral myopathy by the presence of fibrosis of the intestinal smooth muscle and the absence of a vacuolated honeycombed appearance. Remaining muscle cells appear normal or atrophic. The changes in scleroderma are patchier than those found in...
patients with primary myopathies. In severe disease, it may be impossible to distinguish between a primary myopathy and scleroderma based solely on histologic examination. However, the clinical features serve to separate the two disorders, as does serologic testing.

**FIG. 10.42.** Scleroderma. The muscle layers may demonstrate a prominent eosinophilic infiltrate between the smooth muscle cells.

**Treatment and Prognosis**

Since there is no effective treatment for scleroderma, therapy is directed at supportive symptomatic treatment. Antireflux measures help alleviate the symptoms of reflux esophagitis and are important in preventing its complications. Early muscle dysfunction is partially reversible with prokinetic drugs. In addition, prokinetic drugs decrease the acidity of the refluxate, increase lower esophageal sphincter pressure, and increase gastric emptying. Patients with end-stage disease (characterized by severe muscle fibrosis) are not amenable to pharmacologic functional restoration. The main therapeutic options for bacterial overgrowth consist of antibiotics and nutritional supplementation. Approximately 19% of patients require total parenteral or enteral nutrition.

**Diabetes Mellitus**

Diabetic neuropathies encompass a group of clinical syndromes affecting both somatic and autonomic peripheral nerves (195). The term diabetic gastroenteropathy describes a generalized diabetes-associated gastrointestinal motility disorder. Diabetic gastroparesis is diabetes-associated delayed gastric emptying occurring in the absence of mechanical obstruction (Fig. 10.43) (195). Diabetic gastroparesis affects as many as 20% to 50% of diabetics, especially those with longstanding, poorly controlled disease.

Gastrointestinal diabetes-related alterations occur via several mechanisms: A visceral neuropathy involving the parasympathetic or sympathetic nervous system; a microangiopathy; abnormal plasma glucose and electrolyte levels; increased susceptibility to infections and bacterial overgrowth; altered production of insulin, motilin, pancreatic polypeptide, somatostatin, gastrin, and glucagon; and ischemic effects (195,196). The predisposition to accelerated atherosclerosis is a risk factor for developing mesenteric ischemia and intestinal infarction. The most important underlying condition appears to be the visceral autonomic neuropathy that causes decreased motility, hypotonia, and diminished secretions. Diabetic gastroparesis involves a neuropathy, a myopathy, and decreased ICCs. The latter may result from reduced insulin/insulinlike growth factor (IGF)-1 signaling, which may also result in smooth muscle atrophy and reduced stem cell factor production (197).

The gastrointestinal effects of diabetes are not commonly appreciated. Many diabetics, especially patients with type I diabetes, develop gastrointestinal problems, including gastroparesis, diarrhea, constipation, delayed esophageal and intestinal transit, megacolon, chronic nausea, weight loss, and fecal incontinence (195,196,197,198,199). Diabetic gastroparesis manifests as postprandial fullness, vague epigastric pain, nausea, vomiting, heartburn, bloating, early satiety, excessive eructation, and anorexia. Symptom onset is usually insidious. Bezoar formation and pulmonary aspiration may be complications. Additionally, small intestinal stasis and bacterial overgrowth lead to fat malabsorption, steatorrhea, and diarrhea. Incontinence affects up to 24% of diabetics (195).
hyperplasia of the muscularis propria develops secondary to denervation injury following neural damage. Although these cases are uncommon, they can be seen in patients with P.585

Plexus, and ganglionic vacuolization. Remaining neurons appear shrunken, with clubbed, swollen processes. Often the myenteric plexus becomes inflamed (Fig. 10.47). Degenerative changes also involve the submucosal plexus and include axonal ballooning and neural degeneration. Atrophy or degeneration of ganglion cells without extensive deposition of amyloid in the enteric plexus.

TABLE 10.20 Gastrointestinal Amyloidosis

<table>
<thead>
<tr>
<th>Protein</th>
<th>Associated Disease</th>
<th>Forms of Amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin light chain (AL)</td>
<td>Multiple myeloma and other monoclonal B-cell and plasma cell proliferations</td>
<td>Primary amyloidosis: Systemic disease associated with plasma cell dyscrasia (deposits in heart, kidney, gut, liver, and spleen), especially around blood vessels and sometimes between muscle fibers; gastrointestinal involvement is common with massive submucosal involvement</td>
</tr>
<tr>
<td>Serum amyloid-associated protein (AA)</td>
<td>Associated with chronic disease</td>
<td>Secondary amyloidosis: Systemic chronic disease; amyloid deposits in blood vessels and in the mucosa; lamina propria deposits cause mucosal nodularity</td>
</tr>
<tr>
<td>Transthyretin, AA prealbumin (AF)</td>
<td>Hereditary amyloidosis</td>
<td>Hereditary familial amyloidosis: Small intestine commonly involved; perireticular deposition throughout muscle fibers and in neural plexuses; single organ amyloid deposition</td>
</tr>
</tbody>
</table>

Amyloidosis is usually diagnosed on H&E-stained sections and its presence is confirmed with a Congo red stain and the presence of a characteristic apple-green birefringence when examined under polarized light. It can also be confirmed ultrastructurally, in which case the amyloid fibers exhibit their characteristic periodicity. The different forms of amyloid may be distinguished using immunostains for the specific protein.

Drug-Induced Motility Disorders

A number of drugs affect gastrointestinal motility, causing neural and/or muscular injury (Figs. 10.45 and 10.46). The most common drugs that cause motility problems include tricyclic antidepressants, phenothiazines, anticholinergic drugs, opiates, methadone (203), theophylline (204), and antineoplastic drugs. All of these drugs can cause severe constipation, ileus, and pseudo-obstruction. It is unclear whether the drugs cause the symptoms or unmask an underlying gastrointestinal motility disorder.

Laxative-Induced Injury

Cathartic colon is an end-stage colon that no longer effectively contracts, presumably due to extensive myenteric plexus damage induced by long-term cathartic use (abuse). Motility disorders, chronic constipation, and pseudo-obstruction all complicate chronic laxative use. Patients with cathartic colon tend to present with chronic constipation, abdominal bloating or distension, pseudo-obstruction, abdominal pain, and incomplete evacuation. These result from toxic effects of the drugs on neural structures in the bowel wall with secondary muscle damage. Narcotic use often aggravates the symptoms. Severe constipation leads to the formation of hard fecaliths that can cause local chronic inflammation, acute inflammation, stercoral ulceration, bleeding, and perforation. Concomitant medication use and previous intestinal surgeries complicate the clinical picture.

In early cases of cathartic colon the mucosa appears mildly inflamed and glandular atrophy may develop. Esophagitis and mucosal ulcers may be present. Myenteric plexus abnormalities include neuronal swelling and pallor. Later, there is neuronal loss, axonal fragmentation, gliosis of the myenteric plexus, and ganglionic vacuolization. Remaining neurons appear shrunken, with clubbed, swollen processes. Often the myenteric plexus becomes inflamed (Fig. 10.47). Degenerative changes also involve the submucosal plexus and include axonal ballooning and neural degeneration. Atrophy or hyperplasia of the muscularis propria develops secondary to denervation injury following neural damage. Although these changes have been ascribed to laxatives, it is possible that they represent a primary disorder of the enteric plexuses that causes the initial constipation and subsequent laxative ingestion.
Chapter 10

FIG. 10.45. Specimen from a patient on long-term morphine showing inflammation and degeneration of the myenteric plexus.

FIG. 10.46. Severe muscle atrophy in an AIDS patient on long-term azidothymidine (AZT). The fibers of the external layer of the muscularis propria show marked variations in the size of individual muscle fibers. Many are surrounded by fibrous tissue. The myenteric plexus (M) appears more or less normal and the small portion of inner circular muscle that is seen is histologically normal.

FIG. 10.47. Patients with toxic neural damage due to laxative abuse show inflammatory cells in the myenteric plexus.

Radiation Effects
Intestinal pseudo-obstruction, gastroparesis, or esophageal motility disorders may be induced by previous radiation. Histologically, there is evidence of vascular ectasia and sclerosis, serosal fibrosis, neuronal proliferation within the submucosa, and degeneration of the myenteric plexus and muscle fibers of the muscularis propria.

References
Chapter 11
Inflammatory Bowel Disease

Chronic idiopathic inflammatory bowel disease (IBD) includes two chronic gastrointestinal disorders of unknown etiology: Ulcerative colitis (UC) and Crohn disease (CD). The natural history of IBD differs from patient to patient. Disease severity at its onset, disease extent, and patient age at the time of diagnosis, along with other variables, determine overall disease severity and the likelihood of subsequent morbidity and mortality. Once established, IBD patients suffer episodic acute attacks that become superimposed on chronic disease. As a result, the patient is likely to suffer from disabling disease for decades.

General Clinical and Epidemiologic Features of Inflammatory Bowel Disease

The annual incidence of IBD in the United States is approximately 6 cases per 100,000 persons (1). Both CD and UC are predominantly diseases of young adults, with a peak incidence occurring between 15 and 30 years of age. Age-specific incidence rates by sex are slightly greater for males with UC and for females with CD (2). At age 10, both diseases rapidly increase in incidence. Overall, both UC and CD show three peaks in incidence rates. The first and highest peak occurs between ages 20 and 24, the second at ages 40 to 44, and the third at ages 60 to 64 years. In females, the first peak appears at ages 15 to 19, 5 years younger than in males (3). By age 60, the incidence of UC exceeds that of CD.

Ethnicity

Epidemiologic studies show that the incidence and prevalence of IBD vary significantly depending on geographic location and patients' racial or ethnic backgrounds. IBD occurs worldwide and exhibits a relatively low incidence in Asian, Mediterranean, and Middle Eastern countries and a higher incidence in European countries, the United States, Canada, Australia, and New Zealand. This may reflect racial, ethnic, and genetic factors. Prevalence rates for IBD among non-Caucasians in the United States are lower than rates for Caucasians. In one study, the prevalence of Crohn disease was 43.6 per 100,000 population for Caucasians, 29.8 per 100,000 for African Americans, 5.6 per 100,000 for Asians, and 4.1 per 100,000 for Hispanics (4). A study of African-American children reported a Crohn disease incidence of 7 to 12 cases per 100,000 (5). However, recent data indicate that the incidence of IBD among African Americans and second-generation South Asians is increasing (6). Among ethnic groups, Jews in the United States have the greatest risk for developing IBD compared with non-Jewish Caucasians. The incidence rate is two to four times greater and the prevalence two to nine times greater in this group. Ashkenazi Jews exhibit a particularly high IBD risk, especially those originating in Middle Europe, Poland, or Russia.

Etiology

Chronic IBD is a common inflammatory disorder of unknown etiology. The intrinsic complexity of IBD and its variable manifestations hampers progress in understanding its pathogenesis. However, currently favored theories implicate genetically determined, immunologically mediated mechanisms of injury. The fundamental pathogenic question could be: Does the chronic recurring inflammatory activity in IBD reflect an appropriate response to a persistently abnormal stimulus (a structural alteration of the intestine or causative agent in the environment) or an abnormally prolonged response to a normal stimulus (aberrant regulation of immune responses) (Fig. 11.1)? It is conceivable that some factors initiate the disease, whereas others sustain the inflammatory process or possibly even reactivate it.

Genetic Factors

There is considerable evidence that the development of both CD and UC is determined, at least in part, by genetic factors. Overwhelming evidence exists that both ulcerative colitis and Crohn disease cluster within families. In population-based studies, 5% to 10% of individuals with IBD report having an affected family member (7). In fact, having a family member with IBD represents the greatest risk factor for developing the disease. Individuals with a first-degree relative with IBD have a 10- to 15-fold increased risk of also developing the disease compared with those without an affected family member (8).

Approximately 75% of families with multiple affected members show concordance for disease type (i.e., all affected family members have CD disease or all have UC). In the remaining 25%, some members have CD while others have UC (9). This finding suggests that UC and CD may have some common, as well as distinct, susceptibility genes. Twin studies show that monozygotic twin concordance for CD ranges from 42% to 58% (10). In contrast, concordance in dizygotic twins is only 4% (11). Monozygotic twin concordances are significantly lower for UC (10). These findings suggest that although there is a strong genetic component that determines susceptibility to inflammatory bowel disease, there are also environmental factors that play an important role in disease development.
Genetic linkage studies have identified a number of potential genetic susceptibility loci for inflammatory bowel disease. Some of these genes appear to confer a general risk for development of IBD, while others confer specific risk for either UC or CD. These are listed in Table 11-1.

**IBD1**

The IBD1 locus is located in the pericentromeric region of chromosome 16 and shows disease linkage only for CD, not for UC. This locus contains the gene NOD2/CARD15 that has now been definitively identified as the gene responsible for disease linkage to this chromosomal region. The family of Nod proteins includes NOD2/CARD15 as well as several additional regulatory proteins. The Nod proteins contain a central nucleotide-binding domain and an N-terminal caspase recruitment domain (12). In addition, they possess a C-terminal leucine-rich repeat (LRR) region that bears a high degree of homology with plant genes known to be involved in disease resistance. This finding suggests that Nod proteins may play a similar role in mammals (12).

NOD2 is expressed in monocytes, intestinal epithelial cells, and intestinal Paneth cells. This protein recognizes and binds muramyl dipeptide, the biologically active moiety of bacterial peptidoglycan, resulting in activation of the proinflammatory cytokine NF-κB (13). It is the leucine-rich repeat region of the protein that functions in peptidoglycan recognition. Human mutations in NOD2 occur in both the LLR and in the central nucleotide-binding domain. Three major mutations have been described in the LRR, all of which are associated with Crohn disease (14,15). Interestingly, these mutations occur predominantly in Caucasian populations and are extremely rare in Asian and African-American populations (16,17). Mutations in the nucleotide-binding domain result in Blau syndrome, a rare disease characterized by early-onset granulomatous arthritis, uveitis, and skin rash.

Patients who have one defective copy of NOD2 demonstrate a two- to fourfold increased risk for the development of Crohn disease, while homozygous mutants show a 20- to 40-fold increased risk (15,18). Approximately 8% to 17% of CD patients carry two mutant NOD2 alleles. NOD2 mutations are associated with disease onset at a young age, disease located in the small intestine, and strictureing and fistulizing forms of the disease (14,15,19,20). The Crohn disease–associated mutations in the LRR of NOD2 all result in inactivation of the protein with a resultant defect in the cellular response to peptidoglycan (16). This abnormality on monocytes could result in an inability of the innate immune system to recognize bacterial products and a subsequent overreaction to bacteria by the adaptive immune system. In addition, defective NOD2 function in intestinal epithelial and Paneth cells may result in an abnormal immunologic response to normal commensal bacteria within the gut (21).
Locus Designation | Chromosomal Location | IBD Type | Candidate Genes
--- | --- | --- | ---
IBD1 | 16q12 | CD | NOD2
IBD2 | 12q13 | UC | VDR, IFN-γ
IBD3 | 6p13 | CD, UC | MHC I, MHC II, TNF-α
IBD4 | 14q11 | CD | TCR α/δ complex
IBD5 | 5q31-33 | CD | IL-3, IL-4, IL-5, IL-13, CSF-2
IBD6 | 19p13 | CD, UC | ICAM-1, C3, TBXA2R, LTB4H
IBD7 | 1p36 | CD, UC | TNF-R family, CASP9
IBD8 | 16p | CD | Unknown
IBD9 | 3p26 | CD, UC | CCR5, CCR9, nMLH1
Other | 7q | CD, UC | Multidrug resistance 1
Other | 10q23 | CD | Drosophila discs large homolog 5
Other | 9q32-33 | CD, UC | Toll-like receptor-4
Other | 1q41-42 | CD | Toll-like receptor-5
Other | 7p14 | CD, UC | NOD1/CARD4

CD, Crohn disease; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; UC, ulcerative colitis.

### IBD2

The IBD2 gene locus lies on chromosome 12 and appears to be more closely linked to the development of UC than CD (22). A number of possible candidate genes are located in this region, but investigation of several of these has yielded negative results.

### IBD3

Several studies have linked the IBD3 locus, located on chromosome 6, to both ulcerative colitis and Crohn disease (22,23). Recent data suggest that this region may be specific to men (24). This region contains the major histocompatibility complex (MHC), as well as the tumor necrosis factor (TNF) gene. Several human leukocyte antigen (HLA) associations with IBD are well known. Among Caucasians, susceptibility to ulcerative colitis has been convincingly linked to the HLADRβ1*0103 allele. In addition, this allele is associated with severe colitis and extraintestinal manifestations of UC. In Japanese and Jewish populations, susceptibility to UC has been linked to the HLADRβ1*1052 allele. Polymorphisms in TNF-α and their relationship to Crohn disease risk are also under current investigation.

### IBD5

The IBD5 locus resides on chromosome 5q31-q33. It was identified by a genomewide scan of Canadian families with early-onset CD. Heterozygous carriage of the risk alleles increased the risk for developing CD twofold, while homozygous carriage increases this risk by sixfold (25). IBD5 may also be associated with risk for development of UC (25). The specific causative gene has not yet been identified. Candidate genes include organic cation transporter genes 1 and 2, interferon regulatory factor isoform 1, PDZ and LIM domain protein (PDLIM4), and prolyl 4-hydroxylase (P4HA2).

### Immunologic Factors

Both CD and UC represent, at least in part, disorders of both innate (macrophage, neutrophil) and acquired (T and B cell) immunity. It is currently believed that the main abnormality responsible for the development of inflammation in these disorders is a loss of tolerance to enteric commensal bacteria or other pathogens (26). In normal individuals, tolerance is mediated by regulatory T cells, B cells, natural killer T cells, and dendritic cells that produce transforming growth factor beta (TGF-β), interleukin (IL)-10, interferons, and prostaglandin J2. In IBD, lamina propria macrophages and dendritic cells are increased in number, demonstrate an activated phenotype, and express many proinflammatory cytokines and chemokines. In addition, expression of costimulatory molecules and adhesion molecules, vital to the extravasation of macrophages and neutrophils from the vasculature, is also increased in both CD and UC (27).

### TABLE 11.2 Cytokine Production in Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Locus Designation</th>
<th>Chromosomal Location</th>
<th>IBD Type</th>
<th>Candidate Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD1</td>
<td>16q12</td>
<td>CD</td>
<td>NOD2</td>
</tr>
<tr>
<td>IBD2</td>
<td>12q13</td>
<td>UC</td>
<td>VDR, IFN-γ</td>
</tr>
<tr>
<td>IBD3</td>
<td>6p13</td>
<td>CD, UC</td>
<td>MHC I, MHC II, TNF-α</td>
</tr>
<tr>
<td>IBD4</td>
<td>14q11</td>
<td>CD</td>
<td>TCR α/δ complex</td>
</tr>
<tr>
<td>IBD5</td>
<td>5q31-33</td>
<td>CD</td>
<td>IL-3, IL-4, IL-5, IL-13, CSF-2</td>
</tr>
<tr>
<td>IBD6</td>
<td>19p13</td>
<td>CD, UC</td>
<td>ICAM-1, C3, TBXA2R, LTB4H</td>
</tr>
<tr>
<td>IBD7</td>
<td>1p36</td>
<td>CD, UC</td>
<td>TNF-R family, CASP9</td>
</tr>
<tr>
<td>IBD8</td>
<td>16p</td>
<td>CD</td>
<td>Unknown</td>
</tr>
<tr>
<td>IBD9</td>
<td>3p26</td>
<td>CD, UC</td>
<td>CCR5, CCR9, nMLH1</td>
</tr>
<tr>
<td>Other</td>
<td>7q</td>
<td>CD, UC</td>
<td>Multidrug resistance 1</td>
</tr>
<tr>
<td>Other</td>
<td>10q23</td>
<td>CD</td>
<td>Drosophila discs large homolog 5</td>
</tr>
<tr>
<td>Other</td>
<td>9q32-33</td>
<td>CD, UC</td>
<td>Toll-like receptor-4</td>
</tr>
<tr>
<td>Other</td>
<td>1q41-42</td>
<td>CD</td>
<td>Toll-like receptor-5</td>
</tr>
<tr>
<td>Other</td>
<td>7p14</td>
<td>CD, UC</td>
<td>NOD1/CARD4</td>
</tr>
</tbody>
</table>
Table 11.2

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Crohn Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate immune response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>TNF</td>
<td>Markedly increased</td>
<td>Increased</td>
</tr>
<tr>
<td>IL-6</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>IL-8</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>IL-12</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>IL-18</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>IL-23</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>IL-27</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Acquired (T cell) response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>IL-5</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>IL-13</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>IL-17</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>IL-21</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Crohn disease is associated predominantly with TH1 cytokine production (28). Ulcerative colitis, on the other hand, does not fit clearly into either the TH1 or TH2 category, although an atypical or modified TH2 response seems to occur in established UC (26). Although the types of cytokines produced in UC and CD differ somewhat (Table 11.2), both diseases are associated with abnormal immune responses to nonpathogenic commensal bacteria within the gut. Cross-reactivity of peripheral blood and colonic lamina propria CD4+ T cells with indigenous flora in patients with UC and CD suggests that abnormal T cell-specific immune responses to the normal flora of the host are important in the pathogenesis of both diseases (29).

In normal individuals, pathogens are recognized by germline encoded pattern recognition receptors on epithelial cells, neutrophils, macrophages, and dendritic cells. These pattern recognition receptors include lectins, mannose receptors, complement receptors, scavenger receptors, Nod proteins, and toll-like receptors (TLRs). At least ten different TLRs have been described, each of which recognizes a different bacterial factor. Activation of TLRs ultimately results in expression and activation of NF-κB (30). NF-κB is activated in the tissues of IBD patients, where it is thought to have proinflammatory activity. NF-κB stimulates expression of many molecules that likely play a role in IBD including IL-1β, TNF, IL-6, IL-8 and other chemokines, ICAM1 and other adhesion molecules, CD40, CD80, CD86, and the T-cell stimulator ICOS (31). NF-κB also stimulates expression of protective molecules including TNF-induced protein 3, CARD15, cyclo-oxygenase 2, β defensins, and peroxisome proliferator-activated receptor (PPAR)-γ (31).

Activated T lymphocytes are regulated by both effector and regulator T-cell subpopulations in healthy gut mucosa. Effector T cells are capable of inducing intestinal inflammation, while regulator T cells are able to control or prevent inflammation. The immunosuppressive function of the regulator cells is mediated through production of IL-10 and TGF-β. These regulator cells are thought to play pivotal roles in mediating tolerance toward luminal antigens. Genetically engineered IL-10–deficient mice develop severe transmural inflammation of the small and large intestine reminiscent of CD (32). In addition, studies suggest that defects in the IL-10 and TGF-β regulatory signaling pathway may exist in humans with UC (33).

Activation of effector cytotoxic T cells and cytokine release result in generation of activated matrix metalloproteinases, enzymes that are mediators of tissue destruction. In addition, cytokines act directly on the microvasculature, up-regulate adhesion molecules, and enhance recruitment of additional effector cells including neutrophils and macrophages, which amplify and perpetuate the inflammatory response and contribute to additional tissue injury.

As a result of these immunologic events, the mucosa becomes heavily infiltrated by inflammatory cells. Soluble inflammatory mediators produced by neutrophils, lymphocytes, monocytes, fibroblasts, mast cells, neuroendocrine cells, and nerves generate many of the functional and histologic changes that characterize the disease (Fig. 11.2). One sees a large number of activated T and B cells, increased immunoglobulin secretion, the presence of antigen antibodies (34), and aberrant expression of class II HLA molecules (35).

T-cell profiles differ between patients with Crohn disease and those with ulcerative colitis. As previously mentioned, CD is characterized primarily by a TH1 response. TH1 responses are mediated by IFN-γ, the production of which is stimulated by IL-12. Patients with CD also exhibit a TH17 response, associated with IL-17 production. IL-17 expression is stimulated by IL-6, TGF-β, and IL-23. In patients with ulcerative colitis, the T-cell profile has been more difficult to characterize, but may represent an atypical TH17-type response. This atypical TH17 response may be mediated by natural killer T cells that secrete IL-13 (36).

Autoantibodies

Populations of mucosal B cells and plasma cells increase in UC, a finding that initially suggested that the disease was antibody mediated and complement dependent. In addition, patients with UC demonstrate...
circulating autoantibodies including those directed against human intestinal tropomyosin isoform as well as anticolonocyte antibodies (34,37). This production of antiself antibodies is now thought to represent a phenomenon that is a secondary protective response aimed at clearing apoptotic cells.

Patients with UC also commonly demonstrate the presence of circulating antineutrophil cytoplasmic antibodies (ANCAs) (38,39). Antineutrophil cytoplasmic antibodies were initially described as sensitive and specific markers for active Wegener granulomatosis but are now known to occur in a wide range of diseases. The antigens recognized by ANCAs are by definition cytoplasmic, predominantly localizing to the primary granules of neutrophils. ANCAs exhibit two distinct patterns on ethanol-fixed human neutrophils: (a) a coarse granular cytoplasmic staining (C-ANCA) or (b) a perinuclear staining pattern (P-ANCA). The perinuclear staining pattern results from redistribution of the cytoplasmic antigen to the nucleus. Serine proteinase 3, cathepsin G, and elastase are the antigens to which C-ANCAs react and myeloperoxidase is the usual antigen to which P-ANCAs react in patients with vasculitis. In contrast, a unique subset of P-ANCAs characterizes UC patients. The identity of the antigen is unclear. The prevalence of a positive P-ANCA in UC patients ranges from 49% to 86% (40,41). The perinuclear ANCA pattern is 93% to 97% specific (39), but only 46% to 60% sensitive for the diagnosis (42). P-ANCAs are also found in up to 25% of patients with CD (40,43). Titers of these antibodies, however, do not correlate with the degree of severity of the associated colitis, and although they may serve as a convenient clinical marker for UC, their role in the pathogenesis of the disease is unclear. Interestingly, a recent report suggests that P-ANCA in UC may represent a cross-reacting antibody to an antigenic target of *Escherichia coli* and *Bacteroides* bacterial strains (44).

The absence of P-ANCAs in the serum defines one population of CD patients, whereas a smaller number of patients are positive for P-ANCA. CD patients with serum P-ANCA expression exhibit a UC-like clinical phenotype (45). One hundred percent of CD patients with P-ANCA have symptoms of left-sided colitis with clinical and histopathologic features of UC. The patients also express a rare allele (R241) of the intercellular adhesion molecule-1 (ICAM1) gene, suggesting the possibility that R241 is a marker for a CD–UC overlap syndrome (46).

**Apoptosis**

In normal mucosa, the inflammatory response is terminated by induction of apoptosis in activated T cells once the pathogen has been eliminated. However, in CD, mucosal T lymphocytes are resistant to apoptosis, leading to their accumulation and persistence of the inflammatory response (19,47). In UC patients, T cells are more susceptible to Fas-mediated apoptosis. In addition, Fas ligand is strongly expressed by T cells in active UC, but not in CD, suggesting the Fas-Fas ligand-induced apoptosis contributes to mucosal damage in UC (48).

**Exogenous Agents**

Numerous data suggest that environmental factors play a role in the development and progression of both forms of IBD. Susceptibility genes for both UC and CD are known to demonstrate incomplete penetrance. As noted earlier, concordance rates for monozygotic twins are >50% for Crohn disease and <10% for UC. This finding suggests that factors other than genotype must be involved in the pathogenesis of IBD. In addition, the incidence of IBD has increased in the...
developed parts of the world over the last 50 years, and is now becoming increasingly common in less developed countries as they become more industrialized and the standard of living improves. Environmental changes that might affect development of the mucosal immune system or the indigenous enteric flora include improved hygiene, consumption of sterile or at least noncontaminated foods, childhood vaccinations, and increased age at first exposure to a variety of intestinal pathogens.

Exogenous agents, including diet, infections, smoking, and other environmental factors, all may play an etiologic role in IBD. Environmental influences related to certain forms of industrial pollution may also account for the recent increase in CD incidence in certain countries.

**Food Antigens**

Numerous studies have demonstrated that exposure to food-associated antigens plays an important role in the gastrointestinal inflammation that occurs in patients with CD. In addition, patients treated with simplified or elemental diets containing proteins in the form of amino acids or small peptide fragments improve symptomatically and show decreased endoscopic or serologic evidence of inflammation (49). Rectal exposure of CD patients to a series of food antigens resulted in increased rectal blood flow and lymphocyte proliferation in comparison to non-CD control patients (50), a finding that suggests that patients with CD show gut-specific sensitization to food antigens. Reactions were seen with yeast and citrus antigens, although individual patients reacted also to other antigen groups. Although it is possible that this sensitivity to food antigens is merely a reflection of exposure to antigens through mucosal defects, the absence of similar sensitivities in patients with UC makes this possibility unlikely (50). It is not likely, however, that exposure to food-associated antigens represents the primary abnormality in patients with CD. Instead, exposure to food in the proximal gastrointestinal tract may lead to sensitization and stimulation of the immune system in genetically susceptible individuals.

**Infectious Agents**

For many years investigators have been suspicious that IBD may have an infectious etiology. These suspicions are based on several observations. First, CD patients have an increased incidence of childhood infections including pharyngitis, tonsillitis, and rhinitis (51). In addition, gastroenteritis in early infancy has been linked to later development of CD (52). Furthermore, studies have shown that patients with CD tend to have increased serum levels of antibodies directed against nonpathogenic as well as pathogenic enteric organisms (53). Many studies have attempted to link IBD to infections with *Mycobacteria*, *Yersinia*, and several viruses. However, no definitive link with any one infectious agent has ever been made.

Current evidence, instead, suggests that the resident bacterial flora of the gut may be a factor in initiating and propagating the inflammation in IBD. In CD patients, T lymphocytes are hyperreactive to bacterial antigens, a factor that suggests that local bacterial tolerance mechanisms may be abnormal in these individuals (54). Patients with both UC and CD show higher numbers of bacteria attached to their intestinal mucosa than do unaffected individuals (55). In addition, bacterial invasion of the mucosa has been reported in both UC and CD patients (56). IBD patients also have increased mucosal production of IgG antibodies directed against a wide range of commensal organisms (57). The clinical observation that, in some patients, disease flares may be ameliorated by antibiotic administration is supportive of a bacterial role. Finally, recent evidence suggests that the NOD2 CD susceptibility gene is involved in regulation of host responses to bacterial organisms (12). Overall, many view inflammatory bowel disease as a disease initiated by a general loss of tolerance for the commensal bacteria of the gut.

**Tobacco Use and Exposure**

The association between tobacco use and development of IBD is well established. Smoking decreases the risk for the development of UC, but exacerbates and aggravates Crohn disease (58,59). Former smokers have a lower risk of UC than do those who never smoked. In addition, exposure to passive smoke also appears to confer a lessened risk of developing UC relative to nonexposed nonsmokers (60).

Overall, the effect of smoking appears to be dose dependent (61). Interestingly, nicotine has been shown to have an inhibitory effect on TH2 lymphocyte function, the type of cells most implicated in UC (62). Former smokers have a lower risk of UC than do those who never smoked. In addition, exposure to passive smoke also appears to confer a lessened risk of developing UC relative to nonexposed nonsmokers (60). Indeed, nicotine-based enemas have been demonstrated to be beneficial in patients with milder forms of distal colitis. Nicotine has no effect on TH1 cells characteristic of the Crohn inflammatory response.

**Intestinal Permeability**

Increased intestinal permeability may play a role in the pathogenesis of CD. Increased permeability not only occurs in the intestines of patients affected by the disease, but also in their unaffected first-degree relatives (64). It has been suggested that this increased permeability may represent a predisposing factor to the development of CD because a leaky intestinal barrier may intensify antigen absorption, leading to exaggerated systemic immune stimulation.

**Appendectomy**

Appendectomy early in life (before the age of 20) has been shown in several studies to decrease the risk of developing UC (65,66). Interestingly, the risk for UC is reduced only in patients who undergo appendectomy for acute appendicitis, and not in those whose appendices are removed because of nonspecific abdominal pain or incidentally during surgery for other causes. This finding suggests that the appendicitis that results in appendectomy, rather than appendectomy itself, is protective. Alternatively, there may be other factors among patients destined to develop UC that prevent those individuals from developing appendicitis. A recent report suggests that the risk for Crohn disease may also be decreased in patients who have undergone appendectomy (67).

**Other Environmental Factors**
Epidemiologic data suggest that use of nonsteroidal anti-inflammatory drugs (NSAIDs) can exacerbate existing UC, and may even induce it de novo (68). This effect was initially attributed to the cyclooxygenase (COX)-1 inhibitory effect of the drugs, but recent reports suggest that even COX-2–specific inhibitors also demonstrate this effect (69). Possible mechanisms by which NSAIDs exert these effects include inhibition of protective mucosal prostaglandin production and increased leukocyte migration and adherence. It has been estimated that NSAID use increases the risk of IBD exacerbation by as much as 30%. As many as 40% of UC patients report that psychological stress represents a trigger for their disease (70). There is evidence to link psychological stress with increased susceptibility to infection and illness through stress-related impairment of the immune system. Some animal models suggest that stress may play a role in the development of colitis. Cotton-top tamarinds, primates that spontaneously develop colitis and serve as a model for human IBD, develop colitis only in long-term captivity (71).

**Occupation**

Differences in IBD incidence exist among individuals with different occupations. Occupations involving work in the open air and physical exercise appear to protect against development of IBD, whereas exposure to air-conditioned, artificial working conditions or extended and irregular shifts can confer an increased IBD risk (72).

**Crohn Disease**

**Incidence**

As noted previously, there has been a steady rise in the incidence and prevalence of CD in Western Europe, Canada, and the United States over the past several decades. The incidence of CD ranges from 3.4 to as many as 14.6 per 100,000 in differing Western countries (1,73). CD affects all ages and both sexes, but its incidence peaks in the 2nd and 3rd decades of life. A second minor peak in incidence occurs in patients aged 50 to 70 years. Crohn disease is more common among Caucasians than among other racial groups, and is more frequent in Jewish than non-Jewish populations (4,5).

**Multiple Forms of Crohn Disease**

Recent epidemiologic evidence suggests that there are two forms of CD: One inherently indolent (nonperforating), which tends to recur slowly, and another inherently aggressive (perforating), which tends to evolve more rapidly. Patients with the relatively aggressive “perforating” type of CD are more prone to develop fistulae and abscesses, whereas the more indolent “nonperforating” type tends to lead to stenotic obstruction. The latter associates with an exaggerated inflammatory response and an exaggerated proinflammatory cytokine response (74). Host responses determine which form of CD becomes manifest in any individual, and differences in cytokine expression between the two forms of CD might have diagnostic, investigative, and therapeutic implications (74).

**Clinical Features**

The signs and symptoms of CD are often subtle, frequently resulting in a delay in diagnosis until months, or sometimes years, after symptom onset. However, the diagnosis can usually be made on the basis of a careful clinical history, physical examination, and diagnostic testing. The presentation of a patient with CD depends in large part on the location, extent, and severity of gastrointestinal involvement. Crohn disease most frequently affects the ileocecal region, followed (in decreasing order of frequency) by the terminal ileum alone, diffuse involvement of the small bowel, and isolated colonic disease (75). Because the clinical manifestations of CD are very diverse, both in the sites of tissue involvement and in the severity of the inflammation, a wide spectrum of clinical manifestations results (Table 11.3).

**TABLE 11.3 Clinical Features of Crohn Disease Related to Site of Bowel Involvement**

<table>
<thead>
<tr>
<th>Isolated small intestinal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Early satiety</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Postprandial cramping</td>
</tr>
<tr>
<td>Variable diarrhea</td>
</tr>
<tr>
<td>Lactase deficiency</td>
</tr>
<tr>
<td>Zinc deficiency</td>
</tr>
<tr>
<td>Ileal disease (or resection)</td>
</tr>
<tr>
<td>Vitamin B12 malabsorption</td>
</tr>
<tr>
<td>Fat-soluble vitamin malabsorption</td>
</tr>
<tr>
<td>Colonic involvement</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Cramping</td>
</tr>
<tr>
<td>Urgency</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Ileocecal involvement</td>
</tr>
</tbody>
</table>
Patients with ileocolonic disease experience intermittent episodes of crampy, often postprandial, abdominal pain. Pain may be referred to the periumbilical region, especially in children (75). The abdominal discomfort may be accompanied by loose stools. Stools are small, frequent at night, loose to watery, but not usually overtly bloody. Such symptoms are often attributed to dietary factors or irritable bowel disease. The past history commonly includes perirectal or perianal abscesses and fistulae. Physical examination may localize tenderness to the right lower quadrant. Occasionally, an inflammatory mass may be palpable. Patients with diffuse small intestinal Crohn disease present with diffuse abdominal pain, diarrhea, anorexia, and weight loss. Malabsorption may also occur. These patients demonstrate diffuse abdominal tenderness on physical examination. Colonic CD may mimic ulcerative colitis. Patients complain of diarrhea often containing blood and/or mucus and crampy lower abdominal pain that may be relieved with defecation. Crohn colitis is characterized by more extensive bleeding, more perianal disease, and less pain than Crohn ileitis.

Growth retardation occurs in many pediatric patients with CD, and may occur before other disease signs or symptoms develop. The growth failure and malnutrition result from inadequate dietary intake, malabsorption, and increased nutritional requirements, and, in treated patients, from drug therapy, particularly corticosteroids. Progressive transmural inflammation with scarring and deep ulceration may ultimately lead to symptoms associated with intestinal obstruction, perforation, bleeding, or fistula formation. When obstruction develops, it usually does so in the distal ileum. Extensive mucosal ulceration predisposes the patient to bacterial translocation with all of its complications, including a predisposition to bacterial endocarditis (76). Patients also demonstrate altered small intestinal motility with abnormal receptor-mediated small intestinal contraction (77). Deep linear ulcers or fistulae may sometimes give rise to profound lower GI bleeding. A sudden worsening of clinical symptoms and/or an unusual disease presentation should alert one to the possibility of ischemia or viral infection superimposed on pre-existing CD. Ischemia may develop secondary to vasculitis, or may occur because of endothelialitis resulting from infection with cytomegalovirus (CMV), particularly if immunosuppressive therapy has been utilized.

**Anorectal Disease**

Anorectal complications are common in patients with CD. In some patients, these anorectal symptoms may be the most troubling aspect of their disease. Approximately one quarter of patients with CD involving the small bowel and three quarters of individuals with colonic CD will have an anal lesion sometime during the course of their disease (78). Anorectal complications are more likely to occur during severe attacks when the colon is extensively involved. Perianal involvement may predate, postdate, or develop concurrently with primary intestinal CD.

**Jejunal Disease**

The term *regional jejunitis* is used to describe a variant of CD that manifests initially or predominantly as jejunal disease. It rarely coexists with duodenal CD. More often it occurs as part of diffuse jejunoileitis. It
also manifests as a particularly devastating and sometimes fatal pattern of CD recurrence following surgery for ileitis. The lesion may be confused with ulcerating jejunitis.

Appendiceal Disease

Sometimes CD initially presents in the appendix (Fig. 11.3), making it very difficult to differentiate from ordinary appendicitis because of the similarity of the clinical symptoms. The distinction between these two entities is most easily made if granulomas are found in the appendix.

Esophageal Disease

Esophageal CD occurs, although it is rarer than oral, pharyngeal, or laryngeal involvement. Esophageal disease affects 6% of CD patients (80). Esophageal lesions include aphthous ulcers measuring 2 to 3 mm in size, strictures, esophagitis, esophageal ulcers, and granulomas. The diagnosis should not be made unless typical lesions are found elsewhere in the gut.
Gastric Disease

Gastric CD typically involves the distal stomach producing thickening and granulomatous inflammation of the gastric wall, which results in pyloric obstruction and vomiting. Patients often have concomitant duodenal disease. Gastric CD may antedate small bowel involvement, and some of the reported cases of isolated granulomatous gastritis may actually represent early gastric CD. The diagnosis can only be made with certainty if there is associated CD in the small bowel or colon.

Endoscopy exhibits antral stenosis and rigidity; aphthous ulcers; nodules; thickening and blunting of the gastric folds associated with mucosal cobblestoning and denudation; fibrosis; and ultimately stricture formation. Antral stenosis is the most characteristic feature of gastric involvement. Gastric fistulae usually originate from the intestine with direct extension to the stomach (81). Features of gastric CD grossly and radiologically mimic gastric carcinoma or other inflammatory conditions.

Duodenal Disease

CD produces pathologically and radiologically typical lesions in the duodenum in approximately 0.5% to 4% of patients (81). Duodenocolic or duodenoileal fistulae develop, originating in the diseased duodenum or from previous ileocolic anastomoses. Duodenal–enteric fistulae also complicate CD arising in other parts of the gastrointestinal (GI) tract. Usually, but not invariably, duodenal CD coexists with ileal involvement and the duodenal lesions frequently extend proximally to involve the gastric antrum or distally into the jejunum (Fig. 11.4). The clinical features include symptoms of duodenal obstruction and/or ulceration. Duodenal CD predisposes patients to develop pancreatitis. Rare patients with duodenal disease develop massive upper GI hemorrhage.

Crohn Disease in the Elderly

About 5% of patients develop CD after age 60 (82). Older patients range in age from 64 to 85, tend to have a longer delay in diagnosis, have more hematochezia, and have a higher incidence of coexisting diverticular and vascular disease. Elderly patients often have less pain, a palpable abdominal mass, less small bowel disease, less drug treatment, and no family history of IBD; elderly patients are also less likely to have small intestinal disease. In some series, nearly all patients presenting with CD after age 60 have large bowel involvement (83). Older individuals may have more distal Crohn colitis (Fig. 11.5) than younger patients, who tend to have more extensive colonic involvement. Coexisting anorectal disease may clinically masquerade as diverticulitis. The most reliable hallmarks of CD in older persons include the presence of anorectal disease, rectal bleeding, and fistulae. The anal area may show edematous skin tags, ulcers, fissures, and fistulae. Elderly patients require total colectomy more frequently than those in the younger age groups (84).
FIG. 11.5. Proctocolectomy specimen in an elderly individual with Crohn disease. A: The sigmoid has become relatively featureless and atrophic, as indicated by the star. The most distal portion of the rectosigmoid is involved by active disease. B: Higher magnification showing the prominent severe distal disease. The arrows indicate the boundary of the normal and the involved portion by active disease, as verified by histologic examination. Significant anorectal disease is present.

**Patient Misdiagnosis**

Some patients are diagnosed with CD who do not have the disease. Two major reasons account for such a mistaken diagnosis: (a) diseases in organs adjacent to the ileocecum produce a clinical syndrome of acute right lower quadrant pain and inflammation, which could suggest the diagnosis; and (b) neoplastic, vascular, infectious, or other small intestinal diseases mimic CD. Table 11.4 lists diseases that can mimic CD clinically.

**Association with Other Diseases**

CD associates with extraintestinal diseases that represent part of the inherent disease process (see Extraintestinal Manifestations). Additionally, CD associates with other diseases as listed in Table 11.5.

**Extraintestinal Manifestations**

Approximately 25% of patients with known CD have a history of at least one extraintestinal manifestation. Multiple extraintestinal manifestations occur in the same patient more frequently than would be expected by chance. Large bowel involvement and longer disease duration predispose the patient to extraintestinal manifestations.

<table>
<thead>
<tr>
<th>TABLE 11.4 Diseases Clinically Mimicking Crohn Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Yersinia infections of the ileum, appendix, and cecum</td>
</tr>
<tr>
<td>Tuberculous infections of the ileum, appendix, and cecum</td>
</tr>
<tr>
<td>Acute appendicitis</td>
</tr>
<tr>
<td>Appendiceal abscess</td>
</tr>
<tr>
<td>Appendiceal mucocele</td>
</tr>
<tr>
<td>Meckel diverticulitis</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>Ovarian cysts and tumors</td>
</tr>
<tr>
<td>Cecal diverticulitis</td>
</tr>
<tr>
<td>Carcinoma of the cecum spreading to ileum</td>
</tr>
<tr>
<td>Ileal carcinoid</td>
</tr>
<tr>
<td>Ileal lymphomas, plasmacytoma, and Hodgkin disease</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Acute terminal ileitis</td>
</tr>
<tr>
<td>Ischemic ileitis</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Radiation enteritis</td>
</tr>
<tr>
<td>Ileocecal tuberculosis</td>
</tr>
<tr>
<td>Amebiasis</td>
</tr>
</tbody>
</table>

| TABLE 11.5 Crohn Disease: Associations |

file:///F|/Gastro/Chapter%2011%20IBD.htm (11 of 134)2/4/2009 2:03:30 PM
Need for Surgical Intervention

The majority of patients with CD undergo surgery at some time during their lives. Approximately 42% of children with CD require surgical intervention as compared with only 5% of those with UC (85), and approximately 20% require surgical intervention within the first year of diagnosis (86). The remainder undergo surgery at a rate of 5% per year (87). CD patients typically require repeated operations, with 63% of patients undergoing a repeat operation by the 15th postoperative year.

In general, radical resection does not decrease the recurrence rate of the disease, and repeated resections place patients at risk for the development of short bowel syndrome. Therefore, conservative surgical techniques have evolved in recent times to treat patients with CD-associated complications not amenable or responsive to medical therapy. Surgery in CD patients is indicated for treatment of abdominal abscesses, internal or external fistulae, bleeding, and bowel obstruction secondary to strictures, and in patients with medically intractable disease. Many patients experience recurrence of their disease, but many also report an overall improvement in their quality of life following surgery.

Recurrence of Crohn Disease

CD is a recurring chronic illness, with 94% of patients experiencing recurrent disease. Nearly all patients have a recurrence within 10 years of their initial diagnosis. Recurrence occurs most commonly in patients with ileocecal disease (53%) compared with isolated colonic disease (45%) or isolated small bowel disease (44%) (88). Patients who have undergone surgical procedures are particularly prone to recurrent disease. Ileal recurrence is determined in part by the retrograde reflux of the colonic fecal stream, microvascular injury, and ischemia (89,90). Additionally, increased use of acetaminophen and other nonnarcotic analgesics and increased consumption of simple sugars sometimes heralds the development of recurrent disease. For patients whose original disease was ileitis, recurrent disease almost invariably appears just proximal to the ileocolonic anastomosis. For those with an initial colitis or ileocolitis, recurrence develops on either side or both sides of the anastomosis.

Patient Survival

Patients with Crohn disease develop a large number of complications, some of which impact patient survival. Patient survival is not influenced by disease extent at the time of diagnosis. Patients die both from their underlying IBD as well as from associated diseases, including GI cancer, respiratory diseases, and other GI diseases.

Gross Features

The gross features of the bowel reflect the stage of the disease, with the most severe lesions being seen in advanced transmural disease. Patients with severe disease are those most likely to come to resection. Thus, the pathologist is only likely to see the gross pathology of advanced disease.

Lesion Distribution

CD classically involves the distal 15 to 25 cm of the terminal ileum, often in association with disease involving the right colon, but any part of the GI tract may become involved (Table 11.6). Thus, CD can involve the mouth, esophagus, stomach, duodenum, proximal jejunum, ileum, large intestine, and anus. Ileocolic, small intestinal, and upper gastrointestinal CD occurs in approximately 30% to 50%, 25% to 50%, and 5% to 30% of all cases, respectively. Disease limited
to the colon affects 15% to 30% of patients (91,92). The terminal ileum is involved in about 5% of Crohn colitis patients. The involved segments of small intestine vary from 5 to 76 cm in length with an average of 20 cm. Transition from involved to uninvolved areas is usually abrupt in the small bowel, but is less well defined in the large intestine.

**TABLE 11.6 Gastrointestinal Forms of Crohn Disease**

<table>
<thead>
<tr>
<th>Acute ileitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic regional ileitis</td>
</tr>
<tr>
<td>Localized disease of small bowel, not in terminal ileum</td>
</tr>
<tr>
<td>Extensive small intestinal disease</td>
</tr>
<tr>
<td>Ileocolitis with skip lesions</td>
</tr>
<tr>
<td>Crohn colitis</td>
</tr>
<tr>
<td>Anorectal Crohn disease</td>
</tr>
<tr>
<td>Gastric, esophageal, and duodenal Crohn disease</td>
</tr>
</tbody>
</table>
FIG. 11.6. Crohn disease. A: Serosal surface of Crohn disease demonstrating the presence of numerous fine adhesions and erythema on the entire serosal aspect. A portion of a fistulous tract was transected in the removal of the specimen from the patient (arrows). B: Unopened ileocectomy specimen in patient with Crohn disease. The colon lies to the left and shows prominent taenia coli. The appendix coils around the specimen. The distal ileum is covered with shaggy exudates and portions of transected adhesions (arrows). This process extends into the cecum. In the area of the ileocecal valve there is an abscess. C: The specimen shown in B has been opened, and the ileocecal valve is cut in cross section (arrows). The cecum and ascending colon are present on the left-hand side of the photograph and the terminal ileum is on the right. The portion immediately adjacent to the cecum is markedly stenotic and the terminal ileum lumen is almost completely occluded by the disease (star).

Grossly, colonic CD shows three major patterns: (a) diffuse (almost total involvement), (b) stricture formation, and (c) disease mainly confined to the rectum. Any of these forms can exist in isolation or can coexist with other gastrointestinal lesions, especially those involving the terminal ileum. In the colon, diffuse mucosal disease with relatively less involvement of deeper structures can produce an inflammatory pseudopolypoid mucosal pattern indistinguishable from UC, except for its patchy distribution. Patients with CD have a normal rectum in approximately 50% of cases.

External Gross Features

The external surface of the bowel appears reddened, hyperemic, and covered with serosal exudates producing serositis (Fig. 11.6). Areas of serositis appear rough and nodular, often coexisting with dense fibrous adhesions between bowel loops or fixation of the bowel to other abdominal organs, pelvic organs, or the abdominal wall. Fat encircles the antimesenteric serosal surface, producing a pattern known as “creeping fat” (Figs. 11.7 and 11.8). Miliary serosal lesions, the macroscopic equivalent of granulomas, may be seen. The miliary lesions appear as multiple, minute, white nodules resembling peritoneal seeding by carcinoma or the serosal tubercles characteristic of tuberculosis. They are usually distributed along the serosal lymphatics and may be seen on the surface of the adjacent mesentery and peritoneum. These may represent an early stage of the disease. Initially, the intestinal wall remains pliable, even though it may appear slightly thickened (Figs. 11.7 and 11.8). With disease progression, the bowel becomes increasingly fibrotic and rigid (Fig. 11.8). Eventually, strictures may develop, usually in the area of the distal ileum at the area of the ileocecal valve (Fig. 11.6). Large inflammatory pseudotumors may form at this site, simulating a carcinoma (Fig. 11.6). Granulomata within the lymph nodes are grossly visible as tiny gray-white specks (Fig. 11.9).
Chapter 11

FIG. 11.8. Mucosal thickening in Crohn disease. A: Opened small bowel in a patient with Crohn disease. In the central portion of the photograph the bowel wall is markedly thickened and edematous. Creeping fat is seen at the margin of the cut. At both the right- and left-hand margins the bowel widens out and is more normal. B: Opened ileal segment in Crohn disease. The bowel wall is markedly thickened. The thickening predominantly is due to dense fibrous tissue. The bowel lumen is almost totally occluded by the scarring process.

Internal Gross Features

The earliest grossly visible mucosal change consists of the formation of an aphthous ulcer overlying lymphoid tissue. As these ulcers enlarge, they may develop a hemorrhagic rim that makes them visible. In their early stages, aphthous ulcers are most easily seen in the colon (Fig. 11.10) because villi tend to obscure their presence in the small intestine. It is important to note that aphthous ulcers are not specific for CD, but may also occur in infectious enterocolitis (see Chapters 6 and 13). In some patients, these tiny ulcers are the only or predominant sign of the disease, whereas in other patients they associate with more severe changes elsewhere in the bowel. Recognition of discrete ulcers in areas of otherwise normal mucosa may precede the development of more flagrant changes of CD by weeks or years. The small, stellate, aphthous ulcers enlarge into discontinuous, serpiginous, or linear ulcers that then enlarge to form wide-based ulcers (Fig. 11.11). At this stage the mucosa appears reddened and swollen. The ulcers ultimately coalesce longitudinally and transversely. Grossly, the disorder is characterized by segmentally or diffusely arranged serpiginous or longitudinal furrowed ulcers with areas of intervening normal-appearing mucosa. The deep fissuring ulcers of CD differ from the superficial ulcers present in UC. The mucosa demonstrates islands of nonulcerated mucosa interspersed among ulcerated areas (Fig. 11.11), producing a cobblestoned appearance. This feature is also not specific for CD because it occurs in other conditions, such as ischemia.

When the linear ulcers heal, long railroad track–like scars remain (Fig. 11.12). Ulcers often lie close to the resection margins of the specimen and, if left in the patient, may form the basis of recurrent disease. Transmural inflammation predisposes the longitudinal ulcerations to become fissures or fistulae secondarily involving adjacent organs or the abdominal wall. Eventually, dense adhesions form.
FIG. 11.9. Crohn disease. A: The mucosa is at the top of the photo. A fistulous track (arrowheads) extends from an abscess coursing through the mesenteric fat. B: Cross section through a fixed specimen of ileum in Crohn disease. The loops of bowel are adherent to one another as a result of scarring and fibrosis. C: The bowel wall appears markedly thickened with irregular linear ulcers covered by hemorrhagic exudate. Numerous pseudopolyps are present. In addition, a lymph node containing white specks corresponding to granulomas is present (arrowhead).

FIG. 11.10. Endoscopic view of aphthous ulcers. Aphthous ulcers appear as erythematous “pimplelike” mucosal lesions. The aphthous ulcers are outlined by the arrows.
With disease progression, the cut surface of the bowel demonstrates full-thickness inflammation, scarring, and fibrosis of the submucosa, muscularis propria, and serosa. The fibrosis is superimposed on other macroscopic features. Intervening normal bowel separates diseased bowel segments, creating skip areas. This patchy pattern of inflammation contrasts with the continuous pattern of inflammation and prominent rectal involvement seen in UC. The mucosa may even become atrophic in longstanding disease.

**Abscesses, Fissures, and Fistulae**

Fistulae and adhesions (see Figs. 11.9 and 11.13) occur less commonly in patients with colonic involvement than in those with small intestinal disease. Internal and external fistulae form in up to 60% of patients (93). Fistulae occur spontaneously, and are more frequent in patients who have had previous surgery and who had residual diseased bowel. If the process remains localized, an abscess forms (Fig. 11.14). Vaginal fistulae commonly occur because of the anatomic proximity of the diseased rectal mucosa to the vagina. They may also result from extension of perirectal abscesses.

**FIG. 11.11.** Crohn disease. *A:* Large serpiginous ulcers are present. The ulcers contain granulation tissue and a fibropurulent exudate. The ulcerations extend deep into the bowel wall. The remaining mucosa appears edematous. *B:* Numerous geographic ulcers are present surrounded by mural edema. *C:* Closer magnification picture demonstrating the presence of sharp punched-out ulcers with clean, pearly bases.
Chapter 11

FIG. 11.12. Crohn disease. The bowel is opened. Prominent linear ulcers are present. The combination of ulceration and edema produces long linear ulcers, which produce “railroad tracks” when they heal. Since both linear and transverse ulcers are present, the mucosa has a cobblestone appearance.

Intra-abdominal abscesses develop in patients with CD. These abscesses may be intraperitoneal or, less commonly, retroperitoneal. There is marked preponderance of males in the retroperitoneal abscess group (93).

Perforation only affects 1.5% of CD patients (see Fig. 11.13) (94) because the inflammatory process penetrates the tissues slowly, causing loops of inflamed bowel to adhere to one another, thereby walling off any free perforation that might occur. Perforations result from deep penetration of fissures or fistulae through the bowel wall, from ingestion of some medicines, or from complicating ischemia (Fig. 11.15) or superimposed infection. Patients may also undergo spontaneous free rupture of an abscess into the peritoneal cavity.

Strictures

CD is characterized by strictures in the small and large intestine and in the anorectum. These strictures commonly lead to partial, intermittent obstruction. Strictures and fistulae are more common with ileitis, ileocolitis, and perianal disease than with disease predominating in the colon. The nature of the obstructive symptoms depends on the part of the bowel that is affected. The most severe stenosis usually affects the ileocecal valve. Multiple strictures may be present (Fig. 11.16). The strictures result from transmural inflammation, fibrosis, scarring, and fibromuscular proliferation. Rectal strictures are not unique to CD because they also complicate other disorders (Table 11.7).
FIG. 11.13. Crohn disease. A: Ileum with area of stenosis (arrowheads). The proximal bowel became dilated and ruptured (arrow). B: Portion of ileocolectomy with fistula communicating between the small bowel and the colon (arrows). The colon is densely adherent to the small intestine. The small intestine lies to the right of the photograph and shows prominent thickening of the wall. The colon nearby is dilated.
FIG. 11.14. Colonic abscess in a patient with Crohn disease. A large submucosal abscess is present. It expands and occupies the majority of the submucosa on the left-hand and middle portions of the photograph.

**Pseudopolyps**

Pseudopolyps develop in CD. Many of these are inflammatory in nature, whereas others represent residual mucosal islands (Fig. 11.17). Giant pseudopolyps sometimes form in the colon. These large polyps measure up to 5 cm in height and 2 cm in diameter, and project into the colonic lumen. The lesions have a predilection to involve the transverse colon and splenic flexure, but they occur anywhere in the large intestine. The surfaces exhibit a cribriform appearance and may contain inspissated feces. In addition to the presence of bulky, lobulated polyps, one may also see narrow, tall, filiform polyps.
FIG. 11.15. Crohn disease complicated by ischemic colitis. The ischemic area is in the upper right-hand portion of the mucosa and is covered by a fibrinous pseudomembranous exudate.

P.609

FIG. 11.16. Strictures in Crohn disease. A: A several-inch-long strictured area is present in the ileum. The lumen immediately proximal to it is markedly dilated. B: This is the same specimen shown in A after fixation highlighting extension of the disease into the surrounding fat. C: Numerous strictures are present in the small intestine of this patient. The area just above the ileocecal valve shows several inches of stenosis marked by focal dilation (upper white arrow in the middle of the photograph). Immediately beneath this is another area of stricturing. The remaining arrows indicate the presence of fistulous tracts.

**Histologic Features**

**General Comments**

The ease of making the diagnosis of CD depends on whether one examines biopsy or resection specimens. Resection specimens are more likely to exhibit all of the classic changes of CD, especially those that typically affect the deeper layers of the bowel wall (Table 11.8). The features of CD were originally described in the landmark article published by Crohn and Ginsberg in 1932 (95). Irregularly distributed aphthous-type ulcers, nodular lymphoid aggregates, irregular hypertrophy of the muscularis mucosae, proliferation of submucosal nerves, and loosely organized granulomas occur in various combinations within the mucosa and the submucosa (Fig. 11.18). The biopsy diagnosis of CD remains more problematic because only the mucosa and superficial submucosa are available for examination. In addition, many of the histologic features, including the presence of granulomas, are relatively nonspecific. The pattern and distribution of changes in biopsies are frequently characteristic enough to allow one to suggest that CD is present and/or enable one to exclude other diagnoses that might be in the differential diagnosis.

**TABLE 11.7 Rectal Strictures: Etiology**

<table>
<thead>
<tr>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Ischemic colitis</td>
</tr>
<tr>
<td>Chlamydial infections</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Status postradiotherapy</td>
</tr>
</tbody>
</table>
Epithelial and Mucosal Changes

The patchy distribution of CD results in an epithelium that exhibits a range of changes, depending on whether or not the tissues are examined early or late in the course of the disease and whether the tissues come from more normal or more diseased parts of the bowel. The epithelium ranges in appearance from completely normal, to acutely damaged, to regenerative (Fig. 11.19). In longstanding CD, the crypts and villi show marked distortion of the normal architecture. Distorted glandular architecture is characterized by areas of glandular irregularity and branching (Figs. 11.20 and 11.21). This feature is best appreciated in sections of crypts cut in a plane perpendicular to the muscularis mucosae. In sections cut parallel to the muscularis mucosae, regenerated crypts can be recognized by the presence of cross sections of glands that show variable diameters (Fig. 11.22) and an uneven distribution.

FIG. 11.17. Mucosal polyposis. Irregularly sized cobblestonelike structures are present. They represent residual islands of mucosa. The clefts between them represent linear ulcers.

<table>
<thead>
<tr>
<th>TABLE 11.8 Resection Features That Suggest a Diagnosis of Crohn Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmural inflammation</td>
</tr>
<tr>
<td>Focal or segmental ulceration</td>
</tr>
<tr>
<td>Deep fissures with knifelike clefts passing into the bowel wall</td>
</tr>
<tr>
<td>Deep sinus tracts that extend into or through the muscularis propria</td>
</tr>
<tr>
<td>Focal lymphocyte collections (lymphoid nodules) in all bowel layers, including the serosal fat</td>
</tr>
<tr>
<td>Submucosal widening</td>
</tr>
<tr>
<td>Lymphangiectasia, especially in submucosa</td>
</tr>
<tr>
<td>Confluent linear ulcers</td>
</tr>
<tr>
<td>Perivascular inflammation along the perforating vessels (vascular tracking)</td>
</tr>
<tr>
<td>Intestinal wall thickening secondary to fibrosis</td>
</tr>
<tr>
<td>Inflammation of the superficial muscularis propria strongly suggests the presence of Crohn disease</td>
</tr>
<tr>
<td>Neuronal hyperplasia</td>
</tr>
<tr>
<td>Increased vasoactive intestinal polypeptide content in nerves</td>
</tr>
<tr>
<td>Serosal inflammation (sometimes including granulomas and lymphoid nodules)</td>
</tr>
<tr>
<td>Absence of known etiology (i.e., infection or ischemia)</td>
</tr>
</tbody>
</table>
FIG. 11.18. Whole mount sections of Crohn disease. The mucosal surface demonstrates thickening with areas of ulceration and denudation. The submucosa is considerably thickened and contains numerous prominent lymphoid aggregates as evidenced by the darker circular areas. The muscularis propria appears hypertrophic. There is a prominent serosal exudate. Lymphoid aggregates are also seen on the serosal surface. This photograph demonstrates transmural inflammation.

Distorted glands often show epithelial hyperplasia (Fig. 11.23), crypt abscesses, epithelial cell degeneration, and ulceration (Figs. 11.24 and 11.25). In the small intestine, villi become distorted or atrophic and one commonly sees pyloric metaplasia, especially in the ileum. The presence of distorted villi and/or crypts and areas of pyloric metaplasia or increased numbers of Paneth cells, especially in the left colon, indicates that the disease is chronic in nature.

The mucosa often appears cobblestoned and mildly polypoid, but not to the extent seen in UC. Although focal crypt abscesses affect patients with CD, they are often not as numerous as in UC. Regenerative changes occur at ulcer margins, but the mucosa away from ulcers may appear normal except for a lymphoplasmacytic infiltrate in the basal part of the lamina propria. Goblet cell depletion and reactive epithelial cells are present only in areas of severe inflammation. Active apoptosis affects the deeper parts of the glands. Areas of mucosal fibrosis may be predictive for CD. In patients with chronic disease, the mucosa may exhibit localized areas of hyperplasia lined by prominent and hyperplastic goblet cells (Fig. 11.23).

**Aphthous and Other Ulcers**

Two distinctive types of ulceration affect both the small and large intestines. The first is the histologic equivalent of the grossly evident aphthous ulcer. This lesion develops even before inflammatory cells diffusely infiltrate the lamina propria.

Antigen entry into M cells might lead to the proliferation of antigen-sensitized cells and granuloma formation. The underlying lymphoid nodule may contain giant cells or granulomas. As the lesion progresses, it superficially ulcerates, obliterating its associated lymphoid follicle (Figs. 11.24 and 11.25). A thin stream of mucus, neutrophils, and inflammatory debris exudes from the ulcer mouth and empties into the bowel lumen (Figs. 11.24 and 11.25). The ulcers progressively enlarge, forming a continuum with the larger ulcers normally seen in CD (Fig. 11.26). Larger ulcers may eventually become lined by a single layer of atrophic cuboidal epithelial cells. There is an associated reduction in the number of crypts and loss of villi in the small bowel.

The second type of ulcer is the knife-like fissure, which occurs at right angles to the long axis of the bowel (Fig. 11.27). These may extend through the bowel wall and are likely the basis for fistula formation. Fissures branch and penetrate deeply into the underlying bowel wall, producing adhesions, fistulae, abscesses, and peri-intestinal inflammatory pseudotumors (Fig. 11.28). Fissures contain acute inflammatory cells and a granulation tissue lining with conspicuous pale, plump histiocytes. The latter resemble the epithelioid histiocytes seen in granulomas. Giant cells may also be present. Healed ulcers result in architectural distortion, pyloric metaplasia (Fig. 11.29), and a thickened or duplicated muscularis mucosae often associated with a marked dense submucosal fibrosis. As a result, it is often impossible to distinguish the muscularis mucosae from the submucosa or underlying muscularis propria. Fibroblasts and myofibroblasts proliferate in these areas of fibrosis, usually with accompanying chronic inflammatory cells. Fibrosis extends from the bowel wall to involve adjacent structures and traps within it lobules of fat that may demonstrate variable degrees of fat necrosis.
**FIG. 11.19.** Variable histologic features of Crohn disease (CD). *A:* This picture is from a resection specimen and shows prominent mucosal and submucosal inflammation with marked lymphangiectasia. Areas of re-epithelializing ulceration are present at the right-hand portion of the photograph. *B:* Portion of colonic mucosa in a patient with CD showing essentially normal histologic features. *C:* Portion of small bowel showing marked regenerative changes at the bases of the crypt and extension of the proliferative zone up along the sides of the crypt. Focal chronic inflammation is present, particularly at the right-hand side of the photograph. The villi are fused, hyperplastic, and irregularly shaped.

### Mucosal Metaplasia

Patients with chronic disease often develop pyloric metaplasia (Fig. 11.29), especially in the ileum. The large intestine often develops Paneth cell metaplasia. In the small bowel, the number of Paneth cells may increase, although they are normally present in this location.

The cells in pyloric metaplasia, also known as aberrant pyloric glands, have also come to be known as ulcer-associated cell lineage (UACL) cells (96). This distinctive cell lineage typically arises in sites of enteric ulceration, most notably in the ulcerated gut in CD. The pyloric glands usually occur singly or in clusters in the mucosa adjacent to ulcer margins. They are also found near single discrete ulcers in the edematous segments away from involved mucosal areas.

These cells share many features of pyloric and Brunner glands, although they do not extend deeper than the muscularis mucosae, a feature that distinguishes them from Brunner glands. The regular acinar glands have a coiled tubular neck and therefore the entire neck is rarely seen in a single section. They extend down to, but usually not through, the muscularis mucosae and have a number of terminal branches that are given off at right angles to the neck,
so that they are usually seen in cross section. The glands are lined by clear or pale-staining columnar cells containing indistinct neutral mucin granules. The nuclei appear oval or round and are located near the base of the cell. The glandular structures have a looser architectural pattern than either pyloric or Brunner glands (96).

**FIG. 11.20.** Histologic features of Crohn disease. *A:* A portion of small intestine from a resection specimen showing the focality of the changes. The epithelium on the right-hand side of the photograph is greatly simplified and edematous. On the left-hand side of the photograph, one sees an expansion of the mucosal thickness due to the presence of large numbers of pyloric glands. The villi appear atrophic and the lamina propria is infiltrated with mononuclear cells. The underlying muscularis mucosae appears markedly distorted. *B:* Crohn colitis from a resection specimen. The mucosa demonstrates variable inflammation. The epithelium appears markedly regenerative and mucin depleted. The underlying muscularis mucosae is fused with the muscularis propria.
Lymphatic Dilation (Lymphangiectasia)

Another notable feature of CD is submucosal lymphatic dilation (Fig. 11.30), which commonly coexists with edema and lymphoid hyperplasia. Plasma cells, eosinophils, and neutrophils may infiltrate along the dilated vessels. In more advanced stages of the disease, fibrous tissue replaces the edema.

Nature of the Inflammatory Infiltrate

Early morphologic lesions include increased numbers of mucosal plasma cells, lymphocytes, macrophages, mast cells, eosinophils, and neutrophils in all layers of the bowel wall. A basal lymphocytic–plasmacytic infiltrate occupies the lower part of the mucosa (Fig. 11.31). In active IBD, one sees a constant emigration of neutrophils and monocytes from the circulation into the inflamed mucosa and through the epithelium into the intestinal lumen. Neutrophils infiltrate the intestinal epithelium, forming the lesion known as cryptitis.

Collections of granulocytes within the crypt lumens are called crypt abscesses (Fig. 11.32). Variable edema and/or fibrosis are present, depending on the stage of the disease (see Fig. 11.18). The inflammatory infiltrate often also surrounds submucosal and serosal lymphatics and blood vessels, where they penetrate the muscularis propria. Denser lymphocytic aggregates also lie in the submucosa away from the lymphatics or they may appear scattered throughout all layers of the bowel wall (see Fig. 11.18).
FIG. 11.22. Diagrammatic representation of the appearance of regenerative crypts. **A:** Regenerative branched crypts are relatively easy to recognize when they are cut in a plane perpendicular to the muscularis mucosae. One sees crypt after crypt demonstrating irregular branching often with other features of chronicity, such as Paneth cell metaplasia or pyloric metaplasia. One must be careful in making the diagnosis of regeneration based on the finding of a single “branched crypt,” since the edges of mucosal territories may appear branched. For this reason, one would like to see several branched crypts in a row to make the diagnosis. **B:** Crypts cut in cross section are more difficult to recognize as being regenerative. Clues to their regenerative nature include variability in crypt diameter when one measures each through an equatorial plane. Additionally, the presence of back-to-back glands in the absence of significant cytologic atypia also suggests regeneration.
FIG. 11.23. Mucosal hyperplasia in Crohn disease. A: Low-power magnification photograph of a portion of the terminal ileum showing complex glandular structures cut in cross section. These represent sections through villi. The villi are lined by cells containing hyperplastic goblet cells. The cores of the villi contain dense mononuclear cell infiltrates. B: Higher magnification in an area of junction between the hyperplastic goblet cells (left) and more normal-appearing goblet cells (right).
FIG. 11.24. Progression of aphthous ulcers in Crohn disease. *A:* The colonic mucosa and submucosa contain prominent lymphoid aggregates. The lamina propria is infiltrated with mononuclear cells. Mild regenerative features are present. The goblet cell population is still intact. *B:* Wider-based aphthous ulcer (*arrow*). *C:* Aphthous ulcer. An area of ulceration is noted over a lymphoid aggregate. Inflammatory debris is present in the ulcer tract overlying the lymphoid aggregate (*arrow*). The epithelium on both sides of the ulceration is regenerative (*arrow*).
An early but nonspecific finding of CD is an increased number of eosinophils and macrophages (Fig. 11.33) in the lamina propria beneath the surface epithelium. Eosinophils degranulate in ulcerated areas, leading to deposition of eosinophil cationic protein and cathepsin G. These proteins contribute to the inflammatory process (97). Mucosal and submucosal mast cell hyperplasia and degranulation also represent constant features of both UC and CD. Mucosal mast cells maintain a direct association with substance P (SP)-containing nerves, as well as with capillaries, blood vessels, Schwann cells, nerve fibers, myofibroblasts, and collagen fibers. They also lie along epithelial cells, providing an anatomic basis for communication between nerves and the immune system. Inflammatory mediators released from mast cells contribute to the pathophysiology of CD due to the release of preformed and newly generated inflammatory mediators (98). The bowel develops focal edema and inflammation in the lamina propria, submucosa, and deeper layers, even in the presence of a more or less normal-appearing mucosa.

Dendritic cells lie adjacent to granulomas and fissures. The number of macrophages in the lamina propria increases. They are arranged in bandlike zones at the bottom of ulcers or fissures, perhaps playing a scavenging role directed against microbial agents or dietary substances penetrating the GI wall through the mucosal defects. Aggregates of macrophages lead to the formation of noncaseating granulomas.
Chapter 11

**Lymphoid Aggregates**

Lymphoid aggregates, which may contain germinal centers, generally lie at the mucosal–submucosal junction. Lymphoid aggregates form even in the absence of granulomas, and they may be more helpful than granulomas in establishing the diagnosis of CD (Figs. 11.18 and 11.34). Lymphoid aggregates occur in both CD and UC; however, when they lie in the submucosa or deeper in the bowel and are separated from the muscularis mucosae, and when the lymphoid aggregates coexist with submucosal edema or fibrosis in the presence of an intact mucosa, the diagnosis is more likely to be CD than UC. Prominent lymphoid aggregates also commonly affect the serosal fat in CD. Finally, the lymphoid tissue of the terminal ileum may become hyperplastic, forming multiple lymphoid polyps.

**FIG. 11.27. Ulceration in Crohn disease. A deep knifelike ulcer is present.**

**Granulomas**

Compact sarcoidlike granulomas are the sine qua non for the diagnosis of CD (Figs. 11.35 and 11.36) and, when present, are a reliable histopathologic criterion for differentiating CD from UC. Granulomas assume particular diagnostic significance when seen in tissues remote from areas of ulceration in situations where foreign body granulomas are unlikely. Although the presence of granulomas represents a useful diagnostic feature for CD, they can be seen in various other conditions (see Table 11.9).

<table>
<thead>
<tr>
<th>Mucin granuloma</th>
<th>Fungal infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infections</td>
<td>Chlamydial infections</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Sarcoïd</td>
</tr>
<tr>
<td><em>Yersinia</em></td>
<td>Crohn disease</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Hermansky-Pudlak syndrome</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>Diverticulosis</td>
</tr>
</tbody>
</table>
Pathologists should be cautious when diagnosing a granuloma in biopsy material. Ruptured crypts release mucin into the lamina propria, stimulating the formation of mucin granulomas (Fig. 11.37). Such mucin granulomas may include mature macrophages and foreign body–type giant cells. They can be recognized because of the predominance of giant cells, their association with and orientation around perforated crypts (Fig. 11.37), and their positivity for mucin stains. Mucin granulomas are not specific for CD because they occur in any situation that results in crypt destruction with epithelial cell loss, including UC.
FIG. 11.29. Ileal pyloric metaplasia. A: Low power of the basal portion of the mucosa showing expansion of the mucosal thickness. Prominent pylori glands lie beneath the intestinal epithelium and above the muscularis mucosae. B: Higher magnification of pyloric metaplasia in a different case showing the presence of pyloric glandular collections in the basal mucosa. In the center of the photograph, it connects with an actively regenerating crypt.

FIG. 11.30. Lymphangiectasia in Crohn disease. This section from the ileum of a patient with Crohn disease shows prominent dilation of the lymphatics in the submucosa and deep mucosa.
FIG. 11.31. Basal plasmacytosis in inflammatory bowel disease. The lamina propria of the deep mucosa contains numerous plasma cells. Scattered lymphocytes and eosinophils are also present.

The reported frequency with which granulomas are identified in CD varies markedly between studies. Possible explanations for this include the criteria used to diagnose granulomas; whether or not isolated giant cells are included among granulomas; the number of biopsies obtained; and the number of sections examined. Granulomas are found in the bowel wall in 50% to 87% of colectomy specimens, in 15% to 36% of colonoscopic biopsies, and in 20% to 38% of regional lymph nodes (87,99,100). CD granulomas do not usually affect the regional lymph nodes when they are absent in the bowel wall.

FIG. 11.32. Diagrammatic representation of the different forms acute inflammation takes in inflammatory bowel disease. A: When neutrophils infiltrate the epithelium without causing destruction, the lesion is termed cryptitis. B: When a large number of neutrophils infiltrate the glandular lumen, the lesion is referred to as a crypt abscess. C: Because the neutrophils contain large numbers of lysosomal enzymes, they destroy the underlying crypt and the acute inflammation extends into the surrounding lamina propria. This is sometimes referred to as crypt herniation. D: In time, these changes resolve with new epithelium repopulating the crypt. Epithelial cells migrate upward and again reaccumulate mucin within them. Variable numbers of neutrophils may be present at this stage.

Sometimes the granulomas are quite small (microgranulomas). Microgranulomas consist of only a few histiocytes, and are easily overlooked (Fig. 11.36). In one study, 16% of granulomas were so small as to be seen in only 6 of 90 serial sections. Isolated mucosal or submucosal giant cells are seen in 13% of patients (99).

Fewer granulomas occur in the ileum than in the colon. Granulomas progressively increase in number from the ileum to a maximum number in the rectum (101). The granulomas also occur in various other tissues and organs, including the lymph nodes, pancreas, mesentery,
peritoneum, liver, lung, kidney, and, occasionally, bones, joints, and skeletal muscle. The presence of granulomas does not indicate disease activity, nor does it affect the postoperative recurrence rate.

**FIG. 11.33.** Inflammation in Crohn disease. *A:* Prominent mononuclear cell infiltrate consisting mainly of lymphocytes and plasma cells. There is a mild increase in intraepithelial lymphocytes. *B:* The lamina propria contains a large number of eosinophils and mast cells recognizable by their prominent reddish granules. These cells are actively degranulating. *C:* Localized histiocytic collection surrounded by lymphocytes, plasma cells, and eosinophils.
FIG. 11.34. Crohn disease. Inflammation extends through the full thickness of the bowel wall. Prominent lymphoid aggregates are present within the submucosa and muscularis propria.

The granulomas consist of small, localized, well-formed, loose or more compact aggregates of epithelioid histiocytes with or without Langerhans giant cells, often with a surrounding cuff of lymphocytes (see Figs. 11.35 and 11.36). Nodal granulomas also contain centrally located T lymphocytes and dendritic cells. Older lesions may show varying degrees of hyalinization and fibrosis. The granulomas may be numerous or very difficult to find. Granulomas that have definite foci of necrosis or suppuration, or are restricted to the edges of ruptured crypts, are not specific for CD.

Granulomas may be observed anywhere within the intestinal wall and along blood vessels or nerves, especially in the submucosa (Fig. 11.35), mucosa (Fig. 11.36), and subserosa, and in the regional lymph nodes (Fig. 11.38). Granulomas may lie adjacent to dilated lymphatics, causing compression of the lymphatic wall or projecting within the lumen of lymphatic spaces (Fig. 11.39). Sometimes granulomas are present in the lamina propria or in the wall of microabscesses of aphthoid ulcers.

On those rare occasions when microorganisms are found within the granulomas, they probably represent secondary invaders.

P.619

P.620
FIG. 11.35. Granulomas in mucosal biopsy specimens from Crohn disease patients. A and B are from the terminal ileum, and show the presence of a prominent granuloma just beneath the muscularis mucosae. Figure A provides a low-power magnification overview showing the prominence and nodular arrangement of the granuloma (arrows). The lower left-hand corner of the specimen is more intensely infiltrated with mononuclear cells when compared with the rest of the specimen. B: Higher magnification of the granuloma in the basal epithelium. C and D represent a colonic mucosal biopsy showing a prominent granuloma. The overlying epithelium in C appears regenerative. The granuloma is surrounded by a dense cuff of lymphocytes (arrows). D: Higher magnification of the granuloma.
**FIG. 11.36.** Microgranuloma in a colonic biopsy from a patient with Crohn disease. Note the presence of a compact histiocytic granuloma in the basal portion of the mucosa. The glands surrounding the lesion appear mildly regenerative.

**Vascular Lesions**

Some postulate that CD results from an underlying vascular disease. The changes appear primarily degenerative or inflammatory in nature. Obliterative endarteritis, chronic phlebitis, and other vascular lesions affect approximately 5% of patients (Figs. 11.40 and 11.41). Obliterative changes include intimal proliferation, subintimal fibrosis, medial hypertrophy, medial fibrosis, and adventitial fibrosis, all without a significant inflammatory cell component. Degenerative arterial lesions may narrow the vascular lumen due to duplication of the internal elastic lamina with medial hypertrophy. Venous lesions feature an irregular vascular sclerosis with thickening of the wall due to hyperplasia of fibrous, elastic, and muscular tissues.

The inflammatory lesions consist of perivascular inflammation and chronic inflammatory and/or granulomatous cell infiltrates associated with an obliterative vasculopathy. Lymphocytes and plasma cells infiltrate one or more layers of small arteries or arterioles, leading to interruption of the internal elastic fibers. Areas of thrombosis are rare.

The vascular changes seen in CD must be distinguished from a primary systemic vasculitis involving the GI tract. When a primary vasculitis affects a patient with CD, extraintestinal manifestations of the disorder are usually evident.

**FIG. 11.37.** Early mucin granuloma in a mucosal biopsy from a patient with ulcerative colitis. This specimen shows evidence of basal plasmacytosis, which is most evident in B. A: One sees several crypt abscesses. The right one has ruptured and herniated with extension into the surrounding lamina propria. Histiocytic cells collect at the area of herniation. B: A crypt that has ruptured and is associated with two giant cells intermingling with apoptotic cell fragments and with extravasating inflammatory cells. These lesions have a completely different appearance than the microgranulomas associated with Crohn disease. Compare this photograph with Figure 11.36.
Neural Changes

The autonomic neural plexuses often appear hypertrophic in CD. Large, abnormal, irregular, fusiform nerve bundles and nerve trunks are present throughout the mucosa, submucosa, and muscularis propria (Figs. 11.42 and 11.43). These often contain increased numbers of ganglion cells. Occasionally, striking plexiform neuromatous proliferations associate with tortuous thick-walled arterioles. The nerve fibers contain increased amounts of vasoactive intestinal peptide (VIP) and substance P (102). They express MHC class I antigens (103) and thus the abnormal nerves become infiltrated with mast cells, lymphocytes, and plasma cells (Figs. 11.42 and 11.43). The nerves also show evidence of extensive axonal and dendritic swelling and degeneration.
FIG. 11.39. Granuloma in Crohn disease. This granuloma is arising in association with a dilated submucosal lymphatic. Granulomas in Crohn disease are commonly located adjacent to lymphatics.

Strictures

Stricture formation characterizes CD, especially in the small bowel. These strictures result from fibroblast proliferation and increased collagen deposition in the bowel wall (Fig. 11.44). The fibrosis extends along lymphatics and vascular planes and also involves the serosa and pericolonic tissues. Sclerosing lymphangitis, proliferative endophlebitis, and endarteritis are the end result of many of the inflammatory and fibrosing processes.

Some CD patients develop distinctive polypoid lesions in stricturing areas. These consist of proliferations of vessels, nerves, and muscular tissue, sometimes referred to as neuromuscular hamartomas. Grossly, one sees a cluster of sessile polyps covering normal mucosa. Although the lesions have been described as hamartomas, it is more likely that they represent reparative lesions (Fig. 11.45).
FIG. 11.40. Vasculitis in Crohn disease. A: Submucosal vessel demonstrating sclerosis with mild concentric fibrosis in the submucosa of a patient with Crohn disease. A minimal infiltrate is present within the wall of the vessel (arrows). The intima is expanded. B: This small vessel shows mild sclerosis and the beginning of an organizing thrombus. C: Submucosal vessel showing prominent chronic vasculitis. The entire wall of the vessel is infiltrated by mononuclear cells.
FIG. 11.41. Vasculitis in Crohn disease. Not all cases of vasculitis are as dramatic as those illustrated in Figure 11.40. This patient with CD had only minimal vascular inflammation. Such changes might be seen in a patient with severe ulcerative colitis, so that these features may show histologic overlap.

Pseudopolyps

Several types of polypoid lesions develop in CD. One type consists solely of inflammatory and regenerative tissues (Figs. 11.46 and 11.47). These fingerlike polyps arise in both the small and the large bowel. They contain granulation tissue and variable degrees of inflammation, sometimes covered by regenerating surface epithelium. Sometimes pseudopolyps are removed endoscopically. Other polyps contain mucosa, muscularis mucosae, edematous submucosa, submucosal fibrosis, and smooth muscle hyperplasia. These represent residual mucosal islands.
FIG. 11.42. Neural hyperplasia in Crohn disease. A: Low magnification showing the presence of prominent ganglia and supporting neural elements in this muscularis propria. B: Higher magnification.

Histologically, giant pseudopolyps consist of complex processes that branch and fuse to form a honeycomb pattern (Fig. 11.48). They contain an inflamed mucosa with intramucosal hemorrhage and fibrosis (Fig. 11.48). The lamina propria and surface epithelium become heavily infiltrated by plasma cells, eosinophils, lymphocytes, and neutrophils. The latter sometimes form crypt abscesses. Granulomas may also be present. Erosions, granulation tissue, and pyloric gland metaplasia can also be present. The lamina propria consists of small blood vessels, loose fibrous tissues, and smooth muscle fibers derived from the muscularis mucosae.

**Displaced Epithelium**

It is not uncommon to encounter displaced epithelium in resection specimens of CD patients. This entity is referred to as enteritis cystica profunda or colitis cystica profunda when it affects the small bowel or colon, respectively (Fig. 11.49). Enteritis cystica profunda occurs less commonly than its colonic counterpart, colitis cystica profunda. Displaced epithelium results from epithelial implantation into the submucosa, muscularis propria, or serosa following mucosal ulceration or the formation of mucosal microdiverticula, a common event in CD patients. Mucosal repair following regeneration of an ulcer leaves the detached epithelium buried in the submucosa. It eventually becomes covered by an intact mucosa (Fig. 11.49). Displaced epithelium also results from epithelialization of fissures or fistulous tracts. The displaced epithelium often becomes cystically dilated, containing large mucin accumulations.

FIG. 11.43. Submucosal inflammation in Crohn disease. The photograph is taken at the midportion of the submucosa and shows an intense mononuclear infiltrate and cross sections of numerous hyperplastic neural structures.

Grossly, the bowel wall appears thickened. The cut surface of the bowel discloses the presence of numerous cystic submucosal spaces. These are often quite prominent and glisten because of their mucinous content. The mucosa overlying such lesions usually demonstrates histologic evidence of active or healed CD. Histologically, one sees mucus-filled cysts in the submucosa, muscularis propria, and serosa. These are lined by cuboidal to columnar epithelium containing numerous goblet cells, enterocytes, and Paneth cells, all supported by a normal lamina propria. Sometimes the cyst lining disappears due to pressure atrophy from large intracystic mucinous accumulations.
Chapter 11

Sometimes it is difficult to determine whether the displaced epithelium represents an invasive mucinous carcinoma or merely displaced epithelium, especially when lamina propria does not surround the glands or when the benign epithelium produces excessive amounts of mucin, resulting in large mucinous cysts containing scant epithelial elements (Fig. 11.50). Features that help to rule out malignancy include the absence of desmoplasia, the presence of surrounding lamina propria, and an absence of cytologic atypia within the displaced glands. Cytologic atypia and areas of desmoplasia around angular, irregularly shaped glands characterize invasive cancers, particularly of the nonmucinous type.

In some cases, it may be impossible to determine whether one is dealing with displaced epithelium or an invasive cancer. Sometimes careful sampling and examination of the surface epithelium helps resolve the diagnostic dilemma. If the surface epithelium appears dysplastic, the possibility of an invasive lesion increases.

**Serosal and Mesenteric Changes**

The subserosa becomes considerably thickened, often as the result of hyperplasia of the subserosal fatty tissues, edema, fibrosis, acute and chronic inflammation, and granuloma formation. Nodular lymphoid aggregates are very common, and these may resemble serosal military granulomas grossly. The serosa may also become covered with a fibrinous precipitate or a fibropurulent exudate. The mesenteric changes closely parallel those seen in the serosa. The draining lymph nodes often become enlarged and frequently contain lipogranulomas.

**Superficial Crohn Disease**

The microscopic features of superficial CD are those of classic CD with aphthous ulcers, fissures, hypertrophy of the muscularis mucosae, and submucosal nerves with associated nodular lymphoid aggregates and granulomas in skip areas. However, the Crohn-type inflammatory changes remain limited to the mucosa and submucosa. Microscopically, there is no or minimal transmural inflammation and no fissures extend below the submucosa. Rare lymphoid nodules are present in the subserosa adjacent to the muscularis propria. The diagnosis is based on the association with classic CD in other segments of the same resection specimen.

Patients with both long and short segment superficial CD may have watery diarrhea. Obstructive symptoms and evidence of a stricture affect a small number of such patients, and these patients typically have transmural CD elsewhere in the surgical specimen. The gross mucosal appearance of superficial CD consists of a cobblestoned pattern that is more diffuse and more finely nodular than that seen in classic CD. The bowel wall tends to be thin and pliable rather than thick and rigid.

**Histologic Features of Proximal Gastrointestinal Lesions**

The villous architecture in the proximal small intestine varies from normal to a complete loss of villi and a flattened mucosa covered by an abnormal surface epithelium infiltrated by large numbers of neutrophils. Areas of flattening may lie adjacent to more normal-appearing tissues. In the duodenum, the most severe damage occurs proximal to the ligament of Treitz. The mucosa may contain crypt abscesses, erosions, granulation tissue, pyloric metaplasia, increased numbers of plasma cells, and neutrophils, often in the absence of granulomas. When only minimal changes are present, one sees acute inflammation consisting of focal neutrophilic collections in the lamina propria and surface epithelium. Surface cells vary from normal, to cuboidal, to completely flattened. Some appear vacuolated and others are frankly megaloblastic, presumably due to coexisting vitamin deficiencies. Intraepithelial lymphocytes may be mildly increased, but are not present in the number typically seen in celiac disease. Neutrophils often infiltrate the epithelium in large numbers. Noncaseating granulomas are sometimes seen, and are often present on a background of lymphocytic and plasmacytic inflammation. A normal biopsy does not exclude the possibility of involvement by CD, since the inflammation is usually patchy.
FIG. 11.44. Stricture in Crohn disease. 

A: There is prominent submucosal fibrosis present. In addition, there is marked neural hyperplasia in the submucosa. 

B: The fibrosis extends along the vascular structures into the muscularis propria of the colon. 

C: Serosal fibrosis is also present.
FIG. 11.45. Reactive neural hyperplasia in Crohn disease (CD). *A:* Low magnification of a polypoid lesion in the colon of a patient with CD demonstrating the presence of a prominent proliferation consisting of nerve fibers and fibroblasts. These are arranged in prominent swirling bundles. *B:* Higher magnification showing the structure of these bundles. *C:* S100 stain indicating the presence of neural elements.
FIG. 11.46. Crohn disease. A: Multiple inflammatory pseudopolyps. The mucosa immediately adjacent is essentially normal. B: Filiform polyposis. The mucosa has multiple fingerlike extensions measuring several centimeters in length and extending from the surface. When these fuse, mucosal bridges are produced. C: Pseudopolyp composed essentially of residual, more or less normal colonic mucosa covering an area of ulceration.
Inflammatory pseudopolyps. A: The inflammatory pseudopolyps present in this photograph differ from those shown in Figure 11.46, in that they represent residual islands of mucosa and submucosa. They contain a prominent submucosal core. The surrounding tissues are ulcerated down to the level of the muscularis propria. B: Higher magnification of the pedunculated lesion indicated by the arrow in A. One can see the central fibrovascular submucosal core with a covering of granulation tissue and extravasated red cells. C: Higher magnification of the lesion.

Gastric biopsies show some degree of abnormality in as many as 75% of patients with CD (104,105). The most commonly identified alteration is focal infiltration of the gastric pits and glands by inflammatory cells (Fig. 11.51). These infiltrates may include neutrophils, T lymphocytes, and histiocytes in variable numbers. This focal inflammation affects both the neck region and deep aspects of the gastric glands, and is more commonly seen in the antrum than in the body of the stomach. In addition, granulomas may be seen in from 9% to 16% of patients (104,105) (Fig. 11.51).

Filiform polyp in Crohn disease. This long filiform polyp was one of dozens present in the colon. They are characterized by long submucosal extensions covered by regenerative mucosa.

The major differential diagnosis is with Helicobacter pylori gastritis. H. pylori gastritis may also demonstrate chronic active inflammation, but the infiltrates are almost entirely neutrophilic, and localize to the neck region of the glands. The presence of deep active inflammation should alert the pathologist to the possibility of CD. However, the possibility of H. pylori infection should be ruled out with the use of special stains in all patients demonstrating any form of chronic active gastritis. It is important to note that some patients with CD may have superimposed H. pylori infection.

Crohn disease may affect the esophagus, and when it does, it may be difficult to separate the lesions from other forms of granulomatous esophagitis, especially if one is unaware that the patient has known Crohn disease (Fig. 11.52). Clinically, severe forms of esophageal Crohn disease may simulate carcinoma because of the presence of an irregular, stenotic esophageal segment.

Crohn Disease of the Orogenital System

Oral vesicular lesions and aphthous ulcers affect 49% of patients with CD. Typical CD is usually present in the gut, but occasionally CD first presents as oral lesions. Lesions may develop in the lips, epiglottis, and aryepiglottic folds.
FIG. 11.49. Epithelial misplacement in Crohn disease. A: Whole mount section showing a large knifelike fissure, the mouth of which is indicated by the *arrow*. The thickened bowel wall contains submucosal islands of glands surrounded by lamina propria. B: Higher magnification of the misplaced epithelium. Many of the glands are surrounded by residual lamina propria.
**FIG. 11.50.** Epithelial misplacement in Crohn disease. *A:* The displaced glands in this photo are filled with large amounts of mucin, some of which have extravasated into the wall of the small intestine. *B:* Higher magnification demonstrating the residual epithelium lining the gland. There is no cytologic atypia present, a feature that distinguishes this lesion from invasive carcinoma.

**FIG. 11.51.** Gastric Crohn disease. *A:* Patchy nonspecific chronic inflammation is present in the gastric body of a child with known Crohn disease. *B:* A compact, sarcoidlike granuloma is present. *C:* Duodenal biopsy from the same patient showing patchy inflammation and granulomas.
Chapter 11

**FIG. 11.52.** Esophageal Crohn disease. Figures A and B are from the esophagus of the child whose stomach is depicted in Figure 11.51. A: The esophageal squamous mucosa shows nonspecific inflammation and regenerative changes. B: Although no granulomas were present in this biopsy, a multinucleated giant cell is present in the submucosa.

**FIG. 11.53.** Vulvar Crohn disease. A: Low magnification showing the presence of prominent acanthosis. The underlying submucosa contains numerous collections of lymphocytes and plasma cells. A small fissure containing large numbers of acute inflammatory cells passes through the lower portion of the photograph. B: Higher magnification of one of the areas of inflammation showing the presence of a giant cell.

Oral lesions appear nodular and firm. Biopsy demonstrates the presence of chronic inflammatory cells and granulation tissue. Numerous large, well-formed, noncaseating granulomas containing epithelioid cells, giant cells, and peripheral lymphocytes may also be present. Patients with anal or perianal disease often have vaginal involvement characterized by the presence of nonspecific inflammation, fissures, and fistulae. Occasionally, granulomas are present (Fig. 11.53).

**Evaluation of Resection Margins in Crohn Disease**

Frozen sections of resection margins are unnecessary and should be avoided (280). This is because the rate of recurrence in CD following surgical resection is not influenced by the status of the resection file:///F|/Gastro/Chapter%2011%20IBD.htm (51 of 134)2/4/2009 2:03:30 PM
margins (106). Factors that do affect the risk of postoperative recurrence of CD include extent of disease at the time of surgery and the indication for surgery, with those who failed medical therapy or had perforating disease having a higher risk of recurrence (106,107). Smoking is also a factor affecting disease recurrence (108).

**Complications**

The complications of CD are listed in Table 11.10. The extraintestinal and neoplastic manifestations are discussed later in this chapter. Complications also result from therapy. These include steroid-related osteonecrosis often affecting the hip or knee, as well as secondary viral or bacterial infections.

<table>
<thead>
<tr>
<th>TABLE 11.10 Complications of Crohn Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local intestinal</td>
</tr>
<tr>
<td>Perforation</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Fistulas to adjacent bowel</td>
</tr>
<tr>
<td>Fistulas to urinary bladder (pneumaturia)</td>
</tr>
<tr>
<td>Fistulas to vagina</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
</tr>
<tr>
<td>Enterolith production</td>
</tr>
<tr>
<td>Malabsorption</td>
</tr>
<tr>
<td>Lactose deficiency</td>
</tr>
<tr>
<td>Zinc deficiency</td>
</tr>
<tr>
<td>Enteritis cystica profunda</td>
</tr>
<tr>
<td>Toxic megacolon</td>
</tr>
<tr>
<td>Psoas abscesses</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Emphysema</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Amyloid</td>
</tr>
<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Small bowel carcinoma</td>
</tr>
<tr>
<td>Large intestinal carcinoma</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Renal oncocytoma</td>
</tr>
<tr>
<td>Lymphoma, leukemia, and Hodgkin disease</td>
</tr>
<tr>
<td>Carcinoid</td>
</tr>
<tr>
<td>Squamous cell carcinoma, anus and vagina</td>
</tr>
</tbody>
</table>

**Ulcerative Colitis**

**Incidence**

In recent decades, the incidence of UC in the United States and in Europe has risen, whereas in other countries the incidence has plateaued (2,87,109). It is likely that two factors have contributed to this increase: (a) improved survival of incident cases and (b) diagnosis of milder cases due to increased use of sigmoidoscopy and fecal occult blood testing in the community. UC mostly affects young white people, but there is an increasing recognition that the disease affects many ages and many ethnic groups (2). The incidence of UC inversely correlates with smoking and clinical relapses have been associated with smoking cessation (110).

**Clinical Features**

UC demonstrates a wide clinical spectrum affecting all age groups, with a predominance of the disease in young and middle-aged persons. The peak age of incidence is the 3rd decade. Women are more
Chapter 11

**backwash ileitis**, occurs in continuity with cecal inflammation, and is thought

Inflammation in the terminal ileum occurs in 5% to 17% of patients with ulcerative colitis (115,116). The ileal inflammation, known as **Ileitis** (entamoeba), and amoeba), and ischemic colitis.

**Campylobacter**

Toxic megacolon not only complicates UC, but can also develop in association with any inflammatory condition of the colon including Crohn disease, infectious colitis (**C. difficile, Salmonella, Shigella**, Campylobacter, and amoeba), and ischemic colitis.

**TABLE 11.11 Factors Associated with Relapse or Exacerbation of Ulcerative Colitis Symptoms**

<table>
<thead>
<tr>
<th>Infections</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Upper respiratory viruses</td>
<td>5-Aminosalicylic acid</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>Azodisalicylate</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Ischemia</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Neoplasia</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td></td>
</tr>
<tr>
<td><em>Other enteric pathogens</em></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
<td></td>
</tr>
</tbody>
</table>

Toxic megacolon not only complicates UC, but can also develop in association with any inflammatory condition of the colon including Crohn disease, infectious colitis (**C. difficile, Salmonella, Shigella**, Campylobacter, and amoeba), and ischemic colitis.

**Ileitis**

Inflammation in the terminal ileum occurs in 5% to 17% of patients with ulcerative colitis (115,116). The ileal inflammation, known as **backwash ileitis**, occurs in continuity with cecal inflammation, and is thought
to result from incompetence of the ileocecal valve and reflux of intestinal contents across it. Grossly, the ileal mucosa appears diffusely abnormal, contrasting with the aphthous ulcers and discontinuous and serpiginous ulcerations of Crohn disease. The involved ileum shows inflammation, erosions, and sometimes ulcerations. The ileitis usually resolves following colectomy. Ileitis may develop after colectomy in preanastomotic portions of the small bowel. The disease develops following various types of reconstruction, including ileorectal and ileoanal, with or without a pouch. Patients remain asymptomatic or experience severe pain and diarrhea.

**Perianal Disease**

Some patients first seek medical advice because of the presence of extraintestinal manifestations, such as arthritis or perianal disease. Perianal disease is usually limited to hemorrhoids, anal excoriations, and fissures. Perianal or ischiorectal abscesses, fistulae, and rectovaginal fistulae rarely develop. The complications of UC in the anus are acute and superficial, contrasting with those seen in CD.

**Role of Surgery**

Surgical therapy for ulcerative colitis may be used either for emergencies or as elective treatment. Indications for urgent surgery include failed medical treatment in patients with acute severe colitis, toxic megacolon, perforation, or severe bleeding. There are essentially three indications for elective colectomy for UC: Failed medical treatment, growth retardation in a child with UC, and the development, or concern for, neoplastic transformation in a patient with longstanding disease. Failed medical treatment includes chronic disease, recurrent acute exacerbations, severe symptoms in an otherwise systemically well patient, suboptimal quality of life, steroid dependence, or extraintestinal manifestations of the disease.

In patients undergoing emergency surgery, the most common procedure is colectomy with ileostomy and preservation of the rectosigmoid stump. Under the conditions of elective surgery, several surgical options exist including conventional proctocolectomy, colectomy with ileorectal anastomosis, and restorative proctocolectomy with ileal reservoir.

**Patient Survival**

Since the introduction of effective medical and surgical treatments in the early 1960s, UC has a surprisingly low mortality. Patients with ulcerative colitis have a normal life expectancy compared with persons in the general population (117,118). Severe acute attacks, usually occurring during the first 2 years of disease, are the major killer, especially in patients over 50 years of age (119). Patients with longstanding extensive disease have an increased risk for the development of dysplasia or colorectal carcinoma.

**Gross Features**

Since patients usually undergo resection when they have extensive chronic colitis involving at least the rectum and left side of the colon, or when neoplastic alterations develop in the bowel, most of the described gross features are those that characterize severe forms of the disease. Table 11.12 compares the gross features of UC and CD.

**Disease Location**

Disease extent and involvement vary with the clinical severity of the disease. The distal bowel is always involved, with variable proximal continuous extension. Among patients with UC, approximately 45% have proctosigmoiditis, 20% to 62% have pancolitis, and 17% to 22% have left-sided colitis from the dentate line to the splenic flexure. There is a greater tendency for extension proximal to the descending colon in children than in adults.

**External Features**

UC is primarily a mucosal colonic disease characterized by an inflammatory reaction that remains limited to the mucosa and the superficial portion of the submucosa. For this reason, the external surface of the bowel appears normal unless cancer or toxic megacolon has developed. In chronic disease, the overall length of the bowel may appear contracted. In the case of toxic megacolon, the bowel appears massively dilated and the wall appears paper thin. The extremely thin, friable wall tends to fall apart with the gentlest handling. Frequently, one sees peritonitis as well as fibrinous or fibrinopurulent exudates on the peritoneal surfaces. The descending and sigmoid colon show the most severe acute lesions. Edema widely separates the fibers of the muscularis propria, leading to incipient perforation. Rarely, perforation is seen in patients without megacolon.

| TABLE 11.12 Gross Features of Crohn Disease Versus Ulcerative Colitis |  }
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
Chapter 11

Feature Crohn Disease Ulcerative Colitis

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Segmental; 50% have normal rectum</th>
<th>Diffuse; circumferential continuous with rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal involvement</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Terminal ileum</td>
<td>Often thickened, ulcerated, and stenosed; creeping mesenteric fat; terminal 15–25 cm</td>
<td>Involved 10%; short segment; backwash ileitis</td>
</tr>
<tr>
<td>Mucosal surface</td>
<td>Aphthous ulcers; linear ulcers; cobblestone appearance; fissures</td>
<td>Granular; ulcers</td>
</tr>
<tr>
<td>Mucosal atrophy</td>
<td>Minimal</td>
<td>Marked</td>
</tr>
<tr>
<td>Serosa</td>
<td>Inflamed, creeping fat, adhesions</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Colonic involvement</td>
<td>Predominantly right sided; granulomata</td>
<td>Usually left sided and continuous to right</td>
</tr>
<tr>
<td>Colon shortening</td>
<td>Due to fibrosis</td>
<td>Due to muscle hypertrophy</td>
</tr>
<tr>
<td>Strictures</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Fistulas</td>
<td>10% with enterenteric or enterocutaneous</td>
<td>Rare</td>
</tr>
<tr>
<td>Free perforation</td>
<td>Very rare</td>
<td>Occurs with toxic megacolon</td>
</tr>
<tr>
<td>Pseudopolyps</td>
<td>Occurs</td>
<td>Common</td>
</tr>
<tr>
<td>Oral lesions</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Increased frequency over control population</td>
<td>Increased frequency over control population</td>
</tr>
<tr>
<td>Anal disease</td>
<td>+ +</td>
<td>+ +</td>
</tr>
</tbody>
</table>

aThe appendix can also be involved in the absence of right-sided disease.

Determination of Disease Extent

Typically, when one opens a resected UC colon, blood oozes diffusely from the congested vasculature of the mucosal surface. The disease usually involves the rectum and extends proximally in a contiguous fashion affecting each successive segment of the bowel with a symmetric inflammatory response (Fig. 11.54). The length of the proximal extension varies. UC manifests as proctitis, proctosigmoiditis, left-sided proctocolitis, subtotal proctocolitis, or total involvement of the large bowel (pancolitis). The disease stops abruptly either at the ileocecal valve or in more distal portions of the colon. Variations in the intensity of inflammation may give a false impression of discontinuous focal or skip lesions, particularly in acute UC with patchy full-thickness mucosal loss (Fig. 11.55). One may see ulcerated areas with intervening mucosa that looks macroscopically normal. Additionally, treatment with steroid enemas and mucosal healing may lead to the false gross impression of rectal sparing (Fig. 11.56). However, grossly apparent skip areas or rectal sparing always show histologic evidence of architectural abnormalities characteristic of healed colitis. The only exceptions to this statement are the presence of appendiceal disease in a patient without pancolitis and patients with toxic colitis and a normal right colon who may develop ileal disease.

Similarly, the exact extent of mucosal involvement is not always easy to determine in the excised specimen because microscopic evidence of disease may be found in a macroscopically normal mucosa. Sometimes inflammatory changes of rectal UC go into spontaneous remission, while the proximal colonic inflammation remains active. This gives the gross impression of right-sided disease with rectal sparing. However, again, histologic examination discloses the presence of an abnormal rectal mucosa with regeneration in areas of resolved previous damage. The exact extent of disease in UC can only be accurately judged histologically.

Ulcers

In active UC the mucosa acquires a diffuse, uniformly granular, and erythematous, hemorrhagic appearance (Fig. 11.57). When ulcerations are present, the intervening intact mucosa appears granular and hemorrhagic. Ulcers undermine adjacent intact mucosa to form polypoid mucosal tags or inflammatory pseudopolyps (Fig. 11.58). The presence of broad areas of superficial ulceration covered by an overlying mucopurulent exudate results in partial or complete loss of the mucosa. The ulcers exhibit a linear distribution (Fig. 11.59), particularly in relation to the attachment of the taeniae coli. The ulcers lay bare the underlying muscularis propria (Fig. 11.58) and penetrate it only in fulminant UC. Extensive longitudinal ulcers, especially if connected by transverse ulcers, are not a feature of UC but rather of CD. Perforation occurs when the ulceration penetrates the muscularis completely.
FIG. 11.54. Acute ulcerative colitis. A: Pancolitis with ulceration and numerous pseudopolyps throughout the entire length of the specimen. B: Ulcerative colitis demonstrating the presence of mucosal changes throughout the length of resected bowel. These changes are much more marked in the distal portion of the bowel and decrease in severity as one goes proximally. There are not as many pseudopolyps as seen in A.

FIG. 11.55. Resection specimen in ulcerative colitis. Superficial examination of this bowel suggests that the patient has Crohn disease because grossly skip lesions appear to be present. The arrows indicate two reddened areas that are separated from the main hemorrhagic and erythematous portion of the bowel at the right of the photograph. However, histologic examination disclosed significant colitis in the intervening, apparently grossly normal mucosa.
UC patients who also have diverticulosis may have extension of their mucosal disease into a diverticulum, perhaps obliterating the underlying architecture, resulting in an appearance of a primary fistula and creating changes that mimic CD.

**Chronic Colitis**

In chronic continuous UC the mucosa appears granular with or without inflammatory polyps and the hemorrhagic component is muted or absent. When UC goes into remission, it is possible for the mucosa to return to a normal gross appearance; however, usually microscopic signs of former active disease remain with the mucosa appearing smooth and atrophic, or showing variable granularity.

**FIG. 11.56.** Ulcerative colitis with backwash ileitis. The distal bowel has become completely atrophic. The more proximal portions still contain evidence of active inflammation. The ileocecal valve (*arrowheads*) is incompetent, and inflammation extends into the terminal ileum. In the middle of the specimen extensive ulceration is present.
FIG. 11.57. Hemorrhagic ulcerative colitis. A: The entire resection specimen demonstrates the presence of a diffusely reddened, oozing mucosa that appears essentially the same throughout the entire length of the large bowel. B: Higher magnification showing the diffuse oozing and redness of the mucosal surface.

Sometimes the most striking gross feature is intestinal shortening with loss of the haustral folds, which produces an appearance of a contracted, stiff, thickened bowel (Fig. 11.60). This shortening results from muscular abnormalities and is most obvious in the distal colon and rectum. Fibrosis may cause the mucosa to lose its mobility over the underlying muscularis propria.

**Pseudopolyps**

Pseudopolyps represent discrete areas of mucosal inflammation and regeneration. They complicate various forms of colitis but are most common in UC. These pseudopolyps do not correlate with the disease severity and are not precancerous. Their distribution depends on the extent of the primary disorder. Both localized and diffuse forms of polyposis complicate UC (Fig. 11.58, 11.59, and 11.61, 11.62, and 11.63). Pseudopolyps are numerous only in a minority of cases and are usually present in patients with severe chronic disease.

The pseudopolyps are typically short, measuring <1.5 cm in height. They result from full-thickness mucosal ulceration and almost always represent either the surviving mucosal islands between areas of ulceration (Fig. 11.59) or heaped-up granulation tissue that becomes covered with epithelium. Once formed, pseudopolyps tend to persist and may serve as an indicator of previous episodes of colitis.
Chapter 11

**FIG. 11.58.** Pseudopolyps. *A:* Higher power magnification of the bowel shown in Figure 11.6B. The mucosa is ulcerated all the way down to the level of the muscularis propria, leaving pseudopolypoid islands of mucosa. *B:* Cross section demonstrating the pseudopolyps. Ulcerations can be seen extending all the way to the muscularis propria. In these areas no residual submucosa is evident.

P.636

Pseudopolyps are more prominent in the colon than in the rectum; they can completely spare the distal large bowel. Polyp fusion results from the approximation of two adjacent polyps that become superficially ulcerated. Fibroblasts grow into the granulation tissue between the polyp surfaces. Fused polyps create a labyrinthine appearance and mucosal bridging (Fig. 11.63). The polyps often lie in the direction of the fecal stream, as if accentuated by it (Fig. 11.62).

**FIG. 11.59.** Cobblestoned mucosa that results from loss of the intervening mucosal surface, showing mucosal ulceration.

There are also unusual polyps that attain a large size or have a bizarre architecture. These form a continuum with the more ordinary pseudopolyps but because of their unusual features are separated from them. Pseudopolyps (especially large ones) may produce acute obstruction or intussusception or may mimic carcinomas. Filiform polyposis, which represents an exaggerated form of pseudopolyps, usually coexists with chronic IBD, especially CD and UC. It is characterized by numerous wormy, densely packed, villiform colonic polyps associated with a moderate degree of inflammation and edema. These may grossly resemble villous adenomas (Fig. 11.61) (see Chapter 20). Arborization is a striking feature. The polyps are found anywhere in the colon. Filiform polyps reach heights of 2 to 3 cm. Filiform polyposis frequently spares the rectum.
FIG. 11.60. Mucosal atrophy in ulcerative colitis. This patient shows an atrophic foreshortened bowel due to muscular contraction. Active disease was present histologically.

FIG. 11.61. A: Cross section of the bowel demonstrating the presence of multiple filiform pseudopolyps. B: Cross section through a filiform pseudopolyp demonstrating the presence of a prominent fibroblastic core. The epithelium is inflamed and regenerated.

**Toxic Megacolon**

The internal features of toxic megacolon reflect the external ones, with marked dilation of the bowel lumen and thinning of the intestinal wall (Fig. 11.64). Severe extensive mucosal ulcers lead to almost
Chapter 11

complete mucosal denudation. Deeper ulcers that penetrate the mucosa lay the muscularis propria bare. The latter may become covered by only a very thin layer of granulation tissue.

**FIG. 11.62.** Filiform polyposis in ulcerative colitis. Picture demonstrating a thickened, contracted bowel and numerous filiform polyps (arrows). They all line up in the direction of the fecal flow. The distal rectum is to the right-hand portion of the picture.

**Ileal Disease**

The terminal ileum becomes involved only in continuity with total colitis in 5% to 20% of specimens, and no more than 10 to 25 cm proximal to the ileocecal valve is involved by the disease. Macroscopically, the ileal mucosa appears diffusely abnormal (see Fig. 11.56), contrasting with the terminal ileitis of CD, which shows aphthous ulcers and discontinuous and serpiginous ulcerations. The diseased ileum shows inflammation, erosions, ulcerations, and sometimes strictures.

Inflammation occurring in the setting of colectomy followed by ileostomy is usually not due to the UC per se but is secondary to the ileostomy. It is called *prestomal ileitis*. In this disorder, one sees ulcers scattered throughout the ileum and jejunum with the intervening mucosa appearing normal or edematous. Because these ulcers have a tendency to perforate, peritonitis and fistulae develop, and the lesions may prove fatal.

**FIG. 11.63.** Mucosal bridge in ulcerative colitis. Gross specimen demonstrating the presence of pseudopolyps, filiform polyposis, and mucosal bridging resulting from fusion of pseudopolyps.
FIG. 11.64. Toxic megacolon. A shaggy hemorrhagic mucosa and colonic dilation as evidenced by the increased width of the specimen.
FIG. 11.65. Active chronic ulcerative colitis. *A:* The lamina propria shows an intense infiltrate of lymphocytes and plasma cells. There is evidence of glandular distortion. A prominent crypt abscess is seen. *B:* Crypt herniation. The crypt at the right-hand side of the photograph has ruptured and is spewing its contents into the surrounding lamina propria.

**Histologic Features**

The histologic appearance varies with the clinical phase of the disease, allowing one to classify UC into three stages: Active colitis, UC going into remission (resolving colitis), and colitis in remission. UC is characteristically a mucosal and submucosal disease. Table 11.13 compares the histologic features of UC and CD. Table 11.14 compares the major changes seen in acute, resolving, and chronic colitis.

**Features of Active Colitis**

**Cryptitis, Crypt Abscesses, and Ulcers**

The mucosa in active UC is characterized by an intense inflammatory cell infiltrate, crypt abscesses, mucin depletion, and surface ulceration. The hallmark of acute activity in UC is the presence of neutrophils infiltrating the lamina propria and crypt epithelium. The term *chronic active colitis* serves to indicate the presence of acute activity superimposed on a background of chronic changes.

An early feature of active colitis is the formation of cryptitis, which evolves to crypt abscesses and crypt ulcers (Fig. 11.65).

As in CD, cryptitis reflects migration of neutrophils into crypt epithelium. A collection of neutrophils in the crypt lumen represents a crypt abscess (see Fig. 11.32). Crypt abscesses may be relatively isolated and present in a background of intense infiltration by mononuclear cells (Fig. 11.65) or they may be part of a more diffuse process (Fig. 11.66). Crypt ulcers represent areas of crypt destruction from the inflammation. Once the crypt ruptures (crypt herniation) (Figs. 11.65 and 11.67), the luminal contents and mucus extravasate into the surrounding lamina propria, sometimes creating histiocytic collections around the area of rupture. Such histiocytic collections may simulate or suggest a diagnosis of CD. However, these histiocytic collections lack the typical features of compact granulomas more characteristic of CD (compare Figs. 11.35 and 11.37). The presence of acute inflammation, primarily based in the epithelium rather than the lamina propria, and the presence of changes associated with chronic injury serve to distinguish UC from acute self-limited colitis.

**TABLE 11.13 Microscopic Features of Ulcerative Colitis Versus Crohn Colitis**
<table>
<thead>
<tr>
<th>Feature</th>
<th>Crohn Colitis</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Skip lesions; transmural</td>
<td>Diffuse; mucosal and submucosal; 20% transmural including toxic megacolon</td>
</tr>
<tr>
<td>Submucosa</td>
<td>Normal, inflamed, or reduced width</td>
<td>Normal or reduced width</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>Seldom prominent</td>
<td>Prominent</td>
</tr>
<tr>
<td>Lymphoid hyperplasia</td>
<td>Common; separated from muscularis mucosae; transmural and pericolonic tissue; associated with submucosal edema and fibrosis</td>
<td>Rare; mucosa and submucosa; not associated with submucosa, edema, and fibrosis</td>
</tr>
<tr>
<td>Neutromatous hyperplasia</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Edema</td>
<td>Marked</td>
<td>Minimal</td>
</tr>
<tr>
<td>Crypt abscess</td>
<td>Uncommon; when present, few in number</td>
<td>Common</td>
</tr>
<tr>
<td>Cytoplasmic mucin</td>
<td>Slightly reduced</td>
<td>Mucin depleted; greatly reduced</td>
</tr>
<tr>
<td>Paneth cell metaplasia</td>
<td>Occurs</td>
<td>Common</td>
</tr>
<tr>
<td>Granulomas (sarcoidlike)</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Fissures and sinuses</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Focal lymphoid aggregates in submucosa</td>
<td>Presence suggests Crohn, especially when deep</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Granulomas</td>
<td>Reactive hyperplasia</td>
</tr>
<tr>
<td>Ileal lesions</td>
<td>More than half</td>
<td>Minimal, not more than 10 cm</td>
</tr>
<tr>
<td>Anal lesions</td>
<td>Granulomas</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Dysplasia and cancer</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Inflammatory pseudopolyps</td>
<td>Less common than in ulcerative colitis</td>
<td>Common</td>
</tr>
<tr>
<td>Filiform polyposis, giant polyps</td>
<td>Occurs</td>
<td>Occurs</td>
</tr>
<tr>
<td>Accuracy rate of rectal biopsy</td>
<td>40%</td>
<td>70%</td>
</tr>
</tbody>
</table>
FIG. 11.66. Crypt changes in ulcerative colitis. A crypt abscess (*small star*) and herniating crypt abscess (*large star*) are both present in this example of active ulcerative colitis.

<table>
<thead>
<tr>
<th>TABLE 11.14 Histologic Features of Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute (active) stage</strong></td>
</tr>
<tr>
<td>Vascular congestion</td>
</tr>
<tr>
<td>Mucin depletion</td>
</tr>
<tr>
<td>Cryptitis, crypt abscesses</td>
</tr>
<tr>
<td>Epithelial loss and ulcers</td>
</tr>
<tr>
<td>PMNs, eosinophil and mast cell infiltrates</td>
</tr>
<tr>
<td>Luminal pus</td>
</tr>
<tr>
<td>Basal plasma cells</td>
</tr>
<tr>
<td>Vascular congestion</td>
</tr>
<tr>
<td><strong>Resolving stage</strong></td>
</tr>
<tr>
<td>Less vascular congestion than seen in the active phase</td>
</tr>
<tr>
<td>Gradual disappearance of PMNs</td>
</tr>
<tr>
<td>Gradual disappearance of crypt abscesses</td>
</tr>
<tr>
<td>Continued basal plasma cells</td>
</tr>
<tr>
<td>Epithelial regeneration</td>
</tr>
<tr>
<td>Expansion of the mitotically active cells</td>
</tr>
<tr>
<td><strong>Chronic healed stage</strong></td>
</tr>
<tr>
<td>Architectural distortion</td>
</tr>
<tr>
<td>Atrophy</td>
</tr>
<tr>
<td>Branching</td>
</tr>
<tr>
<td>Crypt shortening</td>
</tr>
<tr>
<td>Villous transformation</td>
</tr>
<tr>
<td>Metaplasia</td>
</tr>
<tr>
<td>Pyloric</td>
</tr>
<tr>
<td>Paneth cell</td>
</tr>
<tr>
<td>Lymphoid hyperplasia</td>
</tr>
<tr>
<td>Filiform polyposis</td>
</tr>
<tr>
<td>Epithelial displacement</td>
</tr>
<tr>
<td>Increased mononuclear cells in the lamina propria</td>
</tr>
<tr>
<td>Endocrine cell hyperplasia</td>
</tr>
<tr>
<td>Squamous metaplasia</td>
</tr>
<tr>
<td>PMNs, polymorphonuclear leukocytes.</td>
</tr>
</tbody>
</table>

* An individual patient may have all three stages present in the same specimen.
The diagnosis of UC primarily based on the presence of crypt abscesses is hazardous because crypt abscesses occur as part of acute inflammation associated with many disorders, including CD or acute self-limited colitis. Although crypt abscesses are not specific for UC, when they are very prominent and involve nearly all the crypts, the disease is much more likely to represent UC than CD. In contrast, the presence of isolated crypt abscesses with chronic inflammation and completely uninvolved crypts, particularly with neutrophils in the lamina propria, is more common in CD (100).

The crypt abscesses play a role in the generation of the ulcerations that occur in severe disease because when they burst into the surrounding tissues, they spread laterally and beneath the mucosa, which then sloughs, leaving an ulcer. Ulcers may also spread into the submucosa and undermine adjacent, relatively intact mucosa. Except in severe colitis, these ulcers tend to be grossly small and generally shallow. When severe, the ulcers extend to the muscularis propria (Fig. 11.68), but deep penetration of the muscular layer or serosa only occurs in toxic megacolon. The crypt abscesses also contain mucous debris and bacteria. Because the crypt abscesses rupture into the bowel lumen, one finds white cells in the feces. Secondary infection of an already damaged mucosa by organisms present in the fecal stream further extends the damage.

The microscopic findings also include mucin depletion from goblet cells (Figs. 11.65, 11.66, and 11.67), epithelial cell necrosis and regeneration, reduced goblet cell numbers, Paneth cell metaplasia, and dense infiltration of the lamina propria by neutrophils, plasma cells, and other acute and chronic inflammatory cells. At the height of a severe attack, goblet cells disappear completely. Because of the mucosal loss, the epithelium actively regenerates and the proliferative fraction of cells in the crypts increases to compensate for the cell loss. Patients with active disease show expansion of the proliferative compartment as demonstrated by Ki-67 immunostaining (Fig. 11.69) (120) as well as by flow cytometric analysis.
FIG. 11.68. Fulminant colitis. In fulminant colitis, the ulceration may extend down to the level of the muscularis propria leaving residual mucosal and submucosal islands forming pseudopolyps.

FIG. 11.69. Ki-67 immunoreactivity in active ulcerative colitis. Note the expansion of the proliferative zone along the lengths of the crypts in the actively regenerating mucosa. The intense stromal staining corresponds to the proliferation of lymphocytes.
**Inflammatory and Stromal Changes**

Basal accumulations of lymphocytes and plasma cells (referred to as basal lymphoplasmacytosis) (Fig. 11.70), together with hyperplasia of lymphoid tissue, probably represents an early immunologic manifestation of the underlying disease process. The chronic inflammatory cells may also infiltrate the superficial mucosa (see Fig. 11.65). A subset of patients with predominantly rectal disease has a high number of IgE-bearing plasma cells (121). Dendritic cells lie in a bandlike infiltrate under the mucosal surface and near lymphoid follicles, if present. Hyperplastic mucosal lymphoid follicles may be quite prominent, especially in the rectum. The inflammation remains superficial and primarily mucosal (Fig. 11.71). Occasionally, this inflammation extends into the superficial submucosa (Fig. 11.71). Deeper inflammation may occur in areas adjacent to or underlying ulcers. The lamina propria contains a dense infiltrate of lymphocytes and plasma cells (Fig. 11.72). Mast cells and eosinophils increase in number, and the tissue histamine content rises (122). Both mast cells and eosinophils degranulate in areas of active inflammation, suggesting that inflammatory mediators released from them contribute to the pathophysiology of the disorder (122). Mast cells also release heparin and proteolytic enzymes, thereby exaggerating and facilitating the spread of the inflammation and necrosis. As the intensity of inflammation increases, the mucosa becomes extensively superficially ulcerated. The mucosal contour becomes irregular and covered with pus, blood, and exfoliated cells.

**FIG. 11.70.** Biopsy specimen from a patient with ulcerative colitis. The patient shows basal plasmacytosis. There is mild widening of the distance between the base of the crypts and the muscularis mucosae. The muscularis mucosae appears frayed. The inflammation spills into the upper submucosa. Some inflammation is diffusely present in the muscularis mucosae.
FIG. 11.71. Regenerating colonic epithelium in ulcerative colitis. The epithelium appears mucin depleted. Much of the acute inflammation has subsided, but one sees an intense mononuclear cell infiltrate in the mucosa. The cells at the base of the crypt appear more hyperchromatic and more immature than those higher up in the crypt.
**FIG. 11.72.** Inflammatory infiltrate in ulcerative colitis. The lamina propria contains a dense infiltrate of lymphocytes and prominent plasma cells.

Mucosal capillary congestion and vascular ectasia with intramucosal hemorrhages are common, especially in severe disease (Fig. 11.73). The entire intestinal vasculature becomes congested, but this feature is most prominent in the mucosa. The vascular changes associate with varying degrees of epithelial necrosis and regeneration.

**Neural Changes**

The nerves may show mild hyperplasia, but never to the extent seen in CD. In contrast to the situation that occurs with CD, the mucosa of patients with UC shows a deficit of substance P–containing and VIP-containing nerves. They are decreased (sometimes almost completely absent) in the areas of severe inflammation (123,124). The loss of VIP correlates with the degree of inflammation.

**Features of Resolving Colitis**

Active disease resolves spontaneously or in response to therapy. Initially, one sees a reduction in the vascular dilation and disappearance of the active inflammation and crypt abscesses (Figs. 11.74 and 11.75). During the healing phase, the epithelium actively regenerates, epithelial continuity is restored (Fig. 11.75), the inflammatory infiltrate and abscesses begin to resolve, and the epithelial mucin content begins to be restored. Epithelial regeneration extends from the base of the crypts (Fig. 11.76) and from the edge of the ulcers (Fig. 11.77). As the cells regenerate, they exhibit syncytial-like qualities with large amounts of cytoplasm. They may appear flattened at first and then they generally increase in height, first becoming cuboidal and then eventually columnar in shape. During these phases, the epithelium is devoid of mucinous secretions. As the epithelium matures and the inflammation subsides, the columnar epithelium begins to produce mucins again. The crypts begin to appear branched (Fig. 11.78).

**FIG. 11.73.** Telangiectasia in ulcerative colitis. There is prominent dilation of both submucosal and mucosal blood vessels.

Lymphocytes and plasma cells decrease in number and tend to become more focal as the inflammation subsides. Variable numbers of acute and chronic inflammatory cells, Paneth cells (Fig. 11.79), and endocrine cells are also present during this phase. Some patients develop endocrine cell hyperplasia. The mucosal inflammation is confined to the increased lymphocytic and plasma cell content of the lamina propria and occasional crypt abscesses in an intact mucosa. Mucosal lymphoid follicles increase in number, particularly distally. Resolution of the chronic inflammation may produce a patchy infiltrate that can resemble CD in biopsy specimens.

It takes weeks to months for active disease to become quiescent. If the resolution is complete and if the initial damage was minimal, complete architectural restoration occurs. More commonly, permanent architectural abnormalities persist, which represent useful signs of former active disease (Fig. 11.80). Histologic recovery, however, is often incomplete and microscopic evidence of inflammation is common (Fig. 11.80) even in patients with clinically and sigmoidoscopically quiescent colitis.
Chapter 11

FIG. 11.74. Resolving colitis. A: Prominent epithelial regeneration is almost complete. The lamina propria is still acutely inflamed, and large numbers of proliferating blood vessels are present. B: A prominent regenerating gland is present. The surrounding mucosa is inflamed.

Prominent crypt branching, surface villiform transformation, and persistence of mucus-depleted epithelial cells with nuclear changes may lead to confusion with dysplasia in the setting of UC. Early regenerative features can be readily distinguished from dysplasia when the number of epithelial cells is not increased. The cytoplasm appears attenuated, the nuclear chromatin appears relatively sparse and finely distributed, and the nuclear-to-cytoplasmic ratio favors the cytoplasm (Figs. 11.75, 11.76, and 11.77). The use of proliferation markers may help to distinguish between the lesions. Other reparative lesions are more difficult to differentiate from dysplasia.

FIG. 11.75. Regeneration in ulcerative colitis. A gland is present in which one half is intensely hyperchromatic. The remainder of the gland is more typically regenerative.

Features of Fulminant Colitis

Patients with fulminant colitis usually have pancolitis. Microscopic examination shows mucosal denudation; highly vascular granulation tissue; heavy infiltration by histiocytes,
plasma cells, lymphocytes, and neutrophils; and marked submucosal edema. The inflammation extends to the circular and longitudinal layers of the muscularis propria with varying degrees of muscle degeneration and necrosis. Often, individual muscle fibers appear shortened and rounded with aggregates of eosinophilic staining cytoplasm within the myofibrils. The myenteric plexuses may be distorted and edematous, particularly in the areas adjacent to extensive mucosal ulceration. The bowel wall lacks fibrosis or the prominent lymphocytic aggregates seen in CD. Prominent lymphoid follicles can be seen in the submucosa in UC in this setting, but they should not be present in areas away from the ulceration.

**FIG. 11.76.** Resolving ulcerative colitis. This mucosal biopsy shows resolving inflammation with transition toward a villiform pattern. The bases of the crypts appear regenerative. The epithelium at the surface contains mucin and some appear hyperplastic.
FIG. 11.77. Active regeneration. The epithelium covering the lamina propria on the right-hand portion of the specimen shows a gradient of differentiation from the bottom of the picture to the top. The cells toward the base of the crypt (bottom) appear much more hyperchromatic and immature. The cells at the free surface have a large amount of cytoplasm. Several apoptotic bodies are present within the epithelium. Immediately opposite the more mature eosinophilic epithelium on the right-hand side are elongated, multinucleated, syncytial-like epithelial cells covering an area of previous ulceration. A small gland abscess is in the lower middle of the photograph.

Features of Inactive (Quiescent) and Chronic Healed Colitis

The changes that characterize active colitis, including superficial ulceration, diffuse acute and chronic inflammation of the mucosa and superficial submucosa, goblet cell depletion, and telangiectasia, disappear during the resolving or quiescent phases of the disease. In quiescent disease, the mucosa becomes diffusely atrophic with architectural changes resulting from damage that occurred during active disease. Mucosal atrophy (Fig. 11.81) takes the form of loss of crypt parallelism with branching or a severe reduction in the number of crypts per unit area. The crypts characteristically shorten and the space between the base of the crypts and the luminal surface of the muscularis mucosae widens (Fig. 11.81). The atrophy may become so extreme that the mucosa consists of little more than a single layer of surface columnar epithelium with only a few very short crypts. Because of the repeated episodes of ulceration followed by periods of healing, glands become embedded in the submucosa (Fig. 11.82). This epithelial herniation into the submucosa may represent a consequence of sustained contractions of the muscularis mucosae. This change affects as many as 40% of patients. The muscularis mucosae thickens and frays (Fig. 11.81) due to previous ulceration and muscular regeneration. Paneth cell metaplasia distal to the hepatic flexure, pyloric metaplasia (Fig. 11.81), and endocrine cell hyperplasia often indicate a long history of colitis.
FIG. 11.78. Chronic ulcerative colitis. The crypts appear branched, a sign of previous injury.

FIG. 11.79. Regenerated mucosa. The glands are almost completely restored. Prominent Paneth cells are present at the band of the crypts.
FIG. 11.80. Chronic ulcerative colitis in relapse. The mucosa has a regenerated architectural appearance. Evidence of cryptitis with early crypt abscess is seen within the central branched crypt (arrow). In addition, the lamina propria is infiltrated with a large number of eosinophils.

The atrophic mucosa exhibits a variably increased inflammatory cell infiltrate, sometimes associated with focal accumulations of lymphocytes and plasma cells. In some cases, the mucosa shows no increase in inflammatory cells. Bizarre multinucleated stromal giant cells derived from fibroblasts sometimes appear in the colonic mucosa in biopsy specimens from patients with longstanding quiescent UC (125). The changes are most marked distally, but they may affect the entire bowel, with the proximal changes usually being less severe than the distal ones unless the patient has been given steroid enemas to treat the disease.

FIG. 11.81. Quiescent colitis. A: The mucosa has regenerated. An enlarged telangiectatic vessel is present in the lower portion of the mucosa. In addition, one of the crypts runs parallel to the level of the muscularis mucosae rather than perpendicularly. The overall architecture is simplified. B: Subtotal rectal atrophy with diminished numbers of glands and a thinned mucosa. A prominent lymphoplasmacytic infiltrate is also seen straddling both sides of the muscularis mucosae.

Ileitis

Backwash ileitis shows acute and chronic inflammation resembling that seen in the cecum. Crypt abscesses may be present (Fig. 11.83). Histologically, any areas of ulceration are shallow, contrasting with the deep, fissuring ulcers seen in Crohn disease. Characteristically, skip lesions are absent and all contiguous uninvolved segments are unaffected by the inflammatory response.

Strictures

Disagreement exists concerning the frequency of benign strictures in chronic UC. UC-associated strictures develop as a result of muscular hypertrophy and thickening of the muscularis mucosae and muscularis propria rather than from fibrosis. The hypertrophic muscle remains in a spastic or contracted state, resulting in intestinal hypomotility. In addition, there are secondary changes that occur in the
muscle that lead to motility abnormalities, shortening, and contraction of the large intestine and loss of the haustral folds. When fibrosis does develop in the setting of UC, it never develops to the same extent as seen in CD, even when there is deep ulceration with destruction of the muscularis mucosae.

Other strictures form in UC, but these have an ischemic origin. Ischemic strictures show extensive fibrosis, and the mucosa and submucosa become replaced by dense cicatrizing granulation tissue. Ischemia may complicate concurrent CMV infection.

**Pseudopolyps**

Inflammatory pseudopolyps are typically covered by normal or at least nondysplastic colonic epithelium. The histologic features of the pseudopolyps vary, depending on whether or not they represent residual islands of mucosa separated by wide-based ulcerations, as illustrated in Figure 11.81. In this situation, one sees all of the normal structures of the bowel wall (Fig. 11.84). In other situations, one may see localized expansions of the mucosa with marked infiltrates of mononuclear cells expanding the lamina propria and creating a polypoid elevation of the mucosa, as illustrated in Figure 11.85. In still other cases, the mucosa may exhibit exuberant regeneration with exophytic, highly branched, filiform polyps composed of regenerated glands, as illustrated in Figure 11.85. Finally, the polyps may represent polypoid collections of granulation tissue that extend upward into the gastrointestinal lumen.

**Toxic Megacolon**

When patients develop toxic megacolon, the most striking histologic feature is the relative lack of involvement of the mucosa by acute inflammation and the very marked expansion of the submucosa by edema. Deep ulcers may be present in other portions of the bowel wall and perforations may be present as well (Fig. 11.86).
FIG. 11.83. Backwash ileitis in ulcerative colitis. A: Low-power photomicrograph showing preservation of the normal villous architecture of the small bowel. There is patchy active inflammation present. B: A crypt abscess is seen on higher magnification. Features of chronic injury, however, are not present.

FIG. 11.84. Pseudopolyp. Protuberant mucosal masses that extend above the original height of the mucosa. The lamina propria is expanded by a mononuclear cell infiltrate.

**Ulcerative Appendicitis**

Ulcerative appendicitis, the appendiceal counterpart of UC, is present in 50% to 87% of colectomy specimens from patients with pancolitis due to UC. Appendiceal involvement represents part of the continuous inflammatory process that characterizes UC. Appendiceal inflammation also affects 15% to 86% of patients without pancolitis (126,127,128). Additionally, some patients demonstrate patchy cecal inflammation or appendiceal orifice inflammation associated with left-sided colitis (128). Studies suggest that such “skip lesions” are of no clinical significance, and should not be misinterpreted as features of Crohn disease in patients with otherwise typical ulcerative colitis. Additionally, some patients have what is known as a cecal patch that may represent the cecal equivalent of the appendiceal disease. In some patients, the appendiceal disease appears more active than the cecal disease. One should not be deterred from rendering an unequivocal diagnosis of UC when encountering ulcerative appendicitis as the skip lesion or a more severe lesion in a colectomy specimen that is otherwise absolutely characteristic for UC. The histologic features of ulcerative appendicitis are illustrated in Figure 11.87.
FIG. 11.85. This pseudopolyp represents a more marked extension of the process seen in Figure 11.84, with large numbers of regenerative glands. Such lesions must be examined carefully for the presence of dysplasia, particularly when they appear so cellular.
Upper Gastrointestinal Involvement

Rare cases of chronic active duodenal or gastric inflammation have been reported in association with ulcerative colitis (129,130,131). It is as yet unclear whether these cases represent an unusual manifestation of ulcerative colitis or a separate associated disorder. Longer follow-up of the reported cases is required before such a determination can be made.
Ulcerative appendicitis. A: The appendix shows changes similar to those that were present in the colon in this patient. There is prominent crypt architectural distortion present and active inflammation involving the mucosa. B: Higher magnification showing active inflammation and numerous crypt abscesses.

Ulcerative Colitis with Superimposed Infections

UC patients experience a significantly higher incidence of infections than control patients. These may induce a relapse of the UC or a superimposed ischemic colitis. Common infections include CMV and C. difficile. If a patient unexpectedly experiences a relapse of the disease, stool cultures or toxin assays may detect a complicating infection. The pseudomembranous characteristics of C. difficile infection in the noncolitic patient do not occur in UC (Fig. 11.88). CMV infections cause endothelialitis, formation of small intravascular thrombi, and ischemic necrosis. Biopsies taken from such patients exhibit deeper inflammation than usually characterizes UC (because of the ischemia), and chronic changes when severe may obscure the underlying UC. This is particularly problematic when a biopsy is seen for the first time in an emergent setting because of sudden worsening of the disease and previous biopsies are unavailable for review. In this setting, one must decide whether the clinical diagnosis of UC is correct, whether other changes are superimposed on the pre-existing disease, or whether the patient has CD or some other disorder. This distinction is of more than academic interest because the clinician often faces a critical clinical treatment decision as to whether to increase immunosuppressive therapy to control the UC. If the diagnosis of UC is made without recognizing a coexisting CMV infection, the clinician is likely to increase the dose of steroids or azathioprine, drugs that will only worsen the infection. In contrast, if one makes a diagnosis of CMV, the patient may receive ganciclovir or a related drug. Failure to recognize a CMV infection may eventually lead to more generalized ischemic damage and even perforation (Figs. 11.89, 11.91, and 11.92). The diagnosis of CMV infection is made by detecting the presence of viral inclusions within the endothelium, macrophages, or epithelium. Most typically, the viral inclusions are in the stromal cells, particularly the endothelial cells. Fibrin thrombi and endothelialitis are often present. When thrombi occur, features of ischemia are superimposed on the ulcerative colitis.

Clostridium difficile colitis superimposed on ulcerative colitis. There is patchy withering of the colonic crypts and other features reminiscent of ischemic injury. The patient had documented C. difficile colitis. The typical volcanolike eruptions of neutrophils from the eroded mucosal surface and pseudomembranes were not present in this case.

Effects of Therapy

Various therapies used to treat IBD, whether they be local instillation of corticosteroid enemas or systemically administered anti-inflammatory agents, may suppress some of the more classic gross or histologic features associated with the diagnosis of UC. Suppression of rectal inflammation can lead to the false impression of a rectal-sparing disease such as CD. Therapy may also predispose the intestine to develop secondary complicating features, such as a CMV infection, with or without secondary endothelialitis, and ischemia. Patients who undergo steroid withdrawal may develop an acute ileus simulating intestinal obstruction.
FIG. 11.89. Resection specimen in a patient with ulcerative colitis, a cytomegalovirus infection, ischemia, and perforation. The area of perforation lies adjacent to the ileocecal valve (arrow). In this patient, it appears as though the disease is more severe on the right side of the colon than on the left. This is due to the fact that ischemic injury was present from the ileocecal valve to the midtransverse colon and to the fact that the distal disease was more quiescent in nature.

FIG. 11.90. Histologic features from the resection specimen shown in Figure 11.88. One sees misplaced glandular epithelium within the submucosa. Barium (the greenish material indicated by the arrows) lies near the misplaced epithelium. Note the prominent irregular submucosal inflammation and the submucosal telangiectasia.
Indeterminate Colitis and Combined Crohn Disease and Ulcerative Colitis in the Same Patient

Only about 5% to 20% of IBD patients exhibit overlapping features falling into the category of “indeterminate” or “mixed” colitis. Judging from material seen in consultation, the diagnosis of indeterminant colitis is overused and generally reflects inadequate clinical information on the extent and distribution of the disease, information from radiographic or endoscopic studies, or unfamiliarity with some of the nuances of both diseases or the effects of intercurrent infections of therapy (Table 11.15). UC and CD may coexist. As noted in a previous section, CD patients with serum P-ANCA expression exhibit UC-like phenotypes, and this may account for the presence of both histologic features in the same patient.
### TABLE 11.15 Difficulties in Differentiating Ulcerative Colitis (UC) from Crohn Disease (CD)

- Limited morphologic expression in the colon
- Incomplete expression of the disease
- Occurrence of indeterminate colitis with features of both UC and CD
- Clinical mimicry of UC and CD by other inflammatory diseases
- Absence of rectal involvement in otherwise classic UC
- Simultaneous occurrence of both CD and UC
- Modification of the pathologic features by therapy
- Presence of second complicating disease, such as ischemia or infection
- Lack of adequate clinical information
- Small biopsy size
- Inadequate number of biopsies to evaluate disease distribution and extent
- In unfamiliarity of the pathologist with the full range of morphologic findings in both diseases

### Diagnosis of Inflammatory Bowel Disease in Endoscopic Biopsies

Some of the most common biopsies seen in a surgical pathology practice involve the histologic assessment of colonic inflammatory conditions. Often the surgical pathology requisition states, “Rule out acute self-limited colitis (ASLC), rule out UC, rule out ischemia.” Alternatively, the requisition may request one to distinguish UC from CD. The diagnosis of IBD is best distinguished from the other forms of colitis by a systematic approach (Tables 11.16 and 11.17). It is always helpful if one examines biopsies in a standardized way in order to assess each diagnostic feature. In this way, one is unlikely to miss a helpful parameter that might be present. Such a systematic approach involves evaluation of several parameters, including epithelial alterations (whether acute or chronic), changes in the lamina propria, vascular changes, and changes in the muscularis mucosae. Signs of chronicity include architectural alterations with prominent crypt branching or atrophy, a villiform structure, Paneth cell or pyloric metaplasia, lymphoid follicles, or prominent plasma cells above the muscularis mucosae. The diagnosis of different forms of colitis does not rely solely on the histologic features that are present. Knowledge of the endoscopic appearance, the clinical features, and the disease distribution are essential. Such a diagnostic approach facilitates distinction of UC from the diseases that mimic it (Table 11.18).

### TABLE 11.16 Features To Be Consistently Evaluated in Biopsies for the Diagnosis of Inflammatory Bowel Disease

#### Architectural changes
- Crypt orientation (distortion)
- Crypt length
- Distance of crypt bases from muscularis mucosae
- Intercryptal distance
- Crypt branching
- Villiform transformation of crypt surface
- Ratio crypt surface/lamina propria surface

#### Epithelial changes
- Mucus content
- Presence of Paneth or pyloric cells
- Presence or absence of intraepithelial lymphocytes or eosinophils
- Cryptitis
- Endocrine cell hyperplasia
- Presence or absence of specific microorganism

#### Lamina propria changes
- Presence or absence of inflammation

---

file:///F|/Gastro/Chapter%2011%20IBD.htm (83 of 134)2/4/2009 2:03:30 PM
Table 11.17 Differences in Biopsy Appearances of Ulcerative Colitis and Crohn Disease

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative Colitis</th>
<th>Crohn Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution of inflammation or mucosal atrophy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse or segmental</td>
<td>Diffuse</td>
<td>Segmental, especially among several biopsies</td>
</tr>
<tr>
<td>Most marked distally</td>
<td>Typical</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Proximal change with distal sparing</td>
<td>Noa</td>
<td>Sometimes</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uniform intensity in each biopsy</td>
<td>Typical</td>
<td>Occasional</td>
</tr>
<tr>
<td>Marked focality within and between biopsiesb</td>
<td>Uncommon</td>
<td>Usual</td>
</tr>
<tr>
<td>Neutrophils diffusely attack crypts</td>
<td>Typical</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Neutrophils free in the lamina propria, crypt sparing</td>
<td>Very uncommon</td>
<td>Typical, focal</td>
</tr>
<tr>
<td>Disproportionate submucosal inflammation</td>
<td>No</td>
<td>Typical but uncommon</td>
</tr>
<tr>
<td>Granuloma</td>
<td>Only to foreign material</td>
<td>Characteristic when present (maximum 50%)</td>
</tr>
<tr>
<td>Submucosal inflammation</td>
<td>Rare—continuous</td>
<td>Common, often patchy</td>
</tr>
<tr>
<td>Muscularis mucosae</td>
<td>If present is continuous</td>
<td>No</td>
</tr>
<tr>
<td>Noncaseating, compact</td>
<td>No</td>
<td>Typical</td>
</tr>
<tr>
<td>Focal ulceration with minimal adjacent inflammation</td>
<td>Fulminant disease only</td>
<td>Typical</td>
</tr>
<tr>
<td>Mucosa sinus tracts</td>
<td>No</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Epithelial features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villous</td>
<td>Common</td>
<td>Occasional presence favors ulcerative colitis</td>
</tr>
<tr>
<td>Diffuse mucin depletion in active disease</td>
<td>Usual</td>
<td>Occasional</td>
</tr>
<tr>
<td>Paneth cell metaplasia</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Pyloric metaplasia in the ileum</td>
<td>Absent</td>
<td>Typical but uncommon</td>
</tr>
<tr>
<td><strong>Stromal changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Absent unless concomitant cytomegalovirus</td>
<td>Occasional</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Neural hyperplasia</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

*a The use of rectal steroid-containing enemas may create the appearance of rectal sparing.

*b A false impression of focal disease can be obtained from biopsies of inflammatory polyps and biopsies of granulation tissue at anastomotic lines.

*c The absence of granulomas does not exclude the diagnosis. The presence of loose mucin granulomas does not establish the diagnosis.
Patients with UC and CD share many similarities, but there are also significant differences that create the need to distinguish between them. Different surgical approaches are used to treat IBD patients depending on the nature of the underlying disease. Surgical techniques for continent ileostomy or ileoanal anastomosis with construction of a pouch reservoir allow one to avoid an ileostomy following colectomy. The operation is designed to improve the quality of life in UC patients by preserving fecal continence. However, this procedure is not generally used to treat CD patients. Total proctocolectomy in a UC patient with backwash ileitis allows the ileum to heal, but the same operation in a patient with CD ileocolitis may leave residual disease or may be followed by a high incidence of stomal dysfunction and recurrent ileitis. As a result, pathologists are under great pressure to distinguish UC from CD on biopsies before the patients undergo surgical intervention.

### TABLE 11.18 Diseases Clinically Mimicking Colonic Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infection</td>
</tr>
<tr>
<td>Escherichia coli 0157:H</td>
</tr>
<tr>
<td>Salmonella</td>
</tr>
<tr>
<td>Shigella</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Clostridium</td>
</tr>
<tr>
<td>Campylobacter</td>
</tr>
<tr>
<td>Gonorrhea</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Staphylococcal enteritis</td>
</tr>
<tr>
<td>Yersinia</td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
</tr>
<tr>
<td>Fungal infection</td>
</tr>
<tr>
<td>Histoplasmosi</td>
</tr>
<tr>
<td>Chlamydial infection</td>
</tr>
<tr>
<td>Chlamydial colitis–proctitis</td>
</tr>
<tr>
<td>Viral infection</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Protozoan infection</td>
</tr>
<tr>
<td>Amebiasis</td>
</tr>
<tr>
<td>Schistosomiasia</td>
</tr>
<tr>
<td>Anisakiasia</td>
</tr>
<tr>
<td>Ischemic colitis</td>
</tr>
<tr>
<td>Polyarteritis</td>
</tr>
<tr>
<td>Large vessel disease</td>
</tr>
<tr>
<td>Drugs digitalis (contraceptives, potassium salts)</td>
</tr>
<tr>
<td>Colitis-complicating obstruction</td>
</tr>
<tr>
<td>Other specific diseases</td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td>Behçet syndrome</td>
</tr>
<tr>
<td>Uremic colitis</td>
</tr>
<tr>
<td>Immunodeficiency syndromes</td>
</tr>
<tr>
<td>Collagenous colitis</td>
</tr>
</tbody>
</table>
Chapter 11

Radiation colitis
Diverticulitis
Solitary ulcer syndrome
Inflammation due to therapeutic interventions
Enemas and laxatives
Drug-induced colitis
Colitis in graft vs. host disease
Antibiotic-associated colitis

When the diseases are well developed, UC and CD have unique and distinguishing features that allow their separation from one another (see Tables 11.12 and 11.13). Because no one feature is invariably present, and because the features change with disease evolution, all of the pathologic features need to be assessed in aggregate. Reasons for difficulty in differentiating UC from CD are summarized in Table 11.15. Separating IBD from other causes of enterocolitis can also be quite difficult due to the significant overlap that may exist in the clinical, radiologic, endoscopic, and pathologic manifestations of the inflamed intestine (see Table 11.14).

The presence of several specific histologic features correlates with a high predictive probability of diagnosing IBD. The confidence ratio is 87% to 100% when the histologic findings include distorted crypt architecture (Fig. 11.93), increased numbers of both round cells and neutrophils in the lamina propria (Fig. 11.93), a villous surface (Fig. 11.76), crypt atrophy, basal lymphoid aggregates, and basally located isolated giant cells (Fig. 11.35). The presence of villous surface, basal lymphoid aggregates, crypt atrophy, and surface erosions all favor the diagnosis of UC, whereas the presence of granulomas favors the diagnosis of CD. Because CD is a focal disease, it is important to note that a patient with CD may have biopsy specimens that show a completely normal mucosa, a focal or diffuse colitis, or granulomas. Giant cells occur as often in ASLC as in IBD.

When a series of biopsies shows a consistent pattern of focal inflammation (Fig. 11.94) or when the biopsy shows an ulcer, erosion, or crypt destruction with crypt abscess formation in one focus and relatively normal adjacent mucosa, the possibility of UC is essentially ruled out and the diagnosis of CD is confirmed. However, it should be emphasized that many biopsies from CD patients show diffuse inflammation indistinguishable from UC.

Preservation of colonic mucin is a common feature of CD (Fig. 11.94), but it may only represent a manifestation of an essentially focal disorder, and it may not distinguish CD from UC. Its main value is to distinguish a normal biopsy from specimens showing IBD.

The prototypic biopsy for UC comes from a patient with classic endoscopic features (and this information has been transmitted to the pathologist) who has evidence of diffuse colonic mucosal damage that may straddle the muscularis mucosae to involve the upper submucosa. The diagnosis of UC is easiest when one finds increased numbers of lymphocytes and plasma cells within the lamina propria and a basal plasmacytosis in association with characteristic cryptitis or crypt abscesses. Some patients with UC show an inflammatory infiltrate that crosses the muscularis mucosae to involve the upper submucosa. This inflammation occurs in a bandlike fashion and is continuous with the overlying mucosal inflammation (Fig. 11.95). If there is a gap between the mucosal and submucosal inflammation or if the submucosal inflammation is focal in nature (Figs. 11.94 and 11.96), the more likely diagnosis is CD. The presence of focal fibrosis in a setting that otherwise suggests inflammatory bowel disease is consistent with CD. The presence of any significant ileal disease establishes the diagnosis of CD rather than UC with backwash ileitis. Ileocecal valve incompetency in UC can produce ileal changes (backwash ileitis), but the involved ileal segment should be short and the bowel should lack other characteristic features of CD.

P.653
FIG. 11.93. Mucosal biopsy in a patient with Crohn colitis. A: A biopsy specimen with mild glandular irregularity and an intense infiltrate in the submucosa. The inflammation is more or less diffuse. The amount of submucosal inflammation is out of proportion for what would be seen in ulcerative colitis unless one were in the area of a lymphoid follicle in which follicular structures should be seen. The arrows indicate the muscularis mucosae, the boundary between the mucosa and the submucosa. B: Histiocytic cells in the lamina propria adjacent to the glands. The upper lamina propria contains large numbers of mononuclear cells.

The diagnostic value of rectal biopsies in CD is proportional to the distance of the diseased segment from the anal margin. When disease is distal to the splenic flexure, 50% of biopsies will be diagnostic. When primarily ileal disease is present, the rectal biopsy is diagnostic in only 12% of patients. The diagnostic accuracy rate of rectal biopsies for CD ranges from 15% to 40% as compared to 70% for UC (133,134). The low diagnostic accuracy rate for CD relates to the sampling error inherent in diagnosing a patchy disorder with discontinuous pathologic features (133). The yield of a positive diagnostic finding directly relates to the presence of sigmoidoscopic or radiologic abnormalities in the distal colon and rectum.

FIG. 11.94. Mucosal biopsy in Crohn colitis. A: This mucosal biopsy shows mild glandular irregularity suggestive of mild previous damage and an area of focal inflammation that extends into the underlying submucosa (arrow). B: Another biopsy from the same patient showing patchy muscular inflammation (arrow). The patchiness of the inflammation in the mucosa and involvement of the muscularis mucosae suggests a focal process. This distinguishes the lesion from ulcerative colitis but does not rule out other entities, such as ischemia. A knowledge of the clinical context in which the biopsy was taken would be critical to its interpretation.
In some studies, the presence of lymphoid aggregates discriminates patients with IBD (135). On average, one lymphoglandular complex occurs approximately every 2 cm in normal subjects and one every 0.7 cm in patients with colitis (136). However, Theodossi et al found that lymphoid follicles had a similar frequency in patients with CD, in patients with UC, and in normal individuals (137).

The range of agreement over the final diagnosis of UC versus CD ranges from 40% to 76% (133,137). The low accuracy rate for diagnosing CD is attributed to the sampling error inherent in the diagnosis of a patchy disease. There is good agreement in discriminating between normal mucosa and IBD. However, for normal slides, the term "nonspecific inflammation" is often applied without any consistency. In addition, true CD is often thought to be UC. Frei and Morson concluded that in practical terms an accuracy rate in CD of 40% is probably adequate. The rate of false-positive diagnoses was 5% (133).

**FIG. 11.95.** Submucosal inflammation in ulcerative colitis. A: Some patients with ulcerative colitis demonstrate prominent superficial submucosal inflammation that could be misinterpreted as representing Crohn disease. This patient had longstanding disease with a distribution pattern of ulcerative colitis. B: Higher power magnification. The muscularis mucosae appears discontinuous in this area.

There will be some circumstances in which it is not possible to distinguish between UC and CD.

**Extraintestinal Complications of Inflammatory Bowel Disease**

A large percentage of IBD patients suffer from one or more extraintestinal complications at some time during the course of their disease. These complications affect many organ systems and may be of little clinical consequence or they may be severe, disabling, and critical determinants in directing the patient therapy (Fig. 11.97).
FIG. 11.96. Large mucosal biopsy in Crohn disease. This biopsy is deeper than many and contains superficial submucosa. In this setting, it is possible to see the prominent lymphoid aggregates and also the lack of mucin depletion.

Musculoskeletal Complications

Table 11.19 lists the musculoskeletal complications of IBD. The most common extraintestinal manifestation of IBD is arthritis, the incidence of which ranges from 7% to 25% (138,139,140). The incidence varies, depending on whether the diagnosis is made only in patients with objective findings and abnormal radiographs diagnostic of arthritis, or whether it also includes patients with symptomatic arthralgias. Musculoskeletal complaints may predate the onset of intestinal symptoms. Peripheral arthritis occurs with greater frequency in patients with CD than with UC, and it affects patients with colonic CD more frequently than those with only small intestinal involvement. The joint manifestations of CD cannot be distinguished from those associated with UC. Arthritis usually does not affect patients with quiescent disease, but it does accompany disease exacerbations and frequently associates with aphthous ulcers, skin lesions, and iritis. The peripheral arthritis affects the hips, ankles, wrists, and elbows in decreasing order of frequency. Small joints of the hands and feet are less commonly involved. Synovial biopsies demonstrate a nonspecific synovitis with changes including loss of synovial cells and inflammation.

![Diagram of the extraintestinal manifestations of inflammatory bowel disease.](image)

**TABLE 11.19 Musculoskeletal Complications of Inflammatory Bowel Disease**
Peripheral arthritis, arthralgia
Sacroiliitis
Ankylosing spondylitis
Finger clubbing
Granulomatous myositis (rare)
Septic arthritis
Osteomyelitis

The major manifestations of sacroiliitis include narrowing of the joint space, erosions, and sclerosis of the sacroiliac joints. There is a high incidence of silent IBD in patients with spondyloarthropathy. Twenty-five percent of patients have early features of CD (141). An increase in intraepithelial T cells suggests that augmented mucosal antigen handling and involvement of the MHC plays a role in the pathogenesis of spondyloarthropathy-related gut inflammation in CD (141).

It is well established that IBD associates with osteoporosis in from 2% to 30% of cases (142). Osteopenia occurs in an even larger number of patients. Many factors play a role in IBD-associated bone loss, including malnutrition, calcium, and vitamin D deficiency attributable to small bowel disease or surgical resection. Steroid therapy is also a contributing factor.

Hepatobiliary Disorders

Up to 50% of patients with IBD have minor liver and biliary tract abnormalities or elevated liver enzymes, but probably no more than 5% to 10% have clinically significant liver disease (143). Hepatobiliary complications overall occur with comparable frequency in UC and CD patients, even though different frequencies exist for specific complications. The frequency and severity of hepatobiliary diseases correlates with the extent, duration, and severity of the underlying IBD. Table 11.20 lists the major IBD-associated liver diseases.

**TABLE 11.20 Hepatobiliary Diseases Complicating Inflammatory Bowel Disease**

<table>
<thead>
<tr>
<th>Liver</th>
<th>Biliary tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty liver</td>
<td>Pericholangitis</td>
</tr>
<tr>
<td>(steatosis)</td>
<td>Chronic active hepatitis</td>
</tr>
<tr>
<td>Pericholangitis</td>
<td>Liver abscesses</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>Fibrosis and cirrhosis</td>
</tr>
<tr>
<td>Liver abscesses</td>
<td>Hepatic granulomas</td>
</tr>
<tr>
<td>Fibrosis and cirrhosis</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Hepatic granulomas</td>
<td>Nodular regenerative hyperplasia</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Abscesses and pylephlebitis</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
<td>Biliary tract</td>
</tr>
<tr>
<td>Abscesses and pylephlebitis</td>
<td>Pericholangitis</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Pericholangitis</td>
<td>Bile duct carcinoma</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>Cholelithiasis</td>
</tr>
<tr>
<td>Bile duct carcinoma</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>Portal vein thrombosis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Occlusion of hepatic acini</td>
</tr>
</tbody>
</table>

Steatosis

Steatosis affects approximately 30% of IBD patients (144). Extensive fatty infiltration usually affects seriously ill patients and resolves with patient recovery. The fat is of the macrovesicular type with large lipid
droplets in liver cells. The fat exhibits a diffuse, centrilobular, and periportal distribution. The pathogenesis is unknown, but it may result from malabsorption or a generally poor nutritional status. It may also result from bacterial metabolites released when bacteria gain access to the portal system secondary to the mucosal ulcerations. Other etiologic factors may include anemia, drugs, toxins, or other “toxic” substances absorbed through an eroded inflamed intestinal mucosal surface.

**Pericholangitis**

Pericholangitis is the most common bile duct lesion complicating IBD (Fig. 11.98); it affects both children and adults (145). The disorder represents a variant of primary sclerosing cholangitis that involves the smaller intrahepatic bile ducts. Pericholangitis affects patients with extensive colonic involvement and develops in three phases: (a) an acute phase, (b) a subacute phase with early periportal fibrosis, and (c) a chronic lesion with circumducal fibrosis. When the disease first presents, patients may have minimal signs and symptoms of liver disease.

Histologically, one sees portal triad enlargement, edema, bile ductular proliferation, and an inflammatory cell infiltrate, usually consisting of lymphocytes, plasma cells, occasional neutrophils, and eosinophils (Fig. 11.98). The heaviest infiltrate surrounds the interlobular bile ducts, but it may also be evenly distributed throughout the portal spaces. A loose proliferation of fibroblasts surrounds the interlobular bile ducts and dense circumducal fibrosis becomes more marked as the disease progresses. In many patients harmless periductal fibrosis replaces the inflammation. In others, the lesion progresses to chronic liver disease, even to biliary cirrhosis.

![FIG. 11.98. Pericholangitis in inflammatory bowel disease. A: The portal tracts are widened with beginning bridging fibrosis and prominent chronic inflammatory cells surround proliferating bile ductules, which are inconspicuous and difficult to see. B: As the lesions progress, increasing amounts of fibrosis surround the ductal structures and the portal tracts because pericholangitis and sclerosing cholangitis often go hand in hand. The expanded portal tracts also show a heavy infiltration of chronic inflammatory cells around the sclerotic portal tracts.](image)

Patients with cholangitis develop heavily thickened bile duct basement membranes and translucent areas containing bilelike material. The extravasated bile enhances the development of periductal fibrosis progressing to sclerosing cholangitis (146). Intracanalicular bile thrombi and bile inclusions may develop in the hepatocytes.

**Primary Sclerosing Cholangitis**

Primary sclerosing cholangitis (PSC), a serious chronic progressive cholestatic liver disease characterized by inflammation and fibrosis of the bile ducts, strongly associates with a diagnosis of UC. PSC affects 2% to 7% of UC patients (63,147). Conversely, most patients with PSC have UC (70% to 80%). The risk of PSC is higher in patients with pancolitis and is greater for UC than CD (148). The converse
association is much stronger, with up to 80% of individuals with PSC having UC (149). PSC primarily affects young males who usually present with progressive fatigue, pruritus, jaundice, and a cholestatic biochemical profile. The lesion is most easily demonstrated by cholangiography.

An immunologic abnormality might underlie the development of the lesion. The association of sclerosing cholangitis with Riedel thyroiditis, retroperitoneal fibrosis, mediastinal fibrosis, and pernicious anemia is cited as indirect evidence for an immune-mediated etiology (150). Additionally, a colitis-associated immunoglobulin antibody cross-reacts with an antigen on colonic and biliary epithelium (151), and an ANCA occurs in both UC and PSC (152). ANCAs may serve as a prognostic indicator for the development of PSC (153).

The familial occurrence of PSC and UC suggests that genetic factors also play a role in the etiology of the disease, especially because it associates with a high incidence of B8 and DRW3 haplotypes of the major histocompatibility system (154). Liver biopsies often fail to diagnose the lesion but are useful for staging once the disease is diagnosed.

PSC is characterized by a progressively sclerosing obliteratorive process involving the extrahepatic bile ducts and, occasionally, the intrahepatic bile ducts (Fig. 11.99). The liver may appear normal or reveal acute, subacute, and chronic pericholangitis, cholestasis, or cirrhosis (Fig. 11.100). Histologically the fibrotic thickening of the bile duct wall contains a diffuse mononuclear infiltrate, which is predominantly lymphocytic.

P.657

in nature. A lesion classified as small duct primary sclerosing cholangitis consists of hepatobiliary lesions within the intrahepatic bile ducts. The histologic features resemble those of large duct sclerosing cholangitis. Some patients go on to develop cirrhosis.

PSC serves as a marker for the development of colorectal cancer in UC. UC patients with PSC are five times more likely to develop dysplasia than those without it (63,155).
Cholelithiasis

Gallstones affect IBD patients more frequently than those in the general population (140). Distal ileal dysfunction may predispose to the secretion of lithogenic bile.

Pancreatic Abnormalities
Pancreatic abnormalities occur with increased frequency in IBD, complicating either the disease itself or sometimes the drug therapy. Clinically significant and non–drug-related pancreatitis affects two subgroups of IBD patients: (a) patients with duodenal CD who develop reflux of duodenal contents into the pancreatic duct through an incompetent ampulla or through direct ampullary involvement (157), and (b) UC patients with sclerosing cholangitis or pericholangitis who develop pancreatitis on the basis of ductal inflammation. Occasionally, patients with CD present with acute relapsing pancreatitis (157). Also, some patients with CD have evidence of compact sarcoidlike granulomas in the pancreatic tissue.

Amyloid
Secondary amyloidosis is a rare complication of IBD, most often affecting CD patients (158). The amyloid deposits in multiple organs, including the liver and kidneys. Some patients may die of renal failure. The amyloid that develops in patients with UC may resolve, making this form of amyloid unique (159).

Skin Lesions
Many mucocutaneous lesions complicate IBD. Cutaneous lesions affect 10% of patients at the time of IBD diagnosis, and up to 20% throughout the course of their disease (138). IBD-associated cutaneous manifestations may be divided into three types: Granulomatous, reactive, and secondary to nutritional deficiency (140).

Erythema Nodosum
Erythema nodosum affects about 3% to 8% of patients with IBD and 1% to 2% of patients with CD limited to the small bowel (138). It represents the most common extracolonic manifestation of IBD in children. Women are affected three or four times more frequently than men. The lesions may appear before the diagnosis of IBD and their presence often correlates with activity of the bowel disease. The characteristic lesions present as raised, red or reddish-blue, warm, tender nodules, predominantly distributed on the lower legs, especially on the anterior surfaces (Fig. 11.102). They may also be present on the lateral or posterior surfaces of the legs and occasionally on the arms. Some lesions ulcerate. Erythema nodosum is thought to result from hypersensitivity reactions but the specific inciting antigens are unknown. Histologically, erythema nodosum may undergo endothelial cell necrosis, thrombus formation, and ulceration. Oral aphthous ulcers, iritis, and peripheral arthritis sometimes accompany the erythema nodosum.

Pyoderma Gangrenosum
Pyoderma gangrenosum is a serious lesion that occurs exclusively in IBD patients. Pyoderma gangrenosum affects approximately 1% to 5% of patients with UC and is roughly three times more common in UC patients than CD patients (160). The presence of the lesions correlates with the presence of active disease. Eighty-five percent of patients with pyoderma gangrenosum have pancolitis. Symptoms usually occur before the diagnosis of IBD is made. The lesions may recur after initially responding to medical treatment and are rare following colectomy. Patients usually give a history of preceding minor trauma. The lesion most commonly involves the pretibial region, although it may be seen on any part of the body, including the face and scalp. Patients also develop peristomal pyoderma gangrenosum.

The skin lesions are macroscopically described as single or multiple deep discrete ulcerations with a necrotic center, an undermined border, and violaceous skin surrounding the lesion. Individual lesions evolve from small pustules that coalesce into painful ulcers, frequently in a few days.

FIG. 11.102. Erythema nodosa on the forearm.
Histologic features are not characteristic and include necrosis, suppuration, angitis with fibrinoid necrosis, thrombosis, and sometimes granulomas. The lesions are sterile and contain a dense dermal neutrophilic infiltrate. If left untreated, the lesions may penetrate deeply causing osteomyelitis, even necessitating amputation of an extremity.

**Pyoderma Vegetans**

The presence of pyoderma vegetans is highly suggestive of IBD (161). Patients may have associated sclerosing cholangitis (162). Pyoderma–pyostomatitis vegetans is an annular, pustular eruption that involves the oral mucosa, groin, axillae, face, scalp, lower trunk, and limbs. The oral lesions are the most easily recognizable on clinical examination and are virtually pathognomonic (161). Pyoderma vegetans initially begins in intertriginous areas with vegetating plaques and vesicular pustules that resolve with postinflammatory hyperpigmentation. Multiple pustules occur on an erythematous base and may coalesce and undergo necrosis to form a characteristic snail-track appearance. Patients typically demonstrate peripheral eosinophilia. Histologically, the main features include pseudoepitheliomatous hyperplasia with intraepidermal abscesses containing neutrophils and eosinophils. Pyoderma vegetans may represent an incomplete form of pyoderma gangrenosum.

**Cutaneous Crohn Disease**

Ulceration of the skin around colostomies or ileostomies usually represents a reoccurrence of the CD and can be cured by resection or revision of the ostomy. Cutaneous disease also results from direct extension of IBD from the perianal area onto the perianal skin. Granulomas separated from the GI tract by normal skin are called distant cutaneous CD. This uncommon cutaneous manifestation of CD presents as subcutaneous nodules, plaques with or without ulceration, ulcerated patches, lichenoid papules, or intertriginous ulcerations and erysipeliaslike lesions (163). Histologically, one sees dermal and sometimes subcutaneous noncaseating granulomas that may be perivascular in location. As with other extraintestinal cutaneous manifestations, distant cutaneous CD affects patients whose CD involves the colon.

**Vesiculopustular Eruptions**

Localized or generalized vesiculopustular eruptions affect some UC patients (164). The lesions consist of grouped erythematous vesiculopustules (3 to 5 mm) that sequentially crust and heal with postinflammatory hyperpigmentation. Some consider this to represent an abortive form of pyoderma gangrenosum. Histologic examination reveals intraepidermal neutrophilic abscesses with mixed inflammatory dermal infiltrates.

**Other Cutaneous Lesions**

Zinc deficiencies in CD lead to acrodermatitis enteropathica, a psoriasislike lesion that responds to zinc therapy. Alopecia areata associates with UC, has a familial aggregation, and has an HLA association common to both disorders (165). Cutaneous vasculitic gangrene affects IBD patients and differs in appearance from pyoderma gangrenosum. The underlying cause of the vasculitis often remains unclear.

**Mucosal Lesions**

Oral lesions, both symptomatic and asymptomatic, affect 6% to 20% of CD patients (166). Similar lesions in UC are less well documented. Most oropharyngeal manifestations of IBD occur in patients with active intestinal disease and their presence frequently correlates with disease activity. Recurrent aphthous ulcers are the most common oral manifestation of IBD (Fig. 11.103). The cause of oral aphthous ulcers is multifactorial. They may result from nutritional deficiencies of iron, folic acid, and vitamin B₁₂. Discrete punched-out superficial ulcers begin shortly before or during acute exacerbations of the IBD and may associate with other extraintestinal complications, including arthritis, erythema nodosum, and iritis. In patients prone to develop aphthous ulcers, the development of a new crop of oral ulcers often heralds flare-up of the bowel disease. The ulcers may be painful, interfering with eating and drinking. These lesions must be differentiated from oral candidiasis, which also complicates severe IBD, particularly in a patient treated with steroids and antibiotics.

CD patients develop diffuse swelling of the lips and cheeks, inflammatory hyperplasias of the oral mucosa, indurated polypoid taglike lesions in the vestibular and retromolar mucosa, persistent deep linear ulcerations with hyperplastic margins, and indurated fissuring in the midline of the lower lip. CD patients may also develop the oropharyngeal lesions and lesions of the epiglottis and aryepiglottic folds characterized by palatal submucosal edema, lymphatic dilation, and nonspecific perivascular chronic inflammatory cell infiltrates. Lymphoid nodules and microgranulomas consisting of clusters of histiocytes and occasional multinucleated giant cells also develop. Oral findings in UC patients include ulcers analogous to pyoderma gangrenosum of the skin and pyostomatitis vegetans.
FIG. 11.103. Aphthous ulcers involving the buccal mucosa in a patient with Crohn disease.

### TABLE 11.21 Eye Lesions in Inflammatory Bowel Disease Patients

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uveitis</td>
<td>Chorioretinitis</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Keratitis</td>
</tr>
<tr>
<td>Iritis</td>
<td>Blepharitis</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Retinal detachment</td>
</tr>
<tr>
<td>Marginal corneal ulcers</td>
<td>Uveitis</td>
</tr>
<tr>
<td>Antral serous retinopathy</td>
<td>Scleromalacia</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>Ischemic optic neuropathy</td>
</tr>
<tr>
<td>Orbital myositis</td>
<td></td>
</tr>
</tbody>
</table>

Some patients develop ulcerative tracheobronchitis years after colectomy for UC (167), and severe upper airway stenosis affects some UC patients (168). UC patients also develop oral hairy leukoplakia (169), a lesion more commonly associated with AIDS. The lesion may serve as a marker of severe immunosuppression.

**Eye Lesions**

Approximately 10% of IBD patients develop ocular complications (140). The most common eye lesions are listed in Table 11.21. Eye lesions often appear early in acute episodes or relapses of the bowel disease, and they subside as the disease goes into remission. Orbital myositis, a nonspecific inflammation involving the ocular muscles, develops in some patients.

**Gynecologic Features**

CD patients have a number of gynecologic problems (Table 11.22). The lesions are typified by chronic granulomatous inflammation with exudation and marked tissue destruction (see Fig. 11.53). Special stains for acid-fast bacilli, fungi, and Donovan bodies are negative in vulvar CD. Vulvovaginal disease has also been complicated by the development of Bowen disease in the area of CD (170). CD involving the labia may present as unilateral labial hypertrophy, especially in young children.

### TABLE 11.22 Gynecologic Problems of Inflammatory Bowel Disease Patients

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal disease</td>
<td></td>
</tr>
<tr>
<td>Labial hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Special stains</td>
<td></td>
</tr>
<tr>
<td>Acid-fast bacilli</td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
</tr>
<tr>
<td>Donovan bodies</td>
<td></td>
</tr>
<tr>
<td>Vulvar CD</td>
<td></td>
</tr>
<tr>
<td>Bowen disease</td>
<td></td>
</tr>
</tbody>
</table>

CD involving the labia may present as unilateral labial hypertrophy, especially in young children.
Vulvar, vaginal, perineal, or labial lesions
- Ulcers
- Granulomas
- Fistulas
- Bowen disease
- Infertility
- Adnexal masses
- Preterm deliveries

TABLE 11.23 Vasculitides Associated with Inflammatory Bowel Disease.

<table>
<thead>
<tr>
<th>Vasculitides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Takayasu disease</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td>Large vessel disease with aneurysm formation</td>
</tr>
<tr>
<td>Gastrointestinal vasculitis</td>
</tr>
<tr>
<td>Cutaneous vasculitis</td>
</tr>
</tbody>
</table>

IBD patients also sometimes present with an acute abdomen or with an adnexal or pelvic mass that may be incorrectly diagnosed as pelvic inflammatory disease, as acute appendicitis, or even as an ovarian cyst. Pregnant patients may have an increased incidence of preterm delivery (171), and 30% to 50% of pregnant women have an exacerbation of their IBD during their pregnancy and postpartum period.

**Vasculitis**

Vasculitis (Table 11.23) affects different parts of the body in patients with different forms of IBD. Some believe that vascular lesions represent a universal intestinal finding in CD, playing an important role in the development of the pathologic features of the disease (172). Cutaneous, systemic, and cerebral circulations are affected. No specific clinical features distinguish patients with vascular involvement from those without this phenomenon.

**Cutaneous Vasculitis**

Both necrotizing (leukocytoclastic) vasculitis and benign cutaneous polyarteritis nodosa occur in IBD patients (173). Cutaneous or systemic polyarteritis nodosa associates with CD. The vasculitis results from deposition of immune complexes in blood vessel walls, and presents as purpuric skin lesions or as visceral disease. The usual sites of involvement are the legs and acral areas. Mixed cryoglobulinemia may be demonstrated in some patients. Histologic examination shows a typical necrotizing panarteritis with granulomatous features when associated with CD, and leukocytoclasis, hemorrhage, and vessel wall damage.

**Large Vessel Disease**

Large vessel disease leads to aneurysm development, often affecting the major intestinal vasculature, including the superior mesenteric artery. Aneurysms also develop in the iliac and brachiocephalic vessels and in the aortic arch. Histologic examination shows the presence of intimal and medial fibrosis, extensive degeneration of the medial elastomuscular lamellae, and adventitial inflammation, predominantly consisting of a mononuclear cell infiltrate.

**Takayasu Arteritis**
Takayasu arteritis, an inflammatory and stenotic disease of medium-sized and large arteries with a strong predilection for involvement of the aortic arch and its branches, the pulmonary artery, and cerebral arteries, affects a small number of UC patients (174).

**Giant Cell Arteritis**

Giant cell arteritis has also been described complicating IBD (175). The disease presents as recurrent erythematous, tender, painful cords and subcutaneous nodules that tend to ulcerate, involving the skin of the lower and upper extremities. Most patients are in their 20s, with patients ranging in age from 13 to 31 years. Histologically, one sees granulomatous panarteritis involving the muscular arteries of the subcutis and adjacent dermis, as well as vessels of peripheral nerves and skeletal muscle.

**Genitourinary Complications**

Genitourinary (GU) complications affect 4% to 23% of IBD patients (176). The three most common GU complications are urinary tract calculi, ureteral obstruction, and vesicle fistulae (176). These most commonly affect patients with severe, longstanding CD. Nephrolithiasis affects 2% to 10% of patients (177), contrasting with an incidence of <1 per 1,000 in the general population. Frequently implicated lithogenic factors include oliguria, diminished water absorption, urinary tract infection, abnormal urate excretion, alterations in oxalate absorption and excretion, steroid administration, hypercalcemia, prolonged bedrest, and decreased intestinal sodium absorption with concomitant decreased urinary sodium (177). Proctocolectomy with ileal pouch–anal anastomosis increases the risk of stone formation. Severe diarrhea or profuse ileostomy discharge following colectomy leads to a low volume of concentrated urine, often with a low pH secondary to intestinal bicarbonate loss. These factors contribute to the formation of urate stones. In addition, ileal resections or extensive ileal disease, as occurs in CD, often causes hyperoxaluria. Obstructive hydronephrosis affects CD patients; it results from ureteral compression by abscesses or inflammatory masses, retroperitoneal extension of intestinal inflammatory processes originating as perforations or fistulae.

Bladder involvement by CD results from direct extension of the inflammatory process from a contiguous segment of inflamed bowel, with or without intervening abscess formation. When fistulae develop, patients may experience pneumaturia and urinalysis may reveal pyuria and infection.

**Thromboembolic Complications**

Thromboembolic complications affect 1.3% to 6.4% of CD and UC patients (Fig. 11.104) (178). Both venous thromboembolism and arterial thrombosis develop. Arterial thrombosis, however, is rare, occurring most commonly following surgery. Extensive arterial thrombosis (179) occasionally occurs in UC patients. Portal vein, mesenteric vein, and hepatic vein thrombosis also associate with a high mortality.

**FIG. 11.104.** Portal vein thrombosis in a patient with a hypercoagulable state and inflammatory bowel disease.

Cerebral venous thrombosis is an extremely rare complication of IBD with only a small number of cases reported in the literature. When it develops, the outcome is poor (180). In most instances, permanent neurologic sequelae or death results (179). Even young infants may develop central nervous system thrombosis (180). Thromboembolic episodes more commonly affect the deep peripheral veins or result in pulmonary emboli. The risk of thrombotic complications increases with disease activity or other precipitating events. In some series, 64% of patients have active disease at the time of thrombosis (172). The thrombosis in IBD is generally considered to result from the presence of a hypercoagulable state. Other contributing factors include bedrest, toxemia, and surgical procedures. Hemostatic abnormalities include thrombocytosis, elevated fibrinogen, factors V and VII, vitamin K, and decreased protein C and S, factor XIII, and antithrombin III levels (172,181,182). Sixty-three percent of CD and 25% of UC patients demonstrate free protein S deficiency. Protein C deficiency also occurs. Protein C activity may return to normal on disease remission or following subtotal colectomy (183). Other abnormalities include the
presence of fibrin microclots. Platelets circulate in an activated state in IBD, and the increased platelet activation and aggregation found in this disorder may contribute to the risk of systemic thromboembolism and mucosal inflammation secondary to ischemia. Circulating immune complexes contribute to the development of vasculitis (184), which then predisposes to thrombosis. Additionally, patients might have CMV infections that can precipitate localized clotting secondary to an endothelialitis.

**Pulmonary Complications**

Respiratory disorders complicating IBD include pulmonary vasculitis, localized interstitial fibrosis, apical fibrosis, panbronchiolitis, chronic suppurative bronchitis, and bronchiecstasy involving both large and small airways. The lung may also represent a latent site of involvement by CD based on the demonstration of a lymphocytic alveolitis and granulomatous lung disease (185). Patients also develop sulfasalazine pneumonitis (186).

**Hematologic Abnormalities**

Hematologic abnormalities affect many IBD patients, with iron deficiency anemia due to GI blood loss representing the most common abnormality. As many as one third of IBD patients have hemoglobin levels <12 g/dL (187). Macrocytic anemia develops as the result of folate deficiency during sulfasalazine therapy or with impaired B12 absorption in patients with terminal ileal CD (188). CD patients also produce inadequate amounts of erythropoietin because cytokines, such as interleukin-6, suppress erythropoietin production (189). Patients also spontaneously develop autoantibodies directed against red cells or develop Coombs-positive autoimmune hemolytic anemias as a result of sulfasalazine therapy (190). Azathioprine therapy causes bone marrow toxicity with thrombocytopenia and leukopenia (191). IBD patients also present with refractory anemia and myelodysplasia (192).

**Other Lesions**

Perineuritis resulting in a peripheral neuropathy may represent an autoimmune manifestation of the disease (193). Patients with pericarditis develop asymptomatic pericardial effusions and cardiac tamponade (194). The pericarditis associated with IBD may represent an adverse drug effect. Some patients also develop hyperthyroidism (195). A rare patient has also been described who had selective IgA deficiency, UC, and celiac disease (196).

**Complications of Inflammatory Bowel Disease Therapy**

**Complications of Drug Therapy**

Because patients with UC and CD often have lifelong problems associated with their inflammation, they are treated with many drugs to reduce the inflammatory response. This can predispose patients to infections, including *C. difficile* and CMV. Sulfasalazine treatment results in pneumonitis or a Coombs-positive autoimmune hemolytic anemia (190). Mesalazine causes interstitial nephritis (197). Long-term steroid therapy leads to all of the well-known problems associated with steroid use, including osteonecrosis. Therapy may also mask the usual histologic features of IBD.

**Changes Seen with Fecal Stream Diversion**

Fecal stream diversion induces inflammation in the defunctionalized intestinal segment. The changes are predominantly mucosal and they may generate histologic confusion, especially when granulomas develop. Rectal stumps typically show such features as follicular hyperplasia (which may sometimes be quite extensive), transmural inflammation, granulomas, fissures, and changes akin to ischemia with pseudomembranous colitis (Fig. 11.105). Even though the patient's underlying disease may be UC, the changes may mimic CD.
Changes in Ileostomies

Ileostomies are prone to develop pathologic lesions, including inflammatory polyps and adenocarcinomas (Fig. 11.106).

Additionally, a small percentage of patients will require ileostomy revision because of prolapse, tightening of the stoma, or localized sepsis. Histologic evaluation of the resected ileostomy shows variable mucosal atrophy and inflammation. The mucosa may also appear ulcerated. When carcinomas develop, they are sometimes surrounded by large intestinal mucosa.

Complications of Restorative Proctocolectomy (Pouchitis)

Abdominal colectomy with ileal pouch–anal anastomosis has become the surgical treatment of choice for most patients with uncontrollable UC. This procedure removes all of the diseased mucosa while preserving continence and transanal defecation. With the creation of ileal pouches, the primary function of the terminal ileum changes from absorption to fecal storage. The most common long-term complication of the procedure is nonspecific inflammation of the ileal reservoir, commonly known as pouchitis. This complication affects 15% to 47% of patients (198,199) and becomes chronic in 5% (200). Complications of pouchitis are likely to be much more severe if patients had histologic evidence of CD. Pouchitis is also more common in patients with primary sclerosing cholangitis, with a cumulative probability of developing the condition of 79% at 10 years (201). Smoking appears to be protective against pouchitis in patients with UC (202).

Bacterial overgrowth resulting from stasis is thought to play a major role in the development of pouchitis (203). Anaerobic bacterial concentrations in ileal pouchitis correlate with the presence of nonspecific histologic changes, including villous atrophy and chronic inflammation. Fecal stasis and aerobic and anaerobic bacterial overgrowth may contribute to the development of colonic metaplasia. Other factors that may play a role in the development of pouchitis include the presence of volatile fatty acids, fecal bile acids, oxygen-free radicals, ischemia, platelet-activating factor, and hormonal factors (199,203,204).

Definition

In some centers, pouchitis is defined clinically as the following: (a) a syndrome of frequent watery and often bloody stools associated with fecal urgency, incontinence, abdominal cramps, malaise, and fever; and (b) symptoms present for 2 or more days that respond promptly to metronidazole (199,205). At St. Mark's Hospital, pouchitis is defined as the triad consisting of (a) diarrhea, (b) endoscopic features of inflammation in the pouch, and (c) histologic evidence of active inflammation (204).
Sandborn et al developed a pouchitis disease activity index (PDAI) (198). The PDAI was significantly greater in patients with clinical features of pouchitis than it was for patients who did not have pouchitis. Such a pouchitis disease activity index may be useful in prospective studies to facilitate valid comparisons between medical centers and to objectively measure the response in therapeutic trials.

**Clinical Features**

Clinical symptoms of pouchitis include diarrhea, rectal bleeding, abdominal cramps, urgency, tenesmus, and malaise. In severe cases, these symptoms may be accompanied by incontinence and fever (198). Endoscopic findings include edema, mucosal erythema, granularity, friability, bleeding, loss of the vascular pattern, and the presence of a mucus exudate with small superficial areas of ulceration (204). Generally, a significant relationship exists between the endoscopic and the histologic features.

The endoscopic findings are also similar to those in UC including edema, granularity, friability, bleeding, loss of the vascular pattern, and the presence of a mucus exudate with a trend toward mucosal ulceration (206).

**Mucosal Adaptation**

Three basic patterns of mucosal adaptation develop in pelvic ileal pouches: (a) normal mucosa or mild villous atrophy with no or mild inflammation, (b) transient atrophy with temporary moderate or severe villous atrophy followed by normalization of architecture, and (c) constant atrophy with permanent subtotal or total villous atrophy and severe pouchitis (Fig. 11.107). The pouch mucosa converts to one with a colonic phenotype in 80% of cases (207) and pouchitis most commonly affects those in whom metaplasia has developed (200). The greater the degree of colonic metaplasia in the pouch mucosa, the more likely one is to see histologic pouchitis (200). The metaplasia is detected in a manner similar to its detection in ileostomies.
FIG. 11.107. Pouchitis. A and B show a low and high magnification of a biopsy from a patient with pouchitis. The villi appear distorted and broadened with beginning colonic metaplasia. The mucosa is infiltrated with acute and chronic inflammatory cells. Cryptitis is present and is shown at higher magnification in the center of B. This patient had undergone an ileoanal anastomosis following resection for ulcerative colitis. The changes resemble those seen in active ulcerative colitis. In contrast, C shows mucosal biopsies from another patient who underwent an ileoanal anastomosis and who developed severe pouchitis. Here the changes more closely resemble those seen in Crohn disease because of the nodular lymphoid aggregates found in the submucosa. Review of the original specimens in the patient confirmed that the previous disease was ulcerative colitis.

Histologic Features

Patients with pouchitis have a pattern of mucosal inflammation similar to that seen in UC. Early changes consist of neutrophilic and eosinophilic inflammation with architectural distortion, Paneth cell metaplasia, and a partial transition to the colonic mucinous phenotype, as well as an increased proliferative index (208). These features remain relatively stable after 6 months, except for a greater degree of mononuclear infiltration and a progressive increase in eosinophilic inflammation. Additionally, various infections may be present, including Candida.

Refractory chronic pouchitis may resemble Crohn disease. However, review of the colectomy specimen usually shows unequivocal UC, and the patients do not have any other clinical, radiologic, or pathologic evidence to support a diagnosis of CD. However, because of the histologic resemblance to CD, one should exclude the presence of transmural inflammation, granulomas, fibrosis, or strictures in areas distant from the anastomosis. Review of previous biopsy material also proves helpful in delineating the true nature of the inflammatory process. Sometimes, an analysis of serologic markers may also be useful in difficult-to-distinguish cases. A correlation exists between pouchitis, primary sclerosing cholangitis, and extraintestinal manifestations of IBD (198,199).

Aphthous ulcerations are one of the earliest lesions affecting the neoileum in CD. They develop in approximately 80% of patients within 1 year of ileal resection (209). Fistulae also develop as a result of previously unrecognized CD. These usually extend from the pouch to other sites such as the vagina or bladder.

Cancer Complicating Inflammatory Bowel Disease

General Comments

Patients with IBD, including both UC and CD, are at increased risk for the development of gastrointestinal carcinoma, particularly colorectal adenocarcinoma (210,211,212). The incidence of carcinoma is estimated to be 10 to 20 times greater for the small bowel and 4 to 20 times greater for the large bowel than in the general population. Cancer affects 4.8% of patients with CD and 11.2% with UC. The cancer risk positively correlates with disease duration and the anatomic extent of the colitis. Patients with left-sided colitis develop both their colitis and their cancers about a decade later than those with extensive disease, and the mean duration of the colitis before a cancer diagnosis ranges from 17 to 21 years (213,214,215). The cancer incidence is greater in persons with extensive UC (i.e., those in whom the disease extends proximally to the midtransverse colon). Multiple carcinomas develop with equal frequency in CD and UC (11% and 12%, respectively) (215). Patients also develop carcinomas outside of the GI tract.

Relationship to Disease Duration and Age at Diagnosis

The median duration of disease to diagnosis of cancer is long (CD 15 years and UC 18 years). Most cancers develop after more than 8 years of disease (CD 75%, UC 90%). The average age at the time of diagnosis of carcinoma is approximately 10 to 20 years earlier than carcinomas arising in patients without IBD. The median age at diagnosis of colorectal cancer in IBD patients is 54.5 years for CD and 43 to 45 years for UC patients (215,216). The risk is 20 to 30 times higher in individuals with pancolitis of 10 or more years’ duration than in a control population. The risk of cancer complicating colitis is 0.5% per year for 10 to 20 years after diagnosis and 0.9% for 20 to 30 years, and 1.5% thereafter (217). Some data suggest that an increased risk exists for patients who develop IBD at an early age, although this remains controversial (218).
Chapter 11

Cancer Arising in the Setting of Ulcerative Colitis

UC associates with an increased colon cancer risk. Carcinoma in UC affects young patients and is associated with a high incidence of multicentricity. Among 1,248 UC patients seen at the Cleveland Clinic and followed for a mean duration of 14.4 to 21 years (216), 66.5% developed colorectal cancer and 3.8% had extracolonic malignancies (216). Most cancer patients are men (2:1) with extensive (90%) and long-lasting (20 years or more) colitis. The colitis was inactive before the diagnosis of cancer in 48% of patients. The cumulative risk of colorectal cancer is significantly higher in patients with extensive colitis than in those with left-sided disease (11.9% vs. 1.8% at 20 years, and 25.3% vs. 3.7% at 30 years) (215). Although the carcinomas arise predominantly in the left side of the colon and in the rectum, there may be a higher incidence of right-sided colon cancer than in the noncolitis population. The diagnosis was suspected clinically in 64% of cases (215). Among those with extracolonic malignancy, the incidence of bile duct carcinoma, leukemia, bone tumors, and endometrial cancer is significantly greater than expected, whereas that of lung cancer is significantly lower.

PSC patients represent a subset of UC patients who exhibit a markedly increased incidence of colonic neoplasia. Patients with both PSC and colitis, but not cholangitis alone, have a 10-fold elevated colorectal cancer risk (219). DNA aneuploidy in nonneoplastic mucosa in UC patients predicts a high risk for future development of neoplasia (220). Patients with both PSC and UC are six times more likely to exhibit mucosal aneuploidy than patients with UC alone (155).

Cancer Arising in the Setting of Crohn Disease

Patients with longstanding CD (>7 years) have an increased incidence of large bowel carcinomas (221,222); these are sometimes multiple (223). The risk of developing cancer in CD is similar in magnitude to that found in UC patients with left-sided colitis but is much less than that found in UC patients overall. As in UC, the cancers tend to develop in patients with longstanding disease and in patients who are younger, on the average, than those with intestinal carcinoma in the general population (224). Cancers develop in the large intestine, small intestine (Fig. 11.108 and 11.109), and anus.

The relative risk for developing colorectal cancer in CD patients overall is 3.4. Patients with extensive colitis exhibit a relative risk of 18.2 (225). Patients with CD also evidence an excess number of cancers of the upper GI tract, mainly represented by an increased number of small intestinal cancers. Risk factors for developing small intestinal carcinoma include surgically excluded small bowel loops, chronic fistulous disease, and male sex. A relationship also exists between cancer development and certain occupations, particularly those that involve exposure to halogenated aromatic compounds, aliphatic amines, asbestos, cutting oils, solvents, and abrasives (214).

**FIG. 11.108.** Gross features of dysplasia in inflammatory bowel disease. Portion of the transverse and descending colon from a patient with ulcerative colitis. Note the presence of a large plaquelike lesion (arrows) occupying much of the left-hand side of the photograph. Several smaller plaquelike lesions are present. All of these were dysplastic histologically.
FIG. 11.109. Carcinoma arising in the small intestine of a patient with Crohn disease. A and B come from the same patient; C comes from a second patient. In A, one sees a large area of dysplasia on the right-hand portion of the mucosa. In B, one can see a polypoid exophytic lesion with a carcinoma invading into the underlying submucosa. In both A and B, the epithelium has become so atrophic that it resembles colonic mucosa. C: Dysplasia and invasive carcinoma. The dysplastic epithelium to the left of the photograph replaces the normal villous structure of the small bowel. A mucinous carcinoma has developed in the right-hand side of the photograph. It invades the superficial portion of the submucosa.

Unlike sporadic small intestinal carcinomas that commonly involve the duodenum, small intestinal carcinomas complicating CD arise in the distal small bowel in areas involved by CD. The distribution of GI cancers in CD is 25% in the small bowel (30% in the jejunum, 70% in the ileum), 70% in the large bowel, and 5% in the remaining sites (223). Crohn disease patients also develop carcinomas within their ileostomy stomas (226).

Patients who develop anorectal carcinomas have longstanding severe CD. There is also an increased incidence of urinary bladder carcinoma (227).

Risk Factors and Pathophysiology of Cancer Development

There is considerable interest in the relationship between oxidant stress and the development of cancer. As noted previously, both UC and CD are associated with increased reactive oxygen metabolites (ROMs). ROMs can cause oxidative DNA damage leading to base changes, strand breaks, and enhanced protooncogene expression; oxidative stress can induce malignant transformation (228). Factors such as the rate of damage, the status of antioxidant defenses, DNA repair mechanisms, and the necessity for multiple steps (initiation, promotion, and progression) all play a role in whether or not cancer develops.

**Dysplasia as a Marker for Cancer Risk**

Dysplasia was first postulated to be a precursor of carcinoma in UC by Warren and Sommers in 1949 (229); its histologic appearance in polypoid lesions was described in detail by Dawson and Pryse-Davies in 1959 (230), and in 1967 Morson and Pang (231) demonstrated that dysplasia could be detected on biopsy, thereby identifying patients who are likely either to have or to develop carcinoma.

The evidence supporting the concept of dysplasia as an indicator of malignancy in UC derives largely from two types of observations. First, retrospective analyses of resected colons harboring carcinomas from patients with UC almost uniformly disclose coexisting dysplasia, either adjacent to, or remote from, the carcinomas. The relationship between colon cancer and dysplasia is stronger when the dysplasia is adjacent to the cancer and when the dysplasia is high grade (232). Second, studies of patients who have undergone colectomy following biopsy demonstration of dysplasia often have a coexisting suspected (or
Chapter 11

unsuspected) carcinoma in the colectomy specimen (233). Patients with CD also develop dysplasia resembling that seen in UC. Precancers in CD histologically resemble those seen in patients with UC (Fig. 11.110). One often finds multifocal precancer characterized by epithelial dysplasia, adenomatous growth patterns, and villiform transformation of the mucosa. These signs are identical to those associated with UC and are present both adjacent to and distant from infiltrating cancers. The dysplasia ranges from widespread multifocal disease to focal dysplasia (234). The more severe the dysplasia, the closer a lesion is to becoming an invasive carcinoma. However, carcinomas may rarely arise from areas of low-grade dysplasia. The finding of low-grade or high-grade dysplasia indicates that the colon is at high risk for malignant changes, although the time frame between the onset of dysplasia and malignant transformation may vary. Dysplasia-associated lesions or masses (DALMs) (Figs. 11.108 and 11.111) are the most consistent indicator of carcinoma (232,235).

Despite the usefulness of dysplasia in predicting neoplastic transformation and cancer development, the concept of dysplasia predicting cancer development has the following drawbacks: (a) it involves a certain degree of subjectivity and skill to make the diagnosis and to grade the dysplasia; (b) the dysplasia has a patchy mucosal distribution, so that a negative rectal biopsy does not exclude large bowel neoplasia; (c) dysplasia is not always grossly visible or the gross features may be atypical; (d) a proportion of IBD patients develop cancers in the absence of demonstrable dysplasia; and (e) not all patients with dysplasia develop cancer.

Options for Reducing the Cancer Risk

The recognition that IBD has a malignant potential places the responsibility on clinicians to minimize or eliminate the risk that these patients will die from colonic cancer. Although most agree that patients with high-grade dysplasia have a strong risk for either concomitant cancer or the development of cancer, not all agree on the management of such patients.

Endoscopic Surveillance

Surveillance programs have been accepted as the standard of care for UC patients. Carcinomas detected in surveillance programs tend to be of lower stage than those occurring in patients not undergoing surveillance (236). Surveillance increases life expectancy due to earlier cancer detection (214). The death rates in patients with cancers detected in and out of surveillance programs are 11% and 60%, respectively (236).

Patients who develop colorectal carcinoma when under surveillance develop them mainly in the left colon (237,238). Most failures in surveillance programs, as evidenced by the presence of extensive cancer, usually develop in individuals who are referred for the first time for colonoscopic surveillance screening. Such patients have often been lost to follow-up before they were eligible for surveillance or had been remote from the medical system (214).

Since areas of dysplasia and cancer are equally distributed throughout the colon, total colonoscopy is required to detect their presence. The best method of surveillance involves regular colonoscopy, allowing visualization and biopsy of the entire colon. A recent consensus statement provides guidelines for surveillance in patients with IBD (239). In patients with UC, an initial screening colonoscopy should be performed 8 to 10 years after the onset of symptoms, following which a regular program of surveillance should begin. Patients with extensive colitis or left-sided colitis who have a negative screening colonoscopy should be seen within 1 to 2 years. With two negative examinations, the screening interval may be increased to up to 3 years until the disease duration reaches 20 years. At this time the surveillance interval should be decreased to every 1 to 2 years since the risk for colon cancer increases with long duration of colitis (240). Patients with primary sclerosing cholangitis should undergo initial screening colonoscopy at the time of diagnosis of PSC, and then should have annual surveillance colonoscopy thereafter. Individuals with only ulcerative proctitis (no macro- or microscopic disease proximal to 35 cm) may be screened according to the guidelines for colorectal screening for the general population.

P.668
Abnormal findings on surveillance colonoscopy are followed up in a variety of ways depending on the degree of dysplasia present. All diagnoses of dysplasia should be confirmed by an experienced gastrointestinal pathologist.

**Indefinite for Dysplasia**

Patients with confirmed diagnoses indefinite for dysplasia should be followed up with repeat surveillance colonoscopy in 3 to 6 months.

P.669
Controversy exists about the management of low-grade dysplasia because the natural history of this lesion is unknown. For patients complying with a strict surveillance program, finding flat low-grade dysplasia during surveillance may not carry the same high risk of progression to high-grade dysplasia or cancer as finding flat low-grade dysplasia on initial screening examination (241,242). There is evidence that with low-grade dysplasia as the worst histologic diagnosis at colonoscopy, an unrecognized synchronous colorectal cancer may already be present in up to 20% of individuals (241,243). Therefore, competing options should be discussed with each patient. A prophylactic colectomy should be offered given the possibility of a synchronous adenocarcinoma, particularly if the number of colonoscopic biopsies is insufficient.

A patient confirmed to have multifocal flat low-grade dysplasia (two or more biopsies from a single surveillance examination) or repetitive flat low-grade dysplasia (two or more examinations with at least a single focus of low-grade dysplasia) should be strongly encouraged to undergo prophylactic total proctocolectomy. Regardless of the focality of flat low-grade dysplasia, if colectomy is deferred and the patient elects to continue with surveillance, a repeat examination should be performed within 3 months and no later than 6 months from the discovery of the low-grade dysplasia. Repeat examinations should include sufficient sampling so that there is no error in the histologic diagnosis. A subsequent negative examination is not sufficiently reassuring to return to routine surveillance (242,243). Therefore, continued examinations at 6-month or shorter intervals should be pursued.

Patients with high-grade dysplasia should undergo total proctocolectomy given the high rate of synchronous and metachronous adenocarcinoma associated with this diagnosis (241,244).

Raised lesions encountered within areas of colitis may include one or more polyps that visually resemble sporadic adenomas and may be amenable to complete polypectomy (245). If polypectomy is complete and biopsies of surrounding mucosa (four biopsies taken immediately adjacent to the raised lesion and submitted separately) are negative for dysplasia and there is no dysplasia elsewhere in the colon, a follow-up examination should be performed within 6 months, with regular surveillance resumed if no dysplasia is found. However, if dysplasia is present in the surrounding mucosa, or if the dysplastic polypoid lesion is unresectable or does not resemble a typical adenoma, a high risk of associated synchronous colorectal cancer would justify recommending complete proctocolectomy.

The surveillance approach to patients with colonic CD is similar to that of patients with UC (239). Patients with CD...
confined to the small intestine are not considered to have an increased risk for colorectal cancer, and as such may be followed using the general guidelines for colorectal cancer surveillance in the general population.

**Pathologic Identification of Dysplasia**

In recent years, attention has focused on the identification of precancerous epithelial dysplasia in the large bowel as a histologic marker for identifying individuals at increased cancer risk and as a potential indicator for patients who should undergo colectomy. However, diagnosing dysplasia is a complex process due to the fact that its diagnosis is not straightforward and even experienced pathologists may disagree as to whether a change represents dysplasia or not. The diagnosis of dysplasia is difficult due to the recurrent and persistent inflammatory changes associated with the underlying IBD.

In 1983, the Inflammatory Bowel Disease—Dysplasia Morphology Study Group focused its attention on (a) developing standardized definitions of terms pertaining to IBD and dysplasia, (b) establishing criteria for diagnosing dysplasia and for differentiating it from other epithelial changes occurring in IBD, (c) developing a system for grading and classifying dysplasia, (d) assessing the accuracy and precision of the grading system for dysplasia, and (e) formulating guidelines for the clinical management of IBD patients (234). The classification scheme developed by this group is still in use today, with some modifications. The classification system contains three major categories: Negative for dysplasia, indefinite for dysplasia, and positive for dysplasia (Table 11.24). The study group defined dysplasia as an unequivocal neoplastic alteration of the intestinal epithelium (Fig. 11.110). Dysplasia presents with various gross appearances, including (a) a flat mucosa that is unremarkable except for loss of mucosal folds (Fig. 11.108), or that has a granular or pebbly appearance (Fig. 11.108); (b) a velvety appearance due to mucosal villiform transformation (Fig. 11.112); and (c) a spectrum of plaques (Fig. 11.111), nodules, and other polypoid excrescences that may resemble adenomas (Fig. 11.113). The dysplasia is itself neoplastic and may coexist with an invasive malignancy.

**FIG. 11.112.** Appendiceal cystadenoma in inflammatory bowel disease. *A:* Note the large, plaquelike cecal lesion, which represents a dysplasia-associated lesion or mass. Its borders are indicated by the *arrows*. The extension to the left of the photograph represents the appendix (AP). The AP contained a papillary noninvasive neoplasm, which is seen best in B when it is cut in cross section. *B:* Several serial cross sections of this papillary lesion are shown. *C:* Histologic features of this papillary cystadenoma.

<p>| TABLE 11.24 Biopsy Classification of Dysplasia in Inflammatory Bowel Disease |</p>
<table>
<thead>
<tr>
<th>Negative for dysplasia</th>
<th>Positive for dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mucosa</td>
<td>Low-grade dysplasia</td>
</tr>
<tr>
<td>Inactive (quiescent)</td>
<td>High-grade dysplasia</td>
</tr>
<tr>
<td>Active colitis</td>
<td></td>
</tr>
</tbody>
</table>

Histologically, one bases the diagnosis of dysplasia on a combination of microscopic features, including architectural alterations that exceed those resulting from reparative processes and cytologic abnormalities (Fig. 11.110). The architectural alterations often result in glandular arrangements that may resemble adenomas. The cytologic abnormalities principally consist of cellular and nuclear pleomorphism, nuclear hyperchromatism, loss of nuclear polarity, and marked nuclear stratification (Fig. 11.110) (234). Epithelium negative for dysplasia appears completely normal or it exhibits a range of destructive or regenerative changes. These result from the recurrent episodes of ulceration and repair characteristic of both forms of IBD.

FIG. 11.113. Adenomatous polyp occurring on the background of ulcerative colitis. A: The gross specimen demonstrates the presence of areas of scarring, pseudopolyp formation, and adenomatous growth, which is indicated by the arrow. B: Histologic sections through the adenoma show the presence of typical adenomatous epithelium. In addition, there were areas of dysplasia in the surrounding bowel mucosa.

**Mucosa Indefinite for Dysplasia**

Various factors alter the mucosa, making it impossible to classify some epithelial changes as unequivocally positive or negative for dysplasia. Odd growth patterns and unusually florid areas of active inflammation and/or regeneration may be classified as equivocal for dysplasia. In other cases, the use of picric acid– or mercury-based fixatives that enhance nuclear details creates worrisome nuclear hyperchromasia (234). The diagnosis of “indefinite for dysplasia” is made when the cytologic changes appear to exceed what one would expect to see in an active colitis but are insufficient for a definitive
diagnosis of dysplasia.

When the reparative processes associated with active colitis reach the point where the epithelium appears columnar, the chance of confusing regenerative atypia with dysplasia increases. At this stage the nuclei tend to acquire more chromatin, particularly around the nuclear membranes; they become elongated and may retain large eosinophilic nucleoli. (Mitoses can be found in both regenerating and dysplastic mucosa and they do not distinguish between regeneration and dysplasia.) If the nuclei are increased in number and are markedly stratified, the appearance may be so similar to dysplastic epithelium that a part of a single crypt examined in isolation, as in biopsy material, may be difficult to distinguish from true dysplasia (Fig. 11.114). In large biopsies, one might be able to evaluate the overall histologic context in which the changes are occurring. In such biopsies, one often observes a junction between the regenerating epithelium and the nonulcerated epithelium in the same or adjacent crypts, allowing one to diagnose such areas as reactive. In small biopsies, this may be impossible. Reparative changes may be particularly exuberant in children and young adults (234).

FIG. 11.114. Mucosa indefinite for dysplasia. This biopsy could be interpreted as indefinite for dysplasia, probably reactive. The gland at the far left (arrow) contains more mucin than the glands immediately to its right. In addition, it exhibits much less nuclear stratification at the same level in the mucosa. For this reason, the glands to the right of the one indicated by the arrow might be interpreted as indefinite for dysplasia, probably reactive, because the nuclear features are not atypical, and yet the epithelium shows more nuclear stratification and less mucin production than the gland to its left in the absence of any evidence of active inflammation.
Unusual growth patterns may also cause concern because they are commonly observed in colons harboring definite areas of carcinoma or dysplasia, but they have not been observed to give rise directly to invasive carcinoma. In one of the patterns, the crypts fail to differentiate into normal mature cell types and the nuclei appear uniformly enlarged. This pattern is recognized by the presence of columnar epithelium and a marked reduction in the number of goblet cells (Figs. 11.115 and 11.116) (234). Whether such crypts contain absorptive cells only or only relatively undifferentiated intermediate cells is unknown. In one variant of this pattern, every cell contains small mucin droplets. In another variant, goblet cells become rounded and displaced from the luminal aspect of the crypt. As a result, they resemble signet ring cells. Such cells are called dystrophic goblet cells. Dystrophic goblet cells may occasionally be found in nondysplastic mucosa, but when they are numerous they should alert one to the possibility of the presence of dysplasia.

In other specimens, the superficial parts of the crypts contain a serrated or saw-toothed pattern similar to that seen in sessile serrated and hyperplastic polyps, or they may acquire a villous architecture but lack the classic changes seen in villous adenomas. A complete spectrum of epithelial alterations exists in these serrated lesions, ranging from negative for dysplasia (Fig. 11.117) to clear-cut dysplasia (Fig. 11.118). The dysplasia is often confined to the basal portion of the crypts, with the upper part containing more mature cells and a serrated pattern, but the entire thickness of the mucosa may be involved. Villous lesions are likely to be dysplastic. As with other unusual growth patterns, the presence and the degree of dysplasia should be determined principally on the basis of the nuclear features. These lesions often resemble serrated adenomas.
FIG. 11.116. Indefinite for dysplasia. This epithelium, like that in Figure 11.115, shows no evidence of glandular maturation. In contrast to Figure 11.115, the nuclei appear more hyperchromatic and they contain enlarged, prominent nucleoli. One cannot be certain that this does not represent the end part of a regenerative process.

Another pattern that sometimes causes difficulty and places lesions in the “indefinite for dysplasia” category is the presence of unusual lesions covering prominent lymphoid follicles (Fig. 11.119), usually in the rectum. Often, the crypts overlying these follicles appear markedly distorted and exuberant regeneration of the surface epithelium is present. This complex arrangement may mimic dysplasia.

Finally, in other cases, the epithelium shows features of dysplasia, but because they are associated with prominent active inflammation in a background of a regenerating mucosa or because the nuclear features do not cross a person’s threshold for neoplasia (Fig. 11.120), one is not completely certain that the lesion is not reactive. Although it may be possible to diagnose dysplasia in the presence of acute inflammation and ulceration, one should exercise extra caution under these circumstances and be absolutely certain that dysplasia is present before making the diagnosis.

P.673
FIG. 11.117. Indefinite for dysplasia, serrated glandular pattern. A and B represent two separate lesions with glandular serration. A: The epithelium mostly resembles that seen in hyperplastic polyps and is probably not dysplastic. B: The serrated pattern is more prominent with glandular hyperplasia and occasionally dystrophic goblet cells. This pattern represents an area truly indefinite for dysplasia.

**Mucosa Positive for Dysplasia**

By definition, the category “positive for dysplasia” includes mucosa that is unequivocally neoplastic. This diagnosis therefore indicates that a lesion may be associated with, or may subsequently give rise to, an invasive adenocarcinoma. Although invasive carcinoma is probably more common in cases with severe or high-grade dysplasia, it may also be found in colons containing lesser degrees of dysplasia. Operationally, dysplasia is divided into low-grade and high-grade forms based on its degree of deviation from normal colonic epithelium.
FIG. 11.118. Villiform changes. A: Ulcerative colitis with an area of villous dysplasia resembling a villous adenoma. This was one of multiple areas of low-grade dysplasia in the bowel of this patient with a long history of pancolitis. B: Area of unusual villiform transformation (left) with atypia at the basal part of the mucosa (right) and evidence of maturation toward the surface. It is indefinite for dysplasia, probably positive.

Low-grade Dysplasia

Low-grade dysplasia is characterized by mucosal changes resembling those found in adenomas (Figs. 11.120 and 11.121). The involved crypts usually appear uniformly lined by tall epithelial cells with elongated hyperchromatic pseudostratified nuclei that evidence failure to differentiate into normal goblet cells and absorptive cells at the free surface. Some mucin may be produced by the neoplastic cells, but it is usually reduced in amount. Dystrophic goblet cells may be present. The surface of low-grade dysplasia may be villous or flat (Fig. 11.121). Mitotic activity is unrestricted and is found at all levels of the low-grade and high-grade dysplastic crypt. However, some basal polarity of the nuclei is maintained in low-grade lesions. Low-grade dysplasia can be accompanied by endocrine cell hyperplasia and Paneth cell metaplasia. Acute inflammation should be minimal.

FIG. 11.119. Follicular proctitis. A: The epithelium overlying the lymphoid follicle is simplified. It has some resemblance to the incomplete maturation shown in Figure 11.52. However, evidence of goblet cell differentiation is seen. This does not represent a dysplastic change. B: A prominent hyperplastic lymphoid follicle is seen at the junction of the mucosa and submucosa (left). Overlying this is a mucin-depleted gland with some nuclear stratification (right). This lesion is probably reactive in nature.
FIG. 11.120. Low-grade dysplasia. Sections of two glands are seen along their longitudinal axis. The epithelium becomes progressively cytologically more atypical as one proceeds from the left-hand portion of the photograph to the right-hand part. The nuclear changes increase as one progresses in this direction, as does the degree of nuclear disorganization. The gland on the left does not contain any definite dysplasia despite the presence of occasional enlarged nuclei with irregular chromatin. The right-hand gland shows changes on its left side that could be diagnosed as indefinite for dysplasia, probably dysplasia, due to the nuclear stratification and the irregularity. The right-hand portion of this gland is definitely a low-grade dysplasia, as evidenced by the jumbled architectural arrangement of the nuclei, the presence of dystrophic goblet cells, nuclear stratification, and the increased nuclear:cytoplasmic ratios.

FIG. 11.121. Low-grade dysplasia. The dysplastic epithelium lies at the superficial portions of the mucosa, resembling that seen in an ordinary tubular adenoma.

When the dysplastic epithelium is restricted to the upper portion of the mucosa, one sees a disturbed pattern of cellular maturation as evidenced by the presence of large numbers of mitotically active cells near the free surface (Fig. 11.121). Crypt architecture tends to be preserved, and distortion, if present, is mild; the nuclei may be stratified, particularly near the base of the crypts, but this stratification does not reach the crypt lumen; nuclei are crowded and hyperchromatic (234).

Most examples of low-grade dysplasia pose few diagnostic problems because they bear a strong histologic resemblance to tubular adenomas (Fig. 11.121). Potential problems in diagnosing low-grade dysplasia exist at either end of the spectrum. It may be difficult to decide whether a biopsy specimen should be classified as “indefinite for dysplasia” or as “low-grade dysplasia.” However, this is of no
consequence since both diagnoses require an early repeat biopsy. At the other end of the spectrum are specimens that contain areas of both low- and high-grade dysplasia; in these it is best to rate the lesion according to the higher grade (234).

**High-grade Dysplasia**

In most cases, the diagnosis of high-grade dysplasia is relatively straightforward. The distinction from low-grade dysplasia depends primarily on the degree of cytologic atypia present. High-grade dysplasia shows true nuclear stratification. The level of the nuclei in the epithelium helps distinguish low-grade from high-grade lesions (Fig. 11.122). In contrast to low-grade dysplasia, in which fairly regular nuclei are confined to the basal halves of the cells, most cases of high-grade dysplasia show nuclear stratification that extends beyond the midportion of the cells. High-grade dysplasia also evidences a greater degree of cytologic variability (Figs. 11.122 and 11.123), nuclear hyperchromasia, and pleomorphism, and the epithelium more resembles the cells seen in invasive cancers than the regular tall cells of adenomas. In high-grade dysplasia, the nuclei lose their polarity, and instead of being elongated with the long axis of the nucleus perpendicular to the basement membrane, the nuclei round out and develop prominent nucleoli. High-grade dysplasia often coexists with low-grade dysplasia, and there is a tendency for the cells to form expansile nests that appear to push the cells with an adenomatous appearance to the side. In some patients villous dysplasia is present (234). The category “high-grade dysplasia” includes carcinoma in situ. One recognizes carcinoma in situ by the presence of a cribriform glandular pattern (Fig. 11.123). DALMs usually contain high-grade dysplasia (Fig. 11.123).

**FIG. 11.122. Dysplasia.** A: Low-grade dysplasia. The hyperchromatic nuclei occupy less than one half of the distance of the epithelial height. B: High-grade dysplasia with nuclei extending all the way to the lumen of the gland and early glandular budding. C: High-grade dysplasia with nuclear irregularity and a back-to-back cribriform pattern.

One judges the severity of the dysplasia based on the worst changes present and not the predominant ones. However, the appearance of high-grade features in just one or two crypts probably does not justify upgrading the dysplasia into a higher category if this is all that is present (234). As a general rule of thumb, evidence of dysplasia in three crypts or more is sufficient for the diagnosis.

**Polypoid Areas of Dysplasia and Adenomas in Inflammatory Bowel Disease (Dysplasia-associated Lesions or Masses)**

By convention, the dysplastic tissue that precedes the development of carcinomas in sporadic colon cancer is referred to as an adenoma, whereas polypoid areas of dysplasia occurring in the setting of IBD are diagnosed as DALMs.
FIG. 11.123. High-grade dysplasia. A: A whole mount section of the lesion. The entire surface of the colon is replaced by dysplastic epithelium. It is seen in higher magnification in B. B: Portion of the mucosa as it joins the submucosa, indicating that this back-to-back configuration remains confined to the area above the muscularis mucosae.

True adenomas similar to those seen in non-IBD patients may be encountered in IBD patients, particularly in patients over age 40 (Fig. 11.124). The incidence of adenomas increases in this age group, just as it does in the normal population, and the presence of an adenoma may have nothing to do with the underlying IBD. However, the significance of isolated polypoid adenomas in patients with UC remains controversial. The major difficulty concerns patient management and follow-up. The options are to treat IBD patients with adenomas found in the setting of IBD as polypoid areas of dysplasia, and interpret them as signals for the presence of synchronous or subsequent carcinoma. Alternatively, they could be regarded as having a significance no greater than that of the sporadic adenoma in the general population. In such patients it is important to determine whether additional dysplasia is present in the nonpolypoid mucosa. If the dysplasia is confined to the polypoid lesion in a well-sampled colon, then it may be possible to treat the patient as one would treat a noncolitic patient with an adenoma. If the dysplasia is present in the adenoma and in the surrounding mucosa or elsewhere in the bowel, then the case must be considered as dysplasia in the IBD setting (Fig. 11.125).

**Dysplasia in Inflammatory Pseudopolyps**

Dysplasia in inflammatory pseudopolyps is rare, but it does occur. As with the nonpolypoid mucosa, an entire spectrum of features, ranging from inflammatory changes to high-grade dysplasia, may exist in inflammatory pseudopolyps. The major problem is that the polyps frequently have areas of residual regeneration that may be difficult to distinguish from true dysplasia. When dysplasia is suspected in what appears to be an inflammatory pseudopolyp, additional specimens obtained from the surrounding flat mucosa should be examined to determine whether the polyp is part of a larger area of dysplasia (234).

**Agreement on the Diagnosis of Dysplasia**

The degree of observer variation in detecting and grading dysplasia in the setting of UC, even among experienced pathologists, is poor. The best agreement is for slides that show no dysplasia. The level of agreement in the diagnosis of dysplasia varies depending on how it is assessed. The agreement between whether dysplasia is present or absent is better than agreement among various degrees of dysplasia; it ranges from 68% to 84%. The level of agreement for “atypia present” (including reactive atypia and low- and high-grade dysplasia) versus “no atypia” achieves a consensus of >90%. Agreement on the diagnosis of high-grade dysplasia ranges from 100% to as low as 33% (246). Nonetheless, dysplasia does represent a successful marker in clinical practice. Pathologists should have access to previous slides from the same patient and adequate clinical information before reporting biopsies as positive for dysplasia because of the clinical implications of the diagnosis.
FIG. 11.124. Portion of a polypoid mass in a patient who underwent resection for dysplasia and ulcerative colitis. The patient had numerous other areas of dysplasia. The lesion resembles a sporadic adenoma.

FIG. 11.125. Polypoid dysplasia in a patient with ulcerative colitis. A: Low-power view showing a polypoid area of dysplasia resembling somewhat an adenomatous polyp. B: The adjacent flat mucosa, however, also shows low-grade dysplasia. This finding confirms that the polypoid dysplasia is inflammatory bowel disease associated and not a sporadic adenoma.

Ancillary Tools for Diagnosing Dysplasia
Because of the difficulty in reliably diagnosing dysplasia, various alternative approaches have been employed to make the diagnosis more objective. These techniques have included the use of enzyme assays, immunophenotypic markers, ultrastructural examination, immunohistochemistry, flow cytometry, genetic probes, and mucin and lectin staining. Markers such as carcinoembryonic antigen, secretory component, and epithelial IgA are not useful in distinguishing regenerative from dysplastic lesions (246). To date, of the markers that predict subsequent cancer development, clearly histologic identification of dysplasia continues to be the best predictor.

**Mucin Stains**

Mucins have also been used to distinguish dysplastic from regenerative changes. Sialomucins increase in UC and dysplasia (247,248). However, since sialomucins increase in both inflammatory dysplasia and cancer, they are not specific for a diagnosis of neoplasia.

**Flow Cytometric Analysis**

Cellular aneuploidy represents a common development in the pathway to dysplasia and cancer in UC. The degree of DNA aneuploidy correlates well with the presence and grade of dysplasia (249,250,251,252,253). Detailed mapping studies carried out on colectomy specimens show that as many as 14 or 15 different and overlapping regions of aneuploidy may be present in the colonic mucosa (253). The presence of multiple aneuploid stem cell lines suggests that a high level of genomic instability is present and that the patient probably has a higher risk of progressing to colorectal carcinoma (253). Although dysplasia correlates closely topographically with DNA aneuploidy, aneuploidy also occurs without concomitant dysplasia. Changes in nuclear DNA content occur earlier than dysplasia and malignant transformation of the colorectal mucosa in UC. Aneuploidy also occurs in 2% of biopsies from mucosa classified as normal (252) and in 10% to 42% of biopsies with inflammation, hyperplasia, or atrophy; in 20% to 100% of polyps and in biopsies with dysplasia; and in the majority of adenocarcinomas. The presence of aneuploidy in nonneoplastic mucosa may help select patients who should undergo surveillance colonoscopies. Approximately 32 biopsies are required to achieve a 90% confidence that a histologic abnormality is detected or about 55 biopsies for a 95% confidence. Similarly, a total of 20 biopsies analyzed flow cytometrically are required for a 90% confidence that aneuploidy will be detected if present, and 30 biopsies for a 95% confidence (220). These levels are clearly not within the realm of what can be done for standard diagnostic purposes.

**Proliferative Markers**

We have found that because cell proliferation is abnormally regulated in neoplastic lesions, immunostaining in problematic areas with MIB-1 immunostains helps to delineate areas of dysplasia from a regenerative mucosa. Statistically significant differences in the pattern of MIB-1 immunoreactivity occur between nonneoplastic and neoplastic lesions. In regenerative mucosa, MIB-1 immunoreactivity localizes to the bases of crypts and the proliferative zone appears expanded. In dysplasia, immunoreactivity is prominent in the cells in the superficial mucosa as well as in the crypt base. In some dysplasias and all invasive carcinomas, MIB-1 staining is diffusely distributed throughout the crypts, suggesting complete deregulation of normal cell proliferation. Additionally, the intensity of the staining and the percentage of cells staining positively tend to be greater in areas of dysplasia (120,254,255).

**Carcinomas**

Carcinoma in UC commonly arises throughout the colon. It may develop in multiple sites, and it often does not produce clear-cut symptoms before advanced disease has developed. Cancer may also arise in the retained rectum after colectomy. Patients with cancer or dysplasia in the colon at the time of colectomy are at increased risk for the later development of rectal cancer (256).

**Gross Features**

Most carcinomas develop in areas of macroscopic disease. The gross appearance of the neoplasms may resemble ordinary intestinal carcinomas arising on an atrophic but grossly more or less normal bowel (Fig. 11.126). Often the tumors are flat or slightly depressed, poorly circumscribed, and spreading, and can be more easily felt than seen (Figs. 11.127 and 11.128). In this regard, they resemble gastric cancer of the diffuse type. In some instances, the lesions appear somewhat raised.
Histologic Features

Intestinal stem cells may become hyperstimulated due to the inflammation inherent in IBD, which leads to hyperplasia or neoplastic transformation. Such a process could explain the broad spectrum of tumor types that arise in IBD, including adenocarcinomas, small cell carcinomas, and carcinoid tumors (257,258,259,260). It can also explain the presence of widespread dysplasia and the occurrence of multiple carcinomas and multiple carcinoid tumors that one sees in the setting of IBD. Intramucosal carcinoma falls within the realm of high-grade dysplasia. Intramucosal carcinomas may represent focal lesions or may be present diffusely in large patchlike areas. Very exceptionally, one encounters a form of intramucosal carcinoma analogous to that seen in the stomach, in which signet ring cells infiltrate the lamina propria but do not extend beyond the muscularis mucosae (Fig. 11.129). The metastasizing potential of this lesion is unknown.

Adenocarcinomas arising in a setting of UC may show any degree of histologic differentiation (Figs. 11.130, 11.132, and 11.133), but there is a higher proportion of poorly differentiated and mucinous tumors in IBD patients as compared to sporadic colon cancers. In one study, 54% of tumors had mucinous features and 27% had signet ring cells (216). Mucinous and signet ring cell features are as common in CD as in UC (Fig. 11.134). In CD, dysplasia and cancer may be exclusively located in the small bowel, whereas other cases may be found in the colon.
FIG. 11.127. Superficially invasive carcinoma developing in ulcerative colitis. A: This carcinoma would have been impossible to find had one not palpated the bowel and/or examined cross sections of it. The specimen was bread-loafed. These serial, several-millimeter cross sections demonstrate an area of whitish discoloration that extends into the underlying submucosa corresponding to the invasive cancer (B). C: A section from a second slice from the lesion showing the invasive carcinoma. This bowel had four other invasive carcinomas. The pen marks on the slide in B and C indicate the area of cancer. Carcinoma extends into the submucosa in both of these areas. Dysplasia surrounds the invasive cancer.

Carcinoid tumors affect both sexes equally. Patients also develop single (257) or multiple microcarcinoids, sometimes in association with synchronous carcinomas (258). The neoplasms tend to occur in inflamed areas or in tissues that show evidence of previous damage. Microcarcinoids measure <2 mm in diameter and are not generally grossly visible. These resemble gastric microcarcinoids seen in patients with autoimmune gastritis and pernicious anemia (258).

FIG. 11.128. Carcinoma extending into the submucosa. Note that the surface is covered by a broad area of dysplasia. An invasive carcinoma underlies the dysplasia. No dysplasia-associated lesion or mass is present in this area.

The coexistence of an intestinal carcinoid (incidence 1 to 1.3 per 100,000) and UC incidence (2 to 10 per 100,000) or CD (1 to 6 per 100,000) could be fortuitous (261) because the clinical profile of patients resembles that of patients with sporadic carcinoid tumors. Some patients have a long history of CD or UC with extensive involvement of their bowels when their carcinoid is first described and others have a relatively short history (618). Adenocarcinoid tumors also arise in pre-existing UC (261).

**Role of Cytology in Ulcerative Colitis**

Brush cytology of the colon and rectum may aid in cancer detection in IBD patients (262), especially in patients with strictures or in whom there is widespread neoplasia. The malignant cells show marked
anisocytosis, pleomorphism, and nuclear hyperchromasia, and appear in loosely cohesive clusters or in single forms in an inflammatory and necrotic background. In some cases, moderate or severe atypia is found in brushing specimens when biopsies only reveal mildly reactive changes. The two diagnostic techniques are complementary to one another (263).

**Prognosis**

Some have said that cancers arising in the setting of UC behave more aggressively than sporadic colon cancers. Poor prognosis results in part due to the difficulty of early diagnosis of cancer in these patients and because the patients are often young and the cancers are highly malignant. Others have shown that there is no significant difference in 5-year survival among colitis and noncolitis patients with colorectal carcinoma when matched for stage (262). Multivariate analysis shows that the stage is the best prognostic indicator, followed by tumor differentiation and DNA ploidy status. Tumor location, number of cancers, duration of disease, age, and sex do not correlate with prognosis (216). Other factors associated with significantly poorer prognosis include larger tumor size, infiltrating and ulcerating configuration, and higher mucin content.

**Extraintestinal Cancers**

Patients with IBD have an increased incidence of extraintestinal carcinomas. The extraintestinal neoplasms may coexist with intestinal carcinomas. The proportion of extraintestinal cancers is greater in CD than UC, 43% versus 12%. The incidence of gastrointestinal cancer increases with duration of disease in both CD and UC, but extraintestinal cancers show less correlation with increasing disease duration. Extraintestinal cancers include cancers of the breast, thyroid, bladder, brain, skin, stomach, hepatobiliary system, lymph nodes, larynx, and uterus, and Kaposi sarcoma (264,265,266).

Patients with IBD show an increased risk of reticuloendothelial neoplasms with an excess of leukemias in UC and an excess of lymphomas in both UC and CD. Additionally, there is an increased incidence of squamous cell cancers of the perianal region, an incidence 30 times greater than expected, as well as an increased incidence of squamous cell cancers of the vagina. Lymphomas, leukemia, squamous cell carcinomas, and Kaposi sarcoma all occur in excess in immunosuppressed or irradiated patients. Thus, one can speculate that the increased incidence of these neoplasms in patients with ileitis and colitis may result from underlying immunologic deficiencies associated with IBD, or to the long-term administration of steroids or other immunosuppressive medications.

Atypical lymphoid lesions and true lymphomas complicate both UC and CD (265,267,268,269). Lymphomas range in incidence from 0.43% in UC to 0.27% in CD. UC patients sometimes develop gastrointestinal and extraintestinal non-Hodgkin lymphoma. These tumors represent a heterogeneous group with tumors displaying both B-cell and T-cell phenotypes, although lymphomas complicating UC are usually B-cell lesions.

Squamous cell carcinoma in situ (Fig. 11.135) and invasive squamous carcinoma arise in both CD and UC, but they are more common in the setting of CD (270). Most commonly, they associate with fistulae or they occur in the anal region.

**Molecular Changes Associated with Cancer Development**

Cancer development in IBD is a multistep process and the molecular abnormalities have been better defined in UC than in CD. Numerous genetic alterations exist in dysplasias and carcinomas arising in IBD.
patients. Molecular abnormalities also exist in mucosa that is not obviously dysplastic, suggesting that their identification may serve as an aid to predicting increased cancer risk in IBD patients. These involve many of the same genes that are abnormal in sporadic colorectal tumors. These include multiple sites of allelic deletion, microsatellite instability (271,272,273,274,275,276,277), telomere shortening (278,279), and mutations of SMAD2, SMAD4 (280), and p53 genes (281,282,283). Ras, APC, and DPC4 mutations are more common in IBD-associated neoplasia than in sporadic colorectal cancers (284,285). The frequency and order of genetic alterations in UC-associated colon carcinomas may differ from those seen in sporadic tumors, suggesting that neoplastic progression in UC might proceed by different mechanisms than in sporadic cancer.

Chromosomal Instability

Chromosomal instability in IBD occurs at many sites. Fluorescence in situ hybridization (FISH) has demonstrated losses or gains on chromosomes 8, 11, 17, and 18 in patients with IBD-associated dysplasia or cancer. These chromosomal changes precede the development of histologically identifiable dysplasia, supporting the concept of a large field effect with a mutator phenotype in these patients. Comparative genomic hybridization studies also show widespread chromosomal instability in patients with IBD-associated neoplasia. Such studies have also shown loss on chromosome 18q, the site of the deleted in colon cancer (DCC) gene, SMAD2, and SMAD4 (273,286). Chromosomal instability in colonic mucosa from UC patients has also associated with telomere shortening (279). Telomere alterations are also seen in nondysplastic mucosa from patients who ultimately progressed to develop dysplasia or carcinoma (278).

FIG. 11.132. Carcinoma arising in ulcerative colitis. Some carcinomas appear to drop off the mucosa and invade the underlying submucosa. In this photograph, the overlying epithelium appears villiform without significant dysplasia. A microinvasive carcinoma extends into the underlying submucosa. The invading glands appear neoplastic.

**p53 Alterations**

Numerous studies have shown that p53 overexpression and/or mutation occur in various colonic lesions in patients with ulcerative colitis (281,282,283,287). p53 mutations occur in from 0% to 29% of nonneoplastic colonic mucosa, 3% to 41% of lesions indefinite for dysplasia, 30% to 75% of dysplasias, and 41% to 100% of carcinomas (282,283,288,289). p53 overexpression is reported with a somewhat higher frequency than p53 mutation. Interestingly, increased levels of p53 have recently been reported in the serum of UC patients (290). The significance of this finding is not yet clear.
FIG. 11.133. Invasive ileal carcinoma in a patient with Crohn disease. The tumor appears so well differentiated that it might be difficult to distinguish from displaced epithelium. This tumor had infiltrated the entire ileal wall and had metastasized to the regional lymph nodes.

FIG. 11.134. Colonic adenocarcinoma in a patient with Crohn disease. The tumor cells are poorly differentiated and infiltrate as single cells, some of which have a signet ring appearance.

Microsatellite Instability

Studies of microsatellite instability (MSI) in IBD have shown variable and even discordant results. These studies are difficult to compare, as the types of patients studied, the methods used, and the samples analyzed vary tremendously among studies. In addition, the microsatellite markers used and criteria defining MSI are also highly variable among studies.

Overall, it appears that MSI does play some role in IBD-associated neoplasia, but this role is probably not the same as that associated with sporadic colorectal cancers. Ulcerative colitis cancers may not display as high a level of MSI as is seen in sporadic colon cancers, and sites of MSI in IBD versus sporadic colonic neoplasia appear to differ. For example, transforming growth factor-β receptor II mutations are common in sporadic MSI-high colon cancers, while islet cell autoantigen 1 (ICA1) mutations are more frequent in UC (274). In addition, the underlying causes of instability in IBD may be different. In sporadic
colorectal cancers, MSI results most commonly from hMLH1 promoter hypermethylation. In contrast, hMLH1 methylation is less common in MSI-positive tissues from IBD patients (291).

Finally, MSI in ulcerative colitis is commonly of the low type (MSI-L). Interestingly, studies have shown that oxidative injury may inactivate the mismatch repair system in a dose-dependent fashion, providing an explanation for the higher frequency of MSI-L in UC (292).

Methylation
An increasing number of genes are being described whose silencing through promoter methylation occurs in IBD-associated neoplasia. High levels of methylation occur in the estrogen receptor, MyoD, p16, p14, E-cadherin, and CSPG2 genes in IBD-associated dysplasia (293,294,295,296,297,298,299). In addition, some of these genes are hypermethylated in nondysplastic tissues from IBD-related cancer patients. Methylation abnormalities are not observed in the colonic tissues of UC patients without dysplasia or cancer, raising the possibility that some of these markers could be useful for IBD surveillance.

Specimen Handling
Resection specimens are received for one of two major reasons: (a) the bowel has developed acute complications as a result of the inflammatory process, including obstruction, perforation, fistula formation, toxic megacolon, or concomitant ischemia or infection; or (b) the development of carcinoma or dysplasia. The approach to handling the specimen varies, depending on the reason for the resection. Those specimens removed for inflammatory complications that demonstrate perforations or changes out of proportion to the rest of the disease should be searched for evidence of ischemia and/or viral infections.

In resections that are done in patients with longstanding disease who harbor areas of dysplasia or carcinomas, it is helpful to record and photograph all of the pertinent features present in the mucosa and to extensively sample unusual lesions, particularly those that are polypoid or firm. Because cancers develop in multiple sites and because they are hard to detect, it is helpful to divide the bowel into quarters and then to remove the pericolonic or peri-intestinal fat and dissect the groups of lymph nodes individually from each of the quarters. In this way, one can accurately stage individual carcinomas should more than one be present. Once the pericolonic or peri-intestinal fat has been removed from the specimen, it is helpful to palpate the intestine because carcinomas may be more easily felt than seen and all firm areas should be sampled. Although it is a tedious process, each quadrant of the bowel should be bread-loafed into several-millimeter sections and the cut surfaces examined for unusual areas of whitish discoloration that extend below the muscularis mucosae. These areas usually turn out to be carcinoma. If there are no definable lesions in the bowel, then sections should be taken approximately every 10 cm in progressive order from the right side of the bowel to the left.

The presence of dysplasia in intestinal biopsies of patients with CD should arouse the suspicion of a carcinoma and force one to take multiple sections of stricture and polypoid lesions. Detection of tumors arising in CD is difficult due to the fact that CD typically is a transmural process. Diffuse thickening of the bowel wall makes cancer detection more difficult. Additionally, neoplasms in CD patients may develop at sites remote from the bowel in fistulae and fissures.

References


Chapter 12
Polyposis and Hereditary Cancer Syndromes

Polyposis Syndromes

Introduction

Polyps develop throughout the gastrointestinal (GI) system either as sporadic lesions or as part of a polyposis or hereditary cancer syndrome. The most common syndromes are those that involve neoplastic intestinal adenomas. These include familial adenomatous polyposis, MYH polyposis, and hereditary nonpolyposis colorectal cancer syndrome. Less common polyposis syndromes involve development of hamartomas and include Peutz-Jeghers, juvenile polyposis, Bannayan-Riley-Ruvalcaba, neurofibromatosis 1, and Cowden syndromes. Another hamartomatous polyposis syndrome, Cronkhite-Canada syndrome, is nonfamilial. Other syndromes, such as hyperplastic polyposis and hereditary mixed polyposis, include both adenomatous and nonadenomatous polyps. Some rare forms of polyposis involve proliferations of lymphoid or mesenchymal tissues and are discussed elsewhere in this text.

Less than 1% of all GI malignancies result from intestinal polyposis syndromes. One classification scheme of polyposis syndromes is shown in Table 12.1. In order to diagnose a specific polyposis syndrome, one must be aware of (a) the number of polyps a patient has and their location, (b) the patient's age, (c) the family history, and (d) other clinical information that identifies a patient as having a specific syndrome. Overlap exists between several syndromes.

Hereditary Adenomatous Polyposis Syndromes

Familial Adenomatous Polyposis and Its Variants

General Comments

Familial adenomatous polyposis (FAP) (OMIM entry #175100) is a generalized growth disorder that includes intestinal polyposis as well as numerous extracolonic manifestations. Overlap exists among the different adenomatous polyposis syndromes, and the varied extraintestinal manifestations of FAP have led to confusion in their nomenclature. Gardner syndrome was the term applied to patients with colonic polyposis, epidermoid cysts, osteomas, and desmoids. Turcot syndrome was diagnosed if the patient had colonic polyposis with brain tumors. However, our current understanding of these disorders indicates that FAP, Gardner syndrome, and Turcot syndrome all represent variations of the same disease rather than distinct entities, and result from defects in a single pleiotropic gene with variable expressivity.

Genetic Features

The FAP-associated gene is located on chromosome 5, and is called APC for adenomatous polyposis coli (1,2,3,4). APC has 15 exons (Fig. 12.1) and encodes a protein of 2,843 amino acids (2,4). The large size of the gene may account for the high frequency of new mutations that occur in it. Germline mutations in APC account for most cases of FAP (2,3,5). Every cell in an FAP patient contains one inactive APC allele; an alteration in the other allele gives rise to intestinal tumors. Inactivation of the second allele occurs in the earliest recognizable phase of the tumors, including some lesions containing as few as two adenomatous crypts, confirming that inactivation of the second APC allele occurs early in neoplastic development.

APC germline mutations are notable in that they are almost exclusively single base pair (bp) changes leading to termination codons, or small (one to four bp) deletions, insertions, or splicing mutations causing translational frame shifts and subsequent downstream stop codons (2,3,6). Even though 45% of patients have detectable germline defects in exon 15, mutations are located throughout the length of the APC gene. Most mutations disrupt the coding sequence in the 5' half of the FAP open reading frame (7).

The first clue to the function of the APC protein came when immunoprecipitation experiments showed that anti-APC antibodies precipitated β-catenin (8). APC and β-catenin are part of a complex signaling pathway, the Wnt pathway, that controls many cellular processes including proliferation, differentiation, apoptosis, and body patterning during development (Fig 12.2). In addition to its role in mediating β-catenin degradation, APC also stabilizes microtubules, promoting chromosomal stability. Loss of APC function results in defective mitotic spindle formation and abnormal chromosomal segregation (10).

<table>
<thead>
<tr>
<th>TABLE 12.1 Classification of Intestinal Polyposes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial Disorders</strong></td>
</tr>
<tr>
<td>Adenomatous</td>
</tr>
<tr>
<td>Familial adenomatous polyposis and its variants</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>MYH polyposis</td>
</tr>
<tr>
<td>Multiple adenomas</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer syndrome</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Muir-Torre syndrome</td>
</tr>
<tr>
<td>Hereditary mixed polyposis</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Chapter 12

Hyperplastic polyposis

Disease Expression

Patients with FAP exhibit considerable phenotypic variability of their colonic and extracolonic lesions, even within the same family. This suggests that the nature of the inherited genetic defect is only one parameter determining patient phenotype. Inactivation of APC may provide affected cells with a proliferative growth advantage (6), allowing the colon to then acquire additional genetic abnormalities, thereby facilitating disease progression. Environmental factors may also be important. Bile from FAP patients appears to be more mutagenic than that from non-FAP patients (11), perhaps inducing secondary changes both in APC and other genes in the adenoma–carcinoma sequence (see Chapter 14). Many manifestations of FAP may be partially controlled by hormonal status and other genetic factors. Data supporting such a postulate include (a) stimulation of polyp growth during puberty, (b) adenoma inhibition by sulindac (12), (c) the preponderant development of thyroid carcinomas in women (13), and (d) the association of repeated trauma with the development of desmoid tumors (see Chapter 19).

FIG. 12.1. The APC gene with its 15 exons shown as blue boxes. Mutations occurring within the part of the gene designated by the red line result in a congenital hypertrophy of the retinal pigment epithelium (CHRPE)-negative phenotype. Those occurring in the area designated by the yellow line are associated with CHRPE lesions. The yellow arrow indicates the region of the gene in which mutations begin to result in the appearance of CHRPE lesions. The orange area of the gene is associated with formation of desmoid tumors. Mutations in the green and purple areas result in the attenuated APC and full-blown APC phenotypes, respectively. AAPC, attenuated adenomatous polyposis coli.

Relationship of APC Mutations to Disease Expression

Mutations in specific regions of APC produce different clinical phenotypes, and the length of the truncated gene product influences the severity of the colonic disease and the presence of eye lesions or desmoid tumors (Fig. 12.1). Patients with mutations toward the 3' end of exon 15 who produce longer protein products have a more severe phenotype than patients with mutations toward the 5' end of the gene (exons 3 and 4). Patients with less severe forms of the disease are referred to as having attenuated adenomatous polyposis (discussed below). Patients with the severe form of the disease tend to have large numbers of polyps that arise early in life (14,15,16). The commonly observed deletion of five

P.693

bp at codon 1309 within exon 15 associates with early onset of colon cancer (1) and the early development of colonic adenomas.
Chapter 12

FIG. 12.2. Diagram of the Wnt signaling pathway. A: In normal cells, most endogenous β-catenin is bound to the intercellular adhesion molecule E-cadherin on the cell membrane. Any unbound, cytoplasmic β-catenin is quickly targeted for degradation by a protein complex that includes the proteins Axin, protein phosphatase 2A, protein kinases GSK3β and CK1α, and APC. Phosphorylation of β-catenin by this complex targets it for ubiquitin-mediated destruction. B: Stimulation of the wnt receptor by its ligand results in the destruction protein complex, which is inactivated, allowing cytoplasmic β-catenin to enter the nucleus and interact with the Tcf family of transcription factors. The result is expression of WNT target proteins and increased cell proliferation. C: In patients with familial adenomatous polyposis, the dysfunctional APC protein disrupts the activity of the multisubunit destruction complex, and results in accumulation of free β-catenin in the cell. β-Catenin is free to enter the nucleus of the cell where it interacts with Tcf, resulting in sustained expression of c-Myc, cyclin D1, and other Wnt target proteins.

Attenuated Adenomatous Polyposis

A less severe form of FAP, known as attenuated adenomatous polyposis coli (AAPC), is characterized by a relatively low number of adenomas (15). AAPC is associated with a germline APC mutation in approximately 10% of affected patients (17). This syndrome differs significantly from classic FAP in that affected individuals have fewer adenomas that tend to cluster on the right side of the colon where they appear flat rather than polypoid. The number of adenomas varies among family members, ranging from 1 or 2 to 100. Upper gastrointestinal lesions, particularly fundic gland polyps, are almost invariably present. In addition, affected patients exhibit a reduced risk for colorectal cancer compared with those with classic FAP.

The lifetime penetrance of colon cancer is high in AAPC families, however, even among members with relatively few adenomas. When colorectal cancers do develop, they arise later than in classic FAP. The average age of colon cancer onset in AAPC patients is approximately 15 years later than that of patients with classic FAP and approximately 10 years earlier than individuals with sporadic colorectal cancer. Table 12.2 compares classic FAP and AAPC.

Clinical Features

FAP is the most frequent genetic polyposis syndrome, affecting 1 in 6,850 to 29,000 live births. It is transmitted as an autosomal dominant disorder with up to 90% penetrance. Fifty percent of the children of an affected individual and a normal individual will inherit the polyposis gene and will develop the disease. Ten to thirty percent of patients with FAP have no familial history and represent spontaneous new mutations. FAP patients develop at least a few adenomas by age 21. The adenomas almost always involve the rectosigmoid, where they tend to develop rapidly and in large numbers. Males and females are equally affected (18).

As noted above, variation in the expression of the FAP phenotype within families exists, and may result from dietary or environmental factors. Even more variation exists between families, presumably due to the fact that APC mutations occur at multiple sites in the gene and that different mutations confer different phenotypes.

Adenomas are not present at birth in FAP patients. Most affected individuals remain asymptomatic until puberty, at which time the polyps begin to appear (19). In untreated, unscreened patients, the mean age of polyp development is 24.5 years, symptom onset is 33 years, polyp diagnosis is 35.8 years, cancer diagnosis is at 39.2 years, and death from cancer averages a mean of 42 years (19). Young patients present with a small number of polyps, the number of which progressively increases with time. Eventually, the entire length of the colon becomes carpeted with adenomas. By the time a patient comes to colectomy, he or she may have hundreds to tens of thousands of polyps. Progression to cancer is inevitable; by age 30, approximately 75% of FAP patients will have developed colon carcinoma unless a prophylactic colectomy is performed. Most untreated patients die of cancer by the 5th decade of life.

TABLE 12.2 Comparison of FAP and AAPC Colorectal Cancer Syndromes
### Classic FAP vs. AAPC

<table>
<thead>
<tr>
<th>Classic FAP</th>
<th>AAPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of colonic adenomas</strong></td>
<td>Usually 1–50; seldom more than 100</td>
</tr>
<tr>
<td><strong>Gross features</strong></td>
<td>Flat or slightly elevated plaques</td>
</tr>
<tr>
<td><strong>Invisible to polypoid adenomas</strong></td>
<td>Flat adenomas</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Location of colonic adenomas</strong></td>
<td></td>
</tr>
<tr>
<td>Throughout the colon</td>
<td>Predominantly located proximal to splenic flexure</td>
</tr>
<tr>
<td><strong>Location of colon cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Throughout the colon</td>
<td>Predominantly located proximal to splenic flexure</td>
</tr>
<tr>
<td><strong>Average age of cancer onset</strong></td>
<td>39</td>
</tr>
<tr>
<td><strong>Fundic gland polyps</strong></td>
<td>55</td>
</tr>
<tr>
<td>Present</td>
<td>Almost invariably present</td>
</tr>
<tr>
<td><strong>Extracolonic cancers</strong></td>
<td></td>
</tr>
<tr>
<td>Periampullary carcinoma, papillary thyroid carcinoma, sarcomas, brain tumors, small bowel cancer</td>
<td>Periampullary carcinoma</td>
</tr>
<tr>
<td>AAPC, attenuated familial adenomatous polyposis; FAP, familial adenomatous polyposis.</td>
<td></td>
</tr>
</tbody>
</table>

Adenomas also develop in extracolonic sites, most commonly in the duodenum around the ampulla of Vater. Patients less frequently develop adenomas in the stomach or in other portions of the small intestine. Carcinomas may subsequently arise in these sites, but are relatively rare. Gastric cancers are more common in FAP patients living in parts of the world where gastric cancer rates are high. Fifty percent of Japanese FAP patients develop gastric adenomas, and gastric carcinoma is more common in these patients than ampullary cancers. In contrast, Western gene carriers exhibit a higher rate of ampullary than gastric neoplasms (20). Colonic adenomas are often present for years before giving rise to symptoms including rectal bleeding, colicky abdominal pain, diarrhea, and mucous discharge (19). Seventy-five percent of polyposis patients without cancer have rectal bleeding, and 63% have diarrhea (19). When symptoms are severe enough to cause concern, two thirds of the patients have already developed a carcinoma. Very rarely, patients develop severe electrolyte depletion as a result of diffuse polyposis (21). Acute pancreatitis develops secondary to obstruction of the pancreatic duct at the ampulla of Vater by adenomas. Intussusception due to the adenomas may also occur.

### Diagnosis of Familial Adenomatous Polyposis

The diagnosis of symptomatic patients is usually not difficult because they present with bleeding, diarrhea, or abdominal pain. Surveillance of children in affected kindreds results in earlier adenoma detection and in a lower cancer incidence. Today the tendency is to diagnose the presymptomatic individual by genetic testing and then confirm the diagnosis by sigmoidoscopy. Some advocate beginning flexible sigmoidoscopy by age 10 to 12 and continued yearly examinations until age 35 (22). Upper GI endoscopy should begin once the diagnosis of FAP is made and should be continued every 3 years thereafter in the absence of gastroduodenal adenomas (23). Genetic techniques will detect 50% of carriers of APC mutations (24). The child of an FAP patient has a 50% likelihood of inheriting the genetic mutation. Prescreening strategies can be designed to detect mutations at the 12 most commonly mutated loci, which account for nearly 40% of germline mutations in FAP patients (25). The use of DNA extracted from archival specimens of affected available FAP patients increases the number of at-risk individuals who can be diagnosed presymptomatically (25). The association of the DNA markers and the presence of congenital hypertrophy of the retinal pigment epithelium (CHRPE) make it possible to identify gene carriers even in the absence of rectal polyps. CHRPEs affect up to 90% of classic FAP patients, especially those with both upper gastrointestinal and extraintestinal manifestations (26). They may be single or multiple, bilateral or unilateral, and are easily identified on funduscopy examination. These congenital lesions are observed in very young or even preterm infants, and represent the earliest diagnostic stigma of FAP. If one family member has CHRPE, all family members with the disease will have CHRPE. Similarly, other kindreds exist in which no family members have the retinal lesions.
FIG. 12.3. Gross features of familial polyposis. A through D demonstrate the different forms this disorder may take. A: Numerous sessile, small rounded polypoid lesions are present, often on the mucosal folds. Large intervening areas of apparently normal colon are present. B: Clusters of pedunculated adenomatous polyps, larger than those seen in A, are present. They tend to pull up the mucosal folds into stalks. C: Numerous sessile and pedunculated polyps are scattered over the mucosal surface. D: The bowel is carpeted by numerous larger raspberrylike pedunculated polyps.

Cancer Development
Carcinoma invariably develops in FAP patients if the colon is not resected by age 40 or 50. Indeed, FAP is the “experiment of nature” that provides support for the colonic adenoma–carcinoma sequence (Fig. 12.3). Adenomas also represent the precursor for small intestinal cancer, but small intestinal adenomas are less likely to become malignant than are colonic lesions. Adenomas and carcinomas also develop in the retained rectum following colectomy.

Carcinomas develop approximately 6 years after symptom onset. The incidence of carcinoma is approximately 10% in patients observed for 5 years and 50% in those observed for 20 years. Each 10-year age group has a 2.4-fold increase in cancer risk (27). Multiple cancers are frequent, with synchronous lesions affecting 41% of patients and metachronous lesions affecting 70%. Polyp count and patient age, but not sex, predict cancer risk. Patients with >1,000 polyps have a 2.3 times greater risk of cancer than those with <1,000 polyps. Patients who undergo prophylactic colectomy may still die of other tumors, including ampullary cancers, brain tumors, hepatoblastomas, and desmoid tumors (28).

Treatment
Because of the high cancer risk, FAP patients undergo prophylactic total colectomy once the diagnosis is established. The procedure is timed so as not to interfere with psychosocial development, if the individual is a teenager or younger. It is recommended that the procedure be performed by age 20 to 25 (29). Patients have four surgical options: Total proctocolectomy, continent ileostomy (Koch pouch), total abdominal colectomy with ileorectal anastomosis, and ileoanal reservoir procedure. Total proctocolectomy with ileostomy eliminates the possibility of rectal carcinoma, but this procedure is unacceptable to many patients. The ileoanal reservoir procedure removes the bulk of the colorectal mucosa at risk for developing cancer while preserving the anal sphincter, but the cancer risk continues in the retained rectum. Rectal preservation is an ideal therapy for patients with relatively few rectal polyps because such patients are less likely to develop rectal carcinoma than those with numerous rectal adenomas (30). Patients with a retained rectum undergo semiannual sigmoidoscopic screening with removal of all polyps that develop. According to some, more than 50% of patients will develop carcinoma in the rectal stump despite semiannual sigmoidoscopic surveillance and removal of all polyps (30).

A trend is emerging to treat FAP patients with nonsteroidal anti-inflammatory drugs (NSAIDs), as these drugs associate with disappearance of rectal polyps (31). However, sulindac treatment does not prevent the development of adenocarcinomas in the rectal segment (32).
the density appear greater in this region (19). Rarely, the rectum is spared, especially in AAPC. When extensive, the entire large bowel becomes carpeted with adenomas (Fig. 12.3). Adenomas show gradations in size and shape from pedunculated tumors 1 cm or more in diameter, to smaller, broader-based nodules, to tiny lesions 1 mm or less in size. Adenomas tend to be larger in propositi (Figs. 12.3, 12.4, and 12.5) than in patients undergoing screening surveillance (Fig. 12.5). In classic FAP, the number of polyps ranges from <100 (Fig. 12.3) to >5,000 with an average of 1,000, depending on when one sees the patient (19). Colorectal carcinomas may be multifocal and more frequently develop on the left side of the colon (33). Patients with AAPC develop flatter, nonpolypoid adenomas than are seen in classic FAP. They arise throughout the colon, with preferential involvement of the right colon. They also originate in the retained rectum following colectomy.

**FIG. 12.4.** Resection specimen in a familial adenomatous polyposis patient. There is a large fungating tumor present that represented an invasive carcinoma. Numerous pedunculated adenomas are seen in the surrounding mucosa.

**FIG. 12.5.** Resection specimen from a patient who was part of a surveillance program. The patient has numerous small nodular lesions only mildly elevated over the mucosal surface. The lesions are smaller in patients undergoing surveillance than those who are not part of surveillance programs.
Pathologic Features of Adenomas

Adenomas and carcinomas in FAP patients grossly resemble their sporadic counterparts. Endoscopically, very small adenomas resemble hyperplastic polyps (Figs. 12.3 and 12.5). It is only when they become larger that the typical raspberry-like configuration of an adenoma becomes evident. As in sporadic colon cancer, the incidence of malignancy relates to adenoma size.

In the early stages, adenomas consist of small groups of adenomatous tubules. They range from unicryptal, bicryptal, or tricryptal lesions in grossly normal-appearing mucosa (Figs. 12.6 and 12.7) to the more typical multicryptal grossly visible polyps seen in patients without FAP (Fig. 12.8). The presence of unicryptal, bicryptal, and tricryptal adenomas strongly suggests the diagnosis of FAP. Even in unicryptal adenomas, the entire tubule is completely lined by neoplastic epithelium (Fig. 12.7). Proliferation throughout the entire length of the adenomatous crypt leads to branching, budding, infolding, and mucosal elevation. As the lesions enlarge to a grossly visible size, they become tubulovillous. Pure villous adenomas are rare in FAP patients.

FIG. 12.6. Cross sections of the grossly apparently normal mucosa in patients with familial polyposis. A: Low-power picture showing two foci containing adenomatous glands. A unicryptal adenoma is present above the star. A tricryptal adenoma is illustrated by the arrow. B: A tricryptal adenoma is illustrated.
FIG. 12.7. Longitudinal section of the mucosa showing the presence of a unicryptal adenoma (arrow). Even the single adenomatous crypts are easily visible.

FIG. 12.8. Familial polyposis. Histologic section through the mucosa demonstrating the presence of multiple adenomatous polyps arising on the surface of the mucosa.
Chapter 12

**FIG. 12.9.** Flat adenoma in a patient with attenuated adenomatous polyposis coli. Note that the adenomatous glands (*center*) lie at or below the level of the normal mucosa.

FAP patients develop depressed, flat, or polypoid adenomas (34), with AAPC patients showing a tendency to develop flat lesions. In contrast to pedunculated adenomas, the whole surface of flat or depressed adenomas lies at or below the level of the normal mucosa (Fig. 12.9). Polypoid adenomas are those with convex surfaces. Flat adenomas differ endoscopically and histologically from the usual adenoma. They present as slightly elevated plaques of adenomatous mucosa, not more than twice as thick as the adjacent normal mucosa. Further growth is by radial extension of adenomatous epithelium so that the lesions remain flat. When cancer develops, then one sees a reddish depression surrounded by marginal elevations (35). Occasionally, patients with FAP develop serrated polyps (see Chapter 14) or, more rarely, they develop juvenile polyps.

**Upper Gastrointestinal Lesions**

Nearly all FAP patients have polyps in the upper GI tract, with as many as 90% of patients developing gastric or duodenal adenomas by age 70 (36). Adenomas develop in the gastric antrum, duodenum, periampullary region, and ileum. However, it is the periampullary region that is most commonly involved, and adenomas tend to cluster at this site. More than 50% of FAP patients who undergo upper endoscopy have a grossly polypoid lesion, 90% of which arise in the periampullary region (37), suggesting that bile plays a role in their growth (38). The bile of FAP patients has a greater proportion of chenodeoxycholic and a lower proportion of deoxycholic acid than does the bile of patients without polyps (38) and is more mutagenic. Patients also exhibit fecal flora abnormalities resulting in the possible production of carcinogenic compounds. Periampullary carcinoma is a major cause of death in FAP patients (39), affecting from 2.9% to 12% of all FAP patients (19,39,40) and causing death in 22.2% of patients following colectomy (40).

**Duodenal Lesions**

Duodenal adenomas develop in as many as 100% of patients in Japanese series (40,41) and in 50% in Western countries (19,42,43). Duodenal adenomas develop when patients are in their 2nd to 5th decades of life. The average age of FAP patients with adenomas involving the ampulla of Vater is 31.7 years, compared with 59.6 years in those without FAP. Duodenal adenomas vary in size and appearance from microadenomas in a normal-appearing ampulla to sessile polyps measuring 3 cm in diameter (43). Duodenal adenomas are generally small in screened populations. Over 90% of duodenal adenomas are tubular lesions. Large lesions become tubulovillous with dysplasia ranging from mild to moderate in degree. FAP-associated duodenal adenomas show a significant increase in the number of Paneth cells (Fig. 12.10) and endocrine cells per crypt compared to controls. This specialized cell hyperplasia affects the flat mucosa of FAP patients, regardless of the presence or absence of adenomas, and may represent a primary defect in the regulation of duodenal stem cell differentiation in FAP patients (44).
**Chapter 12**

**Fig. 12.10.** Duodenal adenoma in familial adenomatous polyposis patient showing the presence of adenomatous epithelium and a large number of Paneth cells, as evidenced by the eosinophilic granules within the cytoplasm.

P. 699

**Ileal and Jejunal Lesions**

Adenomas also develop in the ileum and jejunum, but to a lesser extent than in the duodenum. As many as 82% of FAP patients develop ileal adenomas (45). Ileorectal anastomoses, ileostomies, and ileal pouches predispose the ileal mucosa to become neoplastic (32,46,47). The ileal mucosa undergoes colonic metaplasia, which then gives rise to adenomas. Ileal adenomas resemble duodenal, gastric, and large intestinal adenomas. Ileal adenomas tend to be sessile, measuring 1 to 5 mm in size. Multiple lymphoid polyps also develop in the terminal ileum in FAP patients.

**Gastric Lesions**

Gastric polyps develop in approximately two thirds of FAP patients (23). Two different types of polyps arise in the stomach. Antral polyps are usually adenomas, whereas the small polyps arising in the fundus and body are usually fundic gland polyps (see Chapter 4) (48). Fundic gland polyps affect 25% to 60% of FAP patients.

Fundic gland polyps occur earlier than gastric adenomas, presumably because they originate in the existing fundic mucosa without the requirement for intervening intestinal metaplasia. Most patients with fundic polyps are under age 20. Fundic gland polyps are often multiple and small in diameter, appearing sessile or semi-sessile. They are identical to sporadic fundic gland polyps (see Chapter 4) (Fig. 12.11). The gastric mucosa may be studded with numerous small, sometimes eroded polyps that may increase in number and size over a several-year period. Alternately, they may decrease, or even disappear. Lesions that decrease or disappear may be followed by the appearance of a new crop of polyps (48). The fundic gland lesions are generally considered to be benign with little or no malignant potential, yet dysplasias and carcinomas have been described in FAP-associated fundic gland polyps (49,50). Superimposed gastric adenomas may give the false impression of dysplasia arising in a fundic gland polyp.
Chapter 12

FIG 12.11. Fundic gland polyp in a patient with attenuated familial adenomatous polyposis. The lesion is similar in appearance to a sporadic fundic gland polyp.

In Western countries, FAP-associated gastric adenomas and carcinomas are rare, contrasting with the Japanese experience, and supporting the role of environmental or other genetic factors in gastric cancer development. Gastric adenomas develop in the antrum in areas of intestinal metaplasia, a histologic requirement for the formation of gastric adenomas. When one compares gastric adenomas with colonic adenomas, the gastric lesions tend to be smaller and more sparsely distributed. In addition, gastric adenomas occur later in life than colonic adenomas. Gastric adenocarcinomas develop in the adenomas. Finally, FAP patients may develop gastric microcarcinoid tumors (48).

Adenomas and Carcinomas in the Rectal Remnant

Overall, the cumulative risk of developing cancer in the retained rectum ranges from 4% to 59% during a period of 10 to 30 years following surgery (51,52). The cancers may be small, depressed, and restricted to the mucosa. The age of the patient at the time of colectomy, the length of the retained colon, the tendency for spontaneous regression of polyps in the retained rectum, and the presence of carcinoma in the excised colon all influence the subsequent development of rectal cancer. Carcinomas and adenomas can develop, even in patients who are closely followed (32).

Kinetic and Other Biologic Abnormalities

FAP patients have a generalized abnormality of DNA synthesis that eventually results in uncontrolled cellular replication in the GI tract and in extragastrointestinal sites. FAP patients often exhibit increased ornithine decarboxylase activity, an enzyme that is essential for intestinal mucosal proliferation (53). As a result, FAP patients demonstrate increased cell proliferation in the adenomatous epithelium as well as in the nonneoplastic crypts, on the luminal surface, and in the mucosa between adenomatous polyps (54). The markedly increased replication rate and the large number of adenomatous cells available for mutation and malignant transformation increase the likelihood of cancer developing.

APC mutation is a requisite initiating event for the formation of adenomas and provides a permissive environment for the subsequent development of carcinomas. Further steps in the neoplastic progression, including severe dysplasia and invasive carcinoma, associate with somatic mutations in K-ras and p53 (55,56). In addition to mutations, losses of the APC, p53, and DCC also occur (56,57,58). Additionally, c-myc is frequently overexpressed (59). Some patients also develop microsatellite instability (60).

Extraintestinal Manifestations

FAP patients have a high incidence of extraintestinal manifestations, including dental and skin abnormalities and the development of various types of neoplasms (Fig. 12.12). The dental abnormalities include unerupted teeth, supernumerary teeth, dentigerous cysts, and mandibular cysts. Subcutaneous lesions include epidermoid cysts, lipomas, fibromas, neurofibromas, and trichoepitheliomas. The latter appear at an early age, even before polyps appear. Those that occur in prepubertal years are strong indicators for the presence of a polyposis syndrome, and to some represent an indicator for regular sigmoidoscopy, even without a history of polyposis. Epidermal inclusion cysts are often multiple. The epidermoid cysts occur anywhere on the body but most are located on the arms, buttocks, legs, and face, and occasionally in the testis.

Not surprisingly, patients who carry germline mutations in a tumor suppressor gene exhibit tumors in sites other than the GI tract. These are summarized in Figure 12.12. Osteomas commonly occur in the skull or jaw,
although they can affect any bone. These benign tumors rarely become malignant. FAP associates with nasopharyngeal angiofibromas (61). The lesion occurs 25 times more commonly in FAP patients when compared with the general population.

**FIG. 12.12.** Diagram of the various manifestations of familial adenomatous polyposis, which is essentially a systemic disorder. CHRPE, congenital hypertrophy of the retinal pigment epithelium.

FAP patients also develop a number of endocrine and other neoplasms. Thyroid carcinomas, which occur with increased frequency in FAP patients, are all follicular neoplasms, sometimes containing papillary, cribriform, solid, and spindle cell components. FAP-associated thyroid cancers are commonly multifocal and predominantly affect young women. Since multicentricity is unusual for follicular thyroid tumors, it should alert the pathologist to the possibility of FAP (62). Soft tissue lesions include fibromas, lipomas, and desmoid tumors.

Desmoid tumors are a locally invasive form of fibromatosis (see Chapter 19) that affects 9% to 32% of FAP patients (63,64), particularly women (3:1). Affected patients are often young, with a mean age of 29.8 years (65). The overall prevalence of these lesions in FAP is 15%, a risk approximately 850 times greater than that of the general population (65,66).

Desmoid tumors tend to involve members of the same family and associate with mutations in exon 15 of **APC** (Fig. 12.1). Most patients have undergone a previous colectomy (86%). Hormonal factors such as pregnancy and estrogen use may also play etiologic roles in desmoid development. Although the desmoids can develop on the shoulder girdle, buttocks, groin, and abdominal wall, the majority arise within the small intestinal mesentery.
FIG. 12.13. Desmoid tumor in a patient who died of complications from the desmoid. A: Autopsy en bloc resection of the liver, spleen, intestines, and desmoid tumor. One can see that the tumor diffusely infiltrates the abdominal contents and extends up to the liver. Numerous organs were entrapped within this neoplasm, including the biliary tree, large numbers of vessels, and loops of bowel. B: Higher magnification of the neoplasm showing the presence of a fleshy mass with areas of ischemic necrosis.

Desmoid tumors represent an adverse prognostic factor in FAP patients because they associate with a high frequency of complications and tumor recurrence. These nonencapsulated, irregular, infiltrative (Fig. 12.13), locally aggressive lesions do not metastasize, but they can cause significant intestinal obstruction, ureteral or vascular compression, or other local problems. Extensive mesenteric or retroperitoneal involvement leads to recurrent small bowel obstruction. Many patients die from these lesions. In one center, desmoid tumors were second only to colorectal cancer as a cause of death in FAP patients (39). Death results from vascular compromise, small bowel gangrene, perforation, or intra-abdominal sepsis.

Surgery is usually reserved for a specific indication, such as relief of intestinal or ureteric obstruction. Surgery on these lesions is extremely difficult because it is rare for the tumors to be small enough or sufficiently localized to allow resection without sacrificing vital structures. In most cases, attempts at surgical resection are followed by tumor recurrence. The recurrence rate after wide surgical resection is 81% (63). As a result, some have abandoned surgical procedures in favor of other therapies.

Other therapies have been tried including radiotherapy and various chemotherapies. Radiotherapy slows or reverses abdominal wall and mesenteric tumor growth, but the dose is limited by the need to preserve underlying intraperitoneal structures. Hormonal therapy, especially with antiestrogens, has met with minimal success. Tamoxifen has been effective in some patients (67), as has progesterone (68). Recently, NSAIDs have been used to halt the tumor growth, presumably by interfering with prostaglandin metabolism. Treatment with sulindac has resulted in a reduction in tumor size in some patients, but the response is inconsistent (67).

Histologically, desmoids consist of uniform, mature fibroblasts arranged in intertwining bundles. Mitoses are infrequent and never atypical. The extent of vascularization varies and may be prominent (Fig. 12.14). This prominent vascular ectasia, which sometimes occurs in FAP patients, is not a feature in non-FAP individuals and may account for intraoperative hemorrhagic complications. The tumor infiltrates the intestinal loops and peritoneum. The arteries and veins become surrounded by tumor but it does not infiltrate them (Fig. 12.14). The tumor cells actively produce collagen fibers.
FIG. 12.14. Desmoid tumor. A: A highly vascular spindled cell mass is present, which extends up to a large sclerotic vessel but does not invade it. B: Higher magnification showing the haphazard arrangement of the spindled cells. C: A more hyalinized area of the tumor. D: A more vascular portion of the tumor.

TABLE 12.3 Central Nervous System Lesions in Turcot Syndrome

<table>
<thead>
<tr>
<th>Medulloblastoma</th>
<th>Glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavernous hemangioma</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>Spongioblastoma</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Glioma</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Craniopharyngioma</td>
</tr>
</tbody>
</table>

Desmoids in FAP patients contain both germline and somatic APC mutations, suggesting that inactivation of this gene plays a role in the development of the lesions (69). Desmoid tumors also demonstrate deletion of 5q (70).

**Turcot Syndrome**

Turcot syndrome is the association of FAP with malignant tumors of the central nervous system. Central nervous system tumors arise around the time of puberty, often before the diagnosis of FAP (Table 12.3). The brain tumors are often lethal (71). Both familial and nonfamilial cases occur, resulting in a controversy concerning its mode of inheritance. Some suggest an autosomal recessive inheritance pattern (72,73). However, patients often die before having children, making it difficult to test the inheritance pattern. Lewis et al proposed classifying Turcot syndrome based on a study of family pedigrees (74) (Table 12.4).

Patients with Turcot syndrome fall into three groups based on their intestinal lesions: (a) those with a low number of colonic polyps (20 to 200), (b) those with large polyps measuring over 3 cm in diameter, and (c) those with colonic carcinoma developing during the 2nd to 3rd decades. Patients in the second group often have very few polyps. The gastrointestinal adenomas predominantly arise in the colon and rectum, but small intestinal and gastric lesions also develop.

Turcot syndrome is linked to the APC locus. Hamilton et al detected genetic abnormalities in 13 of 14 registry families (75). Germline APC mutations were detected in ten. The glioblastomas and colorectal tumors in three of the families and in the original family studied by Turcot also had replication errors characteristic of hereditary nonpolyposis colorectal cancer (HNPCC). In addition, germline mutations in mismatch repair genes MLH1 or PMS2 were found in two families. Thus, the association between the brain tumors and multiple colorectal adenomas can result from two distinct types of germline defects (i.e., mutation of APC or a mismatch repair gene) (75).

**TABLE 12.4 Lewis Classifications of Turcot Patients**

<table>
<thead>
<tr>
<th>Group I</th>
<th>Patients who have siblings with the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group II</td>
<td>Patients in families in which colonic polyps are found in several generations</td>
</tr>
<tr>
<td>Group III</td>
<td>Isolated nonfamilial cases</td>
</tr>
</tbody>
</table>

Somatic p53 mutations are found in both the brain and colon tumors in Turcot syndrome, although the mutations are not the same in the two sites (76). Gliomas also exhibit allelic deletions of chromosome 17p (77). K-ras
Chapter 12

**Pigmented lesions generally develop by age 2 years. Pigmented macules involve the mucous membranes of the lips and oral cavity.** Macular lesions tend to cluster around the mouth, eyes, and nostrils. They also occur under the tongue and buccal mucosa. Macules have been found in the respiratory and urinary tracts. Pigmented lesions may appear simultaneously in different parts of the bowel.

**The Peutz-Jeghers syndrome (PJS) (OMIM entry #175200) is inherited in an autosomal dominant disorder with pleiotropic inheritance and variable penetrance. PJS has an estimated incidence of 1 in 120,000 births (98).**

**Clinical Features**

The Peutz-Jeghers syndrome (PJS) (OMIM entry #175200) is inherited in an autosomal dominant disorder with pleiotropic inheritance and variable penetrance. PJS has an estimated incidence of 1 in 120,000 births (98). Approximately 50% of cases are familial; the remaining 50% are new mutations. The incidence of PJS is roughly one tenth that of familial adenomatous polyposis (99). The syndrome consists of two major components: (a) gastrointestinal hamartomatous polyps and (b) pigmented macules involving mucous membranes and skin (Fig. 12.16). The pigmentation affects 90% of patients, and polyps may occasionally be absent. Conversely, some patients with 6 to 48 polyps had a carcinoma (86). Many of these patients may in actuality have AAPC or MYH polyposis.

**Nonhereditary Adenomatous Polyposis Syndromes**

**Multiple Colonic Adenomas**

The presence of multiple adenomas (<100 in the colorectum) defines a group of patients without a clear genetic disorder, but who exhibit an increased risk for developing colon carcinoma. Morsøn surveyed patients with intestinal neoplasia at St. Mark’s Hospital and found 1,846 individuals who had multiple adenomas (86). Of these, 27.9% had more than one adenoma; 4.5% had more than five adenomas. In this series, the patients with familial polyposis had a minimum of 200 polyps, whereas the nonfamilial group had a maximum of 48. The percentage of patients with associated carcinoma increased with increasing numbers of adenomas; 80% of patients with 6 to 48 polyps had a carcinoma (86). Many of these patients may in actuality have AAPC or MYH polyposis.

**Hyperplastic Polyposis**

Hyperplastic polyposis (HP) is a rare syndrome first described in 1980 as “metaplastic polyposis” (87). In the original series, seven patients were described, each with more than 50 colonic hyperplastic polyps. None of the patients in the group developed colonic adenocarcinoma. However, numerous reports have subsequently described the occurrence of colorectal cancers in HP patients (88,89,90), suggesting that patients with this syndrome are at increased risk for colon cancer development. Familial aggregation of the disorder has been observed in some patients, but a definite genetic association has not been demonstrated (91).

Patients with hyperplastic polyposis develop not only hyperplastic polyps, but also sessile serrated polyps, serrated adenomas, mixed serrated and adenomatous polyps. This finding suggests that MYH mutations may be an important factor in cancer development. In this group of patients, the disease affects males and females equally. Most patients have more than 30 but fewer than 100 polyps. Molecular studies suggest that at least some patients with hyperplastic polyposis have an underlying defect in DNA methylation, leading to hypermethylation of CpG islands throughout the genome (93).

**Hereditary Mixed Polyposis Syndrome**

As the name implies, hereditary mixed polyposis syndrome (OMIM entry #601228) is characterized by a variety of colorectal tumor types including atypical juvenile polyps, serrated polyps including serrated adenomas, classic adenomas, and carcinomas (94). This disease appears to affect the colon only; no other gastrointestinal or extraintestinal manifestations have been described. Two forms of hereditary mixed polyposis syndrome appear to exist. The first is linked to a genetic locus mapped to chromosome 15 (95,96), and the second to the BMPR1 locus on 10q23 (97).

**Hereditary Hamartomatous Polyposis Syndromes**

**Peutz-Jeghers Syndrome**

**Clinical Features**

The Peutz-Jeghers syndrome (PJS) (OMIM entry #175200) is inherited in an autosomal dominant disorder with pleiotropic inheritance and variable penetrance. PJS has an estimated incidence of 1 in 120,000 births (98). Approximately 50% of cases are familial; the remaining 50% are new mutations. The incidence of PJS is roughly one tenth that of familial adenomatous polyposis (99). The syndrome consists of two major components: (a) gastrointestinal hamartomatous polyps and (b) pigmented macules involving mucous membranes and skin (Fig. 12.16). The pigmentation affects 90% of patients, and polyps may occasionally be absent. Conversely, some family members have only the intestinal polyps. The disease affects males and females equally. The diagnostic criteria for PJS are listed in Table 12.6.

A diagnosis of PJS has been made in an individual as young as 15 days (100). Jejunal and ileal hamartomatous polyps often produce intussusception, leading to abdominal pain, partial or complete intestinal obstruction, or bleeding (99). As a result, most patients have recurrent attacks of crampy abdominal pain. Infants or older patients may present with anal extrusion when large rectal polyps prolapse. Polyps that autoamputate or undergo torsion, intussusception, or prolapse become ischemic, leading to bleeding, anemia, or massive hemorrhage. The polyposis progresses by the intermittent growth of polyps and with new “crops” of polyps appearing simultaneously in different parts of the bowel.

Pigmented lesions generally develop by age 2 years. Pigmented macules involve the mucous membranes of the lips and oral cavity. Macular lesions tend to cluster around the mouth, eyes, and nostrils. They also occur on
the gums, palate, and oropharynx, or the skin of the face, forearms, hands, feet, and perianal area. The pigmented spots on the skin may fade or disappear as the patient ages, often at the time of puberty. This feature may make diagnosis difficult, especially in patients with no symptoms attributable to gastrointestinal polyps. Buccal pigmentation presents as ill-defined, bluish areas. Histologically, these lesions resemble freckles, with hyperpigmentation along the basal epithelial layer due to increased numbers of melanocytes. Although the pigmentation is characteristic for PJS, acquired pigmentation simulating PJS may also affect non-PJS patients with colon cancers (101). A number of other nonneoplastic conditions affect PJS patients (Fig. 12.17). Whether these lesions should be considered part of PJS or merely coincidental findings remains to be determined.

**FIG 12.15.** Hyperplastic polyposis. *A:* Low-power view showing areas of serrated-appearing glands in a patient with hyperplastic polyposis. *B:* Some polyps resemble typical hyperplastic polyps, while others show features of sessile serrated polyps (*C*). *D:* Occasional foci of dysplasia or adenomatous change are present in some polyps.

**Genetic Features**

The PJS gene lies on chromosome 19p13.3 and encodes the serine/threonine kinase STK11/LKB1 (102,103). Germline mutations or loss of heterozygosity in the STK11 gene account for most PJS cases (103). PJS kindreds inherit mutations in STK11 as a single hit on one allele corresponding to the autosomal dominant inheritance pattern. The second hit then occurs in affected PJS tissues. Germline mutations are usually truncating, but missense mutations also occur. Approximately 70% of familial and 30% to 70% of sporadic PJS patients have STK11 mutations (104).
TABLE 12.5 World Health Organization Working Definition of Hyperplastic Polyposis

1. At least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which two are >10 mm in diameter, or
2. Any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual with a first degree relative with hyperplastic polyposis, or
3. Greater than 30 hyperplastic polyps distributed throughout the colon

FIG. 12.16. Photograph of a patient with Peutz-Jeghers syndrome demonstrating the characteristic mucosal pigmentation.

STK11 is a tumor suppressor gene, consisting of nine exons. It is ubiquitously expressed in adults (103). The STK11 gene product localizes to both the nucleus and cytoplasm and is a substrate of cyclic adenosine monophosphate (AMP)-dependent protein kinase (105). The encoded protein, LKB1, interacts with p53 and regulates specific p53-dependent apoptotic pathways (106). Restoring LKB1 activity to cancer cell lines defective for its expression results in G1 cell cycle arrest and induction of the CDK1 inhibitor p21 (107).

Identification of the PJS gene makes genetic screening possible for affected families. Mutation testing is done by full sequencing of the gene. Patients with neoplasia in their hamartomas exhibit 19p LOH, β-catenin mutations, or mutations or LOH at the p53 locus. These findings suggest that mutations of β-catenin gene and/or p53 may help convert hamartomatous polyps into adenomas and carcinomas (108).

TABLE 12.6 Diagnostic Criteria for Peutz-Jeghers Syndrome (PJS)
1. Three or more histologically confirmed Peutz-Jeghers polyps, or
2. Any number of Peutz-Jeghers polyps with a family history of PJS, or
3. Characteristic prominent mucocutaneous pigmentation with a family history of PJS, or
4. Any number of Peutz-Jeghers polyps and characteristic prominent mucocutaneous pigmentation

**FIG. 12.17.** Diagrammatic representation of many of the intestinal and extraintestinal lesions found in patients with Peutz-Jeghers syndrome.

**Gross Features**

Hamartomatous polyps occur throughout the intestinal tract affecting the jejunum, ileum, colon, stomach, duodenum, and appendix in decreasing order of frequency. The distribution of the polyps depends on the patient population. Intestinal PJS polyps usually number in the dozens rather than in the hundreds, and may be sessile or pedunculated with a smooth lobulated outer surface. They range in size from a few millimeters to 6 or 7 cm in greatest dimension (Figs. 12.18 and 12.19), but most measure 0.5 to 1 cm in diameter. Patients who present predominantly with jejunal and ileal polyps most likely have PJS because the other polyposis syndromes...
do not usually produce multiple polyps in these sites.

Gastric PJS polyps usually arise in the antrum, and are often larger than the gastric polyps associated with juvenile polyposis, Cowden disease, or Cronkhite-Canada syndrome. They often resemble gastric adenomas grossly.

**Histologic Features**

Intestinal hamartomas of the PJS type have a fairly distinctive histologic appearance, although grossly they are not easily differentiated from other gastrointestinal polyps. The epithelial component of the polyp resembles the normal epithelium indigenous to its site of origin. Small intestinal polyps consist of crypts and villi of varying lengths divided by arborizing muscle bundles. The muscle fibers branch out from the center of the lesion like branches of a tree (Figs. 12.19 and 12.20). The smooth muscle bands span out into the head of the polyp and become progressively thinner as they project toward the surface of the polyp. Each branch is covered by mucosa (Fig. 12.20). Unlike juvenile polyps, the lamina propria appears normal. Some crypts become cystically dilated, whereas others may show intraluminal papillary projections, producing a serrated pattern reminiscent of that found in hyperplastic polyps or serrated adenomas. Cells of the normal small bowel mucosa, including goblet cells, absorptive cells, enteroendocrine cells, and Paneth cells, line the crypts and villi of small intestinal PJS polyps. Duodenal lesions contain Brunner glands. These cells retain their normal relationships with each other. However, in some foci, one cell type may predominate. The surfaces of PJS polyps often appear acutely inflamed and superficially eroded, with evidence of regeneration. As a result, abnormally long rows of darkly staining replicating cells of the expanded regenerative zone may line elongated crypts.

Mitotic figures usually can be identified in these regenerative areas. Rare polyps contain areas of osseous metaplasia.

**FIG. 12.18.** Peutz-Jeghers syndrome. Gross photograph of a Peutz-Jeghers polyp.
FIG. 12.19. Low-power magnification of a Peutz-Jeghers polyp showing the treelike arborizing pattern of the musculature covered by branched glands.
**FIG. 12.20.** Colonic Peutz-Jeghers polyp. *A:* Low magnification showing the presence of a branching polypoid structure containing the normal elements from the rectum where this polyp arose. One sees a central muscular core, lymphoid follicles, and essentially normal colonic mucosa covering the central cores. *B:* Higher magnification showing the details of the central muscular cores and the covering colonic epithelium.

**FIG. 12.21.** Peutz-Jeghers polyps in the colon. *A:* This lesion has undergone adenomatous transformation. *B:* Wide, smooth muscle bands course through the lesion.

Colonic PJS polyps demonstrate similar, but less complex, features than small intestinal polyps. They contain elongated, occasionally branching crypts (Fig. 12.21). The surface may have a villous architecture. Absorptive and goblet cells line the crypts, with goblet cells predominating in most cases (Figs. 12.19 and 12.20). Elongated zones of immature epithelium and mitoses occur in eroded polyps. Interlacing smooth muscle bands occur less frequently in colonic lesions than in small bowel polyps, and may be absent, especially in small lesions.

Gastric PJS polyps consist of foveolar or pyloric glandular cells intermingled with endocrine cells. Like their counterparts in the colon, gastric PJS polyps may lack the arborizing smooth muscle bundles typical of small intestinal PJS lesions. When the smooth muscle bundles are absent, gastric PJS polyps may resemble gastric hyperplastic polyps.

Benign glands lie within the submucosa, the muscularis propria, or even the serosa in 10% of small intestinal PJS polyps (Figs. 12.22 and 12.23). Such epithelial misplacement does not usually affect gastric or large intestinal lesions. Sometimes the deep glands appear to be connected to the more superficial glands; in other cases, they lack continuity with the superficial part of the lesion. Such lesions may show prominent mucinous cysts at the base (Fig. 12.23). Infoldings of columnar epithelium and dystrophic calcification can be seen in the mucinous pools. The benign appearance of the epithelium differentiates these areas from invasive carcinoma.

**FIG. 12.22.** Histologic features of Peutz-Jeghers polyps (PJP). *A* represents PJP of the small intestine; *B* represents PJP of the colon. Both are distinctive for their irregular architecture and the intimate admixture of glandular epithelium native to the site of origin with bundles of smooth muscle fibers. The small intestinal PJP also contains enterogenous cysts.
FIG. 12.23. A small intestinal Peutz-Jeghers polyp. A: Low-power magnification showing the presence of a broad-based, semi-pedunculated, semi-sessile polyp. A series of glands are entrapped within the proliferative muscle. The central portion of the lesion contains a large cystic area, shown better in B. B: One sees a mucinous collection in the center of the cyst. Much of the cyst is lined by hyperplastic-appearing glandular epithelium, sometimes in association with its lamina propria (arrow). In some places, the mucosa becomes attenuated or almost completely unrecognizable.

Rarely, one encounters glands deep in the bowel wall or in the serosa in the absence of a surface polyp. Grossly, these lesions appear as intramural nodules. Histologically, they may be partially or totally lined by normal goblet cells, columnar absorptive cells, endocrine cells, and/or Paneth cells. Alternatively, the mucinous cysts may lack an epithelial lining. This entity has been termed enteritis cystica profunda (Figs. 12.22 and 12.23). The presence of displaced glands deep in the bowel wall results from one of two processes. First, they may occur as part of the development of these hamartomatous intestinal lesions, or second, they may result from glandular entrapment due to previous trauma, perhaps secondary to episodes of intussusception.

One may also see circumscribed foci of signet ring cells in PJS polyps as a result of intestinal intussusception or polyp stretching or torsion. These events cause focal mucosal ischemia and epithelial sloughing. The sloughed epithelial cells, including the goblet cells, accumulate in mucosal folds in which the surface openings are obstructed. The sloughed goblet cells assume a round shape and signet ring appearance. These benign signet ring cell aggregates superficially simulate signet ring cell carcinomas, but they lack the usual cytologic features necessary to make a diagnosis of cancer.

Extraintestinal Tumors

Patients with PJS exhibit an increased incidence of extraintestinal hamartomas and malignancies (Fig. 12.17). Hamartomatous polyps may occur in the ureter, bladder, renal pelvis, bronchus, and nose. Extraintestinal carcinomas arising in association with PJS most commonly develop in the reproductive organs and breast. Adenoma malignum of the uterine cervix, mucinous ovarian neoplasms, and ovarian sex cord tumors with annular tubules (SCTATs) occur frequently in the reproductive organs of women with PJS (109). SCTATs are an almost constant finding in women and are considered to be a phenotypic expression of the syndrome. The tumors usually occur alone, although all three tumor types may rarely coexist in a single patient (110). Patients also develop bilateral breast cancers (111).

The morphologic features of SCTATs are intermediate between those of a granulosa cell tumor and a Sertoli cell tumor (Fig. 12.24). SCTATs are usually benign, typically bilateral, multifocal, very small, even microscopic in size, calcified, and almost always an incidental finding at the time of surgery in ovaries removed for reasons. SCTATs are characterized by ring-shaped tubules encircling hyaline masses (Fig. 12.24). Other stromal tumors cause sexual precocity or menstrual irregularities due to hyperestrogenism. These tumors differ from SCTATs in that they are large (112) and have a complex histologic appearance, featuring diffuse areas and foci of hollow tubular differentiation, microcysts, and papillae. They contain two predominant epithelial cell types, one with scant and the other with abundant cytoplasm. The combination of patterns and cell types is unique and only occurs in PJS patients (113).

Adenoma malignum is an extremely well-differentiated adenocarcinoma or a minimal deviation endocervical adenocarcinoma. Histopathologically, the tumor consists of benign-looking, irregularly shaped endocervical glands. The tumor invades cervical stroma, nerves, and vessels. Some patients with PJS and adenoma malignum also exhibit mucinous epithelium in the endometrium and fallopian tubes (114), representing direct spread from the adenoma malignum (115). Other types of mucinous lesions affect the fallopian tube, including mucinous metaplasia, in the absence of other ovarian or uterine mucinous lesions, mucinous adenocarcinoma in situ, and mucinous cystadenomas (116).

Male PJS patients develop testicular tumors. The patients are usually children who overproduce estrogen and develop gynecomastia, the equivalent of the ovarian SCTATs. Feminizing Sertoli tumors in boys microscopically consist of greatly enlarged seminiferous tubules packed with ovoid Sertoli-like cells. Prominent eosinophilic basement membranes surround the tubules and intersect between the cells forming hyalinized ovoid globules and microcalcifications. They result in increased estrogen synthesis due to the presence of increased transcription of the aromatase cytochrome P450 gene (117).
Juvenile Polyposis

Juvenile Polyposis of Stomach
- Stomach only
- Present

Juvenile Polyposis of Small Intestine
- Colon and rectum, few in small bowel
- Present in approximately 40%

Familial Juvenile Polyposis of Stomach
- Stomach only
- Present

Table 12.7 Classifications of Juvenile Polyps

<table>
<thead>
<tr>
<th>Type of Polyp</th>
<th>Location of Polyps</th>
<th>Familial History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary juvenile polyp</td>
<td>Colon and rectum only</td>
<td>Absent</td>
</tr>
<tr>
<td>Juvenile polyposis coli</td>
<td>Colon and rectum, few in small bowel</td>
<td>Present in approximately 40%</td>
</tr>
<tr>
<td>Juvenile gastrointestinal polyposis</td>
<td>Stomach to rectum</td>
<td>Present</td>
</tr>
<tr>
<td>Familial juvenile polyposis of stomach</td>
<td>Stomach only</td>
<td>Present</td>
</tr>
</tbody>
</table>

Treatment

Because of the increased risk for cancer, patients suspected of having PJS undergo regular screening. The screening recommendations for gastrointestinal malignancies include colonoscopy beginning with symptoms or in late teens if no symptoms occur (121). The interval is determined by the number of polyps, but it is at least once every 3 years. If multiple polyps are found on initial screening, endoscopy should be performed at least annually until all of the polyps have been removed. Screening for gastric neoplasia consists of upper GI endoscopy every 2 years starting in the midteens (122). Screening for small bowel neoplasms occurs via annual small bowel radiography or capsule endoscopy. Screening for pancreatic cancer involves endoscopic or abdominal ultrasound or computed tomography (CT) every 1 to 2 years after age 30 (122,123). Annual breast examinations and mammography every 2 to 3 years beginning at age 25 are performed to detect breast cancers. Screening for gynecologic neoplasms by annual pelvic examination and Pap smear begins at age 20, and screening for testicular tumors begins at age 10.

Juvenile Polyposis

Juvenile polyps are the most common pediatric gastrointestinal polyps, affecting an estimated 1% of children (124). In the past, juvenile polyps were considered inflammatory lesions, but today they are viewed as hamartomas. Most juvenile polyps are solitary lesions that are not part of a generalized polyposis syndrome. They are usually discovered between the ages of 1 and 10 with a peak incidence between 2 and 4 years of age. A second peak incidence occurs around age 25. Isolated polyps occur with equal frequency in males and females, but there is a male predominance when multiple polyps develop (124). When multiple juvenile polyps are present, the entity is termed generalized juvenile polyposis, multiple juvenile polyposis, familial juvenile polyposis, or juvenile polyposis coli (Table 12.7). Multiple juvenile polyps may also be encountered in patients with Cowden disease or Bannayan-Riley-Ruvalcaba syndrome, but these patients have other abnormalities in addition to juvenile polyps.

Juvenile intestinal polyposis (polyposis, juvenile intestinal [PJI], OMIM entry #174900) occurs in both familial and sporadic forms. It is an autosomal dominant condition, with 20% to 50% of patients reporting a family history of polyps. The disorder is rare, occurring in an estimated 1 per 100,000 births, an incidence 10-fold lower than that of FAP (125). Patients with PJI present with multiple juvenile polyps, which are not limited to the colon, but also occur in the small intestine and stomach. Rare patients demonstrate polyps limited to the stomach, and were at one time considered to have a separate form of polyposis. Familial gastric juvenile polyposis is now
considered to be a variant of PJI per OMIM. The criteria for establishing the diagnosis of juvenile polyposis are shown in Table 12.8.

**Clinical Features**

The clinical course of PJI varies depending on polyp number and location. Eighty-eight percent of polyps lie within 20 cm of the anal verge and are easily detectable by sigmoidoscopy. Patients with gastric involvement exhibit a gastric coating of polyps on upper endoscopy. Patients with PJI become symptomatic during childhood, contrasting with children with FAP (126).

who rarely become symptomatic before puberty. Juvenile polyposis may be divided into several different subtypes based on clinical presentation and disease course (126). Three subtypes are recognized: Juvenile polyposis of infancy, juvenile polyposis coli, and generalized juvenile polyposis. Juvenile polyposis of infancy (also referred to as infantile Cronkhite-Canada syndrome) is characterized by bloody diarrhea, protein-losing enteropathy, hypoproteinemia, anemia, anasarca, failure to thrive, and death prior to 1 year of age. An autosomal recessive pattern of inheritance has been suggested for this form of juvenile polyposis (127).

### TABLE 12.8 Diagnostic Criteria for Juvenile Polyposis

<table>
<thead>
<tr>
<th>No extraintestinal manifestations of either Cowden disease or Bannayan-Riley-Ruvalcaba syndrome are present, and one or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Five or more juvenile polyps are present in the colon.</td>
</tr>
<tr>
<td>2. Any number of hamartomatous polyps are present in a patient with a family history of juvenile polyposis.</td>
</tr>
<tr>
<td>3. Extracolonic juvenile polyps are present.</td>
</tr>
</tbody>
</table>

Patients with juvenile polyposis coli have polyps limited to the colon, while those with generalized juvenile polyposis develop polyps throughout the gastrointestinal tract. Presentation of both of these subtypes usually occurs in the 1st or 2nd decade of life. The most common clinical presentation is painless rectal bleeding, a finding that affects nearly all patients. A minority of patients present with other clinical manifestations including rectal prolapse or polyp extrusion, abdominal pain, anal pruritus, diarrhea, constipation, or hemorrhage. Intussusception, protein-losing enteropathy, malabsorption, and diarrhea may be observed in patients with extensive polyposis. Autoamputation of polyps with passage of tissue also occurs.

Patients with juvenile polyposis may exhibit extracolonic manifestations including digital clubbing, failure to thrive, hypertelorism, and macrocephaly. Fifteen percent of patients, usually those without a family history of polyposis, show associated congenital birth defects including malrotation of the midgut, cardiac and cranial abnormalities, cleft palate, polydactyly, genitourinary defects, pulmonary arteriovenous malformations, pulmonary stenosis, and telangiectasias (128) (Table 12.9). Juvenile polyposis patients have an increased risk for the development of colorectal adenocarcinoma, as well as for cancers of the stomach, duodenum, and pancreas (129,130).

### TABLE 12.9 Abnormalities Associated with Juvenile Polyposis

<table>
<thead>
<tr>
<th>Congenital lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal malrotation</td>
</tr>
<tr>
<td>Meckel diverticulum</td>
</tr>
<tr>
<td>Umbilical fistula</td>
</tr>
<tr>
<td>Mesenteric lymphangioma</td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Ganglioneuromas</td>
</tr>
<tr>
<td>Cardiac lesions</td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Amyotonia congenitum</td>
</tr>
<tr>
<td>Hypertelorism</td>
</tr>
<tr>
<td>Porphyria</td>
</tr>
<tr>
<td>Undescended testis</td>
</tr>
<tr>
<td>Supernumerary toes</td>
</tr>
<tr>
<td>Other lesions</td>
</tr>
</tbody>
</table>
Several families have been described in which an autosomal dominant juvenile polyposis syndrome occurs with pulmonary and cerebral arteriovenous malformations, cutaneous telangiectasia, subarachnoid hemorrhage, hypertrophic pulmonary osteoarthropathy, and digital clubbing (OMIM entry #175050). Many of these patients present in childhood or adolescence with polyps located mainly in the colon and small intestine (126). It is currently unclear whether this entity represents a single gene abnormality distinct from juvenile polyposis or represents coincidental juvenile polyposis and Osler-Rendu-Weber disease.

**Genetic Features**

Approximately one half of families with juvenile polyposis have germline mutations in one of two genes, the dysfunction of which interrupts the transforming growth factor-β (TGF-β) signaling pathway: SMAD-4 and the bone morphogenetic protein receptor 1A (BMPR1A) (131,132,133). Mutations in SMAD-4 and BMPR1A occur with equal frequency, with abnormalities in each being identified in approximately 20% of juvenile polyposis patients (134).

SMAD-4 (also known as MADH4 or DPC4) is located on chromosome 18q21.1. Somatic mutations in this gene occur in 15% of colorectal carcinomas and as many as 50% of pancreatic ductal carcinomas (131,132). The most common mutation is a 4 base deletion in exon 9, but numerous other mutations have been reported (133,134). SMAD-4 encodes a 60.4 kDa protein that acts as a cytoplasmic mediator in the TGF-β signaling pathway. Upon activation of TGF-β or related ligands, serine and threonine kinase receptors phosphorylate proteins of the SMAD family, which then form heteromeric complexes with SMAD-4. These complexes are then transported to the nucleus where they interact with DNA, resulting in growth inhibition and initiation of apoptosis.

BMPR1A is the gene upstream from SMAD-4 in the TGF-β pathway. It encodes a serine/threonine kinase receptor that, when activated through phosphorylation, phosphorylates SMAD protein family members. Many different mutations in BMPR1A have been identified to date in PJI families (134). Mutations usually result in a receptor lacking its intracellular serine–threonine kinase domain, an alteration that results in loss of signaling through SMAD-4.

Some clinicopathologic differences may be observed in SMAD-4 mutation–positive versus BMPR1A mutation–positive patients. Those with SMAD-4 mutations have a higher frequency of upper gastrointestinal polyps and are more likely to have a family history of juvenile polyps than are patients with BMPR1A mutations (135,136).

**Gross and Endoscopic Features**

Patients with juvenile polyposis usually have 50 to hundreds of polyps (137). Juvenile polyps are relatively small lesions, ranging in size from <1 mm to 5 cm, with most measuring 1 to 1.5 cm in diameter. The colonic mucosa between polyps is normal in appearance. The majority of polyps appear pedunculated; only about 25% are sessile. Polyps developing in different parts of the GI tract grossly resemble one another. Large lesions present as grayish-pink-red, spherical, mushroomlike, lobulated lesions. The lobulation results from secondary inflammation and ulceration. If the polyps are received fresh, they often exhibit small white patches due to the presence of underlying cysts filled with mucin. Small lesions have a more rounded shape with a smooth surface. The external gross features of juvenile polyps are often indistinguishable from those of adenomas (Fig. 12.26). However, their cut surfaces display variably sized mucus-containing cysts embedded in a gray fibrous stroma (137) (Fig. 12.26).
**Histologic Features**

Juvenile polyps histologically fall into several categories, including typical juvenile polyps or juvenile polyps containing hyperplastic, metaplastic, ganglioneuromatous, adenomatous, or adenocarcinomatous foci. Typical juvenile polyps consist of gastrointestinal glands indigenous to the site of origin, surrounded by a prominent stroma (Figs. 12.27, 12.28, and 12.29). The large amount of stroma surrounds branched, sometimes cystically dilated, tortuous glands (Figs. 12.27 and 12.28). The glands demonstrate considerable variation in size and shape, and may occasionally demonstrate a serrated pattern (Fig. 12.29) resembling that seen in hyperplastic polyps, serrated adenomas, or sessile serrated polyps. The serrated pattern results from epithelial hyperplasia. The epithelial-lined cysts are empty or filled with mucus or inflammatory cells (Figs. 12.27 and 12.28). Cystically dilated glands herniate, resulting in extension of mucus, inflammatory cells, and debris into the surrounding lamina propria (Fig. 12.30). The lining epithelium appears columnar, cuboidal, or flattened depending on the degree of pressure atrophy present. Sometimes the epithelial lining disappears completely (Fig. 12.30). Paneth cells may be quite prominent. The polyp surface may be covered by a single layer of cuboidal or columnar epithelial cells. Goblet cells are often interspersed between these cells. When the polyps become ulcerated, capillaries proliferate in the superficial lamina propria, forming a granulation tissue cap. With additional ulceration, the glands become more dilated, capillaries show greater degrees of cellular proliferation, and the number of inflammatory cells increases.
FIG. 12.27. Polypectomy specimens of juvenile polyps. A: A pedunculated colonic lesion that was removed by electrocautery. It contains a proliferation of epithelium and large cystic spaces. B: A different specimen containing large amounts of congested stroma and large cystic spaces.

FIG. 12.28. Resection specimen from a patient with juvenile polyps. One can see the marked congestion present within the polyp, as well as a cystic dilation of glands. The specimen contains a disproportionate amount of stroma and an underrepresentation of glands.

Smooth muscle fibers are usually absent except in the center of the lesion. These fibers are more abundant in the neck of the polyp than in the head. In pedunculated polyps, the neck region may contain dense intertwined smooth muscle cells. However, the bundles of smooth muscle cells are much less dense than those found in Peutz-Jeghers polyps (Fig. 12.31).

An edematous, often inflamed stroma separates the glands of the polyp. As a result, the crypts appear widely separated from one another. The amount of stroma usually appears disproportionate to the amount of epithelium. Juvenile polyps contain comparatively more stroma than either Peutz-Jeghers polyps or adenomas. The stroma often contains dilated vessels, areas of hemorrhage or hemosiderin deposition, and variable numbers of inflammatory cells (Fig. 12.32). Neutrophils are particularly prominent around ulcerated edges and dilated telangiectatic vessels (Fig. 12.32). The stroma may also contain prominent lymphoid follicles. When the stalk twists, the polyp undergoes torsion with hemorrhage and ulceration. Metaplastic stromal changes include the presence of ectopic bone or cartilage (Fig. 12.32).

Gastric juvenile polyps consist of hyperplastic foveolae and edematous stroma with inflammatory cells, resembling the more common gastric hyperplastic polyps. They also resemble the polyps seen in Cronkhite-Canada syndrome.
Chapter 12

syndrome. A definitive diagnosis requires knowledge of the clinical background of the patient, including patient age, symptoms, distribution of the polyps, the number of polyps, and associated extraintestinal manifestations. Dysplasia and carcinoma may develop in colonic or gastric lesions.

**Ganglioneuromas in Juvenile Polyps**

The ganglioneuromatous proliferation seen in juvenile polyps is characterized by clusters of mature ganglion cells and hypertrophic nerve fiber bundles in the lamina propria and submucosa (Fig. 12.33). The patients usually do not have a history of neurofibromatosis or multiple endocrine neoplasia type IIB (138), but may have Bannayan-Riley-Ruvalcaba syndrome (macrocephaly, multiple lipomas, and hemangiomata syndrome), one of the PTEN hamartoma syndromes (139). It is unclear whether the ganglioneuromatous proliferation represents a reactive or neoplastic process.
FIG. 12.29. Juvenile polyp. A through D represent different areas of the lesions. A, B: Marked congestion as well as an infiltration of the lamina propria with large numbers of mononuclear cells. In B, the epithelium has become hyperplastic, giving the glands a somewhat tortuous appearance. C: The edge of hyperplastic colonic epithelium and prominent mucin within the gland. The nuclei are pushed to the base of the cell. The surrounding lamina propria contains an intense infiltrate of mononuclear cells. D: Higher magnification of the mononuclear cell infiltrate.

FIG. 12.30. Sections of juvenile polyps demonstrating various aspects of histologic features. A represents an area in which the mucus-filled gland has disintegrated. The lining epithelium is no longer evident. B shows the marked tortuosity that the glands can achieve. C represents a small crypt abscess in an otherwise atrophic gland. In D, marked disorganization of the tissue is evident.
FIG. 12.31. Comparison of juvenile polyps, Peutz-Jeghers polyps, and adenomatous polyps. As can be seen, the juvenile polyp (A) shows far more congestion and a greater percentage of stroma than other polyps (B, C). The Peutz-Jeghers polyps show large numbers of glands with variable amounts of smooth muscle. The epithelia in A through C appear benign, whereas the epithelium in D is hyperchromatic and some of the glands have a back-to-back configuration.

FIG. 12.32. Stromal changes in juvenile polyps. A: The surfaces of juvenile polyps frequently become eroded and ulcerated, as in this case. B: Some polyps undergo osseous or cartilaginous metaplasia, as illustrated in this figure (star).
Chapter 12

FIG. 12.33. Juvenile polyp combined with ganglioneuromatous proliferation. A through C derive from the same polyp. A: Note the presence of atypical epithelium within the polyp. B: Marked hyperplasia and neuromatous proliferation of the myenteric plexus are seen. C: A more typical area of a juvenile polyp with proliferation of neural tissue within the lamina propria, causing the lamina propria to appear more cellular than normal.

FIG. 12.34. Juvenile polyps. A represents mixed hyperplastic adenomatous-type epithelium, in which stratified nuclei are evident, as are serrated lumens. B represents a gland with mild dysplasia.

Relationship of Juvenile Polyps to Dysplasia and Carcinoma

 Relatives of patients with juvenile polyposis, as well as the patients themselves, are at increased risk for developing gastrointestinal carcinoma (140,141). In contrast, patients with solitary juvenile polyps rarely develop colon cancer (140). Coburn et al found a total of 218 PJI patients who developed cancer (140). A family history of polyps was present in 50% of the patients, and 15% had associated congenital malformations. The mean age at diagnosis of carcinoma was 35.5 with a range of 4 to 60 years. Most malignancies were located in the distal colon and rectum with isolated cases of gastric and duodenal carcinoma. Tumor stage at diagnosis was usually advanced, with poor patient survival (140). Bentley found that 8% to 20% of PJI patients have either juvenile polyps containing adenomatous (dysplastic) areas or have both juvenile polyps and adenomas. Approximately 20% to 30% of these patients had cancer (142). Dysplasia is more common in larger polyps (>1 cm in size) (137).

 Dysplasia or adenomatous foci occur in two forms: (a) as a focus of adenomatous change in a juvenile polyp or (b) as an adenoma showing no residual juvenile features. Adenomatous changes occur as early as age 3. Carcinomas arise in the dysplastic adenomatous areas. The histologic features suggest a sequence of early hyperplasia passing through dysplasia to carcinoma (Fig. 12.34). The adenomas and adenomatous foci develop in the colon as well as in the stomach, duodenum, jejunum, and ileum. Carcinoma may also develop in polyps at gastrojejunostomy sites (143). Cancers that develop at an early age have a poor prognosis.

 Colon biopsies are warranted in patients with large lesions and multiple juvenile polyps to exclude the presence of neoplasia. The terminology used to describe these lesions is inconsistent, but it is important to make the distinction between regenerative and dysplastic changes, because the implications for clinical follow-up are different. The diagnosis of dysplasia is often straightforward, especially when the lesions consist exclusively of adenomatous epithelium. However, in mixed lesions it is sometimes extremely difficult to distinguish dysplastic areas from the epithelial atypia associated with reparative responses (Fig. 12.35). One may find small, somewhat eosinophilic, irregular glands lined by mucin-depleted, pseudostratified, columnar epithelium. The cells often exhibit large hyperchromatic nuclei with prominent nucleoli and increased mitotic figures, therefore resembling adenomas.

 The dysplasia found in juvenile polyps is usually low grade. The frequency and severity of the dysplasia correlates with greater polyp diameter in individuals with generalized polyposis (144). Dysplasia is much more likely to be present in villous areas. Jass et al reported a dysplasia incidence of 46.7% in lesions showing a villous architecture, contrasting with only 9% in typical juvenile polyps (144). The dysplasia often resembles that seen...
Lesions that should be examined closely for the presence of dysplasia include those that at first glance do not look like typical juvenile polyps. Often, atypical juvenile polyps contain relatively less lamina propria and more epithelium than are found in typical juvenile polyps (Fig. 12.36). Epithelial dysplasias affect both typical and atypical polyps, but the frequency varies considerably in the two types of lesions.

Patients with single juvenile polyps are treated conservatively. Polypectomy is performed and patients are then discharged from care. Patients with multiple polyps, juvenile polyposis, or polyps containing dysplasia or adenomatous transformation require more rigorous follow-up. Genetic testing is available for juvenile polyposis. Patients with PJH should begin upper endoscopy and colonoscopy in adolescence. If multiple polyps are identified, they should all be removed. Annual surveillance is then indicated. All polyps should be examined by a pathologist to rule out the presence of dysplasia or invasive carcinoma. If no polyps are identified on initial endoscopy, screening should be performed at 3-year intervals. Colectomy may be necessary if polyps are too numerous to be removed, or if dysplasia or carcinoma are identified.

**FIG. 12.35.** Atypical epithelium in juvenile polyp. *A:* One sees the darkly staining epithelium surrounded by a markedly congested stroma. Acute inflammation is absent. Such areas can be designated as atypical. *B:* Higher magnification of another area in this polyp showing an apparent back-to-back configuration of glands that are difficult to distinguish between a regenerative process and early low-grade dysplasia. Such lesions can be classified as atypical epithelium. The presence of the neutrophils suggests that this is in an area of resolving inflammation.

### Familial Gastric Polyposis

Familial gastric polyposis may represent a new autosomal dominant syndrome. Cases without a family history may result from new mutations. Patients show a high incidence of cutaneous psoriasis. Gastric hyperplastic polyposis patients have numerous hyperplastic polyps that average 1 cm in size with most lesions measuring <1.5 cm in diameter. The multiple polyps generally appear uniform in shape and size. When more than 50 polyps are present, the term *hyperplastic polyposis* is applied. Gastric polyps develop in 34% to 60% of affected patients (145).

Histologically, the polyps resemble atypical juvenile colonic polyps, fundic gland polyps, or hyperplastic polyps. They are scattered throughout the gastric fundus and body with less frequent involvement of the cardia and antrum. These polyps tend to remain asymptomatic and there appears to be only a slightly increased risk for the development of gastric cancer over that seen in the general population. Carcinoma develops in the hyperplastic polyps.

### Cowden Disease (PTEN Hamartomatous Tumor Syndrome)

Cowden disease (OMIM entry #158350) is a rare disorder named after the family in which it occurred. Synonyms for this syndrome include Lhermitte-Duclos disease and the recently proposed term *PTEN hamartomatous tumor syndrome.*

Cowden disease results from mutations in the *PTEN* gene. *PTEN* encodes a dual specificity phosphatase that affects apoptosis and inhibits cell spreading via the focal adhesion kinase pathway. Mutations include missense and nonsense point mutations, deletions, insertions, and splice site mutations, and occur scattered over the entire length of the gene.
with the exception of the first, fourth, and last exons (146). Approximately two thirds of the mutations occur in exons 5, 7, and 8, with 40% affecting exon 5.

**FIG. 12.36.** True dysplasia within a juvenile polyp. *A:* A medium magnification of the dysplastic area that resembles adenomatous epithelium. One sees nuclear stratification and an increased number of mitotic figures. In addition, there is a complex glandular branching imparting a back-to-back architectural pattern. *B:* Higher magnification showing the nuclear stratification and the increased number of mitotic figures.

**Clinical Features**

Cowden disease is characterized by hamartomatous neoplasms of ectodermal, mesodermal, and endodermal origin. The estimated incidence of the disorder is 1 per 200,000. Ten to fifty percent of cases are familial, with as many as 90% of patients manifesting signs or symptoms of the disease by age 20 (147). By age 30, 99% of patients demonstrate at least the mucocutaneous features of the disease. The disease affects males and females equally.

Most tumors arising in Cowden disease are benign and commonly develop on the face and in the thyroid gland, breast, or GI tract. Gastrointestinal polyps occur in 60% of patients, and may be histologically indistinguishable from juvenile polyps. However, Cowden disease can be distinguished from juvenile polyposis with knowledge of the extraintestinal manifestations in the affected patient. Other gastrointestinal polyps that occur in Cowden disease patients include ganglioneuromas, lipomatous lesions, and inflammatory polyps.

Facial tricholemmomas are considered pathognomonic for Cowden disease, but affected patients present with other facial abnormalities as well (Fig. 12.37). The skin lesions typically develop between ages 20 and 30.

Thyroid disease is the most common extracutaneous abnormality, occurring in 68% of patients (147). The benign lesions are usually goiters or adenomas. Skeletal abnormalities affect 33% of patients. Bone cysts, syndactyly, and other digit abnormalities have been described. Breast carcinoma is the most common malignancy occurring in patients with Cowden syndrome. It affects 36% to 50% of females with the disease (148).

**Gastrointestinal Lesions**

Patients may have coexisting gastrointestinal polyps, ganglioneuromatosis of the colon, and glycogen acanthosis of the esophagus (147). Polyps affect 71% of patients who undergo evaluation of the alimentary tract (149). These occur anywhere from the esophagus to the rectum, but the distal colon is the preferentially involved site. Intestinal polyps in this syndrome include juvenile polyps (Fig. 12.38), Peutz-Jeghers-type polyps, lipomas, inflammatory polyps,

Lymphoid polyps, hyperplastic polyps, epithelioid leiomyomas, and ganglioneuromas. The lesions are usually small and asymptomatic, and grossly resemble hyperplastic polyps. Microscopically, the polyps contain a mixture of cell types, including fibroblasts and adipose tissue (Fig. 12.39). The most common colonic polyp in Cowden disease contains elongated, irregular, regenerative-appearing crypt epithelium with cystic dilation, mild lamina propria edema, inflammation, and variable fibrosis. Cellular pleomorphism or atypia are absent. One may also see thickening of the collagen table underlying the luminal surface as occurs in patients with hyperplastic polyps or collagenous colitis. Biopsies of the polyps may show only mild glandular architectural distortion with variable fibrosis and inflammation of the lamina propria predominantly consisting of plasma cells, lymphocytes, and eosinophils. Fat cells may be present in the lamina propria. Dysplasia and adenomas are rare.
Polyps may also be found in the stomach. Gastric lesions show foveolar hyperplasia or show a resemblance to Peutz-Jeghers or hyperplastic-type lesions. The polyps in the stomach may also contain neural elements. Other gastrointestinal lesions include duodenal lymphoid polyps, duodenal lymphangiectasia, and jejunal lymphangiomas.

**Treatment and Prognosis**

There does not appear to be a significantly increased risk of gastrointestinal cancer in Cowden disease. As a result, many believe that gastrointestinal examinations are unnecessary unless GI symptoms are present. Screening strategies for extraintestinal tumors should be undertaken, however, since 74% of patients develop some form of malignant disease, most commonly invasive ductal breast carcinomas and thyroid tumors. The mean age at diagnosis of breast cancer is 10 years earlier than that of breast cancer in the general population. Men with Cowden disease are also at risk for development of breast cancers. The risk of thyroid cancer (predominantly follicular carcinoma) may be as high as 10% (147). Patients also have an increased risk of endometrial cancer. Other tumors that develop include brain tumors,
mucocutaneous basal cell and squamous cell carcinomas, melanomas, lymphomas, Merkel cell carcinomas, non–small cell lung cancers, ovarian cancers, renal cell carcinomas, transitional cell carcinomas of the bladder, and osteosarcomas. Rarely, gastric, colorectal, hepatocellular, or pancreatic carcinomas develop (147,148).

**FIG. 12.39.** Colonic polyps in Cowden disease. A: Colonic polyp containing abundant adipose tissue. B: Another polyp in the same patient showing a fibrous proliferation underlying the mucosa. C: Ganglioneuroma in another patient with Cowden disease. The colonic glands are separated by a spindle cell proliferation. D: On higher power, scattered ganglion cells are seen within the mucosal spindle cell areas.

P.723

---

**Bannayan-Riley-Ruvalcaba Syndrome**

Another rare hamartomatous syndrome is Bannayan-Riley-Ruvalcaba syndrome (BRRS) (OMIM entry #153480) (Fig. 12.40), also known as the Ruvalcaba-Myhre-Smith syndrome, Bannayan-Zonana syndrome, and Riley-Smith syndrome. This is a generalized hamartomatous syndrome that mainly affects men, and overlaps with Cowden disease. It is inherited as an autosomal dominant disorder and, like Cowden disease, has been associated in 60% of cases with inherited mutations in the PTEN gene (150,151). Unlike Cowden disease, the PTEN mutations found in BRRS do not occur in the PTPase core motif of the gene. Some BRRS patients have PTEN gene deletions (152).

BRRS is noted at birth or shortly thereafter and is characterized by delayed psychomotor development, ileal and colonic juvenile polyps, lingual lesions, subcutaneous and visceral lipomas and hemangiomas, multiple variable congenital anomalies, mental retardation, ocular abnormalities, skeletal abnormalities, thyroid tumors, and pigmented penile macules (Fig. 12.40) (153). The hamartomatous gastrointestinal lesions resemble juvenile polyps, and may occasionally contain areas of dysplasia (154). A definite association with cancer development has not been demonstrated among patients with BRRS.
Chapter 12

Neurofibromatosis 1

Neurofibromatosis 1 (NF1), or von Recklinghausen disease (OMIM entry #162200), is not classically considered a hamartomatous polyposis syndrome, but affected patients may develop multiple submucosal gastrointestinal neurofibromas. This entity is discussed in Chapter 19.

Nonhereditary Hamartomatous Polyposis Syndromes

Cronkhite-Canada Syndrome

Clinical Features

Cronkhite-Canada syndrome (CCS) is a rare, nonhereditary, adult gastrointestinal polyposis syndrome that occurs worldwide. It affects both sexes equally, with patients ranging in age from 31 to 83 years at the time of diagnosis (155). Eighty percent of patients present after the age of 50. All cases are sporadic, and CCS is not considered a genetic disease. Proposed etiologic theories include nutritional deficiency states, disaccharidase deficiency accompanied by bacterial overgrowth, infection, disturbances of intestinal mucin secretion, or some form of immunologic disorder (156,157).

CCS associates with skin hyperpigmentation, patchy vitiligo, alopecia, onychodystrophy, marked edema, tetany, glossitis, and cataracts (Fig. 12.41). The most common symptoms include diarrhea, protein-losing enteropathy, weight loss, abdominal pain, anorexia, weakness, hematochezia, vomiting, paresthesias, and xerostomia. The diarrhea usually consists of loose, watery bowel movements occurring five to seven times per day. They may be grossly bloody, and the blood loss may be significant enough that the patient requires transfusions. Malabsorption invariably develops, probably due to diffuse small intestinal mucosal injury. Laboratory findings include hypoproteinemia, particularly hypoalbuminemia, hypocalcemia, hypomagnesemia, anemia, occult blood in the stool, and electrolyte deficiencies.

FIG. 12.40. Diagrammatic representation of many of the intestinal and extraintestinal lesions found in patients with Bannayan-Riley-Ruvalcaba syndrome.
Symptom onset may be acute and the course rapidly progressive. The major clinical problem in these patients results from protein loss from the damaged mucosa and variable malabsorption. Profound malnutrition may occur and is a major cause of morbidity and mortality. Aggressive supportive therapy with nutritional supplementation, fluid and electrolyte replacement, and transfusion of blood components is warranted to correct the existing or impending deficiencies. The use of total parenteral nutrition is successful in some patients. The mortality rate is 50% to 60%. While spontaneous remissions may occur, survival beyond 2 years for symptomatic patients is uncommon. Other therapies have included corticosteroids, antibiotics, and surgery, but results are unpredictable.

Since as many as 20% of CCS patients develop an adenoma or carcinoma, colonoscopic surveillance is indicated (155). The neoplasms develop primarily in the colon and less frequently in the stomach. Colonic lesions tend to occur in a proximal location. Surgery is recommended when complications such as bleeding, intussusception, bowel obstruction, malignancy, or prolapse develop.

**Pathologic Features**

Polyps develop throughout the GI tract, sometimes occupying the entire mucosal surface of affected sites. Polyp density is greatest in the stomach and colon, followed by the duodenum, ileum, and jejenum. The polyps vary in color from tan to red, sometimes demonstrating areas of surface ulceration and hemorrhage. Their gross appearance varies from diffuse mucosal micronodularity or granularity to gelatinous-appearing pedunculated polyps. The gelatinous appearance results from the presence of large mucosal cysts (Fig. 12.42).

Polyp morphology reflects the site of origin. The polyps resemble colonic juvenile polyps or gastric hyperplastic polyps. Gastric polyps are broad-based sessile lesions that contain corkscrew-shaped glands. Smooth muscle fibers extend up into the mucosa. The polyps contain an expanded, edematous lamina propria and distended, cystic glands lined by flattened epithelium, variable edema, and chronic inflammation. Gastric polyps tend to occur in the antrum forming hyperplastic gastric folds, some of which mimic Menetrier disease. The lesions can spontaneously regress. Adenomatous changes may be present, as can coexisting colorectal carcinomas. Small intestinal lesions are essentially similar, although the degree of inflammation and edema tends to be greater than in the stomach and the lesions tend to involve the entire bowel wall thickness. Villi and crypts decrease in number. Goblet cells increase in the remaining crypts.
Chapter 12

FIG. 12.42. Cronkhite-Canada syndrome. Sessile pedunculated lesion in a patient with numerous other polyps. Large mucus-filled cysts distort the architecture.

The only reliable distinction between CCS and colonic juvenile polyposis is the pedunculated growth of the latter. However, it is important to note that pedunculation is not always present in juvenile polyps. The diagnosis of CCS polyps, especially when located in the stomach, requires knowledge of the clinical context.

Other Polyposis Syndromes

There are other syndromes associated with the development of gastrointestinal polyps. Ganglioneurofibromatosis may associate with juvenile polyposis or multiple endocrine neoplasia syndrome. The pathologic features of ganglioneurofibromatosis are discussed in Chapter 19. Patients with the basal cell nevus syndrome may develop multiple gastric polyps. Multiple recurrent inflammatory fibroid polyps of the stomach and intestine have been reported in families (158). Affected patients present with repeated bouts of intussusception and the polyps range in size from 0.5 to 8 cm. Multiple inflammatory polyps also complicate various infectious diseases or idiopathic inflammatory bowel disease. These polyps are discussed in Chapters 13 and 11, respectively. Multiple lipomatosis is discussed in Chapter 19. Multiple lymphoid polyps and lymphomatosis are discussed in Chapter 18. Patients with hereditary angiomases may present as a polyposis syndrome. These lesions are discussed more fully in Chapter 19.

Hereditary Gastrointestinal Cancer Syndromes Without Polyposis

Hereditary Nonpolyposis Colorectal Cancer Syndrome

HNPCC, or Lynch syndrome, is the colon cancer family syndrome not classically associated with large numbers of colonic adenomas. The features of HNPCC are listed in Table 12.10. HNPCC-associated lesions are summarized in Figure 12.43. Several international diagnostic criteria have been established for the diagnosis of HNPCC (Table 12.11) (159,160). The Amsterdam criteria were developed to ensure international uniformity and to facilitate comparison of clinical, pathologic, and molecular genetic data in these patients (159). The Bethesda guidelines, and the revised Bethesda guidelines, introduced molecular genetic considerations, and provided criteria to be used to determine which individuals’ tumors should undergo microsatellite instability and/or genetic testing (160,161).

<table>
<thead>
<tr>
<th>TABLE 12.10 Features of Hereditary Nonpolyposis Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant inheritance pattern</td>
</tr>
<tr>
<td>Patients develop cancer at a young age (peak age 45 years) as compared with sporadic colon cancer</td>
</tr>
<tr>
<td>Tumors tend to originate proximal to the splenic flexure</td>
</tr>
<tr>
<td>Tendency to develop multiple tumors</td>
</tr>
<tr>
<td>Abundant mucin secretion by the tumor (in 20% of cases)</td>
</tr>
<tr>
<td>Tumors tend to be diploid</td>
</tr>
<tr>
<td>Tumors tend to be surrounded by prominent lymphoid infiltrates</td>
</tr>
<tr>
<td>Small intestinal cancers arising at sites other than the colon</td>
</tr>
</tbody>
</table>
periampullary region

Frequent association with tumors of other sites, especially the endometrium, urothelium, and stomach


Overall, HNPCC-associated colorectal cancers account for only a small percentage of the total colorectal cancer burden (6% to 15.8%), but they represent the most common form of inherited colorectal cancer (162). HNPCC is five times more common than FAP. It is estimated that the prevalence of HNPCC-associated mutations in the general population in Western countries is between 1 in 200 and 1 in 2,000 (162). HNPCC affects many races, including Europeans, Native Americans, Australians, Asians, and South Americans. First-degree relatives of patients with HNPCC have a sevenfold increased colon cancer incidence compared with the general population. HNPCC patients develop cancer at a younger age than patients with sporadic cancer, with a mean age of 39 years for men and 37 years for women. One difficulty in recognizing an HNPCC patient is that the syndrome gives no hint of its existence in the individual patient unless an increased family incidence of colon cancer has already become evident. In the past, identification of the syndrome required examination of family pedigrees. Today, the use of genetic testing for specific mutations allows the diagnosis of individual cases of HNPCC.

**Genetics of Hereditary Nonpolyposis Colorectal Cancer**

HNPCC is inherited as an autosomal dominant condition, with affected patients carrying germline mutations in a DNA mismatch repair (MMR) gene. The most commonly implicated genes are MLH1 located on chromosome 3p and MSH2 located on chromosome 2p. MLH1 mutations are found in 43% to 63% of HNPCC families, and MSH2 mutations in 25% to 45% (163,164). Less commonly, mutations in other MMR genes occur. Patients carrying HNPCC-associated mutations exhibit a 40% to 80% lifetime risk of developing colorectal cancer (165,166,167). Because the HNPCC genes are not 100% penetrant, one may see the cancer phenotype in the maternal or paternal lineages but not in the patient's parents.

| TABLE 12.11 Clinical and Molecular Criteria for Diagnosis of Hereditary Nonpolyposis Colorectal Cancer (HNPCC) |

---
### Amsterdam I Criteria
At least three relatives with histologically verified colorectal cancer:

1. One is a first-degree relative of the other two
2. At least two successive generations are affected
3. At least one relative is diagnosed with colorectal cancer before the age of 50
4. Familial adenomatous polyposis has been excluded

### Amsterdam II Criteria
At least three relatives with an HNPCC-associated cancer (colorectal, endometrial, stomach, ovary, ureter/renal pelvis, brain, small intestine, hepatobiliary tract, or sebaceous tumor of skin):

1. One is a first-degree relative of the other two
2. At least two successive generations are affected
3. At least one relative is diagnosed with an HNPCC-associated cancer before the age of 50
4. Familial adenomatous polyposis has been excluded

### Bethesda Guidelines for Testing Colorectal Neoplasms for Microsatellite Instability

1. Individuals with cancer in families that meet Amsterdam criteria
2. Individuals with two HNPCC-related cancers including synchronous or metachronous colorectal or extracolonic tumors
3. Individuals with colorectal cancer and a first-degree relative with colorectal cancer, and/or HNPCC-related extracolonic cancer, and/or a colorectal adenoma; one of the cancers diagnosed at age <45 years, or adenoma diagnosed at <40 years of age
4. Individuals with colorectal cancer or endometrial cancer diagnosed at age <45 years
5. Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed at <45 years of age
6. Individuals with signet ring cell–type colorectal cancer diagnosed at <45 years of age
7. Individuals with adenomas diagnosed at <40 years of age

### Revised Bethesda Guidelines

1. Colorectal cancer diagnosed in a patient < 50 years of age
2. Presence of synchronous, metachronous colorectal or other HNPCC-associated tumors (colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, small bowel, brain, and sebaceous adenomas and keratoacanthomas) regardless of age
3. Colorectal cancer with microsatellite instability-high histology (tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet ring cell differentiation, or medullary growth pattern) diagnosed in a patient <60 years of age
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

The MMR genes act as tumor suppressors, with loss of both copies of the gene resulting in unrestrained growth and ultimately neoplastic transformation. HNPCC patients inherit one defective copy of an MMR gene, and the second copy is lost or inactivated as a somatic event. Loss of the second MMR gene often occurs as a result of methylation of the gene promoter rather than through deletion.

The DNA MMR proteins form heterodimers that recognize and repair small sequence errors occurring during DNA replication, including base–base mispairings and insertion/deletion loops or slipped strand mispairings (Fig. 12.44). One result of defective DNA MMR is a phenomenon referred to as microsatellite instability (MSI). MSI occurs in approximately 90% to 95% of cancers in HNPCC (168,169). Microsatellites represent short repetitive DNA sequences scattered throughout the genome. Microsatellite instability is defined as an increase or decrease in the number of nucleotide repeats in a given microsatellite allele in normal tissue versus tumor. The new alleles that are identified in MSI-positive tumors represent small insertions or deletions that occur as a consequence of uncorrected errors in DNA replication.

P.727
Chapter 12

affecting MMR-deficient tumor cells. This heavy burden may decrease the overall viability of the individual tumor cells.

favorable stage at diagnosis. The overall 5-year survival rate is 65% in patients with HNPCC compared with 44% with sporadic carcinomas (182). Their better survival rates may be caused by the heavy mutation burden carcinomas is better than that for sporadic colon cancer (167). Survival rates are better among patients with localized and nonlocalized tumors, discounting the notion that the more favorable prognosis is based on a more proximal to the splenic flexure in 60% to 69% of patients (180).

Before age 50, with 12% developing before age 30. Patients tend to develop multiple tumors. Synchronous and metachronous cancers affect 18% and 24.2% of HNPCC patients, respectively (180). HNPCC cancers occur alterations (181). Patients with MSH2 mutations present latest, with an average age at presentation of 49 years. Eighty percent of colorectal tumors develop MSH6 with MLH1 mutations present earlier than those with MSH2 alterations (181). Patients with MSH6 mutations present latest, with an average age at presentation of 49 years. Eighty percent of colorectal tumors develop

MSH2 and MLH1 mutations. Carriers of MLH1 endometrial cancer is greater in patients with an abnormal gene compared with individuals carrying the APC gene. These different mutations result in different brain tumors.

The average age of onset of colon cancer in HNPCC patients is 45 years (179), contrasting with age 65 in the general population (180). Average age at presentation varies with the genetic defect that is present; patients with either MSH2 or MLH1 mutations. Carriers of MSH2 mutations also have a significantly increased risk of renal and ureteral cancers (relative risk of 75.3), gastric cancer (relative risk 19.9), and ovarian cancer (relative risk 8.0) (159). One phenotypic variation of HNPCC associates with desmoid tumors, a feature more classically associated with FAP (see Chapter 19). Another HNPCC variant associates with glioblastoma multiforme (175). Genetic analyses have shown that patients with Turcot syndrome have mutations in either MMR genes or in the APC gene. These different mutations result in different brain tumors.

Adenomas in Hereditary Nonpolyposis Colorectal Cancer Patients

Despite the name hereditary nonpolyposis colorectal cancer, adenomas do develop in HNPCC patients. Overall, adenomas in HNPCC patients tend to be large (>10 mm), show a villous architecture, contain high-grade dysplasia (176) with a right-sided predominance, develop at an earlier age than sporadic adenomas, and exhibit mucinous differentiation. A high proportion of HNPCC adenomas become malignant (177), and the rate of progression to cancer may be higher than that seen in sporadic adenomas (177). This contrasts with the large numbers of low-grade dysplastic adenomas found in FAP patients (Table 12.12).

In addition to traditional tubular adenomas, HNPCC patients also develop hyperplastic polyps, serrated adenomas, and mixed polyps comprising both serrated and adenomatous components (178). Mixed lesions are larger than adenomas and tend to show pseudo-invasion. They may demonstrate a number of bizarre cytologic features, including multinucleation, atypical mitoses, and chromatin aggregation into coarse clumps.

Colorectal Cancers Arising in Hereditary Nonpolyposis Colorectal Cancer Patients

The average age of onset of colon cancer in HNPCC patients is 45 years (179), contrasting with age 65 in the general population (180). Average age at presentation varies with the genetic defect that is present; patients with MLH1 mutations present earlier than those with MSH2 alterations (181). Patients with MSH6 mutations present latest, with an average age at presentation of 49 years. Eighty percent of colorectal tumors develop before age 50, with 12% developing before age 30. Patients tend to develop multiple tumors. Synchronous and metachronous cancers affect 18% and 24.2% of HNPCC patients, respectively (180). HNPCC cancers occur proximal to the splenic flexure in 60% to 69% of patients (180).

HNPCC-associated malignancies are relatively nonaggressive, despite their tendency to be poorly differentiated and mucinous. Stage for stage, the prognosis for HNPCC-associated carcinomas is better than that for sporadic colon cancer (167). Survival rates are better among patients with localized and nonlocalized tumors, discounting the notion that the more favorable prognosis is based on a more favorable stage at diagnosis. The overall 5-year survival rate is 65% in patients with HNPCC compared with 44% with sporadic carcinomas (182). Their better survival rates may be caused by the heavy mutation burden affecting MMR-deficient tumor cells. This heavy burden may decrease the overall viability of the individual tumor cells.
FIG. 12.45. Mismatch repair protein expression in colon cancer. A: MLH-1 immunostain shows an absence of immunoreactivity in this moderately differentiated colonic adenocarcinoma. B: MSH-2 staining is preserved in the same tumor. C: A different adenocarcinoma shows retention of MLH-1 staining. Note the poor differentiation in this tumor. D: MSH-2 staining is lost in the tumor illustrated in C.

<table>
<thead>
<tr>
<th>TABLE 12.12 Comparison of HNPCC and FAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPCC</td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Onset Early</td>
</tr>
<tr>
<td>Adenoma number &lt;10</td>
</tr>
<tr>
<td>Adenoma histology Tubular adenomas</td>
</tr>
<tr>
<td>Polyp distribution Mainly right side</td>
</tr>
<tr>
<td>Degree of dysplasia in adenoma High grade</td>
</tr>
<tr>
<td>Cancer distribution Mainly right side</td>
</tr>
<tr>
<td>Other cancers See Figure 12.12</td>
</tr>
</tbody>
</table>
### Chapter 12

#### Proportion of adenomas becoming malignant

<table>
<thead>
<tr>
<th>High</th>
<th>Low</th>
</tr>
</thead>
</table>

#### Types of polyps

| Adenomas, serrated polyps, mixed hyperplastic–adenomatous polyps | Adenomas |

FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colon cancer.

**Pathologic Features**

HNPCC-associated colorectal tumors usually arise in the right colon, and may be small, measuring as little as 4 mm in size (182). Many of the colorectal cancers arising in patients with HNPCC demonstrate a solid growth pattern, a feature that accounts for the high proportion of poorly differentiated cancers in these patients. In addition, there is an excess of mucinous and signet ring cell tumors among these patients. The tumors often show an expansile or well-circumscribed tumor border (as compared with infiltrating growth) with marked peritumoral lymphocytic infiltrates (182,183) (Fig. 12.46). In addition, colorectal cancers in these patients often demonstrate large numbers of tumor infiltrating lymphocytes. Some tumors show a “Crohn-like reaction” in which lymphoid aggregates, often with germinal centers, ring the periphery of the invasive carcinoma (Fig. 12.47).

**FIG. 12.46.** This colonic adenocarcinoma shows the pushing border and prominent lymphocytic reaction typically seen in tumors arising in association with hereditary nonpolyposis colorectal cancer.

**Treatment and Surveillance**

Patients with a definitive or suspected diagnosis of HNPCC should undergo surveillance for colorectal cancer and other HNPCC-associated cancers. Colonoscopy should be performed every 2 years beginning at age 20 to 25 years until 40 years of age, at which time screening should be undertaken annually (184). It is important that the colon be well prepped, and any polyps that are present should be completely resected. Patients who develop advanced adenomas can be offered the option of prophylactic subtotal colectomy followed by annual proctoscopy. Annual endometrial cancer screening is recommended for women after age 25 to 35. Screening for other HNPCC-associated malignancies is more controversial (185). Some experts recommend screening for ovarian...
cancer with transvaginal ultrasound and serum CA-125 measurements, as well as screening for gastric cancer in high-risk geographic regions (e.g., Japan) or in families with a known history of gastric cancer (186). Urine cytology and renal ultrasound may also be used to detect lesions in families with histories of genitourinary neoplasms (186).

As in other autosomal dominant conditions, the affected patient should undergo genetic testing to allow for directed testing later in other family members at risk. This should be performed in patients meeting the Amsterdam criteria, or in those who are suspected of having HNPCC and fit the Bethesda guidelines. The affected patient's tumor should first be tested for MSI, as well as for MSH2 or MLH1 expression by immunohistochemistry. If MSI is not found, then sequencing of MMR genes is not warranted. If the tumor is MSI positive or loss of protein expression is found, then sequencing of the mismatch repair genes is indicated. An algorithm for genetic testing and patient follow-up is outlined in Figure 12.48.

**Muir-Torre Syndrome**

Muir-Torre syndrome is a rare autosomal dominant disorder in which affected patients develop skin and other tumors, and exhibit a strong family history of cancer. The tumor spectrum in Muir-Torre syndrome resembles that seen in patients with HNPCC (Lynch II syndrome). Muir-Torre syndrome patients develop colon cancer at an early age. The cancers show a right-sided predominance and have a better prognosis than sporadic colonic cancers. Muir-Torre patients also develop skin tumors associated with their internal malignancies (187). The patients develop sebaceous adenomas and isolated or multiple keratoacanthomas, as well as other skin lesions including benign keratoses, squamous cell carcinoma, basal cell carcinoma, cysts, and fibromas. Sebaceous tumors represent a marker for internal malignancy and should prompt a search for occult cancer in individual patients and their family members (188).
FIG. 12.47. Crohn-like reaction in hereditary nonpolyposis colorectal cancer. **A:** Low-power view of a colonic adenocarcinoma showing a prominent lymphocytic reaction to the tumor. Large germinal centers are seen reminiscent of those occurring in association with Crohn disease. **B:** Higher power view demonstrating the lymphocytic infiltrate around individual infiltrating glands. **C:** Numerous intratumoral lymphocytes are present in this poorly differentiated adenocarcinoma. The tumor showed loss of MSH-2 staining by immunohistochemistry.

Like tumors arising in association with HNPCC, those arising in Muir-Torre syndrome are MSI-H. This finding is observed in both skin tumors and visceral malignancies in these patients (189). Based on this finding, some suggest that the syndrome may represent a variant of HNPCC (190). However, a subset of Muir-Torre patients does exist in which no deficiency in mismatch repair can be identified (191).

**Inherited Susceptibility to Colonic Adenomas and Colorectal Cancer**

An autosomal dominant inheritance pattern affects some patients with discrete colorectal polyps and colorectal cancer. A large Utah kindred that lacked the natural history characteristic of typical hereditary colorectal cancer syndromes was described (192). The patients had an increased colon cancer incidence. The cancers developed at an early age and were frequently multiple, with both synchronous and metachronous colorectal cancers. Patients also developed extracolonic malignancies. The disorder is inherited as a unique syndrome.

**Familial Aggregation of Neuroectodermal and Gastrointestinal Tumors**

Sorensen et al (193) reported a family with multiple tumors, many of which were childhood neoplasms derived from the neuroectoderm. An early onset of colonic cancer was also noted.

P.731
FIG. 12.48. Algorithm for genetic testing and follow-up for patients suspected of having hereditary nonpolyposis colorectal cancer. MMR, mismatch repair; MSI, microsatellite instability.

References


P.732


P.733


Chapter 12

Acquired Abnormalities

Diverticular Disease

**Etiology**

Colonic diverticular disease has become increasingly prevalent in the United States and other economically developed countries. Its incidence varies with national origin, cultural background, and diet, and its frequency increases with advancing age. In Western societies, it affects approximately 5% to 10% of the population over 45 years old and almost 80% of those over age 85 (37). The increased incidence of diverticular disease seen in Japan (38), South Africa (39), and Israel (40) in the last few decades results from incorporation of Western-type foods into the diet in these geographic regions.

Three major forms of diverticular disease exist: (a) one that is associated with classic intestinal muscle abnormalities; (b) a form that complicates connective tissue diseases (41); and (c) forms that complicate neural abnormalities (41). In the most common form of the disease, aging; elevated colonic intraluminal pressure; decreased dietary fiber consumption; consumption of beef, beef fat, and salt; lack of physical activity; and the presence of constipation correlate with its development (42,43). The prevalence of diverticular disease in Western countries increased abruptly 30 years after the introduction of grain milling factories, which decreased the fiber content in grain (44). Decreased luminal fiber and lower stool volume require more colonic segmentation to propel feces forward. The increased segmentation generates greater intraluminal pressures predisposing to diverticula formation. The colonic wall is weakest where penetrating arteries pierce the muscularis propria; this is where the diverticula typically form. Genetic factors may also play a role in the development of diverticular disease since diverticula arise in the right colon in Asians (45) and young patients, contrasting with sigmoid and left colonic involvement among Occidentals and older individuals (46,47). Alternatively, right-sided diverticulosis is a different disease than left-sided predominant diverticulosis. Some patients with solitary rectal diverticula have scleroderma (48). Children with colonic diverticulosis often have underlying Marfan or Ehlers-Danlos syndrome or an association with polycystic kidney disease (49).

**Clinical Features**

Most people with diverticulosis remain asymptomatic, only to be diagnosed incidentally (Fig. 13.26). Ten to twenty-five percent of patients become symptomatic (49), usually due to development of diverticular inflammation (diverticulitis). Diverticulosis affects both sexes equally (45), although complicated diverticulosis more frequently affects obese males (50). Children with diverticulosis often have an underlying connective tissue disease or polycystic renal disease (49). Acute diverticulitis varies in severity. Clinical features include lower abdominal pain, made worse by defecation, and signs of peritoneal irritation, including muscle spasm, guarding, rebound tenderness, fever, and leukocytosis. Symptom duration may be short and rectal examination may reveal the presence of a tender mass. Patients developing diverticulitis at an early age appear to have a more virulent form of the disease than other individuals (50).
Acquired Abnormalities


Rectal bleeding, usually microscopic, affects 25% of patients. Significant bleeding occurs in 3% to 5%. Diverticular bleeding can be sudden in onset, painless, massive, and not accompanied by signs or symptoms of diverticulitis. Bleeding is more common in patients with diverticulosis complicating an underlying connective tissue disease. Although most diverticula arise on the left side, most diverticular bleeds complicate right-sided diverticula (51). The reason for this is unclear. One explanation may be that right-sided diverticula have wider necks than left-sided ones (51). The blood appears bright red, maroon, or melanic, especially if it comes from the right colon. Bleeding most often occurs from a single diverticulum and it stops spontaneously in 80% to 90% of patients (52). Some patients develop recurrent, left lower quadrant, colicky pain without clinical or pathologic evidence of acute diverticulitis. Alternating bouts of constipation and diarrhea result from muscle spasm. Most patients have elevated white blood cell counts, erythrocyte sedimentation rates, and C-reactive protein. When diverticulitis develops, the clinical features reflect host defenses and bacterial virulence.

Complications of diverticular disease are shown in Figure 13.27. They are more common among individuals ingesting nonsteroidal anti-inflammatory drugs (NSAIDs) (53), perhaps because the drugs mask the symptoms of earlier disease or because the NSAIDs interfere with natural mucosal defenses. Life-threatening complications are more common among patients with chronic renal failure or on high-dose steroid therapy (54,55). Complications include bleeding, perforation, fistula formation, peritonitis, obstruction, and peridiverticular abscesses. Fistulae complicate transmural inflammation. When fistulae develop, diverticular disease resembles Crohn disease (CD). Pseudodiverticula result from partial drainage of an abscess cavity into the colon. Patients may die from recurrent pericolic abscesses, peritonitis, fecal peritonitis, bleeding, or bowel obstruction (56).
Acquired Abnormalities

**Giant colonic diverticula** are rare complications of diverticular disease. They are characterized by the formation of large, unilocular, gas-filled cysts measuring 7 cm or more in diameter (Fig. 13.28). Rare lesions measure over 27 cm in diameter. Giant diverticula typically develop on the mesenteric border of the sigmoid colon. Patients range in age from their mid-30s to their 80s. The lesions mimic enterogenous cysts (57).

Barium enema often establishes the diagnosis of diverticulosis. Early changes consist of the presence of fine mural serrations known as the *prediverticular state* or *myochosis*. “Saw tooth” luminal irregularities reflect associated muscle spasm. A contracted haustral pattern may also be seen. The sigmoid becomes shortened and distorted, causing it to acquire a concertinalike appearance with bunched, redundant mucosal folds. These can significantly narrow the colonic lumen and may cause obstruction with dilation proximal to the area of obstruction.

**Pathologic Features**

Diverticula are flask-shaped mucosal outpouchings that develop anywhere in the colon. In the Western world, 90% of patients have involvement of the sigmoid colon and 20% of patients have pancolonic involvement. In contrast, Asians with diverticular disease develop multiple diverticula in the right colon (45). Diverticula usually form where the penetrating arteries pierce the muscular wall. Because the penetrating arteries enter on the mesenteric side of the two lateral taeniae coli, diverticula commonly appear as two parallel rows of beaded outpouchings along the bowel wall (Fig. 13.29). Appendices epiploicae also
Acquired Abnormalities

lie in this location and they may cover diverticula beneath them. The presence of pronounced muscular hypertrophy provides a clue to the presence of the diverticula, since the muscle thickening is the most consistent and striking abnormality. The taeniae coli appear thickened, developing an almost cartilaginous quality; the circular muscle becomes corrugated (Figs. 13.30 and 13.31) (58). The mouths of the diverticula lie between the muscular corrugations as they penetrate the muscularis propria (Fig. 13.32).

FIG. 13.28. Giant sigmoid diverticulum. Double-contrast enema of the sigmoid shows a large air-filled, barium-coated defect projecting from midsigmoid colon that represents a giant sigmoid diverticulum.

Because the diverticula often lack the muscular layer, secretions and fecal material easily enter them where they accumulate because they cannot be expelled (Fig. 13.29). Feces in the diverticular orifice block the outflow of secretions. The resulting obstruction and ulceration (with bacterial invasion) leads to diverticulitis via mechanisms resembling those seen in appendicitis (see Chapter 8). Mucosal ulceration by a fecalith leads to infection, diverticulitis, and bleeding. Bleeding usually comes from uninflamed diverticula (Fig. 13.33) and the exact bleeding point is often difficult to identify. Occasionally, one is lucky enough to see a bleeding point or to obtain a histologic section through a diverticulum that identifies the bleeding source. Arteriolar rupture involves small vessels measuring <1 mm in diameter and always occurs on the side of the vessel facing the bowel lumen (Fig. 13.34) (59). The colonic wall may be thickened by pericolonic fibrosis, grossly simulating a neoplasm or inflammatory bowel disease.

Tonic muscular contractions produce redundant, accordionlike, mucosal folds (Fig. 13.35), which appear as exaggerations of the mucosal folds or as larger, leaflike, smooth-surfaced “polyps” with broad bases (60). When multiple, they form two rows between the diverticula. Repeated trauma to the folds causes mucosal erosion and bleeding. Colonoscopic examination in patients with diverticulosis-associated colitis shows confluent granularity and friability affecting the sigmoid colon surrounding the diverticular ostia. The colonic mucosa proximal and distal to the area of diverticulosis appears endoscopically normal. Not uncommonly, a diagnosis of Crohn disease is entertained due to the segmental nature of the colonoscopic findings. The biopsy can often be differentiated between the two entities if the pathologist is made aware of the presence of diverticulosis in the segment of interest.

The histologic features depend on whether one is dealing with simple diverticulosis or with its complications. The major
Acquired Abnormalities

Pathologic features of uncomplicated diverticulosis include a thickened muscularis propria and the diverticular outpouchings (Fig. 13.32), usually lined by mucosa, muscularis mucosae, submucosa, and variable amounts of muscularis propria (Figs. 13.31 and 13.32). Early diverticula may still possess an outer lining of attenuated muscle. This disappears as the diverticula extend beyond the colonic wall. The mucosa appears normal or may show marked chronic inflammation, with or without acute inflammation producing a pattern sometimes referred to as "isolated sigmoiditis" (Fig. 13.36). Trauma within a diverticulum may induce asymmetric intimal proliferations and scarring of the associated vessels, predisposing them to rupture and bleeding (59). The arterial wall exhibits duplication of the internal elastic lamina and eccentric medial thinning, especially on its luminal side (Fig. 13.34). Some have suggested that the thick-walled vessels are angiodysplastic and that there is an association between angiodysplasia and diverticular disease (61). The myenteric plexus may become abnormal and disorganized (Fig. 13.37), a change leading to secondary motility disturbances.

**FIG. 13.29.** Colonic diverticulosis. **A:** Opened bowel. Two parallel rows of numerous diverticular openings are easily visualized. **B:** The serosal aspect of the specimen in A. Numerous diverticular outpouchings are present. Their relationship with the appendices epiploica is also seen. **C:** Cross section of diverticulosis demonstrating the flasklike outpouchings extending into the colonic fat. **D:** Luminal surface showing two diverticula filled with feces.

When diverticulitis develops, the diverticulum becomes infiltrated with acute inflammatory cells, followed by chronic inflammation. As the inflammation extends, the mucosa ulcerates and abscesses or fistulae form. Granulomas may also be present. Sometimes one receives tissues thought to represent a "serosal mass." It results from the walling-off of an abscess or a diverticulum in which the fibrosis produces a localized, serosal, interlacing matrix of connective tissue surrounding fecal material (Fig. 13.38).
Acquired Abnormalities

Redundant mucosal folds appear polypoid with increased mucosal height, crypt elongation, mucosal distortion, edema, vascular congestion, and hemorrhage, possibly associated with thrombi, hemosiderin deposits, erosions, granulation tissue, and fibrosis (Fig. 13.35). Fibers of the muscularis mucosae extend high into the lamina propria, producing changes resembling those seen in mucosal prolapse.

In isolated sigmoiditis, crescenteric colitis, or diverticular disease–associated colitis (these are all synonyms), the histologic changes may exactly mimic those found in inflammatory bowel disease (IBD). Changes include a lymphoplasmacytic and eosinophilic expansion of the lamina propria with cryptitis, crypt abscesses, basal lymphoplasmacytosis, lymphoid aggregates, distorted crypt architecture, surface epithelial sloughing, focal Paneth cell metaplasia, and granulomatous cryptitis (62). The only way to distinguish this entity from IBD is to interpret the finding in the context of the entire clinical, gross, and endoscopic picture. All of these changes lie near the diverticula and are not present away from the diverticula, distinguishing the changes from ulcerative colitis and Crohn disease (Figs. 13.36 and 13.39). In some cases it may be impossible to distinguish between these entities. The mucosa may also appear hyperplastic or it may appear to have a thickened collagen table mimicking collagenous colitis. This resemblance may be further accentuated if there is associated mild colitis.
Isolated sigmoiditis tends not to cause diagnostic dilemmas when one receives a resection specimen in a patient with obvious diverticulosis or diverticulitis. However, given the frequency with which diverticulosis is encountered in the population and the frequency of colonic biopsies, isolated sigmoiditis may cause diagnostic difficulties in biopsy specimens. This is particularly problematic because the chronic colitis of diverticular disease shows the same distribution as ulcerative colitis (UC). If the endoscopist biopsies both the area around diverticula and areas remote from them, the biopsies will show a patchy distribution of the inflammation, allowing one to distinguish sigmoiditis from UC but not from Crohn disease. However, if the biopsies only come from the areas surrounding a diverticulum, a misdiagnosis of IBD may be made. Finally, because diverticulosis occurs commonly in the Western world, it often coexists with other diseases, including adenomas and carcinomas, idiopathic IBD, and other forms of colitis. Occasionally, the carcinomas appear to arise within the diverticulum and tumors may exhibit differing histologic patterns.

It is important to distinguish between congenital and acquired diverticula, since the latter often result from underlying pathology either in the bowel itself or in a structure outside the bowel. The most important feature distinguishing the two is the absence of an intact muscularis propria in acquired diverticula.

When diverticular disease ruptures forming abscesses and peridiverticulitis, it has features that overlap with those seen in CD. Features that suggest the presence of CD complicating diverticular disease include the presence of ulcers away from the diverticulum, fissures, and internal fistulae other than colovesical or colovaginal fistula. If acute inflammatory masses are present in diverticular disease, they may grossly resemble a carcinoma. Additionally, the colonic wall may become thickened by pericolonic, postinflammatory fibrosis, also grossly simulating a neoplasm or inflammatory bowel disease. To further complicate the matter, patients may have both IBD and diverticular disease. UC patients who also have diverticulosis may have extension of their mucosal disease into a diverticulum, perhaps obliterating the underlying architecture, resulting in an appearance of a primary fistula and creating changes that mimic CD.
FIG. 13.31. Muscular hypertrophy in diverticulosis. A: The corrugated nature of the muscularis propria, particularly the inner circular muscle, is evident. B: The mucosa shows a mild increase in mononuclear cells in the lamina propria. A hyperplastic muscularis abuts the diverticulum and shows a “fish flesh” cracking. C: Myenteric hypertrophy. Both the circular and longitudinal muscles are hypertrophic and thickened.

Torsion and Volvulus

A volvulus is an axial twist of a portion of the gastrointestinal tract around its mesentery. The rotation causes a partial or complete bowel obstruction and variable degrees of arterial and venous obstruction. Colonic volvulus affects both children and adults. Sigmoid volvulus accounts for 40% to 80% of colonic volvulus; volvulus of the transverse colon accounts for only 4% to 9% (63,64). The splenic flexure is the least common site of volvulus since it is fixed in position by the gastrocolic, phrenocolic, and splenocolic ligaments. Cecal volvulus usually complicates inadequate colonic fixation, which allows the colon to freely...
Acquired Abnormalities

rotate around its axis. **Primary volvulus** develops in patients lacking a predisposing anatomic abnormality. **Secondary volvulus** affects patients with an acquired or congenital abnormality that predisposes the bowel to rotate.

Colonic volvulus occurs more frequently in countries where the population consumes a diet high in fiber. In the Western world it is the third most common cause of large bowel obstruction (following cancer and diverticular disease) (65). The high fiber content results in bulky stools with a volume that leads to a persistently loaded, elongated colon. As the sigmoid elongates, its two ends tend to approximate one another, producing a narrower mesenteric attachment, predisposing to volvulus. The actual precipitating cause is often a minor event, such as straining at stool or coughing.

Before age 60, cecal volvulus and sigmoid volvulus have the same incidence; after age 60, the incidence of sigmoid volvulus increases. Elderly individuals, especially those given psychotropic drugs or those with chronic constipation (66), previous surgery (64,67), pelvic tumors or cysts that displace the intestine, and neuromuscular disorders (68), acquire an enlarged, redundant sigmoid colon predisposing to volvulus.

**FIG. 13.32. Diverticulosis.** A: There is prominent muscular hypertrophy and four diverticula extend through the wall of the bowel. B: This trichrome-stained section illustrates the prominent muscular hypertrophy seen in red at the middle portion of the photograph. A long diverticular neck passes through the bowel wall in the area of the penetrating artery and ends in a dilated sac that protrudes into the pericolonic fat (star).


**FIG. 13.33.** Bleeding diverticulum. This relatively unimpressive specimen derives from a patient who bled out several units of blood and required an emergency colectomy. The only bleeding site that was identified is indicated by the tip of the pointer in *A*. The other diverticular orifices that contain bloody material represent blood that extended into the diverticula. *B*: Cross section shows the presence of a diverticulum filled with blood.

In its early stages, a volvulus produces a check valve effect allowing flatus and fecal material to enter the loop but preventing them from leaving, resulting in rapid bowel distension. As the volvulus tightens, a complete closed loop obstruction develops with vascular compression and ischemic necrosis. The muscle often appears hypertrophic and hyperplastic and the bowel wall contains thick-walled blood vessels. The mucosa is variably inflamed and there may be coexisting melanosis coli or even pneumatosis coli.

P.756

P.757

Variable degrees of acute or chronic ischemia may also be present.
FIG. 13.34. Bleeding site in the diverticulum illustrated in Figure 13.33. A: The bleeding site is highlighted by the arrow. B: Higher magnification of this site shows an eroded artery with a blood clot on the surface.
**Acquired Abnormalities**

**FIG. 13.35.** Prolapsing mucosal folds. **A:** Redundant mucosal folds and a branched diverticulum in the right colon. Note the marked hypertrophy of the muscularis propria (*star*) and the accordion-pleated-like mucosal folds. The diverticulum (*triangle*) has the branched shape characteristic of right-sided diverticula. **B:** Patients often exhibit redundant mucosal folds with marked hypertrophy of the muscularis mucosae and almost total obliteration of the submucosal space. The muscularis propria (*star*) shows a typical fish-flesh artifact seen in patients with diverticulosis.

**FIG. 13.36.** Diverticular sigmoiditis. **A:** Low magnification shows a hypercellular lamina propria. **B:** Note the increased number of mononuclear cells in the lamina propria.

A rare type of sigmoid volvulus is referred to as *ileosigmoid knotting.* It is best known in Africa, Finland, and Eastern Europe. A loop of ileum knots around the base of a sigmoid volvulus resulting in gangrenous necrosis of both loops.

**Redundant Sigmoid**

An elongated redundant sigmoid colon predisposes to volvulus formation, intussusception, and focal ischemia (Fig. 13.40). Patients with redundant sigmoid colons often also have associated diverticular disease and the dysmotility may further contribute to the pathologic features. The muscularis propria and muscularis mucosae may fuse, producing redundant mucosal folds. The mucosa appears chronically damaged. Acute inflammation may be superimposed on chronic changes. The submucosal vessels become prominently dilated and collections of chronic inflammatory cells infiltrate the submucosa (Fig. 13.41). The tissue may display profound eosinophilia as in any other chronic forms of colitis.
Intussusception

Intussusceptions occur throughout the large intestine. Specimens obtained from patients with intussusceptions fall into several groups: (a) intussusception associated with segmental ischemic necrosis (Fig. 13.42) occurring in patients with neoplasms or other lesions that act as lead points (Fig. 13.43); (b) appendiceal intussusception, a disorder that presents as a cecal “polyp”; the lesion results from retrograde appendiceal intussusception into the cecal wall; (c) rectal intussusception, which occurs 6 to 8 cm above the anal verge, usually involving the entire rectal circumference, and often developing in connection with straining; and (d) intussusceptions in which underlying motility disturbances cause portions of the bowel to intussuscept into one another. Viral infections are important causes of ileal intussusception into the cecum in children. Adenovirus infections are the most common cause, but acute primary infections with human herpesvirus (HHV)-6, HHV-7, and Ebstein-Barr virus (EBV) are etiologic factors (69). The pathologic features of an acute intussusception are usually dominated by those of ischemic injury as described later.
FIG. 13.38. Portion of tissue removed by the surgeon as a “serosal implant.” The patient had extensive diverticulosis. The “implant” appeared multiloculated and contained fecal material. Individual fecal collections were walled off by a fibrous inflammatory reaction.
FIG. 13.39. Diverticular sigmoiditis. A: Mildly regenerative crypts are separated by a lamina propria containing large numbers of mononuclear cells. B: Higher magnification of the mononuclear cell. C: Other areas demonstrate obvious regenerative changes with branched glands and even early fibrosis. D: Superficial collections of lamina propria macrophages are present.
FIG. 13.40. Redundant sigmoid. A: Low-magnification photograph showing the presence of a buckled muscularis propria (arrow) with the muscularis propria showing a typical fish-flesh separation of the outer muscular layer. The curved arrows indicate mucosal protrusions presenting as polyps. B: Another area from the same resection specimen showing an isolated ischemic ulcer (arrow).
Diagnosing a resected, unreduced intussusception is not difficult. However, recurrent or past intussusceptions that spontaneously reduce may be more difficult to recognize. Histologic clues that point to recurrent intussusception include (a) marked disorganization of the muscularis propria, sometimes showing features of peristaltic drag; (b) fusion of the muscularis mucosae with the muscularis propria; (c) focal submucosal fibrosis; (d) marked telangiectasia; (e) evidence of healed serosal disease, including adhesions; and (f) localized mucosal hyperplasia. Sometimes the bowel wall kinks on itself with only the muscularis propria demonstrating the twisted appearance of the previous intussusception (Fig. 13.44).

Intussusceptions can produce a florid vascular proliferation that can be exuberant enough to raise the possibility of an angiosarcoma. The lesion consists of a lobular proliferation of small vascular channels that extend from the submucosa through the entire thickness of the bowel wall (70). The endothelial cells have minimal cytologic atypia, mitoses are rare, and the vascular channels are not interanastomosing as seen in angiosarcomas (see Chapter 19).
among the four entities are confusing. We advocate that these entities be all lumped together under the term *mucosal prolapse* because the changes often coexist and overlap with one another. Prolapse affects 85% to 90% of patients with SRUS (71) and 54% of patients with PCP (72). Perhaps the easiest way to view this spectrum of diseases is that an ulcer develops first. As the mucosa regenerates, a polypoid lesion develops. At the same time, some of the glands become displaced into the underlying submucosa.

![Lipoma serving as a lead point for an intussusception.](image)

Patients present with signs and symptoms of anorectal disease, usually in their 3rd or 4th decades of life. Symptoms include rectal bleeding, diarrhea, anorectal pain, abdominal cramps, and difficulty defecating. The latter presents as constipation, straining, rectal prolapse, or incomplete rectal evacuation necessitating digital manipulation. Fifty percent of patients have incontinence. Ulcerated and indurated areas are often present on the anterior or anterolateral wall. The ulcers often straddle a rectal fold and vary in size from a few millimeters to several centimeters in diameter. Not all patients have ulcers, and in some the only abnormality is an erythematous area, sometimes associated with polypoid projections (73). Rare patients present with an acute abdomen secondary to perforation.
Acquired Abnormalities

**FIG. 13.44.** Features of chronic intussusception. *A* and *B* are from a colonic resection. The most impressive portions of the resection specimen are not shown but consisted of a pericolonic inflammatory pseudotumor. The only clue as to the underlying etiology of the changes was the curved nature of the muscularis propria and the marked hypertrophy and distortion of the myenteric plexus associated with the specimen. The patient has had a long history of recurrent abdominal problems.

**FIG. 13.45.** Early mucosal prolapse. *A:* An inflammatory polyp is present. *B:* Higher magnification of the lesion shows the marked villiform hyperplasia. A “cap” of fibrin, inflammatory cells, and debris covers the surface.

---

**Rectal Prolapse**

Rectal prolapse is defined as anal protrusion of some or all rectal wall layers. Prolapse first occurs in infants; it becomes uncommon in childhood and early adulthood, only to increase in frequency after age 40. Prolapse is more common in women. The problem in children usually corrects itself as they grow (74). Rectal prolapse is either complete or incomplete (71).

Complete rectal prolapse remains concealed (not externally visible at rest), externally visible with straining, or externally visible without straining. The prolapse involves all of the layers of the rectum, essentially creating a rectal wall intussusception (71). It may complicate other disorders such as underlying neoplasms, lymphoid hyperplasia (75) or malacoplakia (76), severe disabling diarrheal diseases, or anorexia nervosa (77). Patients with underlying mass lesions sometimes suffer from recurrent prolapse.

Presenting symptoms include straining during defecation, a sense of obstruction, defecatory pain, fecal incontinence, mucous discharge, pruritus, rectal bleeding, a sense of incomplete rectal evacuation, perineal or intervaginal pressure, and the need to digitally disimpact the rectum (71). Patients may have a palpable mass on digital examination. Endoscopically, there is mucosal reddening, ulceration, and edema (71). Typical features of SRUS and localized PCP may also be present.

The earliest manifestation of rectal prolapse may consist of nothing more than mucosal erosions or ulcers, or just nonspecific inflammation with thickening of the collagen table mimicking collagenous colitis. Ulceration is heralded by capillary dilation and congestion beneath the surface epithelium. Ulcers covered by a fibrous exudate erupt from the surface mucosa in a volcanolike fashion (Fig. 13.45), reminiscent of pseudomembranous colitis. The ulcers never penetrate deeply into the submucosa. Later, the lamina propria becomes replaced by smooth muscle cells and fibro-blasts arranged at right angles to the muscularis mucosae (Fig. 13.46) (78). The overlying epithelium appears regenerative with mucin depletion, branching, and hyperplasia. These features overlap with those found in inflammatory cloacogenic polyps (see Chapter 15). Ulceration and healing can also lead to the presence of cysts deep in the submucosa (73). Inflammatory polyps also develop.

**Solitary Rectal Ulcer Syndrome**
Acquired Abnormalities

SRUS results from inappropriate anal sphincter contraction during defecation. Repeated straining during defecation, possibly associated with muscular spasm, may create a shear on the rectal mucosa causing traumatic ulceration. Excessive straining also facilitates mild mucosal redundancy in the anterior rectal wall. The term **solitary rectal ulcer syndrome** is a misnomer because ulceration is a late feature of the disease and the ulcers may be multiple. Some of the histologic changes result from an impaired mucosal blood supply during the prolapse. In acute phases, the crypts appear elongated and lined by immature basophilic epithelial cells (Fig. 13.47). Fibrovascular and fibromuscular components proliferate in the lamina propria; telangiectasia is common. The mucosa may become extremely hyperplastic and polypoid, and may even resemble hyperplastic polyps or adenomas, especially if the mucosa acquires a villiform appearance. The submucosal vessels may become ectatic or hyalinized. Smooth muscle fibers extend from the musculis mucosae toward the lumen. The presence of the diffuse mucosal fibrosis is a reliable and discriminating feature between SRUS (Fig. 13.46), UC, and other forms of acute colitis. The fibrosis can be accentuated using trichrome stains. Unfortunately, fibrosis is a late event. Surface ulcers and erosions are present. The ulcers typically do not extend into the submucosa. There may be features of ischemia along with pseudomembranes. These result from vascular compromise during the mucosal prolapse. Inflammatory cap polyps may develop. The lesion may develop in patients with an associated rectal malignancy (79); when this happens the underlying tumor may go unrecognized.

![Image](file:///F|/Gastro/Chapter%2013%20Acquired%20Abnormalities.htm)
Acquired Abnormalities

**FIG. 13.46.** Mucosal prolapse. The mucosa in the various prolapse syndromes share the features of glandular dilation and branching with variable degrees of fibrous and smooth muscle proliferations. Early on, the lesions appear inflamed, as shown in A. B: Later, the muscle bands course through the highly branched glands with less inflammation. C: Medium magnification showing the presence of the hyperplastic fibers of the muscularis mucosae extending upward into the lamina propria (actin immunostain).

**Proctitis Cystica Profunda**

Rectal mucosa displaced into the submucosa is termed *proctitis cystica profunda*. PCP is a benign condition that may mimic a colloid carcinoma (Table 13.1). Patients often present with blood and mucus in the stools. PCP often, but not invariably, associates with rectal mucosal prolapse and disordered puborectalis function (73). PCP may complicate SRUS, developing as the crypts become trapped by reactive fibromuscular proliferations.

**FIG. 13.47.** Mucosal prolapse showing flat hyperplasia covered by a fibrinous membrane.
Patients who develop PCP show mucosal edema; erythema; a lumpy-bumpy mucosa with increased folds; obvious cysts, polyps, or pseudopolyps; mucosal friability; oval, linear, stellate, or serpiginous ulcers; or a cauliflower-shaped mass measuring up to 5 cm in size (Fig. 13.48). Thick mucus may exude from the cysts when compressed. Surface ulceration is uncommon, but loss of superficial lining cells occurs frequently. Tracts extending from the mucosa toward the mucinous cysts are sometimes visible. The remaining mucosa frequently appears scarred, with glandular loss. strictures or stenosis may develop. Sections through the cysts demonstrate gelatinous or mucinous secretions. The histologic features of PCP resemble those of colitis cystica profunda (see below). Other histologic findings reflect ischemia secondary to vascular compression, especially when the prolapse becomes impacted in the upper end of the anal canal.

**Colitis Cystica Profunda**

Colitis cystica profunda (CCP) presents either as a localized lesion or diffusely as multiple lesions. Diffuse CCP involving the entire colon along with enteritis cystica profunda are exceptionally rare, and they may coexist (80). Patients with CCP range in age from 4 to 68 years, with a mean of 33 years. Males outnumber females 7:1. Mucus submucosal retention cysts may follow episodes of bacillary dysentery. The epithelium becomes displaced during mucosal ulceration in the acute phase of the disease (81). Areas near lymphoid follicles may create points of weakness in the muscularis mucosae, facilitating the mucosal herniation (82).

<table>
<thead>
<tr>
<th>Surface mucosa</th>
<th>Features of mucosal prolapse</th>
<th>Neoplastic epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucin pools</td>
<td>Rounded</td>
<td>Irregular</td>
</tr>
<tr>
<td>Lamina propia</td>
<td>Often present</td>
<td>Absent</td>
</tr>
<tr>
<td>Hemosiderin deposits</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Desmoplasia</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Symptoms include rectal bleeding, passage of mucus and blood, diarrhea, tenesmus, and crampy abdominal pain. Endoscopy may demonstrate a nodular mucosa (73). Associated diseases include IBD (82), Peutz-Jeghers syndrome (PJS), and congenital anomalies. The patients develop innumerable prominent, circumferential, polyoid mucosal elevations and submucosal cysts measuring up to 2 cm in diameter. The ascending and transverse colon are diffusely involved (83). Microscopically, flattened epithelium incompletely lines the submucosal, mucin-filled cysts. Complete or incomplete cuboidal columnar epithelium resembling normal colonic mucosa lines newly formed cysts (Fig. 13.49). Serial sections may demonstrate a communication between the cysts and the mucosal surface. Older cysts often lack an epithelial lining and are surrounded by fibrous tissue and/or a polymorphic inflammatory infiltrate, hemosiderin, or foreign body giant cells. The material in the cysts may calcify or ossify. The degree of fibrosis is usually moderate but it can be significant, extending into the muscularis propria or even into the serosa. The cyst lining appears benign, lacking cytologic atypia so that confusion with a malignant process is generally not a problem. However, low-grade dysplasia may be present in the displaced epithelium in patients with longstanding ulcerative colitis (83).

A lesion that may superficially resemble colitis cystica profunda causing localized cystic masses with variable degrees of inflammation is endometriosis (Fig. 13.50). However, the endometrial epithelial lining should not contain mucin and the stroma surrounding the glands should be the denser endometrial stroma rather than the looser lamina propria typical of the intestinal
mucosa.

**Colitis Cystica Superficialis**

Colitis cystica superficialis is a condition in which mucinous cysts remain confined to the intestinal mucosa (Fig. 13.51). These are seen in pellagra and following healing of chronic inflammation, as in UC.

P.764
FIG. 13.48. Proctitis cystica profunda. A: Nodular area of colitis cystica profunda in a proctectomy specimen. The proximal mucosa is uninvolved. B: Cross section shows numerous mucin-filled submucosal cysts surrounded by fibrosis. C: In this Bouin-fixed specimen the mucosa is highlighted (yellow). D: Whole mount of lesion illustrated in C demonstrates the presence of multiple mucus-filled cysts. E: High-power magnification of the lesion illustrated in B. Numerous submucosal cysts are seen. The overlying mucosa is not neoplastic.

Stercoral Ulcers

Stercoral perforation generally develops in the rectosigmoid. Reasons for this include (a) local pressure from structures surrounding the rectosigmoid that keep it from distending; (b) the presence of hard feces in this area; and (c) the presence of a relatively narrow intestinal lumen. Stercoral ulceration with perforation is an uncommon but frequently fatal condition because patients often develop peritonitis. Perforation often occurs during difficult bowel movements. Many patients are renal patients with severe constipation due to ingestion of nonabsorbable antacids, particularly magnesium and aluminum hydroxide gels, and cation exchange resins used to treat their hyperkalemia (84). The inspissated stool causes local pressure, ischemia, necrosis, and perforation. The situation is made worse by loss of normal mucosal barrier function due to coexisting uremia.
**FIG. 13.49.** Colitis cystica profunda. *A:* Cross sections through four submucosal cysts are seen (*stars*). They are lined by variably flattened nonneoplastic colorectal epithelium. The epithelium appears regenerative. *B:* Higher magnification of the central cysts showing prominent hemosiderin deposition with resulting fibrosis. Lamina propria surrounds the cysts.

**FIG. 13.50.** Comparison of colitis cystica profunda and endometriosis. *A:* Colitis cystic profunda. A nonneoplastic mucosa lies above the muscularis mucosae (*MM*). The submucosa contains glands lined by mucin-secreting epithelium with mucin in the cyst lumen. The lower cyst (*star*) has a large accumulation of mucus within it. *B:* Endometriosis. The endometriotic focus lies in the submucosa. It is surrounded by dense stroma and lined by non–mucin-secreting epithelium (*star*). The stroma surrounding the endometrial gland is much denser than the lamina propria surrounding the displaced epithelial glands seen in *A.*
Acquired Abnormalities

FIG. 13.51. Colitis cystica superficialis. Multiple mucosal cysts are present. These are seen at low and high power in A and B.

Grossly, stercoral ulcers are characterized by the presence of longitudinal tears or perforations (Figs. 13.52 and 13.53). One often finds hard feces corresponding in size to the perforation site. Sometimes the hard feces protrude through the perforation site. Histologically, the intestinal wall is acutely and chronically inflamed (Fig. 13.53).

FIG. 13.52. Stercoral ulcer.
Changes Induced by Drugs and Toxins

The etiology of drug-induced colitis varies significantly, as does the underlying pathophysiologic disturbance that results from the drug ingestion. Since drug-induced colitis is likely underrecognized, its true incidence is unknown, especially since the changes induced are usually nonspecific and they mimic many other conditions. Drug-induced injury can cause acute diarrhea soon after the drug is started. Alternatively, chronic diarrhea may appear long after the drug administration. The histologic changes range from a normal-appearing colon to fulminant colitis and extensive necrosis. Drugs can induce ischemia, eosinophilic colitis, necrotizing colitis, microscopic colitis, IBD-like changes, and infectious colitis (Table 13.9).

Laxatives

*Melanosis coli* results from chronic ingestion of anthraquinones and laxatives derived from plants, including cascara sagrada, aloes, senna, frangula, and rhubarb. Evidence is beginning to emerge that melanosis coli does not result solely from laxative use. It can also occur in patients with IBD (both Crohn disease and ulcerative colitis) who have not used laxatives (132) and in individuals with diarrhea unrelated to IBD who have not used laxatives. Anthraquinones concentrate in the colon, particularly in the right colon, where they are potent cellular poisons causing apoptosis, even when taken in small doses (133). The apoptotic bodies are phagocytosed by macrophages and transformed into lipofuscin pigment by lysosomal enzymes (134). The mean apoptotic count is significantly increased in those with melanosis coli compared with a control population. It is said that it takes 4 to 12 months for melanosis coli to be visible and the same amount of time for it to disappear. It is possible that any condition associated with increased apoptosis may result in melanosis coli (135). When present in small quantities, anthraquinones probably stimulate neural tissues leading to their purgative actions. Anthraquinones and other laxatives also damage the myenteric plexus causing neuronal loss, Schwann cell proliferation (133), axonal fragmentation, axonal and dendritic swelling, and smooth muscle damage. This eventually leads to cathartic colon. Bisacodyl, anthraquinone purgatives, phenolphthalein, castor oil, and other agents also cause cathartic colon.

<table>
<thead>
<tr>
<th>TABLE 13.9 Examples of Colonic Toxicity Due to Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause ischemia</strong></td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Estrogen</td>
</tr>
<tr>
<td>Ergotamine</td>
</tr>
<tr>
<td>Amphetamines</td>
</tr>
<tr>
<td>Digitalis</td>
</tr>
<tr>
<td>Vasopressin</td>
</tr>
<tr>
<td>Methysergide</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td><strong>Cause pseudo-obstruction</strong></td>
</tr>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Amitriptyline hydrochloride</td>
</tr>
<tr>
<td>Antineoplastic drugs, especially vincristine</td>
</tr>
<tr>
<td>Tranquilizers</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Ganglionic blockers</td>
</tr>
<tr>
<td>Narcotics</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
</tbody>
</table>

*Cause infectious or necrotizing enterocolitis*

<table>
<thead>
<tr>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Deferoxamine</td>
</tr>
<tr>
<td>Loperamide</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Immunosuppressants</td>
</tr>
</tbody>
</table>

*Cause allergic, cytotoxic, or inflammatory injury*

<table>
<thead>
<tr>
<th>Nonsteroidal anti-inflammatory drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold salts</td>
</tr>
<tr>
<td>Potassium chloride</td>
</tr>
<tr>
<td>Mycophenolate</td>
</tr>
<tr>
<td>a-Methyldopa</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
</tbody>
</table>

**FIG. 13.80.** Severe melanosis coli. The bowel is dilated, has lost its haustral folds, and appears darkly pigmented.

Many patients are symptomless only to be diagnosed following endoscopic examination for other reasons. Individuals with
surreptitious laxative abuse typically present with unexplained chronic diarrhea. Some patients may have an obsession regarding their need to have a bowel “cleansing.”

The colon in patients with melanosis appears dark brownish (Figs. 13.80 and 13.81). Melanosis primarily affects the right colon, but in severe cases the discoloration extends to the left colon or diffusely involves the entire large intestine.

The appendix and terminal ileum may also become affected. Abnormal mucosal proliferations, such as adenomas or colon cancers, arising in a mucosa affected by melanosis coli retain their normal mucosal color rather than becoming pigmented. In severe cases, the entire lamina propria, the submucosa, and even the draining mesenteric lymph nodes contain pigmented macrophages. Migration of pigmented macrophages to regional lymph nodes results in sequential loss of the pigment from the superficial and deep lamina propria (134).

**FIG. 13.81.** High-power melanosis coli showing macrophages containing prominent brown pigment.

The histologic features of laxative use range from mild melanosis coli to severe cathartic colon. Because the autofluorescent pigment of melanosis coli contains melanin as well as glycoconjugates, it has been suggested that the pigment be termed *melanized ceroid* (136). The ceroid pigment develops from the abundant apoptotic epithelial cells, whereas the precursors of the melanic substance may derive from the anthranoids (136). Autofluorescent, refractile, golden brown, pigmented macrophages populate the lamina propria (Fig. 13.81). Occasionally, one also sees inflammation in the lamina propria, increased apoptotic bodies in the lining epithelium, superficial collections of apoptotic debris, and thickening of the muscularis mucosae. The associated inflammation probably represents a nonspecific response to an underlying injury or to stasis that may have been the cause for the laxative ingestion, rather than a direct effect of the laxative consumption. Subluminal microgranulomas often containing pigment may form (Fig. 13.82).

The pigment stains positively with periodic acid–Schiff (PAS), acid-fast, aniline blue sulfate, and Schmorl stains, but it is...
Changes Induced by Drugs and Toxins

The brown pigment may be confused with hemosiderin, which usually appears larger and more refractile than melanosis. Special stains for iron can be used in questionable cases.

Mucosal laceration or perforation with mucosal hemorrhage can complicate enema tube insertion. Devices other than the usual enema nozzle used to administer home enemas may cause erosions, mucosal tears, ulcers, or perforations. Patients utilizing enema solutions with various cleansing agents, including *ethyl alcohol* and *hydrogen peroxide*, may develop a severe proctitis (137,138). Hydrogen peroxide enemas, as used by some naturopaths, may induce a clinical picture resembling ischemic colitis, ulcerative colitis, or pseudomembranous colitis (137). The mucosal damage may result from ischemia secondary to the explosive entrance of the generated gases into the bowel wall. Histologically, one may see pneumatosis intestinalis, intense mucosal congestion, hemorrhage, or frank gangrenous necrosis.

Patients sometimes receive *formalin enemas* to cleanse the rectum either for health reasons or to sterilize the bowel wall during cancer surgery. Fortunately, this practice is very rarely used because 10% formalin causes severe, sharp pain and rectal bleeding within a few minutes of instillation. Within a week, the colonic mucosa becomes edematous, with multiple petechiae and superficial erosions. Histologically, one sees a nonspecific chronic colitis with superficial erosions. The lesions usually heal with a severe fibrosing process that progresses to stricture formation (139).

![FIG. 13.82. Melanosis coli with granuloma formation. Some of the epithelioid cells contain evidence of brown pigment (arrow).](image)

**Kayexalate-Sorbitol Enemas**

Kayexalate-sorbitol enemas, used to treat hyperkalemia after renal transplantation, cause intestinal necrosis. Since Kayexalate causes severe constipation, it is administered along with sorbitol, which acts as an osmotic laxative. The osmotic
load from the sorbitol causes vascular shunting, resulting in mild colonic ischemia. Patients treated with Kayexalate-sorbitol enemas always have underlying renal disease and many are renal transplant patients (140,141). The colonic damage is potentiated by the presence of uremia. Patients present with an abrupt onset of severe abdominal pain within hours of enema administration. In some cases, elimination of the Kayexalate enemas causes resolution of the colonic manifestations. At the time of resection, long segments of (or even the entire) colon and rectum may appear necrotic. Histologically, one sees transmural necrosis as seen in acute ischemic injury without reperfusion. The lesion mimics autolysis, although a mild neutrophilic infiltrate may be present. The presence of dark purple crystals that are PAS positive and stain with acid-fast stains establishes the diagnosis (140,141).

### TABLE 13.10 Colonic Effects of Nonsteroidal Anti-inflammatory Drugs

<table>
<thead>
<tr>
<th>Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic ulcers</td>
</tr>
<tr>
<td>Nonspecific</td>
</tr>
<tr>
<td>Acute eosinophilic colitis</td>
</tr>
<tr>
<td>Ulcerating colitis</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td>Eosinophilic colitis</td>
</tr>
<tr>
<td>Collagenous colitis</td>
</tr>
<tr>
<td>Lymphocytic colitis</td>
</tr>
<tr>
<td>Ischemic colitis</td>
</tr>
<tr>
<td>Chronic bleeding and perforation</td>
</tr>
<tr>
<td>Relapse of inflammatory bowel disease</td>
</tr>
<tr>
<td>Strictures</td>
</tr>
<tr>
<td>? Diverticula formation</td>
</tr>
<tr>
<td>Complicated diverticular disease</td>
</tr>
</tbody>
</table>

**Drugs that Damage the Myenteric Plexus and Cause Stercoral Ulceration**

Many drugs (in addition to laxatives) damage the myenteric plexus and cause severe chronic constipation, pseudo-obstruction, and stercoral ulceration (Table 13.9). Severe constipation leads to formation of hard fecaliths that can cause local chronic inflammation, acute inflammation, ulceration, bleeding, perforation, and abnormal Schwann cell proliferation.

**Nonsteroidal Anti-inflammatory Drugs**

NSAIDs exhibit diverse gastrointestinal effects; their pathogenesis is discussed in Chapter 6. The drugs cause a nonspecific colitis and they exacerbate pre-existing colonic diseases including IBD and diverticulitis. IBD patients may undergo reactivation of their disease, especially those who are allergic to salicylates (142). Colonic complications include those listed in Table 13.10. It is difficult to estimate the exact incidence of NSAID-induced colonic injury. Elderly patients, or those with long-term or high-dose NSAID use, exhibit the highest risk of NSAID-associated complications including large intestinal ulcers, bleeding, and perforation. If one is unaware that the patient is taking NSAIDs, the diagnosis may be difficult.

Several forms of colitis associate with NSAID use. The most common is nonspecific in nature and difficult to distinguish from ulcerative colitis early in its natural history. Fenamates are a common cause for this pattern (143). The likelihood of a drug association increases if there is prominent apoptosis (144) and increased intraepithelial lymphocyte counts (microscopic colitis). The apoptotic biopsies are often seen in the crypt bases and in lymphocytes and monocytes under the luminal surface. Collagenous colitis, eosinophilic colitis, and pseudomembranous colitis can also be seen (Fig. 13.83). The changes may also mimic Crohn disease or ischemia. There may be extensive damage, particularly in the proximal colon, and mucosal bridges or
Changes Induced by Drugs and Toxins

Diaphragms or strictures may develop (145). Diclofenac can cause granulomatous colonic injury (146). Patients taking NSAID-containing suppositories develop localized anorectal erosions, ulcers, and stenosis. The abnormalities usually resolve following cessation of NSAID therapy.

Immunosuppressive Agents

Immunosuppressive agents including steroids, indomethacin, mycophenolate, azathioprine, tacrolimus, and cyclosporine all damage the gastrointestinal tract. Immunosuppressive drugs lead to mucosal erosions and ulcers. Steroid-associated ulcers are usually superficial but deeper ulcers may lead to perforation. Endoscopically, the mucosa appears edematous with a decreased vascular pattern. Patchy erythema and erosive changes are common. Ulcerative lesions, if present, may be discrete and require biopsy to exclude ischemia, CMV, or other opportunistic infections.

Corticosteroids and azathioprine deplete lymphoid tissues, including gut-associated lymphoid tissues (147), causing a decrease in the size of lymphoid follicles and focal small erosions with M-cell necrosis. This predisposes to bacterial invasion and subsequent perforation. The follicular regions become severely B-cell depleted. Steroids also cause inflammation and cellular necrosis. They slow mucosal cell renewal and decrease the reparative activity of fibroblasts, further predisposing to perforation. Patients on steroids are also prone to develop CMV infections, which may result in an acute colitis.

Mycophenolate mofetil is a relatively new immunosuppressive drug that inhibits inosine monophosphate dehydrogenase, a key enzyme in the de novo pathway of purine synthesis. It causes lymphocyte-selective immunosuppression. It is used to prevent allograft rejection and is usually administered together with cyclosporine or tacrolimus and corticosteroids. Its major adverse effects are on the gastrointestinal tract (149). Mycophenolate causes colonic necrosis and secondary regenerative changes (Fig. 13.84) and intestinal changes that mimic graft versus host disease (GVHD) (148). High doses of mycophenolate also inhibit the proliferation of the stem cells in the intestinal tract (149). The drug may also cause a higher rate of CMV reactivation than is seen in control populations (150).

Cyclosporine causes generalized intestinal microvascular injury (151). Tacrolimus, a potent immunosuppressive drug, decreases mitochondrial adenosine triphosphate (ATP) production, increases intestinal permeability by a mechanism similar to that seen with NSAIDs, and predisposes patients to endotoxemia and impaired intestinal absorption (152). Recipients of organ allografts may develop a GVHD-like condition when receiving tapering doses of cyclosporine, a phenomenon possibly related to an autoimmune reaction. Colonic perforation also complicates high-dose interleukin-2 (IL-2) therapy (153).

Heavy Metal–induced Enterocolitis

Heavy metal therapy with arsenic, mercury, silver, and gold causes colitis. Gold salt therapy causes most heavy metal–induced enterocolitis (154,155), a disease associated with mortality rates as high as 42% (155). The enterocolitis usually starts within several weeks of beginning the drug. Patients present with nausea, vomiting, profuse diarrhea, abdominal pain, fever, proteinuria, maculopapular rashes, and hypogammaglobulinemia. Some patients develop toxic megacolon and perforation (154). Twenty-five percent of patients develop peripheral eosinophilia. The enterocolitis results from either a direct toxic mucosal effect or an immune-mediated hypersensitivity reaction (156). Endoscopically and grossly, petechial hemorrhages, focal ulcers, toxic megacolon, or pseudomembranes may be present (157).
FIG. 13.83. Nonsteroidal anti-inflammatory drug (NSAID) injury. A: Low magnification of a mucosal biopsy in a patient with heavy NSAID ingestion. B: High magnification showing a portion of the mucosa demonstrating nothing more than granulation tissue. C: A portion of gastrointestinal mucosa with red cell extravasation into the lamina propria and regenerative superficial lining cells. D: Medium magnification demonstrating the presence of a marked mononuclear cell infiltrate and prominent capillaries.
Patients with gold-induced colitis usually have a more or less preserved glandular architecture, although individual crypts may drop out. Diffuse chronic inflammation, often with a prominent eosinophilic component, infiltrates the mucosa (Fig. 13.85). Patients may also develop pseudomembranous colitis and ulcers.

**Chemotherapeutic Agents**

Some of the most severe drug-induced colitis results from chemotherapeutic agents. Mucosal toxicity varies depending on the type and number of drugs used, their dosage, complicating effects of surgery, extent of tumor involvement, and concomitant radiotherapy. Chemotherapeutic agents primarily affect mitotically active cells, inducing massive cell death. As a result, the mucosa becomes ulcerated and inflamed. The most marked effects result from 5-fluorouracil (5-FU) therapy (158). Additionally, 5-FU, a drug commonly used as an adjuvant in colon cancer therapy, impairs colonic healing, possibly due to reduced collagen synthesis, potentially adversely affecting the integrity of colonic anastomoses following colon cancer surgery. Mucosal injury begins 4 to 9 days after therapy onset. The nuclei in the crypt bases become pyknotic, lose their polarity, and become karyorrhectic (159). Eventually, the damage progresses toward the lumen, resulting in upper mucosal necrosis. Both the crypt epithelium and the lamina propria become
Changes Induced by Drugs and Toxins

inflamed. During the resolution phase, the crypt epithelium appears hyperplastic or the crypts appear disorganized and cystically dilated and lined by bizarre, sometimes flattened epithelial cells (Fig. 13.86). Increased apoptoses may be seen in the crypt bases (Fig. 13.86). Histiocytic cell infiltrates may become quite prominent. Often, colonic biopsies show only nonspecific colitis with cryptitis, ulcers, and acute and chronic inflammation mimicking other forms of acute colitis. Collections of apoptotic cells in the crypt bases, cytologic atypia, and glandular dilation suggest the diagnosis.
FIG. 13.85. Gold toxicity. A: Low-magnification biopsy in a patient with gold toxicity. Note the chronic mucosal damage as evidenced by focal neutrophilic infiltrates, a disorganized muscularis mucosae, and mild glandular distortion. B: Higher magnification demonstrating the presence of acute inflammatory cells, including numerous eosinophils and crypts that appear to be disappearing and are difficult to distinguish from capillaries (star). Flattened epithelial cells still line the residual gland. C: A gland has completely disappeared (star) and is only surrounded by acute inflammatory cells. The adjacent glands appear abnormal and the lamina propria appears inflamed. D: Regeneration begins at the base of the damaged glands lined by flattened epithelium (star). The regenerative epithelium appears hyperchromatic and contains mitotic figures.

FIG. 13.86. Chemotherapeutic injury. A: The mucosa is severely damaged with crypt dropout intermingled with regenerating glands. The cystically dilated glands superficially resemble either lymphatics or blood vessels. These are lined by flattened epithelial cells and represent damaged crypts (stars). B: Cytoxan injury with prominent apoptosis in the crypt bases.

Chemotherapy also predisposes the mucosa to infections, ischemia, hemolytic uremic syndrome, and pseudomembranous colitis. The neutrophilic infiltrate may be less than one would ordinarily expect if the patient has significant bone marrow suppression. Severe cases may progress to neutropenic enterocolitis, which is discussed in a later section. Intestinal trefoil factor plays a major role in the mucosal recovery following the injury (160). Irinotecan induces epithelial apoptosis in the surface and crypt neck cells (161).

Drugs Causing Vasculitis or Ischemic Injury

Colonic ischemia complicates high-dose IL-2 and α-interferon immunotherapy (162) and treatment with immunosuppressive agents, neuroleptics (163), ergotamine, and contraceptives (Fig. 13.87) (164). Rutoside, used in Europe to treat varicose veins, associates with a lymphocytic phlebitis. Estrogen and progesterone cause intravascular thrombi and ischemic colitis.
(165) Alosetron, a drug used to treat irritable bowel syndrome, also can cause ischemic colitis (166). Ischemic colitis also complicates cocaine leakage into the intestines of cocaine body packers. Potassium salts cause venous spasm leading to ischemic ulceration.

**Pancreatic Enzyme Supplements and Fibrosing Colonopathy**

Fibrosing colonopathy affects young children with cystic fibrosis, most of whom take high-strength pancreatic enzyme supplements to control intestinal malabsorption. Use of H₂ blockers, corticosteroids, or recombinant human DNase increases the risk of developing the disease. Patients present with abdominal distention due to intestinal dilation or ascites, frequent passage of watery stools, and severe anorexia. The changes may be restricted to one intestinal segment, or they may affect the entire colon (167). An intense perianal pruritus affects infants. Prolonged colonic mucosal contact with either the enzymes or the enteric coating or the combination of the two leads to the ulcers and inflammation (167). The toxicity may also result from the underlying gastrointestinal abnormalities from the cystic fibrosis. The pH in the small intestine is abnormally low in patients with cystic fibrosis. As a result, the dissolution of the enteric coatings occurs in the terminal ileum or colon leading to injury in these sites (168).

**FIG. 13.87.** Colonic biopsy in a 24-year-old female on contraceptives showing numerous fibrin thrombi in the vessels. The colon showed ischemic colitis.
Changes Induced by Drugs and Toxins

**FIG. 13.88.** Fibrosing colonopathy. These three figures are from the same specimen in a child with cystic fibrosis treated with enzyme supplements. *A:* Gross photograph of the bowel demonstrating the tenacious mucoid material on the colonic lumen (*upper*). The lower portion of the photograph shows a cecum that appears deformed and has large numbers of pseudopolyps. *B:* Higher magnification of the pseudopolyps. A probe has been passed under one of these. *C:* Portions of the colonic mucosa that are ulcerated and regenerated. Note the dense fibrosis in the underlying submucosa and obliteration of the submucosa and other landmarks. (Photographs courtesy of Dr. Kevin Bove, Department of Pathology, Children's Hospital Medical Center, Cincinnati, OH.)

Rectal exploration shows rectal stenosis; the rest of the colon shows widespread, firm thickening, with narrowing at the flexures. The colon develops a cobblestoned appearance, submucosal fibrosis, thickening of the muscularis propria, and subserosal hemorrhages. Biopsies show acute or chronic inflammation (Fig. 13.88). Moderate to severe eosinophil and mast cell infiltrations develop. Active cryptitis is present in some patients. Dense mature collagen occupies the submucosa and thick, nearly hyalinized collagen bands with a keloidal appearance may be present. Changes in the muscularis mucosae range from focal fraying of the muscle fibers to complete disintegration with loss of the normal demarcation between the mucosa and submucosa. Ganglion cells are unusually prominent and can be found in the deep mucosa near crypt bases. The muscularis propria becomes widened and fibrotic with the process preferentially affecting the inner circular layer. In rare patients, the muscle becomes completely attenuated with disappearance of both layers of the muscularis propria (167). Patients also occasionally demonstrate ischemic changes.

**Antimicrobials**

Penicillin, ampicillin, tetracycline, isoniazid, and chloramphenicol all can cause a vasculitis. Penicillin, ampicillin, tetracycline, and erythromycin can all cause Henoch-Schönlein purpura secondary to a drug hypersensitivity reaction. Flucytosine causes an ulcerative enterocolitis due to direct mucosal toxicity. Antibiotics are the major cause of *C. difficile*–associated colitis (described in a later section). Antibiotics may also exacerbate symptoms associated with ulcerative colitis. A proximal colitis presenting with bloody diarrhea beginning 2 to 7 days following administration of penicillin and ampicillin has also been described.

**Injury by Other Therapeutic Agents**

Numerous other drugs cause colon alterations. Most produce nonspecific histologic changes that are easily confused P.795
with idiopathic IBD, ischemia, or infectious colitis, depending on lesion distribution and the clinical presentation. Localized nonspecific proctitis results from suppository insertion (169). Sulfasalazine enemas cause nonspecific proctitis. Methyldopa and penicillamine cause a diffuse colitis (170). Hematomas complicate anticoagulation therapy. Isotretinoin (Accutane) precipitates IBD (171). Isotretinoin and acyclovir cause allergic colitis (171), and toxic megacolon complicates methotrexate. Ergotamine tartrate sometimes causes solitary rectal ulcer formation (172). The phlebotonic drug C3-FORT causes lymphocytic colitis.
Changes Induced by Radiographic Substances

Barium causes three types of gastrointestinal problems: (a) barium granulomas, (b) bolus obstruction, and (c) an allergic or anaphylactic reaction from the carboxymethylcellulose component of the barium sulfate suspension. Barium granulomas are nodules of histiocytes containing barium sulfate, usually localized to the gastrointestinal submucosa. Allergic reactions to barium sulfate affect less than two individuals per million (173). Perforation is an uncommon complication. When perforation occurs, it does so in several settings: (a) perforation following damage caused by previous mucosal disease, such as active colitis or diverticulitis (173,174); (b) mechanical damage caused by introduction of enema tips, balloons, and catheters; and (c) perforation in those with pre-existing diseases.

By far the most common radiographic substance to cause alterations in the gastrointestinal tract is barium. Barium granulomas develop when barium contrast extravasates during barium enemas via mucosal tears, abrasions, or diverticula. Barium incites an inflammatory reaction that is polymorphic and includes histiocytes and foreign body giant cells. Water-soluble radiographic contrast media may also cause an acute colitis (175). Gastrografin may produce a severe colitis, probably due to TWEEN-80, which is used as a wetting agent.

The gross appearance of barium injury differs depending on whether an allergic reaction is present or whether barium has extravasated into the surrounding tissues. Barium granulomas produce brownish-green tumorous masses, fibrosis, and stricturing that may grossly resemble a carcinoma. Most barium granulomas develop in the rectum approximately 10 cm proximal to the anal verge, often on the anterior wall. They vary in size, ranging up to 10 cm in diameter, usually lying in the submucosa. Larger lesions may become centrally umbilicated. Sometimes, the barium forms hard concretions in the bowel lumen. In patients with allergic changes, one may see only the mildest of mucosal changes.

Barium sulfate is sometimes seen in the gastrointestinal lumen, appearing as fine, greenish, nonrefringent granules or as larger, birefringent, rhomboid crystals, sometimes located in granulation tissue (Fig. 13.89). These findings merely indicate prior use of barium in the patient and do not qualify for a diagnosis of a barium granuloma. Barium granulomas consist of collections of macrophages containing brownish-greenish-gray barium sulfate crystals, surrounded by typical foreign body giant cells. There is surprisingly little inflammation due to the inert nature of the barium. Small granular crystals may be found in clusters. The barium sulfate does not bend polarized light but it is refractile and easily seen when the microscope condenser is lowered. Allergic reactions tend to resemble other forms of allergic gastrointestinal diseases. Eosinophils tend to dominate the histologic picture. The mucosa may also appear mildly edematous. When barium gains access to the submucosa, it elicits a granulomatous response (Fig. 13.89). Gastrografin does not elicit an inflammatory response. Morphologically one sees large rectangular or rhomboid light tan-yellow crystals in the bowel lumen, sometimes associated with an occasional giant cell.

Colitis Due to Venoms

Most scorpion and snake venoms contain a mixture of toxic proteins and enzymes that induce circulatory collapse, hemolysis, coagulation abnormalities, and changes in vascular resistance. All of these may lead to ischemic colitis (Fig. 13.90) (176).
Introduction

The large intestine is divided into the appendix; the cecum; the ascending, transverse, descending, and sigmoid colon; and the rectum (Fig. 13.1). Since both the appendix and the anus are distinctive and their diseases differ from the remainder of the large intestine, they are treated separately.

The colon functions as a reservoir, and it also moves its contents caudally toward the anus. As the intestinal contents travel distally, water and electrolytes are absorbed, and some substances are secreted into the lumen. The histologic organization of the colon reflects its functions (i.e., resorption of water and elimination of undigested material, feces). Elimination is facilitated by the secretion of mucus that lubricates and protects the mucosa from the luminal contents. Like the small intestine, the large intestine has immune and endocrine functions. The immune functions are served by the prominent lymphoid follicles in the appendix and rectum and by immune cells in the lamina propria. Endocrine functions are served by a heterogeneous population of endocrine cells.

Embryology

The embryologic midgut gives rise to the proximal colon, including the cecum, the ascending colon, and the first two thirds of the transverse colon. The rest of the colon and rectum derive from the embryologic hindgut. The colon comes to lie in its final position in the abdominal cavity through a complex series of rotations (Fig. 13.2). Early in development, midgut lengthening results in the formation of a dorsal mesentery that suspends the developing intestine from the posterior abdominal wall. Rapid elongation of the midgut results in formation of the primary intestinal loop, which communicates with the yolk sac via the vitellointestinal duct. Concurrent rapid hepatic growth decreases the space in the abdominal cavity, causing the midgut to herniate into the umbilical coelom during the sixth embryonic week. The cecum becomes recognizable as a small diverticulum of the caudal limb of the midgut at approximately 6 weeks’ gestation. The midgut returns to the abdominal cavity during the third fetal month. The small intestine enters the abdomen first, followed by the cecum. During re-entry, the gut rotates an additional 180 degrees, so that the cecum comes to lie in the right upper quadrant. Later, elongation of this portion of the gut results in cecal descent to the right lower quadrant and formation of the ascending colon. The postsplenic colon is pushed to the left side and lies anterior to the small intestine.

Upper hindgut development follows that of the midgut. The hindgut develops into the left transverse colon, descending colon, sigmoid colon, rectum, and upper anal canal. The descending colon becomes fixed. The sigmoid retains a mesocolon that reduces in length as other hindgut derivatives become fixed in the abdomen. The distal hindgut enters the cloaca, the structure that ultimately forms the anal canal and some of the urogenital structures.

At the 20-mm developmental stage the colon is lined by villi resembling those in the small bowel. As the fetus continues to grow, they thicken, shorten, and then disappear until the mucosa resembles that found in the adult.

Gross Features

The large intestine is a hollow muscular organ that begins at the ileocecal valve and ends at the anus (Fig. 13.1). It includes the cecum, with the attached vermiform appendix; the ascending, transverse, descending, and sigmoid colon; and the rectum. It measures approximately 150 cm (5 feet) in length. The diameter of the large intestine is greater than the small intestine. The cecum has the largest diameter and is nestled in the right iliac fossa. The diameter of the colon decreases as it proceeds distally so that the lumen of the sigmoid is considerably smaller than that of the cecum. In the rectum, the diameter widens again slightly.

The junction of the colon with the rectum is not a precise anatomic point, and it is loosely described as the rectosigmoid. This area lies just below the sacral promontory, approximately 15 cm from the anal verge. The rectum is divided into two parts: An upper part that extends from the third sacral vertebrae to the pelvic diaphragm, and a lower part, or anal canal, that continues down to the anus. The latter is discussed further in Chapter 15.

The ascending colon extends from the cecum to the hepatic flexure and lies retroperitoneally against the right P.736
Introduction

The transverse colon is the longest segment of the large intestine, extending across the abdomen from the hepatic flexure to the splenic flexure. It attaches to the stomach by the gastrocolic ligament and contacts the second part of the duodenum, the pancreas, and the spleen. The omentum is attached to its anterior. The descending colon begins at the splenic flexure and lies retroperitoneally along the left posterior abdominal wall, abuts the lateral border of the left kidney, and may have a partial mesentery as it approaches the sigmoid colon in the left iliac fossa. The sigmoid colon lies within the peritoneal cavity and possesses a mesentery that is sometimes called the mesosigmoid or sigmoid mesocolon. The sigmoid colon may rest on the urinary bladder or uterus. As it passes through the peritoneal reflection, the sigmoid colon becomes the rectum. The rectum curves gently downward and anteriorly along the sacrococcygeal concavity onto the pelvic diaphragm, for a distance of about 12 cm. It abuts the prostate or the vagina inferiorly before turning posteriorly and caudad through the pelvic floor to become the anal canal at the dentate line. For most of its path, the colon lies against the posterior abdominal wall, forming a frame around the loops of small intestine.

The muscularis propria consists of longitudinal and circularly arranged smooth muscle fibers (Fig. 13.3). The outer longitudinal layer forms a continuous coat, which thickens into three flat bands called taenia coli. These run from the base of the appendix to the rectum, where the fibers fan out to form a continuous longitudinal coat (Fig. 13.4). Because the taeniae coli are not as long as the colon, they gather the wall into sacculations or haustra. Taenia are absent from the appendix and rectum. The circular muscle layer is continuous from the cecum to the anal canal, where it increases in thickness to form the internal anal sphincter. The circular muscle and taenia are thinner in the cecum than in other parts of the colon. Between the sacculations, the mucosa and submucosa are thrown into crescenteric folds (plicae semilunares) (Fig. 13.5) that project into the lumen. The ileocecal valve consists of two of these folds. The submucosa resembles the submucosa of the rest...
of the gut. Lymphoid nodules straddle the boundary between the mucosa and the submucosa (Fig. 13.6) and may be quite prominent, especially in children, producing a diffusely nodular mucosa.

**FIG. 13.2.** Embryology of the large intestine. **A:** The proximal large intestine derives from the embryologic midgut, which herniates into the umbilical coelom during the sixth fetal week. The midgut loop then rotates around the axis of the superior mesenteric artery to lie in the position illustrated in **B.** **C:** Relative positions of the developing small and large intestines after return of the midgut loop to the abdominal cavity in the third month of gestation.
FIG. 13.3. Normal colon. A: The four layers of the colonic wall, including the mucosa, submucosa, muscularis propria, and serosa, are present. B: Lower portion of a normal crypt and the underlying muscularis mucosae.

FIG. 13.4. Taeniae coli. A: Colon showing a longitudinal band that corresponds to a single taenia coli (arrow). Haustra are also identifiable (arrowheads). B: The whole mount section shows thickenings of the muscularis propria that correspond to the taenia coli (arrow).

FIG. 13.5. Plicae semilunares. A: The colon is thrown into grossly visible folds. B: Histologically, these folds contain mucosa and submucosal extensions.
**FIG. 13.6.** A lymphoid follicle (*arrow*) spans the muscularis mucosae and extends into the submucosa. A normal mucosal cleft with nonparallel crypts lies above it. Trichrome stain.

The serosal surface is incomplete since the ascending and descending colon are retroperitoneal in location. The distal part of the rectum is not covered by peritoneum since it is below the peritoneal reflection. The serosa can contain lobules of fat that form pendulous projections called *appendices epiploicae* (Fig. 13.7).

---

**Innervation**

Like other portions of the gut, the large bowel is innervated by the autonomic nervous system. Parasympathetic nerves stimulate colonic motor activity, whereas sympathetic nerves inhibit motility and decrease blood flow to the mucosa. The cecum and the ascending and transverse portions of the colon are innervated by the vagus nerve, and the descending and sigmoid regions are innervated by pelvic postganglionic parasympathetic nerves. Sympathetic nerves emerge from the superior mesenteric ganglion to innervate the proximal two thirds of the colon. The remainder is innervated by sympathetic fibers derived from the inferior mesenteric ganglion. Sympathetic fibers innervating the distal rectum and anus derive from the hypogastric ganglion.
The appendices epiploicae appear as fatty dewdrops on the external surface of the colon.

In the right colon and transverse colon the preganglionic cell bodies of the sympathetic supply lie in the lateral columns of the lower thoracic segments of the spinal cord. Axons from these bodies synapse in the celiac, preaortic, and superior mesenteric plexuses. Postganglionic fibers pass to the right and transverse colon along the superior mesenteric artery. The cell bodies for the parasympathetic system are in the vagal nuclei. Long preganglionic fibers synapse with the cells in the submucosal and myenteric plexuses. Afferent fibers arise from sensory endings in the colon wall that are sensitive to stretching and spasm. Sympathetic nerves supplying the distal colon lie in the lateral columns of the first three lumbar segments of the spinal cord. They synapse in the ganglia of the inferior mesenteric plexus. The postganglionic fibers then pass to the left colon and rectum via the inferior mesenteric vessels. Parasympathetic nerves arise from the second to the fourth sacral segments and they proceed to the left colon, rectum, and internal anal sphincter, where they anastomose with the intramural cell bodies.

Axons of the parasympathetic, sympathetic, and sensory enteric plexuses contribute to the fiber network and form connections with the intrinsic neurons. Many types of nerves are present and are ultrastructurally differentiated by the types of vesicles seen in the nerve endings. The types of nerves and their functions are discussed further in Chapter 10.

**Blood Supply**

The cecum, ascending colon, and right part of the transverse colon (midgut-derived structures) are supplied by the superior mesenteric artery via the ileocolic, right colic, and middle colic arteries (Fig. 13.8). The left half of the transverse colon, the descending and sigmoid colon, and most of the rectum (hindgut-derived structures) receive their blood supply from the inferior mesenteric artery through the left colic, sigmoid, and superior rectal arteries (Fig. 13.8). The rectum is supplied by the superior rectal branch of the inferior mesenteric artery. Middle rectal arteries arise from the internal iliac vessels and the inferior rectal arteries come from the internal pudendal vessels. Anastomoses exist between the superior and inferior mesenteric arteries. Major branches of the ileocolic, right colic, left colic, and sigmoid arteries anastomose, forming a series of arches. These
Introduction

joined arches form a single continuous artery, referred to as the marginal artery of Drummond. The vasa recta, which supply the length of the colon, derive from this marginal artery. It is fed by branches of the superior mesenteric artery, the inferior mesenteric artery, and the hypogastric artery. The point of junction between superior mesenteric and inferior mesenteric arteries is known as the Griffith point. The junction between the inferior mesenteric artery and the hypogastric vessels is called the critical point of Sudeck. The colon is most vulnerable to ischemia at these two regions (1). In addition, the marginal artery is often small at the area of the splenic flexure, making this area particularly vulnerable to the consequences of reduced blood flow. There is a well-defined capillary network beneath the absorptive cells of the surface epithelium (Fig. 13.9).
Veins draining blood from the colon arise from a well-developed submucosal plexus and from a second less well-developed plexus outside the muscularis propria. The main veins correspond to the major arteries and are tributaries of the portal system. The venous drainage of the cecum, ascending colon, and part of the transverse colon is via the superior mesenteric vein. The left colon drains into the inferior mesenteric vein. These veins form part of the portal system with drainage from the gut going directly to the liver. The proximal rectum is drained by the superior hemorrhoidal vein that flows to the portal system via the inferior mesenteric vein. The middle and distal rectum are drained by the middle and inferior hemorrhoidal veins.

Lymphatic Drainage

The lymphatics begin as a capillary plexus that wraps around the muscularis mucosae (Fig. 13.10). This plexus sends small branches into the mucosa to reach no higher than the bases of the crypts of Lieberkühn (2). These vessels pass into and through the submucosa and form another plexus around the muscularis propria. The efferent lymphatics from this system form increasingly larger channels, which eventually join lymphatic vessels in the mesocolon. There are generally four groups of external lymphatics: (a) epicolic, which lie on the colon; (b) paracolic, located along the marginal artery; (c) intermediate, located along the main colic vessels and their branches; and (d) principal, located along the superior and inferior mesenteric arteries.

The subserosal lymphatics unite, forming collecting lymphatic trunks in the mesentery proceeding centrally toward the paracolic lymph nodes along the marginal vascular arcades. The serosa also contains small foci of lymphocytes. Efferent collecting lymphatic trunks proceed from the paracolic lymph nodes to the intermediate lymph nodes in the midmesentery, near the bifurcations of colic vessels. From the intermediate group, large efferents reach the central or principal lymph node at the root of the mesentery draining next to the inferior and superior mesenteric lymph nodes.

P.740

...and then into the cisterna chyli. The rectosigmoid mesentery is the most richly supplied with lymphatics and lymph nodes.
**FIG. 13.9.** Colonic blood supply. *A:* A penetrating artery extends from the serosa through the muscularis propria into the submucosa. *B:* Large vessels are present in the submucosa. *C:* A proliferation of capillaries is seen immediately beneath the luminal surface.
FIG. 13.10. A dilated lymphatic is seen immediately beneath the muscularis mucosae.
Congenital Abnormalities

Cecal Agenesis

Intestinal agenesis is the failure of a portion of the enteric tube to form. This disorder is rare, occurring in 1 in 50,000 pregnancies. Males are more commonly affected than females. It can affect the rectosigmoid (where it associates with other major caudal anomalies) or the cecum. Cecal agenesis may result from misexpression of the endoderm-specific homeodomain gene IDX-1 (20). IDX-1 binds to CDX-2, the caudal homeodomain factor important in intestinal differentiation (21).

Malrotations

Most large intestinal malpositions (Fig. 13.20) accompany small intestinal malrotations that occur when the contents of the physiologic abdominal hernia return to the abdominal cavity (see Chapter 6). In malrotations, the cecum usually fails to rotate and lies in the left iliac fossa, in the midline of the pelvis, or in the upper abdomen. The ascending colon retains its mesentery and runs upward, just to the left of the midline, to lie below the gastric curvature, where a loop of transverse colon connects to a normally situated descending colon. When rotation occurs beyond 180 degrees, the colon crowds into the left side of the abdomen or the cecum assumes an unfixed position in the right upper quadrant. The transverse colon and splenic flexure may lie posterior to the stomach and anterior to all or part of the pancreas, a location known as pancreatic interposition. They may also lie in a retroesplenic location (22). The entire malpositioned bowel remains unanchored, supported by a single mesentery with a very narrow base that predisposes it to undergo intestinal volvulus (22). The body attempts to correct the unstable state of the malpositioned intestine by forming fibrous bands or adhesions between abdominal structures. These bands and adhesions become sources of future problems.
**Atresia and Stenosis**

Large intestinal atresias and stenoses (Fig. 13.21) occur far less commonly than esophageal, small intestinal, or anal atresias. Atresias of the ascending and transverse colon develop more commonly than distal ones. Colonic atresia may coexist with other gastrointestinal or laryngeal atresias, gastroschisis (23), and Hirschsprung disease (24).

Hereditary multiple gastrointestinal atresias affect the gut from the pylorus to the rectum. Patients with multiple intestinal atresias may also have biliary atresia (23) or immunodeficiency syndromes (25). Cardiovascular and other gastrointestinal malformations constitute the most common associated major abnormalities; these are a major cause of morbidity and mortality. Skeletal and limb defects account for the most common minor anomalies. Atresias and stenoses are described in detail in Chapter 6.

**Duplications, Congenital Diverticula, and Enterogenous Cysts**

Large intestinal duplications (Fig. 13.22), congenital diverticula, and enterogenous cysts are related defects (Fig. 13.23) that affect both children and adults. They resemble their small intestinal counterparts described in Chapter 6. There is partial or
complete formation of a second luminal structure with its own mucosa and submucosa and incomplete separation of the muscular walls of the two tubes. The duplication always lies on the antimesenteric aspect of the bowel. The extent of the duplicated bowel varies from an entire GI duplication to more segmental duplications. These uncommon lesions affect the cecum, transverse colon, and rectum. Hindgut duplications are rarer than other gastrointestinal duplications. As in the small bowel, duplications communicate with the main intestinal lumen in various ways as discussed in Chapter 6. Distal large intestinal duplications fall into two categories: Those associated with urinary bladder, urethral, or anorectal abnormalities and those that occur alone. Cystic rectal duplications are rare and may cause neonatal intestinal obstruction or rectal prolapse (26). Rarely carcinomas develop within them (27). Anorectal abnormalities are discussed in detail in Chapter 15. Most duplications present in the newborn period, although occasionally the lesions remain asymptomatic, only to be detected in adults.

FIG. 13.22. Colonic duplication. A and B derive from an 81-year-old man who was autopsied and died of a myocardial infarction. He had a duplicated intestinal segment that emptied into the rectum (arrow); it ended blindly proximally. B represents a higher magnification of A showing the junction with the rectum.

Eighty percent of solitary congenital cecal diverticula occur within 2.5 cm of the ileocecal valve (28). Patients present with one of three distinct clinical syndromes: (a) distension, pressure, pain, and possibly perforation due to diverticulitis; (b) ulceration and bleeding, usually from the presence of acid-secreting heterotopic gastric mucosa; or (c) intussusception leading to sudden pain and bleeding. Large intestinal enterogenous cysts resemble their small intestinal counterparts (see Chapter 6) and often project into the colonic lumen (Fig. 13.23). They are generally lined by normal colonic epithelium but may contain heterotopic tissues (usually
Heterotopias

Heterotopic Gastric Mucosa

Large intestinal heterotopias are rare and usually complicate malformations, especially duplications. Ectopic gastric tissue is the most common large intestinal heterotopia (Fig. 13.24) (29). When it contains acid-secreting epithelium, peptic ulceration develops in the adjacent colonic mucosa (29). Rectal heterotopic gastric mucosa may cause significant rectal bleeding or present as a polyp (30), a mass, or hemorrhoids. Symptoms include proctitis, pain, mild rectal bleeding, and proctalgia. Rarely, heterotopic gastric mucosa causes hematochezia and perianal or retrovesical fistulae (31). It usually associates with other congenital anomalies, including incomplete colonic rotation and vertebral body defects, Meckel diverticulum, rectal duplication, rectal diverticula, scoliosis, and megacolon (29,30,31).

Gastric heterotopias more or less recapitulate the normal fundic gastric architecture. The gastric epithelium usually contains chief cells, parietal cells, and foveolar cells (Fig. 13.24). Gastric endocrine cells are often absent, but when present reflect their gastric origin (32). Gastric heterotopia may coexist with ectopic respiratory epithelium, presumably representing the equivalent of heterotopic foregut (Fig. 13.24). It differs from the pyloric metaplasia in that it is an acquired lesion that develops in the setting of chronic inflammation. The “pyloric” tissue does not exhibit normal architectural patterns of the gastric antropyloric region.

Heterotopic Pancreas

Large intestinal heterotopic pancreatic tissue resembles gastric heterotopic pancreas seen elsewhere (see Chapter 4).
FIG. 13.23. Cecal enterogenous cyst. A: The cyst appears as an intraluminal polyp. The reddish color is due to the fact that the duplication caused a terminal ileal intussusception. B: Opened cyst. C: Lining of the cyst shows a thickened muscularis and a simplified mucosa. D: The cyst is lined by a simple layer of colonic epithelial cells. Crypts are absent.

FIG. 13.24. Ectopic foregut in rectum. A: This polypoid lesion presented clinically as a hemorrhoid. The left and right sides of the photograph are lined by normal colorectal mucosa. The junction of the colorectal mucosa with gastric mucosa is indicated by arrows. The gastric epithelium consists of shortened pits without colonic crypts. It contains a glandular expansion; some of the glands are cystically dilated. B: Ciliated respiratory epithelium (star) is present along with the dark staining gastric glands. Prominent parietal cells are present. The clear cells are either antral or Brunner glands.
Congenital Abnormalities

**FIG. 13.25.** Ectopic müllerian tissue in the rectum. *A:* The lesion presented as a submucosal mass. The majority of the lesion consists of a proliferation of fibromuscular tissue and a cyst. *B:* Higher magnification of the cysts shows a flattened ciliated epithelium surrounded by smooth muscle.

**Seromucinous Heterotopia**

Seromucinous tissue resembling salivary glands can occur in the rectal wall, either alone or associated with retrorectal cystic hamartomas. The lesions usually contain both serous and mucinous glands, although pure mucinous lesions have been described (33). The lesions may arise from vestiges of the postanal gut (34).

**Innervation Abnormalities**

A number of congenital innervation abnormalities affect the large intestine, usually presenting with intestinal pseudo-obstruction. These are discussed in detail in Chapter 10.

**Cloacal Dysgenesis**

In cloacal dysgenesis, the bladder and rectum fail to separate into distinct and separate structures. As a result, the common cloacal cavity is lined on one side by transitional epithelium and on the other by rectal mucosa. Infants who exhibit this anomaly often have dilated small intestinal segments that contain calcified concretions.

**Embryonic Rests**

Occasionally one receives a rectal biopsy or resection specimen in which residual nests of müllerian or mesonephric ducts that failed to involute lie scattered deep in the rectal wall. These embryologic remnants represent morphologic curiosities without any clinical significance (Fig. 13.25). Usually these lesions are clinically silent, but they may become symptomatic when secondary changes such as abscesses develop (35). Nephrogenic rests may also be present and these may be part of a multiple congenital anomaly syndrome (36).
Connective Tissue Disorders

Marfan Syndrome

Marfan syndrome is a connective tissue disorder that primarily affects the skeleton, eyes, and cardiovascular system. Diverticula develop in children and in young patients with Marfan syndrome presumably due to the defective collagen.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome is a genetically determined, connective tissue disorder that results from mutations in the gene for type III procollagen (COL3A1) (548,549). It has multiple clinically distinct phenotypes, each showing different inheritance patterns and different biochemical abnormalities. The disease is characterized by hyperextensible skin, hypermobile joints, tissue fragility, and wide, thin scars frequently overlying bony prominences. Patient survival is shortened largely secondary to vascular rupture. The age at death ranges from 6 to 73 years with a median lifespan of 48 years (550). Ehlers-Danlos syndrome type IV is particularly lethal and characteristically presents with numerous problems, including rupture of major vessels with colorectal bleeding, prolapse, diverticulosis, diverticulitis, and spontaneous perforation (550,551). Bowel rupture usually occurs in the sigmoid colon and it accounts for approximately a quarter of major complications in young people (550). Small bowel and gastric perforation is much less common. Tissue fragility and poor wound healing contribute to surgical complications or death. Complications include wound dehiscence, evisceration, hemorrhage from abdominal vessels, fistulas, and adhesions. Some patients have recurrent perforations (550). The perforation and diverticulitis result from abnormal motility (451). Histopathologic examination of the arteries in patients with Ehlers-Danlos syndrome exhibits widespread structural abnormalities in the vessel wall in addition to aneurysms and rupture.
Cystic Fibrosis

Cystic fibrosis (CF), the most frequent lethal autosomal recessive disease in Caucasians, is caused by more than 1,000 different mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene listed in the cystic fibrosis mutation database located at https://www.genet.sickkids.on.ca/cftr/. As a consequence of the wide spectrum of mutations that are present, the clinical presentation of CF varies widely from monosymptomatic disease to multiorgan involvement (568). Some CFTR mutations confer residual CFTR function in rectal epithelia, which results in a milder clinical phenotype (569).

The median survival of patients with cystic fibrosis in North America has increased to 31 years and as a result there is an increased incidence of large intestinal complications. The distal intestinal obstruction syndrome is more common in older patients, is a frequent cause of abdominal pain, and may lead to intussusception. The prevalence of Crohn disease in cystic fibrosis patients is 17 times that of the general population. Patients with CF develop various intestinal complications, including rectal prolapse, intussusception, volvulus, pneumatosis, bleeding, fecal impactions (570), and a fibrosing colonopathy from the therapy as discussed in the section on drug injury. Right-sided microscopic colitis may also develop and there may be an increased incidence of colon cancer (571). Intestinal biopsy specimens from these patients may show hyperdistended goblet cells with an abundant layer of mucus attached to the epithelial surfaces. This disorder is discussed in detail in Chapter 6.

Amyloidosis

All known types of amyloid affect the gastrointestinal tract, including amyloid A (AA), amyloid of lambda (AL), or kappa light chain origin, transthyretin amyloid (ATTR), and β2-microglobulin (β2M). They may be distinguished using a panel of immunohistochemical markers (572). A recent study showed that the most common forms of large intestinal amyloid were AL amyloid followed by AA and ATTR. There were also cases in which the classification of the amyloid type was uncertain (572). Gastrointestinal amyloidosis generally presents as a motility disorder, ulcers, areas of hemorrhage, or pseudotumors.

The colorectum also develops α2-microglobulin deposits, the latter affecting patients on long-term dialysis (573). The development of the amyloidosis correlates with the time on dialysis (574). Patients with α2-microglobulin deposits exhibit two patterns of amyloid deposition: A vascular pattern and a gastrointestinal pattern. The vascular pattern may be subtle and not be evident in H&E-stained sections but can be highlighted by stains for amyloid or a microglobulin immunostain (574). The amyloid deposits may associate with mild mucosal abnormalities and regeneration or there may be ischemic damage. The severity of the mucosal changes reflects the severity of the vasculopathy. In the gastrointestinal pattern the amyloid deposits in the interstitium of the mucosa, submucosa, and muscularis propria. This pattern coexists with the vascular pattern. The amyloid deposits range from barely visible amyloid without mural expansion to amyloid tumors in the muscularis propria (573,574,575).

Rectal biopsies are commonly obtained in patients suspected of having amyloidosis, but it is essential that the biopsies be large enough to permit inspection of the submucosal vasculature. In ordinary H&E-stained sections, amyloid appears as a pink, hyalinized thickening of the vessel walls or as a more diffuse eosinophilic infiltrate in the lamina propria, submucosa, or muscular layer (Fig. 13.163). The lesions may be inapparent in mild cases. Tumoral amyloid is often accompanied by giant cells. Special stains for the amyloid include crystal violet (Fig. 13.163),
thioflavin, and Congo red coupled with polarized light to demonstrate the characteristic apple-green birefringence.
Disorders Associated with Granulomas and Macrophage Collections

Granulomas and collections of macrophages complicate various gastrointestinal conditions, as extensively discussed in Chapter 6. Macrophage collections take the form of both compact caseating or noncaseating granulomas or they appear as diffuse infiltrates. Structures that can simulate macrophage collections or granulomas include germinal centers of the lymphoid follicles, cross sections of smooth muscle, or tangential cutting of the pericryptal myofibroblast sheath. Small mucosal macrophage collections are common and represent a nonspecific reaction to low-grade injury. The macrophages contain foamy vacuoles or basophilic granules and they are usually scattered singly or in small clusters in the upper or lower lamina propria (Fig. 13.147). The macrophages often stain with mucin stains (Fig. 13.148) and increase in number following mucosal injury. Small, loose collections of macrophages also lie in the lamina propria adjacent to sites of crypt rupture (mucin granulomas).

Occasional small granulomas can complicate almost any infection. Granulomas with central caseating necrosis constitute the histologic hallmark of tuberculosis or *Yersinia* infections (see Chapter 6). Well-formed granulomas occur in approximately 50% of cases of colonic CD (see Chapter 11) and their detection relates to the disease distribution. Xanthogranulomas and foreign body granulomas complicate the presence of foreign material, such as barium (Fig. 13.89), feces, talc, food, and sutures or reactions to the transmural inflammation associated with appendicitis or diverticulitis. Deep granulomatous lesions can involve the submucosa and contain foamy histiocytes and fibroblastic cells infiltrated by lymphocytes, plasma cells, and foreign material. These occur very commonly beneath invasive carcinomas (Fig. 13.149) or are associated with diverticulosis.

**FIG. 13.148.** Muciphages in the lamina propria stained with mucicarmine stain. These may be quite prominent, particularly in patients with previous mucosal injury.
FIG. 13.149. Granulomas associated with carcinoma. A: A colonic carcinoma invades into the muscularis propria. Its invasive front is surrounded by an inflammatory response, which consists of granulomas and chronic inflammatory cells. B: Giant cells at higher magnification.

One also sees diffuse macrophage collections in *Mycobacterium avium-intracellulare* infections, Whipple disease, histoplasmosis, storage diseases, immunodeficiencies, and even algal infections. Another disorder characteristically associated with granulomatous inflammation is malakoplakia (see below).

**Lamina Propria Muciphages**

Muciphages, as first documented, are macrophages in the lamina propria that contain mucoproteins and are demonstrated by positive reaction with various mucin stains (462). They occur in up to 50% of rectal biopsies (462,463). These cells can be found throughout the colon in various situations and they reflect previous occult and clinically unimportant mucosal damage (463). Patients may present clinically with diarrhea, hematochezia, bowel habit change, constipation, hemorrhoids, and abdominal pain. Endoscopically, they present as nodules or polyps or they may be found incidentally (462,463). The mucosa may show regenerative or hyperplastic changes. In most cases the macrophages are located superficially (463). It may be prudent to stain for fungal or acid-fast organisms if the clinical situation warrants it.

**Xanthomas**

Xanthomas represent collections of PAS-positive macrophages confined to the mucosa or occupying a part of the bowel wall (Fig. 13.150). Most commonly they are small mucosal aggregates of foamy cells lying in the upper lamina propria and resembling gastric xanthomas (see Chapter 4). However, we have seen cases in which there are extensive collections of foamy cells involving multiple areas of the colon and the mucosa and upper submucosa. The foamy cells contain lipidlike material and are mucicarmine negative. They more than likely represent a nonspecific response to a past injury.
Malakoplakia

Malakoplakia is a distinctive rare granulomatous disease that usually involves the urinary bladder. The colon is the most common site of extraurogenital involvement. Patients with colonic malakoplakia range in age from 6 weeks to 88 years and show an equal sex distribution (464,465). This disease is seldom diagnosed clinically. Rather, the diagnosis usually rests on pathologic examination of the tissues. The GI tract, particularly the large bowel, is the dominant site of involvement in children (465). Malakoplakia complicates various diseases (Table 13.24). Recently it has been found to complicate paracoccidiomycosis (318). Most patients are symptomatic. Adults present with rectal bleeding, diarrhea, and abdominal pain (465). Patients with extensive disease experience intractable diarrhea, bowel obstruction, ulcers, fistulae, and even death. Children present with fevers, failure to thrive, bloody diarrhea, and malnutrition. Endoscopically, gastrointestinal malakoplakia assumes three gross forms:

(a) unifocal lesions, (b) widespread mucosal multinodular lesions, and (c) large mass lesions. Surgical resection is usually curative in limited disease.

FIG. 13.150. Colonic xanthoma. The lamina propria is diffusely infiltrated with foamy histiocytes. The specimen was negative for acid-fast bacilli and fungi, and the patient had no history of a storage disease.

TABLE 13.24 Diseases Associated with Colonic Malakoplakia
Disorders Associated with Granulomas and Macrophage Collections

- Inflammatory bowel disease
- Carcinomas
- Villous adenomas
- Lymphoreticular diseases
- Neurofibromatosis
- Immune deficiency
- α-Chain disease
- Miliary tuberculosis
- Infection
  - Tuberculosis
  - *Mycobacterium avium-intracellulare* infection
  - *Klebsiella*
  - *Escherichia coli*

**FIG. 13.151.** Rectal malakoplakia. *A:* The specimen viewed en face shows a lumpy, bumpy mucosal surface. *B:* Cross section through the bowel wall shows the mucosa to the left and the serosa to the right. The process diffusely infiltrates the bowel wall.

Malakoplakia results from an abnormal macrophagic response with defective bacterial degradation. This may result from an immunologic abnormality affecting cellular digestion, absence of the necessary lysosomal enzymes (466), or decreased levels
Disorders Associated with Granulomas and Macrophage Collections

of cyclic guanosine monophosphate (GMP) (467).

Grossly, colonic involvement is segmental or diffuse, with the rectosigmoid and cecum being the most commonly affected sites. Early lesions appear soft, flat, and yellowish tan (Fig. 13.151). Later, lesions become raised and tan-gray, with an irregular hyperemic margin and a central depressed area. Submucosal lesions secondarily elevate the mucosa into soft yellow-tan plaques or nodules. Often the overlying mucosa appears intact. Malakoplakia most frequently presents as one or more polypoid lesions ranging in size from 3 mm to 4 cm. Intestinal lesions extend deeply into the intestinal wall (Fig. 13.152) leading to perforation and fistula formation. The lesion may mimic tumors and/or associate with tumors.

FIG. 13.152. Whole mount photograph showing the extent of the inflammation, which is primarily submucosal.

The focal or diffuse multinodular masses consist of numerous granular cells with eosinophilic cytoplasm called von Hansemann cells, which contain giant polyphagolysosomes. These contain various forms of mineralized debris and partially digested bacteria (466). The presence of characteristic intracellular and extracellular Michaelis-Gutmann bodies clinches the diagnosis (Fig. 13.153). Michaelis-Gutmann bodies vary in size from 2 to 10 µm and have a round, dense, or targetoid appearance due to the presence of concentric laminations. These stain blue with hematoxylin and are highlighted with the Von Kossa stain for calcium or with iron stains. They also contain lipid and are PAS and Alcian blue positive. Because malakoplakia tends to associate with both adenomas and carcinomas, the tissues should be carefully evaluated for the presence of coexisting neoplastic conditions.

Malakoplakia superficially resembles several other disorders, including storage diseases, Whipple disease, MAI, and fungal infections because of the macrophage collections, but none of these disorders contains the pathognomonic Michaelis-Gutmann bodies. Special stains serve to identify the specific infections in fungal or tuberculous lesions.
Disorders Associated with Granulomas and Macrophage Collections

**Malakoplakia.** A: Histiocytic cells intermingle with lymphocytes and plasma cells. B: Higher magnification shows typical Michaelis-Guttman bodies with their characteristic targetoid appearance (arrows).

**FIG. 13.153.**

**Sarcoidosis**

Sarcoidosis is a chronic multisystem granulomatous disease of unknown etiology. The characteristic histologic lesions include noncaseating granulomas containing multinucleated giant cells in the absence of identifiable infectious diseases or foreign bodies. GI disease is uncommon (468). The stomach is the most frequently affected gastrointestinal organ but the colon may become involved (Fig. 13.154). Colonic sarcoidosis usually remains asymptomatic but it may cause constricting obstructive lesions resembling carcinoma on a barium enema. The disease also mimics CD, especially when it involves the ileocecal region (469). Not all patients with GI disease have intrathoracic involvement (470). Systemic sarcoidosis is generally extremely responsive to corticosteroid therapy, with improvement often occurring after only a few days of treatment (468).
Disorders Associated with Granulomas and Macrophage Collections

FIG. 13.154. Colonic biopsy in a patient with known sarcoid. The compact granuloma is noncaseating and surrounded by a cuff of lymphocytes.

<table>
<thead>
<tr>
<th>TABLE 13.25 Definition of AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any patient with one or more of the following reliably diagnosed diseases in the absence of known cause of immunodeficiency; laboratory evidence regarding HIV infection either positive or not available:</td>
</tr>
<tr>
<td>● Candidiasis of esophagus, trachea, bronchi, or lungs</td>
</tr>
<tr>
<td>● Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td>● Cryptosporidiosis with diarrhea persisting more than 1 month</td>
</tr>
<tr>
<td>● Cytomegalovirus disease, extranodal, in patient older than 1 month of age</td>
</tr>
<tr>
<td>● Herpes simplex virus infection with ulceration persisting more than 1 month</td>
</tr>
<tr>
<td>● Kaposi sarcoma in patient under 60 years of age</td>
</tr>
<tr>
<td>● Lymphoma, brain (primary), in patient under 60 years of age</td>
</tr>
<tr>
<td>● Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia in child under 13 years of age</td>
</tr>
<tr>
<td>● <em>Mycobacterium avium-intracellular</em> or <em>Mycobacterium kansasii</em> disease, disseminated</td>
</tr>
<tr>
<td>● Pneumocystosis</td>
</tr>
<tr>
<td>● Progressive multifocal leukoencephalopathy</td>
</tr>
</tbody>
</table>

Any patient with one or more of the following reliably diagnosed diseases plus laboratory evidence of HIV infection:

| ● Bacterial infections, multiple or recurrent, in child under 13 years of age |
| ● Coccidioidomycosis, disseminated |
| ● HIV encephalopathy |
| ● Histoplasmosis, disseminated |
Disorders Associated with Granulomas and Macrophage Collections

- Isosporiasis with diarrhea persisting more than 1 month
- Kaposi sarcoma at any age
- Lymphoma, brain (primary), at any age
- Other non-Hodgkin lymphoma of certain types
- Disseminated mycobacteriosis caused by mycobacteria other than *Mycobacterium tuberculosis*
- Tuberculosis, extrapulmonary
- *Salmonella* (nontyphoid) septicemia, recurrent
- HIV wasting syndrome

**Wegener Granulomatosis**

Wegener granulomatosis is a disease of unknown etiology characterized by the presence of necrotizing granulomas of the upper and lower respiratory tract, vasculitis, and glomerulonephritis (471). Other affected organs include the intestinal tract. Wegener granulomatosis may mimic IBD when it presents as acute granulomatous colitis (471). Patients may develop nausea, vomiting, abdominal pain, and a bloody mucoid rectal discharge. The diagnosis is confirmed by the presence of characteristic palisading granulomas with a central area of necrosis that contains multinucleated giant cells surrounding small arteries and veins.
Effects of Surgery and Therapeutic Procedures

Endoscopic Thermal Injury

Endoscopic resection of colorectal polyps is currently a standard practice. In general, the resection margin passes through the submucosa. Less than 1% of patients perforate following the procedure (615). Perforations could result from the surgical resection of the colonic wall or from thermal injury. The postendoscopic resection sites show a range of mucosal changes including ulceration. Submucosal changes include inflammation, granulation tissue, fibrosis, and vascular proliferations. If changes are present in the muscularis propria, they may have a "skip" appearance. These consist of patchy muscular depletion or necrosis in the inner muscular layer with or without accompanying fibrosis. Ink may also be seen (615).

FIG. 13.177. Diversion colitis. The specimen is from a patient who had a previous resection for Crohn disease. The specimen is from the diverted segment. A: Marked lymphonodular hyperplasia with variable ulceration of the surface. B: This specimen is from an area of marked glandular atrophy. The bases of the glands are widely separated from the muscularis mucosae. The lamina propria is intensely infiltrated by lymphocytes and plasma cells.

Diversion Colitis

The term *diversion colitis* refers to the inflammation that occurs in the defunctionalized intestinal segment following diversion of the fecal stream. The changes may remain asymptomatic or give rise to rectal bleeding or discharge (616,617). Its importance lies in the inability to differentiate it from other types of proctitis, such as ulcerative colitis. The lesion completely resolves following restoration of the continuity of the fecal stream.

The pathophysiology of the changes are thought to relate to a decrease in mucosal nutrition since short-chain fatty acids that derive from the bacterial fermentation of starch and proteins are the main metabolic fuels for colonocytes, especially distally (618). A change in the bacterial flora in the defunctionalized segment may also lead to the inflammation.

Patients with diversion colitis present with continuing GI symptoms, including constipation or diarrhea with mucoid or bloody discharge and crampy abdominal pain. Endoscopically, the bowel may show erythema; petechial hemorrhages; mucosal
Effects of Surgery and Therapeutic Procedures

Friability; mucosal nodularity, sometimes surrounded by aphthous ulcers; nonspecific colitis; and inspissated mucus (619). Patients may also present with the underlying disorder for which the original colonic surgery and diversion were performed, such as IBD.

Inflammation develops in up to 72% of patients (Fig. 13.177). Biopsies taken from the distal diverted intestine show relatively nonspecific changes, including aphthous ulcers, focal crypt abscesses, surface exudates, surface epithelial cell degeneration, and prominent follicular hyperplasia. It is the lymphoid hyperplasia that produces the fine mucosal nodularity. Many of the mucosal lymphoid follicles have overlying small, punctate erosions forming classic aphthous ulcers. With time, the mucosal inflammation becomes more extensive, leading to the development of ulcers and inflammatory pseudopolyps. Inflammation occurs diffusely throughout the lamina propria and is mainly chronic in nature, but it may include some neutrophils with consequent cryptitis and crypt abscess formation. Subsequently, muciphages may become prominent in the lower half of the lamina propria.

The feature that serves to distinguish diversion colitis from other forms of colitis is the consistent presence of lymphoid follicular hyperplasia (620). This lymphoid hyperplasia is particularly striking in patients with CD (Fig. 13.177), even in those who had a lack of histologic evidence in Crohn disease in the defunctionalized rectum prior to diversion. Severe cases of diversion colitis histologically resemble ulcerative colitis. However, the lack of crypt distortion and the presence of lymphoid follicular hyperplasia resembling follicular proctitis should lead to the correct diagnosis in patients without pre-existing IBD. Intramucosal granulomas sometimes form in response to ruptured crypts, possibly leading to an erroneous diagnosis of CD. However, again, the lack of diffuse mucosal inflammation, crypt distortion, and true granulomas should help avoid this diagnosis. In patients who have had pre-existing IBD, particularly CD, the diagnosis is more difficult and clinically the question is whether the inflammation is recurrence of CD or development of diversion colitis. In some instances, it may be impossible to tell the difference and resolution of the question relies on mucosal restoration following reanastomosis.

![Image of histological sections showing lymphoid follicular hyperplasia and intramucosal granulomas.](image-url)
Effects of Surgery and Therapeutic Procedures

**FIG. 13.178.** Colonic tattoo. *A:* Low-mount photograph demonstrating the presence of a collection of India ink in the submucosa dissecting its way through the muscularis propria. *B:* Higher magnification.

### Colostomies

Colostomies undergo various changes. If the patient has had IBD, inflammation may represent disease remission at the colostomy site. Colostomies also develop nonspecific inflammation, usually manifesting as an increase in the number of mononuclear cells infiltrating the lamina propria. The mucosa usually appears chronically damaged as evidenced by the presence of branched or irregularly shaped glands. Focal ischemia and features of mucosal prolapse are generally present.

### Intestinal Effects of Endoscopic Tattooing

GI tattooing is sometimes used to mark specific features of the GI mucosa at the time of endoscopy. It is used to facilitate the location of biopsy sites or other sites of interest at the time of subsequent biopsy or surgery. Permanent tattoos are used for the long-term endoscopic follow-up of polyps or other suspicious lesions. The tattoos are produced by introduction of nondegradable pigments into the submucosa. The most commonly used substance is India ink, but others include methylene blue and indocyanine green. Submucosal injection of sterile ink produces a zone of blue-black discoloration that is grossly visible from both the mucosal and serosal surfaces. Of the various substances used to produce the tattoos, only India ink and indocyanine green persist for as long as 7 days.

Adverse effects following colonoscopic injection of India ink include focal peritonitis, abscess, fat necrosis, and inflammatory pseudotumors (621). The mechanisms by which India ink produces its effects are unknown. Adverse effects may result from the invasion of tissue by GI flora or from toxic ingredients in the preparation itself (622).

Histologically, one sees an architecturally normal mucosa with an irregular circumscribed area of black pigment deposition within the submucosa. The pigment lies within the cytoplasm of histiocytes as well as extracellularly (Fig. 13.178). Early reactions to India ink include necrosis, edema, and neutrophilic infiltrates into the submucosa and muscularis propria. Vessels are inflamed but without fibrinoid necrosis. In contrast, early reactions to methylene blue include ischemic ulceration, necrosis, and eosinophilic infiltration in the submucosa as well as fibrinoid necrosis of the vessel walls. Obliterative intimal fibrosis complicates the repair of the methylene blue injuries. These changes are absent from colons injected with India ink (623).

Because of the inflammation associated with these agents, some advocate that the injection site be completely resected at the time of definitive surgery (623). When handling such specimens, one should report whether the ink site has been completely removed and the extent of the damage associated with the ink.

### Other Effects

*Ureterosigmoidostomy* replaced urinary diversion by ileal conduits. These procedures may be complicated by the development of polypoid lesions at the site of ureteric implantation. The lesions that develop are often multiple and include adenomatous polyps, juvenile polyps, inflammatory polyps, and carcinomas.
FIG. 13.179. Previous biopsy sites. A: A re-epithelializing ulcer. The right-hand portion of the ulcer is lined by granulation tissue and inflammatory cells. The left-hand side is undergoing regeneration. Underlying the regenerating epithelium are entrapped glands (arrows). The submucosa is intensely inflamed. B: An area of a polypectomy site (arrows) that shows an interruption in the muscularis mucosae and an area of increased fibrous density in the submucosa. The overlying mucosa shows granulation tissue and inflammatory cells. C: Higher magnification of the mucosal defect demonstrating the inflammatory cells and giant cells. There is significant glandular distortion to the side of the lesion and one might interpret such a focal lesion as representing Crohn disease, if one did not have the entire history.

Previous biopsy sites may cause interpretive problems, particularly due to features induced by repair. Fortunately, most such lesions are examined in a subsequent resection specimen so that the lesions can be evaluated in their complete clinical context. The area of the biopsy site will vary histologically, depending on the time interval that elapsed between the biopsy and resection or subsequent biopsy. The biopsy may cause displacement of glands into the underlying submucosa. These glands may appear reactive and may cause interpretive problems, particularly if there is a question of invasive carcinoma (Fig. 13.179).

Anastomoses are sometimes examined to exclude the presence of recurrent tumor if a mass develops in the area. If a mass is located low in the rectum, the patient may undergo a needle biopsy to determine its etiology. Many times all one finds is a dense cicatricial fibrosis with no tumor. The mucosa overlying the anastomotic site usually appears hyperplastic and regenerative. One may also encounter suture material in such a site.

Miscellaneous Lesions

Torsion of Appendices Epiploica (Epiploic Appendagitis)

The appendices epiploica lie along the entire colon from the cecum to the upper part of the rectum. Torsion or vascular thrombosis causes their infarction (Fig. 13.180), hemorrhage

P.885
into the fatty tissues, abscess, or stricture formation. Appendices epiploica may also autoamputate and lie freely in the peritoneal cavity, where they may calcify and turn into “peritoneal mice” (Fig. 13.181). Histologically, they consist of fat that may appear infarcted and completely surrounded by a dense fibrous capsule or may show variable degrees of fat necrosis and calcification, again surrounded by fibrous material.

**FIG. 13.180.** Infarcted appendix epiploica (*arrows*). The appendix epiploica hangs by a thin strand from the pericolonic fat. It has undergone torsion and become infarcted, hence its dark color.
Effects of Surgery and Therapeutic Procedures

FIG. 13.181. “Peritoneal mouse.” Cross section of a hard, whitish nodule containing yellowish material in its center, giving it the appearance of a cross section of a hard-boiled egg.

Irritable Bowel Syndrome

Irritable bowel syndrome is the most common gastrointestinal disorder encountered in general and gastroenterology practices (624,625). It is characterized by abdominal pain, altered bowel habits (diarrhea or constipation), bloating, or the passage of mucus per rectum. A number of criteria have been advanced to standardize the clinical diagnosis (626). The condition develops in women more often than men, often in those with underlying depression or anxiety. Subtle but nonspecific histopathologic changes can be found in patients with this diagnosis. These include increased numbers of mucosal lymphocytes, mast cells, endocrine cells, and nerve cells as summarized by Kirsch and Riddell (627).

Submucosal Colonic Edema (Colonic Urticaria)

Colonic urticaria causes a characteristic mucosal distortion consisting of reticular, polygonal, or mosaic radiographic patterns and broad areas of submucosal edema. The condition results from obstruction or hypersensitivity reactions (628). The lesion has been likened to the skin of a giraffe or a leopard (Fig. 13.182).
FIG. 13.182. Colonic urticaria. The bowel wall is edematous, with loss of the normal architecture.

**Pseudolipomatosis**

Snover et al (629) defined the lesion known as pseudolipomatosis. These authors showed that the lesions do not contain fat cells but represent entrapped gas within the lamina propria (Figs. 13.183 and 13.184). The spaces are also not dilated lymphatics because they lack an endothelial lining. Changes of pseudolipomatosis extend from the stomach to the rectum, and involve normal as well as abnormal tissues. It is our belief that this common finding results from the dissection of the intraluminal air that is introduced into the mucosa of the GI tract at the time of endoscopy. The lesion has no known clinical consequence.
FIG. 13.183. Irregular intramucosal cystic spaces are the hallmark of pseudolipomatosis coli. Note the lack of inflammation.
FIG. 13.184. Mucosal pseudolipomatosis. A: High magnification of such a lesion. Numerous air-filled cysts are present between two glands. B: An adenomatous polyp containing mucosal pseudolipomatosis. It is identified as collections of air-filled bubbles in the mucosa.
Elastofibromatous Change

Elastofibromatous change can develop in the large intestine. The tissues demonstrate smudgy, granulofibrillar, eosinophilic deposits (Fig. 13.185). The elastofibromatous changes consist of eosinophilic deposits that do not stain with Congo red stains but exhibit the histochemical and ultrastructural properties of elastic fibers similar to those found in elastofibromas (630). The lesion develops following injury in genetically susceptible individuals. The pathogenesis of the lesion is unclear.

Myxoglobulosis

Myxoglobulosis is a disorder that normally affects the appendix but occasionally occurs in the cecum (Fig. 13.186). The lesion is usually identified grossly by the presence of a collection of opaque globules of variably calcified, amorphous material without an underlying architecture. This material represents concretions of mucin. In the appendix, the lesion typically associates with mucoceles, but there are no known associations in the cecum. This entity is discussed further in Chapter 8.
Endometriosis and Endosalpingiosis

Colonic involvement occurs in 3% to 34% of women with endometriosis. Patients range in age from 28 to 56 years (609). Recurrent, crampy, mild abdominal pain is the most common presenting symptom. Patients may also present with nausea, vomiting, diarrhea, constipation, small-caliber stools, fever, anorexia, weight loss, hematochezia, a mass, intestinal obstruction, and infertility. Because of the predominantly serosal and subserosal location of the tissue, rectal bleeding is infrequent. An episodic and cyclic nature of the intestinal symptoms just prior to menstruation clinically suggests the diagnosis. However, symptoms coincide with menstruation in <50% of cases (610). Extensive and deep involvement of the intestinal wall (Fig. 13.174) or the inflammatory adhesions produced by resolution of recurrent episodes of bleeding may lead to intestinal obstruction, volvulus, or intussusception. Rarely, the disorder presents as an acute abdomen. Terminal ileal disease mimics malignancy, strictures from previous radiotherapy, CD, ischemia, and infections such as Yersinia and tuberculosis (Fig. 13.175).

FIG. 13.173. Reactive fibromuscular proliferations. A through C are from the same specimen. A: Grossly innumerable short, stubby, mucosal projections are present. B: These consist of mucosal elevations by a proliferation of smooth muscle mixed with vessels and nerves. There is complete loss of the demarcation between the muscularis mucosae, submucosa, and muscularis propria. C: Higher magnification showing the obliteration of these normal landmarks.
Intestinal endometriosis commonly affects those parts of the bowel that lie in proximity to genital organs. The sigmoid is the most commonly affected portion of the large bowel, followed by the rectum (611), with these two sites accounting for 70% of cases. The lesions present grossly as intramural masses of strictures or stenosis, polyps, or submucosal masses simulating a carcinoma. The serosal surface is often puckered secondary to extensive subserosal fibrosis. This may lead to secondary stricture formation. The presence of a hard annular growth that usually spares the mucosa may simulate a carcinoma. Adhesions to adjacent structures may develop. Cut sections of the bowel wall may disclose the presence of small intramural tarry or chocolate cysts. Histologically, endometriosis consists of islands of endometrial tissue in the serosa, muscularis propria, submucosa, or rarely the mucosa of the GI tract (Fig. 13.176). Rarely, endometriosis extends into pericolonic soft tissues, invades blood vessels and their lumens, infiltrates nerves, and spreads to the pericolonic lymph nodes. Since the heterotopic endometrial tissue functions in a manner analogous to eutopic endometrial tissue, it cycles through...
both the proliferative and secretory phases of the menstrual cycle, and it may slough as in menstruation. As a consequence of the sloughing and bleeding, there may be regeneration of the endometrial tissues or scarring with evidence of prior hemorrhage.

The diagnosis is easily made when one identifies endometrial glands surrounded by endometrial stroma. The endometrial glands are distinguishable from colonic glands due to their lack of mucin and the presence of ciliated cells. The endometrial stroma differs from normal lamina propria in that the tissue appears more compact and the stromal cells appear elongated with slightly rounded nuclei. There is often a zone of hemorrhage or fibrous tissue containing hemosiderin. In some instances the amount of endometrial stroma is disproportionate to the glandular component. In its most extreme form one may only see islands of extensive fibrosis containing hemosiderin-laden macrophages and it may be difficult to recognize the true nature of the lesion.

The surrounding mucosa may show signs of chronic injury including architectural distortion, lymphoplasmacytic infiltrates, pyloric metaplasia, ischemia, segmental acute colitis and ulceration, and rarely fissures. There may be

| TABLE 13.31 Comparison of Endometriosis and Colitis Cystica Profunda |
|-------------------|-------------------|-------------------|
| **Feature**       | **Endometriosis** | **Colitis Cystica Profunda** |
| Epithelium        | Non-mucin-secreting endometrial glands; sometimes the glands appear dilated | Mucin-producing colorectal epithelium |
| Stroma            | Dense and spindled | Loose lamina propria |
| Stromal changes, hemosiderin and fibrosis | May be present | May be present |
| CEA immunoreactivity | - | + |
| CEA, carcinoembryonic antigen | | |
Endometriosis and Endosalpingiosis

Evidence of mucosal prolapse (609). The intestinal wall may show marked concentric smooth muscle hyperplasia and hypertrophy, neuronal hypertrophy and hyperplasia, fibrosis, and serositis (609). Endometriosis may mimic colitis cystica profunda (see Fig. 13.50), and the distinction between the two lesions can be difficult. The major difference between the two entities lies in the nature of the epithelium and its surrounding stroma (Table 13.31), particularly in the absence of the typical endometrial stroma accompanying the endometrial-lining epithelium. The lesions might also mimic ischemia or CD. This is particularly true when superficial mucosal biopsies are examined that show architectural distortion. The presence of crypt abscesses and cryptitis may further suggest the diagnosis of IBD. Rarely, areas of endometriosis may show extensive myxoid changes that may lead to an erroneous diagnosis of pseudomyxoma peritonei (612). Areas of endometriosis may also give rise to neoplasms including endometrioid adenocarcinomas, müllerian adenosarcomas, endometrial stroma sarcomas, endometrioid adenofibroma with borderline malignancy adenocarcinoma in situ, and atypical hyperplasia (613).

Endosalpingiosis is characterized by the presence of benign glands lined by ciliated tubal-type epithelium. The cells are believed to derive from the peritoneal mesothelial cells as part of the secondary müllerian system. It is one of the triad of nonneoplastic secondary müllerian lesions, the others being endometriosis and endocervicosis (614). It may affect the colon, where it is usually found as an incidental finding. Rarely it presents as a mass simulating a neoplasm (614). The histologic features are illustrated in Chapter 8.

Inflammatory Pseudotumors

Any transmural inflammatory process, such as CD or diverticulitis, may present clinically as a mass lesion. Usually fistulae with an exuberant secondary inflammatory reaction cause the lesions. These inflammatory pseudotumors consist of variable admixtures of fat necrosis and fibrous proliferation. Radiologically, fibrous stranding is seen in the area of the lesion. Mesothelial cells may become entrapped within the inflammatory masses, leading to the development of mesothelial inclusion cysts or inducing marked mesothelial hyperplasia. If the lesion develops as a result of an abscess, one may see the residual acute and/or chronic inflammation associated with the abscess or one may see marked xanthogranulomatous inflammation. Additionally, if the mass results from fistulization from the bowel lumen, foreign material, particularly food or feces, may be present.
Histologic Features

The mucosa is smooth and without folds except distally in the rectum. There are no villi. The mucosal surface is flat and regular with interconnected territories containing 10 to 100 parallel crypt mouths measuring 25 to 50 µm in diameter, separated by deep clefts (3). The orifices of the crypts appear as regularly arranged and spaced round depressions that have a uniform size and diameter. The clefts are known as the innominate grooves and they appear as small depressions surrounded by elevations of luminal cells. Visualization of the normal surface pattern has become more important with the increasing use of chromoendoscopy and magnifying endoscopy to detect neoplastic and preneoplastic lesions at the time of colonoscopy.

The crypts are straight tubular structures that lie absolutely parallel to one another and measure approximately 0.5 mm in length. They are unbranched, and extend from the lumen to the muscularis mucosae. However, sections through the crypts making up the innominate grooves demonstrate a branching or cloverleaf pattern. The epithelial lining is columnar in shape and contains an abundance of enterocytes and goblet cells and a small number of endocrine cells. Mucin flows from the crypt openings and covers the mucosal surface (Figs. 13.11 and 13.12) (3). The colonic epithelium contains undifferentiated cells, goblet cells, absorptive cells, tuft cells, and endocrine cells (4). An orderly pattern of differentiation proceeds from the crypt base to the luminal surface (5). Undifferentiated stem cells in the crypt bases resemble those in the small intestine. The crypt sides are lined by mucus-secreting cells, immature absorptive cells, and rare endocrine cells. Most of the cells lining the middle and upper crypt are in the second replicative zone (i.e., the zone in which partially differentiated cells can still undergo mitosis). The surface epithelium contains goblet cells and mature absorptive cells (5). Cells in the upper 25% of the crypt do not divide but continue to differentiate to form mature absorptive or goblet cells. In addition, M cells are present in the epithelium overlying lymphoid follicles, and intraepithelial T lymphocytes lie scattered within the colonic epithelium.

Absorptive Cells

Absorptive cells outnumber goblet cells 3:1 (Fig 13.13) (6). Mature absorptive cells absorb water and electrolytes; have numerous short, regularly spaced microvilli; and are joined by junctional complexes and lateral desmosomes. The intercellular spaces are variably dilated depending on the physiologic activity of the colon (5). A glycocalyx covers the microvilli on the luminal surface of the epithelial cells. Microvilli increase in number and elongate as the cells mature. Hairlike, loosely packed projections extend perpendicularly from the plasma membrane into the lumen and radiate from the microvilli. Small, round, 30- to 100-nm vesicles, called C bodies, are embedded among the filaments (7). Similar bodies are seen in the apical cytoplasm of mature absorptive cells. These are called R bodies and measure 106 to 250 nm in diameter. As the cells mature, there is a concomitant migration of the R bodies to the apex of the cell. The cytoplasmic microfilaments form a loose, stratified network that retains the same basic organization as that found in the small intestine (8). The apical cytoplasm contains a terminal web composed of microfilaments and core rootlets. Mitochondria, lipid droplets, lysosomes, apical vesicles, and round basally located nuclei are present in the cytoplasm (5). These cells secrete secretory component, which participates in the epithelial translocation of IgA as discussed in Chapter 6.
Goblet Cells

There are more goblet cells in the large intestine than in the small intestine. They are most abundant in the sigmoid colon and rectum, with approximately one goblet cell for every four columnar cells (Figs. 13.12 and 13.13). Their broad shape creates the false impression that they constitute the majority of the cells. As they differentiate, they migrate toward the mucosal surface and become progressively filled with mucus granules. The nucleus is compressed into a small dense structure in the basal region of the cell. Mucus secretion occurs throughout the life span of the cell. The membrane-bound mucin granules migrate toward the apical surface of the cell, where they are released by exocytosis. As the cells become more distended with mucin, the microvilli become sparser. The lateral cell surfaces are interlocked by cytoplasmic processes. Junctional complexes are present at the cell apices, and desmosomes are located at various points along the lateral surfaces.
FIG. 13.12. Numerous goblet cells are identifiable lining the crypt. Goblet cells contain abundant mucin granules that are discharged into the colonic lumen by exocytosis.
Histologic Features


The goblet cell secretes mucin derived from the carbohydrate–protein complex synthesized in the rough endoplasmic reticulum, which is then glycosylated, sulfated, and packaged in the Golgi. These mucins react strongly with Alcian blue at pH 2.5 and 1.0 (9). Sulfomucins predominate in the lower parts of the crypts, whereas carboxymucins are found in the upper crypts and surface epithelium (10).

Gastrointestinal mucins have been extensively studied in recent years, largely facilitated by the large number of immunohistochemical reagents that have become available to characterize them (11). Mucins are glycoproteins that are formed by the sequential addition of monosaccharides into chains attached to polypeptide backbones. Goblet cells secrete MUC1, MUC2, MUC3, and MUC4. Columnar cells secrete MUC1, MUC3, and MUC4 (12).

Other Cells

Tuft cells constitute approximately 1% to 2% of the colonic epithelium. They are characterized by an apical tuft of long, thick microvilli that project into the colonic lumen. The cores of these microvilli extend deep into the cytoplasm, sometimes reaching the basally located nucleus. The function of the tuft cells is unknown, but some speculate that they have a sensory or chemoreceptive function (13). The colon has the least number of endocrine cells of any region of the gastrointestinal (GI) tract. This cell population is discussed further in Chapter 17. Scattered Paneth cells are present in the cecum and proximal ascending colon (Fig. 13.14). They are absent from the remainder of the normal large intestine.
FIG. 13.14. Paneth cells (*arrows*) occur in the cecum, particularly in the area of the ileocecal valve. They are not found in other parts of the large intestine.
Histologic Features

Cell Renewal and Differentiation

Intestinal epithelial cells are one of the most actively replicating populations in the body. The process of intestinal cell renewal involves their proliferation, migration, differentiation, and sloughing or death. The clonogenic compartment consists of a pool of pluripotent GI stem cells and early undifferentiated progenitors that possess a multilineage clonogenic potential (14). Dividing cells lie in the proliferative compartment of the crypts, which is larger than that seen in the small intestine (Fig. 13.15) and involves the lowest two thirds of the crypts. Cells migrate from the proliferative zone toward the gut lumen. This migration takes 3 to 8 days (15). Normal colonic epithelium turns over approximately every 3 to 4 days. Undifferentiated stem cells in the crypt bases give rise to daughter cells committed to differentiate into columnar, goblet, endocrine, and tuft cells. Columnar, goblet, and tuft cells migrate with one another up the crypt wall onto the flat mucosal surface and they are sloughed into the lumen or undergo apoptosis (Fig. 13.16). Epithelial cells synthesize type IV collagen and laminin, contributing to the formation of the underlying basal lamina.

Pericryptal Myofibroblast Sheath

A pericryptal myofibroblast sheath invests the crypts, maintaining the normal morphology and cellular dynamics of the colonic mucosa (Figs. 13.17). The cells are a unique group of smooth musclelike fibroblasts. They arise by mitosis in the crypt base and migrate toward the mucosal surface. Platelet-derived growth factor and stem cell factor are responsible for differentiating myofibroblasts from stem cells. Myofibroblasts play an important role in organogenesis,
Histologic Features

oncogenesis, inflammation repair, and fibrosis and they secrete extracellular matrix molecules, cytokines, and growth factors (16). The myofibroblast sheath maintains a state of differentiation similar to that of the adjacent epithelium and there is synchronized proliferation in the sheath and the epithelium (17).

FIG. 13.16. Scattered apoptotic bodies lie in the superficial mucosa. They appear brown in this TUNEL assay (arrows).

These cells were originally thought to invest the crypts, but it is now clear that they form a syncytium throughout the lamina propria, merging with pericytes surrounding blood vessels that course through the tissues. In the crypts they are oval and scaphoid in appearance and overlap like shingles on a roof (18). At the surface they become stellate and appear like octopi sending cytoplasmic processes toward the basal lamina. Eventually these cells enter the lamina propria (18). There are close contacts between these cells and nerve terminals.
**Lamina Propria**

The lamina propria separates the crypts of Lieberkühn and consists of loose connective tissue containing reticulin fibers, fibroblasts, capillaries, and mononuclear cells, including macrophages, plasma cells, lymphocytes, and scattered mast cells (15). The lymphocytes are predominantly T cells; the plasma cells mainly produce IgA, but IgG- and IgM-producing cells are present as well. The area immediately under the epithelium primarily contains fibroblasts, myofibroblasts, and macrophages. Macrophages are predominantly located in the upper mucosa. They have
Histologic Features

abundant cytoplasmic vacuoles, lysosomes, and irregular nuclei. Mast cells are round with pleomorphic inclusions containing histamine. Eosinophils (Fig. 13.18), when present, can be recognized by their eosinophilic granules. Significant geographic and seasonal variation exists in the number of eosinophils present (19). Few if any neutrophils are seen. Isolated smooth muscle fibers may be seen in the lamina propria, and their presence may be highlighted by staining them with antibodies to actin and desmin.

FIG. 13.19. A: Lymphoid follicles span the muscularis mucosae occupying both the mucosa and superficial submucosa. The overlying crypts are shortened, and the architecture is mildly distorted to accommodate the underlying lymphoid tissue. B: The muscularis mucosae is discontinuous near lymphoid follicles as demonstrated by an actin immunostain.

The lamina propria contains solitary lymphoid nodules that may be large enough to displace the crypts and extend into the submucosa (Fig. 13.19). They may splay apart the fibers of the muscularis mucosae, or the muscularis mucosae may be discontinuous. These follicles have a ring of lymphocytes surrounding a central germinal center. Their size varies with age, being largest in young children and adolescents. The abundance of lymphoid cells and nodules reflects the presence of hundreds of bacterial species that inhabit the large intestine of healthy humans.

Lymphoglandular Complexes

Foci of lymphoid tissue straddle the muscularis mucosae, causing the fibers to splay around them. These domelike aggregates of gut-associated lymphoid tissue have been termed lymphoepithelial complexes or lymphoglandular complexes. They associate with a specialized surface and crypt epithelium referred to as dome epithelium, which participates in the translocation of antigens from the colonic lumen into the mucosa. The dome epithelium contains M cells. M cells are discussed in detail in Chapter 6. The structure of the lymphoid follicles is discussed further in
Chapters 6 and 18.

Submucosa
The submucosa contains collagen, reticulin fibers, elastic tissue, nerves, fat, blood vessels, lymphatics, and small groups of ganglion cells located immediately below the muscularis mucosae and above the muscularis propria.

Muscularis Propria
The muscularis propria contains bands of smooth muscle fibers separated by connective tissue, including elastic and collagen fibers. The smooth muscle cells have a spindle cell shape and have pinocytotic vesicles along the cell membrane. The cells contain actin, myosin, and desmin filaments. Nerves penetrate throughout the muscular layers. The circular muscle is an expanding meshwork of interlinked bands. The muscle of the longitudinal layer, particularly the taeniae coli, is very tough and contains more collagen and elastic tissue than the circular muscle. The muscularis propria is pierced at regular intervals by the main arterial supply and venous drainage. Between the inner and outer muscle layers are the myenteric plexus and the CD34 and c-kit–positive interstitial cells of Cajal. Abundant connective tissue is present inside the inner circular layer and between it and the outer layer.

Serosa
The serosa is located just outside the muscle coat and contains blood vessels and lymphatics in a thin, connective tissue layer covered in many places by peritoneum. A well-defined elastic lamina exists beneath the peritoneal lining cells.
Infectious Colitis

General Comments

The indigenous colonic flora and an intact mucosal barrier represent vital components of the body's defenses against invasion by pathogens. Disruption of these defenses facilitates bacterial translocation and contributes to disease severity. Colonic injury results from the presence of bacteria or their toxins. Pathogenic mechanisms of mucosal injury include bacterial adherence, invasion, and toxin production (see Chapter 6). The pathogens typically hijack the host cell cytoskeleton. Altering the cytoskeleton is crucial for mediating pathogen adherence, invasion, and intracellular locomotion, especially for *E. coli*, *Salmonella*, and *Shigella* (196).

The risk of developing infectious colitis varies considerably throughout the world and depends on local conditions. Populations inhabiting developing countries often live in ramshackle housing without good sanitation. Enteric infections, particularly bacterial, are readily transmitted in this setting. In contrast, most inhabitants of industrialized countries live in a sanitary environment that generally discourages transmission of enteric pathogens. However, in industrialized countries, other practices facilitate bacterial transmission, including large-scale food production, distribution, and retailing practices, which create opportunities for widespread and extensive outbreaks of food-borne enteric infections (fast-food chains) (197). Infants in daycare centers, patients hospitalized in chronic care facilities, AIDS patients, travelers, and military personnel all have an increased risk of infection. Communication with the clinicians regarding patients' travel, immune status, sexual practices, and food intake facilitates the detection of many infections.

Many gastrointestinal infections are acquired through the ingestion of contaminated food and water. The globalization of the food supply makes the effect of an accidental contamination or deliberate attack on it more widespread. If a bioterrorist attack occurs, pathologists could play a critical role in its identification. Table 13.11 lists factors that should trigger a suspicion of widespread food contamination.

Gastrointestinal changes vary from minimal changes to the classic pattern of acute self-limited colitis, or the production of nonspecific features or a necrotizing enterocolitis. Organisms that produce toxins tend to cause less severe morphologic changes than organisms that invade the mucosa (Fig. 13.95) (see Chapter 6). With the exception of enterohemorrhagic *E. coli* (EHEC), colitis-causing bacteria are invasive and include *Shigella*, *Salmonella*, *Campylobacter*, and *Yersinia*.

EHEC causes enterocyte damage via a secreted toxin. EHEC is the third most common bacterial pathogen isolated from stool samples from diarrheal patients, trailing only *Salmonella* and *Campylobacter* infections (198,199). Infective colitis also results from *Yersinia enterocolitica* (46% of cases), *Campylobacter jejuni* (20%), *Salmonella* (13%), and *Shigella* (9%) infections (199). Amebiasis and cytomegalovirus infections account for another 11% of cases (199). Of these infections, *Salmonella* and amebiasis mimic ulcerative colitis, whereas the other pathogens cause a focal colitis resembling Crohn colitis (199).
**FIG. 13.95.** Bacterial colitis. A: There is marked mucosal edema without obvious inflammation in a patient with a toxigenic *Escherichia coli* infection. B: Area of superficial ulceration and lamina propria inflammation. C: A small bulla has formed underlying the surface epithelium. B and C are from patients with two different types of invasive bacterial infections.

**TABLE 13.11 Factors Suggesting Widespread Microbial Food Contamination**
Odd age distributions for common gastrointestinal (GI) diseases
Increased in usual and unusual types of food-borne illnesses
Increased incidence of organisms not typically seen in a geographic area
Unusual temporal clustering of infectious disease
Presence of microbial illness not common to a specific geographic locale
Unusual numbers of patients with signs and symptoms suggesting a GI infectious disease

<table>
<thead>
<tr>
<th>TABLE 13.12 Location of Colonic Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attachment to epithelial luminal surfaces</td>
</tr>
<tr>
<td>Cryptosporidia</td>
</tr>
<tr>
<td>Spirochetes</td>
</tr>
<tr>
<td>Enteradherent Escherichia coli</td>
</tr>
<tr>
<td>Cytoplasmic localization</td>
</tr>
<tr>
<td>Isospora</td>
</tr>
<tr>
<td>Microsporidia</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>Adenovirus</td>
</tr>
<tr>
<td>Histoplasma</td>
</tr>
<tr>
<td>Lamina propria localization</td>
</tr>
<tr>
<td>CMV</td>
</tr>
<tr>
<td>Strongyloides</td>
</tr>
<tr>
<td>Mycobacteria</td>
</tr>
<tr>
<td>Histoplasma</td>
</tr>
<tr>
<td>Microsporidia</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Submucosal localization</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Muscularis propria or myenteric plexus localization</td>
</tr>
<tr>
<td>Chagas disease</td>
</tr>
<tr>
<td>CMV</td>
</tr>
</tbody>
</table>

The diagnosis of various forms of infectious colitis is based on a combination of clinical findings, histologic features, and response to therapy. The pathologic diagnosis of gastrointestinal infection depends on the recognition of several factors, including specific pathogens, specific tissue reactions, and specific cytopathic effects of the infection. The recognition of specific
Infectious Colitis

pathogens results from their localization to specific tissue sites, including the epithelial apical surfaces, the intestinal lumen, the lamina propria, the submucosa, the muscularis propria, or the myenteric plexus (Table 13.12). Special studies help identify specific pathogens. H&E stains often allow one to diagnose viral inclusions, but these may not always be obvious and the use of immunohistochemical reagents or even in situ hybridization reactions for a particular viral genetic sequence may prove informative. Special stains, particularly fungal stains, are often utilized to confirm the presence of infections, particularly in the setting of diffuse histiocytic infiltrates. Fungi may be highlighted with either Gomori or PAS stains. Microsporidia are highlighted by Gram stains or Giemsa stains, and acid-fast bacillus (AFB) stains are useful in identifying tuberculosis or Mycobacterium avium. Trichrome stains may help identify amoebeae. Ultrastructural examination also aids in the identification of microsporidia and some protozoans. Cultures are often useful, as are stool analyses for the detection of specific toxins or the genes encoding those toxins. Increasing numbers of immunohistochemical stains are becoming available, as are probes for in situ reactions and other molecular methodologies.

### TABLE 13.13 Histologic Features of Acute Self-limited Colitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Days 0 to 4</th>
<th>Days 6 to 9</th>
<th>Days 9+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal edema</td>
<td>+ +</td>
<td>+/ -</td>
<td>-</td>
</tr>
<tr>
<td>Surface exudate</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ulcers</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crypt inflammation</td>
<td>+ + +</td>
<td>+ focal</td>
<td>-</td>
</tr>
<tr>
<td>Inflammation lamina propria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>+ + +</td>
<td>+/ -</td>
<td>-</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Mucin depletion</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>

**General Histologic Features of Bacterial Colitis (Acute Self-limited Colitis)**

Histologic features of acute self-limited colitis (ASLC) include the features listed in Table 13.13 (Fig. 13.95). Table 13.14 lists the histologic characteristics at different times in the infection (200). The features of resolving colitis involve a shift from an acute inflammatory response to one that is more chronic in nature. The chronic changes of resolving infections may be more difficult to distinguish from other forms of colitis.
In early infections the mucosa appears expanded by edema and patchy inflammation. Neutrophils are typically prominent in the lamina propria, often near dilated capillaries or alongside the crypts. Marginating neutrophils may be seen in the capillaries. Neutrophils also infiltrate the crypt epithelium, causing cryptitis. Crypt abscesses are not prominent at this stage of many infections. Neutrophils outnumber lymphocytes and plasma cells. The epithelium often appears ragged and degenerating, sometimes with syncytial tufts. The crypt lining may appear mucin depleted, flattened, or reactive. The crypts are arranged in parallel to one another and the upper halves may appear dilated. The lamina propria may contain fresh hemorrhage.

Since ASLC is clinically and endoscopically similar to active idiopathic IBD, pathologists are often asked to distinguish between these two entities (Table 13.15) (see also Chapter 11). An important histologic feature that distinguishes IBD from ASLC is the crypt architecture. When the architecture is normal, ASLC is likely (Fig. 13.5) and IBD is unlikely. Conversely, a distorted crypt architecture strongly correlates with IBD. The ability to correctly diagnose IBD is very high when the histologic findings include a distorted crypt architecture (branched or forked glands not caused by glands bending around lymphoid follicles), increased numbers of round cells and neutrophils in the lamina propria, a villous architecture, epithelioid granulomas, crypt atrophy (shortening and scarcity of glands), basal lymphoid aggregates, plasmacytosis, Paneth cell metaplasia, and basally located isolated giant cells. Villiform surface configurations usually occur in UC (Fig. 13.96). However, they are relatively uncommon and therefore have limited diagnostic value. One caveat with regard to the foregoing is that when ASLC occurs in populations with a high incidence of infectious disease, the patients may develop crypt distortion. This disorder is sometimes referred to as tropical colonopathy. Such patients may show effects of previous infection with organisms known to destroy crypt architecture, such as amoeba, superimposed on an acute bacterial infection.
The nature of the inflammation in the lamina propria also helps differentiate ASLC from acute-onset IBD. *The presence of a pure acute neutrophilic inflammatory infiltrate suggests ASLC because this never occurs in IBD.* However, a mixed acute and chronic infiltrate occurs in both diseases. Inflammatory changes in the basal lamina propria strongly suggest IBD. One reason for this is that the crypt bases are normally relatively acellular, and when plasma cells are increased in this area, they are easily detected. *Both basal lymphoid hyperplasia and basal lymphoid aggregates highly discriminate for IBD because they are more common in IBD patients than in patients with ASLC.* The basal lymphoplasmacytosis affects the lower 20% of the mucosa. Mononuclear cells, including lymphocytes and plasma cells, may increase in ASLC but they are usually not present to the degree found in IBD unless the IBD patients have been treated.

The *resolving form of an acute self-limited colitis* is particularly difficult to distinguish from IBD. Inflammation limited to the superficial one half or two thirds of the lamina propria occurs more frequently in patients with ASLC, but this feature is not always present. The inflammation may form bandlike inflammatory infiltrates preferentially lying in the upper or midzonal parts of the mucosa and sparing the lower mucosa. The inflammation occupies the lamina propria rather than the crypt epithelium as in idiopathic IBD. Edema and hemorrhage, other hallmarks of infectious colitis, are absent or inconspicuous in idiopathic IBD. Focal inflammation occurs more commonly in patients with ASLC than in patients with UC.

P.804

### TABLE 13.16 Granulomas in Bacterial Colitis

<table>
<thead>
<tr>
<th>Granulomas in Bacterial Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
Some infections produce epithelioid granulomas similar to those seen in CD. Others elicit microgranulomas or histiocytic collections lacking giant cells (Table 13.16). Inconspicuous microgranulomas may be seen in ASLC, particularly with Campylobacter and Salmonella infections, although these are rare. Granulomas are more frequent in Yersinia enterocolitica and Mycobacterium tuberculosis infections.

### Specific Bacterial Infections

**Escherichia coli**

As indicated in Chapter 6, humans develop several types of *E. coli* infection. Toxigenic strains tend to cause minimal injury (Fig. 13.97). EHEC infections are discussed here; the remaining *E. coli* infections are covered in Chapter 6.

Enterohemorrhagic colitis results from infections due to Shiga toxin–producing *E. coli*. *E. coli* 0157:H7 is one strain of Shiga toxin–producing *E. coli* (201,202,203) and the one most commonly associated with HUS in the United States. Other strains cause HUS in other parts of the world. Two similar but distinct bacterial cytotoxins (Shiga-like toxins I and II) contribute to the pathogenicity of enterohemorrhagic *E. coli* infections. These toxins have two units that are almost identical in structure to Shiga toxin and cholera toxin. Both toxins interact with the same membrane receptor (202). A unique plasmid-encoded fimbrial adhesin facilitates adherence of *E. coli* 0157:H7 to the intestinal mucosa (203). The organism targets Peyer patches, where it creates an attaching/effacing lesion (204). As a result, EHEC does not invade the epithelium but rather adheres to the luminal surface, where it elaborates a toxin. The absorbed toxins interfere with protein synthesis, causing epithelial and endothelial damage (205). These toxins damage the vascular endothelium of the kidneys and intestines and mediate bacillary dysentery, hemorrhagic colitis, HUS, and thrombotic thrombocytopenic purpura (TTP) in infected patients (206). The damaged endothelium fails to secrete anticoagulants, initiating microvascular thrombosis. Because of the underlying endothelial damage, the tissues often exhibit morphologic changes indistinguishable from ischemic colitis. Not all EHEC strains carry a risk for the development of HUS. HUS develops in 5% to 8% of patients with EHEC infection. High white blood cell counts, elevated C-reactive protein, and fever early in the course of the disease may be indicators of risk for development of HUS (207,208).
Infectious Colitis

**FIG. 13.97.** Toxigenic *Escherichia coli* infection. *A* and *B* are from two different areas of the colon. *A* shows less damage than *B*, which is almost completely denuded. Both figures demonstrate superficial edema with extravasation of red blood cells. The biopsy is from a 17-year-old boy who ate a hamburger at a picnic and whose stool was positive for the *E. coli* toxin.

The mean annual rates of *E. coli* 0157:H7 infection range from 2 per 100,000 to 12.1 per 100,000 in two different parts of the world (209). In the United States, *E. coli* 0157:H7 infections are widespread, as shown by the number of outbreaks and sporadic cases, severe illnesses, and deaths. In one study, *E. coli* 0157:H7 was the fourth most common bacterial stool pathogen (210). Another study by the Centers for Disease Control and Prevention showed that 8% of routine cultures were positive for this organism, with an infection rate higher than that seen for *Shigella* (211). The infection occurs nationwide, although infection rates in the South are lower than those in the rest of the country. Patients range in age from 1 to 80 years, with a median age of 14 years. Populations most susceptible to the infection are the very young and the very old.

The incidence of the infection is highest in the summer, with most cases occurring between May and September (212). *E. coli* 0157:H7 outbreaks usually occur in communities, nursing homes, daycare centers, kindergartens, and children's wading pools (213). *E. coli* 0157:H7 can survive in drinking water and associate with water-borne disease outbreaks (214). The infectious dose of EHEC has been estimated to be fewer than 100 organisms. *Shiga* toxin–producing *E. coli* also associates with the consumption of hamburgers, other beef products, unpasteurized milk, cheese, pork, poultry, lamb, vegetables, and fruits (215,216). Ground beef represents an especially important vehicle of disease transmission (217). *E. coli* 0157:H7 in ground beef is more sensitive to heat than other bacteria, but it survives for months at -20°C (218). For this reason, proper cooking is the preventive measure of choice. Person-to-person transmission is also possible, as is transmission by environmental contamination (219).

Currently, many laboratories do not routinely perform surveillance cultures for *E. coli* 0157:H7 unless the stool specimen is bloody or a specific request is made for it. Therefore, the infection often goes undetected (220). Screening for *E. coli* 0157:H7 is performed with the use of sorbitol MacConkey agar (218).

The mean incubation period is approximately 3 to 4 days and the illness usually lasts for 2 to 9 days. Asymptomatic infections are common, as is a self-limited, nonbloody, afebrile diarrhea. Other patients develop ileocolitis. Young children, the elderly, and immunosuppressed individuals are more susceptible to HUS and TTP. Antimicrobial treatment does not influence symptom duration, nor does it alter the risk of developing HUS or TTP. Patients with colitis develop bloody diarrhea, severe crampy abdominal pain, and low-grade fever. Fecal
Infectious Colitis

leukocytes are absent. Complications include thrombocytopenic purpura, end-stage renal disease, and neurologic damage, including strokes (221). Endoscopy demonstrates the presence of a normal mucosa with oozing of blood. Other changes include mucosal edema and congestion, erosions, ulcers, erythema, a friable mucosa, and the presence of exudates or pseudomembranes. The submucosa appears swollen. The edema may be so marked that obstruction develops, requiring surgical resection. Resection is also used to control bleeding. The lesions often localize to the right colon but pancolitis may develop, particularly in children.

The histologic features demonstrate overlapping ischemic and infectious patterns due to the presence of both epithelial and endothelial injury (Fig. 13.98). Features associated with the ischemic damage include focal marked submucosal edema, hemorrhage, pseudomembranes (221), bland mucosal necrosis, ulceration associated with fibrin thrombi in the mucosal and submucosal capillaries, and abundant intramural fibrin deposits. The ischemia leads to extensive areas of mucosal necrosis, leaving ghosts of crypts with underlying neutrophilic infiltrates. The necrosis may extend to the submucosa or transmurally with an overlying serosal exudate. The intervening mucosa remains minimally affected with mild mucus depletion and occasional neutrophils and capillary platelet thrombi. The intervening mucosa may also exhibit epithelial dropout, fibrin deposition, and adjacent hemorrhage.

FIG. 13.98. Escherichia coli 0157: H7. This patient had a hemorrhagic colitis with pseudomembrane formation.

Histologic features associated with an infectious histologic pattern include a prominent neutrophilic infiltrate within the crypts, lamina propria, and adherent pseudomembranes. The neutrophilic infiltrate may be mild and patchy, or it may infiltrate the crypt epithelium, producing cryptitis or incipient crypt abscesses. Cryptitis occurs more commonly than crypt abscesses, and in all cases the neutrophilic infiltrate is focally accentuated rather than uniform in appearance, and may even appear as solitary inflammatory foci. Patients often exhibit extreme submucosal edema with hemorrhage and fibrin exudation. The focal nature of the neutrophilic infiltrate, along with the predominance of cryptitis over well-formed crypt abscesses, resembles the histologic changes seen in Campylobacter, Salmonella, and early amebic infections. Its focal distribution and the presence of fibrin thrombi distinguish the infection from acute UC. The changes may resemble those present in C. difficile colitis. A disproportionate amount of lamina propria hemorrhage is often present when compared to the degree of inflammation. Glandular distortion, architectural abnormalities, granulomas, and giant cells are usually absent unless there is underlying pre-existing IBD (222). Because the disease is patchy, biopsies may appear normal or only exhibit a focal, mild, nonspecific increase in lamina propria lymphocytes or plasma cells. The histology does not correlate with either disease duration or the course of the illness. Advanced lesions display regenerative mucosal changes and heavy submucosal plasmacytic infiltrates.

The differential diagnosis includes C. difficile colitis and ischemic colitis, which share overlapping features with the E. coli infection. The C. difficile antigen test may be very helpful in excluding C. difficile infections. Culture and serotyping are the mainstays of the diagnosis. Immunohistochemical stains and molecular assays for EHEC exist, but they are not widely available.

Campylobacter Infections
**Salmonella Infections**

As discussed in Chapter 6, *Salmonella* infections cause five clinical syndromes. In this chapter, we will focus on *Salmonella* infections that present as colitis. *Salmonella* gastroenteritis results from infection by *Salmonella enteritidis*, *Salmonella typhimurium*, *Salmonella argona*, *Salmonella javiana*, *Salmonella poona*, *Salmonella oranienburg* and *Salmonella newport*. It varies from a mild to a severe infection, occasionally associated with bacteremia or bacteriuria. *Salmonella* gastroenteritis is acquired by ingestion of infected foods or drinks accounting for up to 80% of food poisonings. Most outbreaks occur through June and July and associate with consumption of contaminated fish, shellfish, cheese, and poultry (224,225,226,227). There is also a high prevalence of *Salmonella* in livestock. The practice of feeding subtherapeutic amounts of antibiotics to improve animal growth has resulted in the emergence of multiple antibiotic-resistant *Salmonella* strains in the animals and an increased incidence of antimicrobial-resistant organisms causing serious human disease. Food handlers who may become human carriers are occasionally implicated in spread of the infection.

The northeastern portion of the United States and parts of Europe has experienced a marked increase in food poisoning due to *S. enteritidis*. *S. enteritidis* is also increasing in South America and Africa (228). The increase relates to increased consumption of infected eggs and poultry. Approximately 400 cases of salmonellosis are reported annually in the United States, with fatality rates ranging from 1.3% to 8.4% (229).

Salmonellosis usually causes a mild self-limited disease that develops 8 to 48 hours following organism ingestion. Signs and symptoms of *Salmonella* gastroenteritis vary widely, but most patients present with nausea, vomiting, abdominal cramps, fever, pain, and diarrhea, which sometimes becomes bloody. Symptoms last for 3 to 12 days. *Salmonella* infections in the elderly have a poorer prognosis than when they occur in younger individuals. This is because the patients are more likely to become septic. Rarely, life-threatening, massive lower GI bleeding occurs. Bleeding usually arises in the small intestine but large intestinal bleeding also occurs (230). Patients not only develop GI symptoms, but also may develop erythema nodosum, reactive arthropathy, and rectal prolapse, particularly those with massive diarrhea. A pseudoappendicitis or ileocecalitis may occur and may be complicated by perforation or toxic megacolon. Infections are particularly virulent in individuals with sickle cell disease or those with HIV infections. Diffuse or patchy mucosal hyperemia, friability, and inflammation may be seen at the time of colonoscopy.

*Salmonella* bacteria are intracellular parasites that enter the host by penetrating intestinal epithelial barriers, usually in the area of Peyer patches in the M cells. Once they are in close contact with the epithelium, the bacteria induce degeneration of the enterocyte microvilli (231), which is followed by profound membrane ruffling in the area of the bacterial host cell contact. Profuse micropinocytosis leads to bacterial internalization (232). *Salmonella* entry into the epithelium requires several chromosomal genes (*inv/spa*) clustered in a pathogenicity island termed SPI1 (salmonella pathogenicity island 1) (233). Additional pathogenicity factors are summarized in the Armed Forces Institute of Pathology (AFIP) fascicle (234). Bacteria enter membrane-bound vacuoles (phagosomes) inside epithelial cells and macrophages where they replicate (235). Replication also occurs in macrophages of the lymphoid follicles leading to bacteremia, reinfection of additional macrophages, and seeding of distant sites. As a result, the lymphoid follicles become hyperplastic, swollen, congested, and ulcerated, often resulting in typical longitudinally oriented ulcers and areas of hemorrhage. Edema, fibrinous exudation, and vascular thrombosis precede the ulceration. Aphthous ulcers sometimes develop.

Histologically mild cases show nonspecific patchy changes consisting of edema, congestion, and focal inflammation (Fig. 13.99). More severe cases show crypt abscesses with prominent neutrophilic infiltrates in degenerating crypts. The neutrophilic infiltration is more intense in the lamina propria than in the glands. Areas of hemorrhage and ulceration are also present. Crypt abscesses may be present in the nonulcerated areas. There may also be extensive areas of mucosal necrosis and hemorrhage with punched-out mucosal ulcers or erosions with elevated borders, crypt abscesses in the nonulcerated areas, and extensive mucosal and submucosal necrosis and hemorrhage (Fig. 13.100). These changes differ from IBD by the relative scarcity of chronic inflammatory cells. Microthrombi fill small mucosal and submucosal venules, creating a picture resembling that seen in acute ischemia. In severe cases, giant cells may populate the inflamed tissues, which, if transmural inflammation is present, might suggest the presence of CD. However, the giant cells do not form compact granulomas, as seen in CD. Occasional patients will show mild crypt distortion and branching, especially in those with persistent diarrhea. There is sometimes a concurrence between salmonellosis and IBD (236), creating diagnostic and treatment dilemmas.

Rectal biopsies show the active inflammation typical of UC (237). The immunosuppression used to treat the IBD may predispose to the infection.
Infectious Colitis

**FIG. 13.99.** *Salmonella* colitis. *A:* The mucosa is inflamed and there is glandular destruction. There are apoptoses in one of the crypt bases mimicking drug injury and graft versus host disease. *B:* The base of several crypts show increased mitotic activity. The surrounding lamina propria appears edematous and the vessels are congested.

**Shigellosis**

*Shigella* is a nonmotile, Gram-negative bacillus that is among the more virulent human enteropathogens. *Shigella* infections are an important cause of morbidity and mortality in developing countries, particularly in tropical areas. It causes approximately 10,000 cases of gastroenteritis each year in the United States (238). *Shigella* infections are more common in AIDS patients. They have a more virulent course and the infection is difficult to treat so that recurrences are common. Outbreaks of shigellosis among men who have sex with men result from direct or indirect oral–anal contact and are usually cause by *Shigella flexneri*. However, there was an outbreak of *Shigella sonnei* in California in 2000–2001 among men having sex with men (239). Person-to-person transmission and ingestion of contaminated food and water also cause the disease (240,241).

*Shigella* infections associate with poor hygiene and overcrowding, and are a significant problem among children in nurseries and mental hospitals. Several *Shigella* species (*dysenteriae, flexneri, boydii, and sonnei*) cause colitis, with diminishing severity from the first organism to the last (242). *S. sonnei*, which produces a mild colitis, is the most common cause of bacillary dysentery in the Western world. Shigellosis results from release of bacterial toxins into the bowel lumen, as well as from direct bacterial invasion of the colonic mucosa (243). *Shigella* produces a potent toxin that inhibits protein synthesis and has cytotoxic, neurotoxic, and enterotoxic effects (244).

Children are the main victims of *Shigella* infections. The two major clinical presentations include watery diarrhea and dysenteric syndromes. The watery diarrhea has a short duration before hospitalization. The dysenteric form presents with bloody mucoid stools (27%), intense crampy abdominal pain (94%), diarrhea (98%), fever (87%), and nausea and vomiting (78%). It has a longer illness duration prior to hospitalization (245). Septicemia, hyponatremia, and hypoglycemia are common (246). The small volumes of dysenteric stool contain blood and pus. Patients with longer symptom duration may develop relative vascular insufficiency, activated lymphocytes, eosinophilic and mast cell degranulation, and antibody-mediated
Infectious Colitis

The severity of *Shigella* infections depends on many factors, including previous exposure to the organism and the infecting dose. The infections are usually self-limited, but dysentery can be a life-threatening illness in infants, the elderly, or malnourished individuals. The usual incubation period ranges from 1 to 3 days. Watery diarrhea, with or without vomiting, is the initial symptom. After 24 hours, the stool becomes mucoid and grossly bloody. Low abdominal pain is common. Severe disease clinically mimics toxic megacolon, with hemorrhage, paralytic ileus, and perforation. Anal or perianal disease, including fissures, fistulae, hemorrhoids, or prolapse (245), complicates severe diarrhea. Serious complications are rare, especially in infections by *S. flexneri* and *S. sonnei*. However, patients with *Shigella dysenteriae* infection may develop bacteremia, sepsis, paralytic ileus, toxic megacolon, disseminated intravascular coagulation, and renal cortical necrosis severe enough to require hemodialysis (247). Shigellosis also causes hemolytic uremic syndrome, a condition associated with a high mortality (248). Circulating endotoxins cause the coagulopathy, renal microangiopathy, and hemolytic anemia. Other complications include toxic megacolon, intestinal perforation, sepsis, encephalopathy, pneumonia, conjunctivitis, and arthritis (249).

FIG. 13.100. Typhoid ulcer extending into the submucosa. The mucosa is inflamed and necrotic.

*Shigella* organisms pass from the mouth to colonize the colon. Small intestinal infections do not occur unless the patient has a motility disturbance. Once they reach the colon, the bacteria penetrate the intestinal mucous layer and invade the epithelium. Multiple genes control epithelial entry (250). The preferential site of entry is through the dome of the lymphoid follicles. An adhesive or invasive phenotype is required for efficient colonization of the M cells of the follicle-associated epithelium. The invasive phenotype causes major inflammation-mediated tissue destruction, whereas the adhesive phenotype causes alterations in the M cells, which become stretched over large pockets containing aggregates of mononuclear cells.
Infectious Colitis

The M cells progressively occupy larger surface areas of the follicle-associated epithelium, causing the enterocytes to come off the epithelial surface (251). The organisms that invade the epithelium reorganize the cell cytoskeleton, a process that requires \textit{Shigella} Ipa proteins. Once inside the cells, bacteria lie within membrane-bound vesicles. Here they multiply, causing mucus secretion and goblet cell depletion and inducing luminal neutrophilic infiltrates. The neutrophils loosen the intercellular barriers, further facilitating \textit{Shigella} invasion (252). \textit{Shigella} bacteria direct their own uptake into the colonic mucosa through membrane ruffling and macropinocytosis in a manner similar to \textit{Salmonella} uptake (253). After engulfment, the bacteria are surrounded by a membrane-bound vacuole within the host cell. \textit{Shigella} rapidly lyses the surrounding vacuole and it is released into the cytosol where it grows and divides (251). Once it escapes from the vacuole it is quickly coated with filamentous actin and ultimately forms an actin tail at one pole of the bacterium (254). This actin polymerization propels the bacterium through the cell cytoplasm (255) and when the pathogen reaches the plasma membrane, it forms a long protrusion into the neighboring cell, which subsequently internalizes the microbe (256). The bacterium again breaks out of the vacuole starting a new cycle of infection in a new host cell (257). The cycle of intracellular and intercellular infection allows colonization of large epithelial surfaces while the bacterium is protected from immune host surveillance mechanisms. Bacilli penetrate the intestinal epithelium and pass through the mucosa in a period of several hours (251). The organism induces apoptosis in macrophages, which in agony release mature IL-1$\beta$. The IL-1$\beta$ attracts neutrophils to the site of infection resulting in the massive colonic inflammation characteristic of the disease (258).

The \textit{Shigella} cytotoxin rapidly reduces epithelial protein synthesis. An endotoxin damages mitochondria, leading to further destruction of cellular organelles, cell death, extrusion, and the formation of microulcers in the surface epithelium. Inflammation results in focal abscess and ulcer formation and, when severe enough, ileus, toxic megacolon, gross hemorrhage, and perforation. Endotoxin absorption in the lumen also leads to thrombosis, hemorrhage, and vascular insufficiency, causing further crypt damage. Endoscopically, the mucosa appears edematous, friable, hyperemic, and ulcerated. All patients have inflammation in the rectosigmoid area. In most patients, the lesions are continuous and diffuse with the intensity of inflammation decreasing as one moves proximally. In severe cases there is a pancolitis with backwash ileitis, which can extend as far as 50 cm from the ileocecal valve (246). There may also be coexisting appendicitis. Serpiginous ulcers develop on the free edge of the mucosal folds oriented transversely to the long axis.

The intervening mucosa appears granular and hemorrhagic. Aphthous erosions may be present (Fig. 13.101). Other causes of aphthous ulcers are listed in Table 13.17. In fatal infections a gray mucopurulent exudate covers the mucosa. Because the findings resemble those seen in \textit{Campylobacter} and \textit{Salmonella} infections and IBD, definitive diagnosis requires stool culture.
Histologic changes in *Shigella* infections include patchy hyperemia and edema with mucosal friability or ragged ulcerations, sometimes associated with pseudomembrane formation. Biopsies of early-stage disease show a surface epithelium that is reduced in height and infiltrated by neutrophils. The epithelial cells then detach from an edematous lamina propria forming mucosulcers. Neutrophils frequently lie below the mucosulcers. Detached epithelial cells, neutrophils, and red blood cells form a layer of purulent exudate on the surface. Microulcers and erosions are present in 85% of biopsy samples taken during the acute stage of the disease (246). Small aphthous ulcers also form. These always arise over the lymphoid follicles because the follicles with their M cells are the portal of entry (Fig. 13.101). Other changes consist of acute inflammation with neutrophilic emigration, superficial crypt abscess formation, early goblet cell depletion, edema, erythema, and mild plasma cell infiltrates (224). *Shigella* bacteria are numerous in the epithelial cells and in the lamina propria of early lesions. Dilated vessels accompany marked edema. As the lesions become more advanced, epithelial necrosis occurs and purulent exudates cover the damaged mucosa. Frank ulceration develops, disturbing the crypt architecture and causing pseudopolyp formation. The changes may remain confined to the mucosa, although they can extend into the submucosa. Patients may show mild crypt distortion and branching. Cellular regeneration progresses from the base of the crypts toward the mucosal surface. Even in the case of extensive mucosal damage, recovery is usually very rapid.

Infectious Colitis

<table>
<thead>
<tr>
<th>Crohn disease</th>
<th>Ileocolic candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yersinia infections</td>
<td>Ulcerative colitis (rare)</td>
</tr>
<tr>
<td>Behçet syndrome</td>
<td>Campylobacter infections</td>
</tr>
<tr>
<td>Shigellosis</td>
<td>Ischemia</td>
</tr>
</tbody>
</table>

In autopsy cases, chronic ulcers of variable size and depth are present in 100% of cases. The ulcers may be superficial, involving only the upper quarter of the mucosa, but they may extend down to the muscularis mucosae. Some patients have wide areas of mucosal denudation and pseudomembranes. Crypt abscesses may be present along with architectural distortion and thrombosis of small vessels in the mucosa or submucosa. Colitis cystica profunda develops in about a quarter of the cases (246).

P.810

Convalescent stage biopsies show residual small superficial ulcers and marked inflammation of the lamina propria. The intensity of the lymphocytic and plasmocytic infiltrate is greater than that of the neutrophils.

**Clostridium difficile**

*Clostridium difficile* is a well-known cause of epidemics and is the most common cause of nosocomial diarrhea. There are four groups of risk factors for the development of the disease: Patient risks, treatment risks, environmental risks, and the *Clostridium difficile* strain (Table 13.18) (259,260). Infants, children, and adults may acquire *C. difficile* infections when they are hospitalized (261,262). The patients often receive antibiotic therapy in a setting where environmental contamination with *C. difficile* spores is commonplace (263). In one study, 21% of patients acquired *C. difficile* during their hospitalizations. Of these, 63% remained asymptomatic; 37% developed diarrhea. Among patients in the community who are treated with oral antimicrobial agents, only 1 to 3 individuals per 100,000 develop *C. difficile* colitis compared with as many as 1 per 100 hospitalized patients treated with similar drugs (263). Immunodeficient patients are particularly susceptible to developing *C. difficile* infections (264).

**TABLE 13.18 Risk Factors for Acquiring Clostridium difficile Infections**

<table>
<thead>
<tr>
<th>Patient risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Severity of the diarrhea</td>
</tr>
<tr>
<td>Previous gastrointestinal disease or surgery</td>
</tr>
<tr>
<td>Failure to mount a sufficient IgG antibody response to toxin A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly antibiotics</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
</tr>
<tr>
<td>Chronic care facilities</td>
</tr>
</tbody>
</table>

*C. difficile* strain
Infectious Colitis

**Production of a binary toxin in addition to toxins A and B**

**Presence of a deletion leading to increased production of toxins A and B**

**Resistance to broad spectrum quinolones**

*C. difficile* spores are heat resistant and may persist in the environment for months. The organism may spread person to person by hands, via fomites, or by general contamination (265). The organism can be cultured from hospital floors, toilets, bedding, and furniture, especially in areas where patients with diarrhea from *C. difficile* infection have been recently treated. Features that determine whether or not a patient develops a *C. difficile* infection include the nature of the fecal flora, the size of the *C. difficile* population, production of the requisite cytotoxins, and the presence of other organisms that affect toxin expression or activity. Host risk factors include advanced age, severe underlying illness, and prolonged hospital stay. Recent studies suggest that immunologic susceptibility has a role in *C. difficile* infection. The presence of an IgG antibody against toxin A protects against the clinical expression of a *C. difficile* infection and against relapse (266,267).

Toxigenic strains of *C. difficile* release two large protein exotoxins, toxin A and toxin B. Both toxins possess cytotoxic activities inducing the disaggregation of actin microfilaments and cell rounding (268). Binding and internalization of toxin A into cells elicits an acute inflammatory cascade via a sequence of activation signals involving the release of substance P and other neuropeptides from sensory nerves (269). Release of IL-8 and other proinflammatory cytokines from immune cells and enterocytes also occurs. The release of IL-8 depends on an oxidative burst originating from mitochondria and is transduced via the NF-κb pathway (270). This is followed by up-regulation of leukocyte adherence molecules on the vascular endothelium and local infiltration of the lamina propria with acute inflammatory cells (269). The end result is a severe necroinflammatory lesion (pseudomembranous colitis) accompanied by massive fluid secretion and mucosal ulceration. Toxin B is also an inflammatory enterotoxin (271). A previously uncommon strain of *C. difficile* with variations in toxin genes has become more resistant to fluoroquinolones and has emerged as a cause of geographically dispersed outbreaks of *C. difficile*–associated disease (272,273). *C. difficile* infections account for 10% to 25% of cases of antibiotic-associated diarrhea and virtually all cases of antibiotic-associated pseudomembranous colitis. The type of antibiotic and the route of its administration influence disease incidence. More cases occur when the drug is given orally than when it is administered parenterally. Clindamycin, ampicillin, and the cephalosporins are most commonly associated with antibiotic-associated pseudomembranous colitis, but virtually any antibiotic may produce the disorder. *C. difficile*–associated diarrhea also complicates the use of chemotherapy.

The laboratory diagnosis of *C. difficile* is based on isolation or detection of components or products of the organism. Stool cultures and assays for *C. difficile* toxin (the preferred method for establishing the diagnosis) are positive in >95% of patients. Cultures performed properly on selected media are the most sensitive method for the detection of *C. difficile*, whereas cell cytotoxin assay for detection of toxin B is the most specific. *C. difficile* may be cultured anaerobically on special antibiotic-containing media selective for it. The organism is readily identified based on colony morphology and microscopic features. Unfortunately, it takes up to 5 days to grow the organism. Additionally, culture detects all *C. difficile* colonies irrespective of their pathogenicity so that colonies that are isolated must be tested for their ability to produce the toxin (274).

**P.811**

The cytotoxic assay diagnostic method exploits the cytotoxic feature of *C. difficile* toxins. In this test, the patient's specimen is added to a cell culture line. Cells are examined for cytotoxic changes after an incubation period. Then, to verify that the cytotoxicity was due to the presence of the toxin, the assay is performed with a neutralizing antibody against the *C. difficile* toxin added to the specimen. This assay is the gold standard because of its high sensitivity (94% to 100%) and specificity (99%) (274). Because there is no clinical correlation between stool levels of the toxins and the severity of the disease, the culture is simply reported as positive or negative.

Enzyme immunoassays are used to diagnose *C. difficile* infections. These assays are designed to detect either toxin A alone or both toxins A and B. They have the advantage of being very rapid to perform (<4 hours) and have a sensitivity of 69% to 87% and a specificity of 99% to 100% (275). *C. difficile* toxin can also be identified by the polymerase chain reaction (PCR). The PCR primers amplify a repetitive sequence of the enterotoxin gene, thereby generating a distinctive ladder pattern. This detection technique is more sensitive than standard culture and has a sensitivity similar to cytotoxin testing (276).

The clinical presentations of *C. difficile* infections, in increasing order of severity, include asymptomatic carriage, antibiotic-associated colitis without pseudomembrane formation, pseudomembranous colitis, and fulminant colitis with catastrophic transmural inflammation and myonecrosis. The most severe forms are the least common. Over 50% of healthy neonates are asymptomatic carriers of *C. difficile*. However, even though children are relatively resistant, they can develop pseudomembranous colitis in the presence of *C. difficile* cytotoxin (277). Children with fatal disease usually have underlying Hirschsprung disease or a hematologic malignancy. Less than 1% of healthy adults are carriers, but approximately 25% of adults recently treated with antibiotics are colonized by the organism. The majority of hospital inpatients infected with *C. difficile* remain asymptomatic (261). When *C. difficile* infection presents as diarrhea, it is usually mild to moderate in severity, sometimes accompanied by lower abdominal cramps. Symptoms usually begin during or shortly after antibiotic therapy; occasionally, they are delayed for several weeks. *C. difficile* toxins are present in the stool at this time but endoscopic and histologic features are frequently
Infectious Colitis almost normal in patients with mild disease. The diarrhea often subsides when antibiotics are stopped. Severe colitis without pseudomembrane formation presents as a profuse debilitating diarrhea, abdominal pain, and abdominal distention. Common systemic manifestations include fever, nausea, anorexia, malaise, and dehydration. Peripheral blood polymorphonuclear leukocytosis and increased numbers of fecal leukocytes are common. Patients may experience occult colonic bleeding; rarely, they develop frank hematochezia. The most dramatic form of the disease, pseudomembranous colitis, clinically resembles *C. difficile* colitis without pseudomembranes except for the fact that the diarrhea, abdominal tenderness, and systemic manifestations are more severe. As colonic muscular tone is lost, toxic dilation or megacolon develops. The development of the paralytic ileus or the colonic dilation results in a paradoxic decrease in the diarrhea. Endoscopy should be avoided in such patients because of the risk of perforation. When severe, pseudomembranous colitis requires surgical resection to avoid perforation.

Patients with early pseudomembranous colitis have focal or confluent yellow-white, raised 2- to 10-mm plaques with erythematous bases and a centrally adherent yellow plaque. Small lesions can be mistaken for mucus or an aphthous ulcer. The intervening mucosa typically appears normal or only mildly erythematous or congested. Patients with severe disease may have plaques that coalesce to cover large mucosal areas. The rectum and sigmoid are typically involved, but in approximately 10% of cases the colitis is confined to the proximal colon (278). Edema, blurring of the vascular pattern, and thickening and blunting of the haustral folds are also present. The lesions are most prominent in the large intestine but the distal small bowel occasionally becomes involved. If pseudomembranes are identified endoscopically, stool specimens should be sent to confirm the presence of the *C. difficile* toxin and biopsies should be obtained in order to confirm the diagnosis because other disorders may produce pseudomembranes (Fig. 13.102).

The earliest lesions (type I lesions) consist of focal areas of epithelial necrosis with neutrophils and nuclear dust in an edematous lamina propria. A shower of fibrin and neutrophils erupts from the mucosal surface (Fig. 13.103). The early lesions reflect local epithelial damage occurring on the luminal surface. Plaque formation is initiated by epithelial breakdown with eruption of an exudate into the lumen. The linear deposition of neutrophils and Gram-positive sporulating bacilli within fibrin strands and mucus represents an almost pathognomonic appearance.

Later lesions (type II lesions) consist of a well-demarcated group of disrupted crypts that lose their superficial lining and are distended by mucin, neutrophils, and eosinophils. Later, epithelial damage extends downward to involve the lower parts of the crypts. The epithelium of affected crypts becomes flattened and progressively lost. Occasional fibrin thrombi are found in superficial mucosal capillaries at this stage (Fig. 13.104). Focal mushroom-shaped or focal volcanic eruptions of a pseudomembrane attach to the necrotic mucosa. The pseudomembranes contain epithelial debris, red blood cells, fibrin, mucus, and polymorphs. The adjacent mucosa appears normal. Type III lesions consist of complete structural mucosal necrosis with only a few surviving glands covered by cellular inflammatory debris, mucin, and fibrin (Fig. 13.105). The lamina propria becomes edematous and bulges into the lumen. Focal congestion and hemorrhage in the lamina propria explain extravasation of blood into the intestinal lumen. In addition to the characteristic mucosal lesions, the colonic specimens show characteristic, marked diffuse mural edema that extends to the muscularis propria (279). When mucosal necrosis becomes confluent, it may be impossible to distinguish *C. difficile*-induced disease from other forms of severe colitis, especially ischemic colitis or severe idiopathic IBD. In fatal cases, organisms can be found in the colon, necrotic mesenteric lymph nodes, and other organs.
**FIG. 13.102.** Pseudomembranous colitis. A through D show progressive degrees of pseudomembrane formation. 

A: Discrete separated pseudomembranous lesions are present. 

B: One sees beginning coalescence of the lesions with little intervening normal mucosa. 

C: Represents further progression of the disease. Some areas of the mucosa are spared. 

D: Shows a mucosa that is virtually completely covered by pseudomembrane.

**FIG. 13.103.** Histologic features of pseudomembranous colitis. 

A: Several volcaniclike eruptions of pseudomembranes overlie the colonic epithelium. 

B: Higher magnification of one of the eruptions demonstrating central fibrin deposition and showers of inflammatory cells expanding from this in a starburst pattern.
FIG. 13.104. Pseudomembranous colitis due to *Clostridium difficile*. The patient had a positive toxin assay. *A*: The superficial lesion with desquamating epithelium and the beginning of ghostlike structures. A pseudomembrane covers a vast area of the surface and there is evidence of intramural red cell extravasation. *B*: The base of the crypts demonstrates crypt abscesses resembling those seen in some infectious disorders, such as *Salmonella*.
FIG. 13.105. Type III Clostridium difficile lesion demonstrating transmural necrosis on the left-hand portion of the mucosa.
FIG. 13.106. Biopsy of *Clostridium difficile*. A: Low-magnification photograph demonstrating the various biopsy fragments of a patient who was toxin positive for *C. difficile*. B: Higher magnification shows what appears to be a chronic colitis in the absence of an overlying pseudomembrane. This region comes from a portion of the biopsy not associated with the pseudomembrane. C: Higher magnification of the lamina propria demonstrating the acute inflammation.

Mucosal biopsies of patients with *C. difficile* are often taken in the area of the pseudomembranes. They may show nonspecific findings demonstrating only evidence of a focal colitis and an inflammatory exudate (Fig. 13.106). Patients who present with a necrotizing enterocolitis pose a diagnostic dilemma because this pathologic picture results from both bacterial and ischemic colitis. Often secondary infections complicate ischemic injury and conversely, bacterial toxins may cause thrombosis and secondary ischemic damage so that it may be impossible to differentiate between ischemia versus a bacterial toxin-induced injury. Areas of focal fibrosis are more likely to associate with ischemia (108), whereas endoscopically visible continuous pseudomembranes are more likely to be associated with *C. difficile* infections (108). Table 13.19 compares the histologic features of three common forms of focal colitis.

Signet ring cells occur in up to 28% of patients with pseudomembranous colitis (280,281), potentially suggesting the diagnosis of carcinoma. However, the cells are confined within the basement membranes, a feature that can be highlighted by cytokeratin immunostains. Furthermore, the nuclei of the signet ring cells are not enlarged and have uniform chromatin and inconspicuous nucleoli, making the diagnosis of carcinoma unlikely. The cells of signet ring cells are negative for p53 and Ki-67 and positive for E-cadherin. In contrast, signet ring cell carcinomas are strongly positive for p53, have a high proliferative rate, and have no or weak positivity for E-cadherin (281).

### TABLE 13.19 Comparison of the Histologic Features of Ischemia, *Clostridium difficile*, and Crohn Disease

<table>
<thead>
<tr>
<th></th>
<th>Ischemia</th>
<th><em>C. difficile</em></th>
<th>Crohn Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal process</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pseudomembranes</td>
<td>+</td>
<td>+</td>
<td>-a</td>
</tr>
<tr>
<td>Mucosal changes of chronicity</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hemosiderin-laden macrophages in lamina propria</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inflammation extending into submucosa</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Crypt abscesses</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Glandular ghosts</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Granulomas</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Atrophic microcysts</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Lamina propria fibrosis</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*a*Unless there is coexisting ischemia.

Patients are generally treated with metronidazole (282). A *C. difficile* toxoid vaccine also has shown promise in treating the disease (283).

**Clostridium Septicum**

*Clostridium septicum*, an unusual inhabitant of the human gut, plays a role in the development of neutropenic enterocolitis, an entity discussed in a later section. The organism is a rod-shaped, spore-forming, saprophytic, anaerobic, Gram-positive bacterium that occurs as an opportunistic infection in immunocompromised hosts. Others especially prone to *C. septicum* infections are those with diabetes or malignancies (284). Devitalized tissues or tumors with a low pH offer a perfect environment for germination of the clostridial spores (285). Severe ulcerating intestinal lesions allow organisms to seed the bloodstream and to penetrate the pericolonic tissues and then pass into the psoas and fascial planes. This results in *C. septicum* bacteremia, gas gangrene, or gangrenous myonecrosis (286). When the spores germinate, they produce liquefaction necrosis in both normal and neoplastic tissues. An infection by this organism may be treated with oral metronidazole (287).

P.815
Infectious Colitis

**Clostridium Perfringens**

Ingestion of food contaminated by large numbers of vegetative cells of enterotoxigenic strains of *Clostridium perfringens* produces an unpleasant, self-limited form of diarrhea (287). Rarely, it produces a more serious, often fatal form of disease known as enteritis necroticans (see Chapter 6). The bacteria multiply in the intestine and sporulate, releasing *C. perfringens* enterotoxin. DNA probes are available for the detection of enterotoxin produced by *C. perfringens*.

**Mycobacteria**

Tuberculosis (TB) is a segmental disease that most commonly involves the ileocecal region or rectum, but the remainder of the colon may also be involved. Perirectal TB often presents as anorectal fissures and fistulae containing giant cells, not always associated with granuloma formation. Stenotic areas measuring several centimeters in length develop in both the rectum and the cecum. Endoscopy reveals nonspecific mucosal friability with nodular changes. In order to establish the diagnosis, multiple deep biopsies of the ulcer bed and its margins must be performed. The differential diagnosis of cecal tuberculous colitis always includes CD and *Yersinia* infection because all three diseases tend to concentrate around the ileocecal valve and all produce granulomatous colitis with strictures, aphthous ulcers, tumorlike lesions, and fistulae. Rarely, tuberculosis associates with a vasculitis (288). Features that distinguish between these three entities are compared in Table 13.20. The clinical and pathologic features of tuberculosis are covered in Chapter 6. *Mycobacterium avium-intracellulare* (MAI) infections rarely exist alone and are seen predominantly in AIDS patients. These infections are also discussed in Chapter 6.

**Yersinia**

*Yersinia enterocolitica* causes an ileocolitis and can affect other parts of the colon as well, where it typically causes patchy disease. The rectosigmoid area is frequently spared. The histologic features of colonic disease tend to lack the granulomas that typically associate with the ileocolitis. The histologic features show a focal nonspecific inflammatory response. This infection is discussed in greater detail in Chapter 6.

**Gonorrhea**

Gonorrheal infections are common in men who have sex with men but in females it may result from spread from the vagina. Perhaps the most common cause of proctitis in individuals who engage in anal intercourse is *Neisseria gonorrhoeae* (289). In a recent study the four most prevalent infectious causes of proctitis among men having sex with men were gonorrhea, herpes simplex, chlamydia, and syphilis, in a decreasing order of frequency (290). Patients may present with anorectal discomfort, mucopurulent rectal discharge, or tenesmus; however, many anorectal gonococcal infections remain asymptomatic. Biopsy findings are nonspecific. Depending on the host's immune response, neutrophils, plasma cells, or lymphocytes infiltrate the lamina propria. The diagnosis is best made by Gram stain and culture of a distal rectal mucosal swab, rather than by biopsy. However, biopsies may serve to exclude the presence of other gastrointestinal pathogens. This infection is discussed further in Chapter 15.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Tuberculosis</th>
<th>Crohn Disease</th>
<th>Yersinia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive chest x-ray</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Change in bowel habits</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ileocecal x-ray</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Ileal involvement</td>
<td>Tends to be short</td>
<td>Tends to be long</td>
<td>Tends to be short</td>
</tr>
<tr>
<td>Stool culture</td>
<td>30% + Tbc</td>
<td>-</td>
<td>Often positive</td>
</tr>
<tr>
<td>PPD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ulcers</td>
<td>Tend to be circumferential</td>
<td>Tend to be linear</td>
<td>Present</td>
</tr>
<tr>
<td>Fistulae</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thickened mesentery</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
**Infectious Colitis**

<table>
<thead>
<tr>
<th>Symptom/Feature</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse fissures</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Edema</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pseudopolyps, rectal bleeding</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Very rare</td>
<td>May be present</td>
</tr>
<tr>
<td>AFB stain</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Usually present in cecum, also commonly present in rectum</td>
<td>Present in 33%-50% of cases</td>
</tr>
<tr>
<td>Number</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Size</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Nature</td>
<td>Caseating</td>
<td>Noncaseating</td>
</tr>
<tr>
<td>Organism demonstrated</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td>Independent of mural involvement</td>
<td>Only present if the wall is involved</td>
</tr>
<tr>
<td>Anal lesion</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Fibrosis muscularis propria</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Strictures</td>
<td>Usually &lt;3 cm</td>
<td>Generally long</td>
</tr>
<tr>
<td>Transmural follicular hyperplasia</td>
<td>Usually absent</td>
<td>Usually present</td>
</tr>
<tr>
<td>Serology of <em>Yersinia</em></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AFB, acid-fast bacillus; PPD, purified protein derivative.

### Syphilis

Syphilitic proctitis results from direct bacterial inoculation of the anorectum. The spirochetes penetrate the epithelium, inciting a focal inflammatory reaction with ulceration and chancre formation that can mimic a carcinoma, solitary rectal ulcer syndrome polyps, or anal fistulae. Unless secondarily infected, the lesions usually remain painless. Patients may have coexisting sexually transmitted rectal infections, including herpes, gonorrhea, or *Chlamydia trachomatis*. Proctitis may be present in secondary syphilis as well. The histologic features are characteristic and include an obliterator endarteritis with a mixed inflammatory infiltrate containing numerous plasma cells. Crypt abscesses and granulomas may also be present. Warthin-Starry silver or immunofluorescent stains identify the organism, but the diagnosis is usually established by conventional serologic tests. The histologic features are described further in Chapter 15. Table 13.21 compares the features of various bacterial forms of colitis.

### Intestinal Spirochetosis

Spirochetosis occurs relatively commonly in men having sex with men, especially those who have an HIV infection. However, spirochetosis also affects up to 7% of healthy individuals who do not engage in anal intercourse and up to 30% of homosexual men without evidence of immunodeficiency. The most common organisms are *Brachyspira aalborgi* and *Serpulina pilosicoli*. Both adults and children may be infected. Patients may remain asymptomatic or they may develop nonspecific symptoms including diarrhea (291). There is no difference in the presence or type of intestinal symptoms, sigmoidoscopic appearance of the mucosa, types of sexual practices, or antibiotic use in men with and without spirochetosis. Debate exists as to whether the spirochetes that colonize the bowel represent true pathogens or not. It has been suggested that they represent enteric commensals that become opportunistic pathogens due to unknown factors. The bacteria may cause various GI disturbances, including longstanding diarrhea, rectal bleeding, constipation, purulent discharge, abdominal pain, and perianal pain. The infection may also be found in asymptomatic individuals. Treatment results in symptom remission in some patients, whereas in others therapy fails to induce any changes.

**TABLE 13.21 Differential Histologic Features of Bacterial Colitis**

---

file:///F|/Gastro/Chapter%2013%20Infectious%20Colitis.htm (24 of 56)2/4/2009 2:03:55 PM
<table>
<thead>
<tr>
<th>Organism</th>
<th>Location in Colon</th>
<th>Ulcers</th>
<th>Granulomas</th>
<th>Pseudomembrane Formation</th>
<th>Blood Vessels</th>
<th>Nature of Cellular Infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>Mostly right sided</td>
<td>Longitudinal</td>
<td>Microgranuloma (rare)</td>
<td>-</td>
<td>Congested, thrombosed</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Shigella</td>
<td>Distal distribution: mimics ulcerative colitis</td>
<td>Free edges of mucosal folds</td>
<td>No</td>
<td>-</td>
<td>Normal</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Yersinia</td>
<td>Ileocecal region</td>
<td>Aphthous</td>
<td>Necrotizing</td>
<td>-</td>
<td>Normal</td>
<td>Histiocytic with granuloma formation</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Ileum and colon</td>
<td>Aphthous</td>
<td>Microgranulomas</td>
<td>-</td>
<td>Acute vasculitis</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Enterohemorrhagic</td>
<td>Patchy</td>
<td>Superficial</td>
<td>No</td>
<td>+/-</td>
<td>Congested</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Patchy</td>
<td>Superficial</td>
<td>No</td>
<td>+/-</td>
<td>Congested</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>Anywhere</td>
<td>Superficial</td>
<td>No</td>
<td>-</td>
<td>Normal</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Clostridium</td>
<td>Anywhere, but preferentially affects ileocolic and rectal region</td>
<td>Circumferential, aphthous, fissures, fistulae</td>
<td>Necrotizing granulomas, intestines, and lymph nodes</td>
<td>-</td>
<td>Normal</td>
<td>Granulomatous</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Anywhere</td>
<td>Unusual</td>
<td>No</td>
<td>-</td>
<td>Normal</td>
<td>Histiocytic collections</td>
</tr>
<tr>
<td>Mycobacteria avium</td>
<td>Anorectal</td>
<td>Superficial</td>
<td>No</td>
<td>-</td>
<td>Normal</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Anorectal</td>
<td>Superficial</td>
<td>No</td>
<td>-</td>
<td>Normal</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Anorectal</td>
<td>Superficial</td>
<td>Chancre</td>
<td>-</td>
<td>Obliterative endarteritis</td>
<td>Lymphocytes and plasma cells</td>
</tr>
<tr>
<td>Toxigenic E. coli</td>
<td>Anywhere</td>
<td>None</td>
<td>No</td>
<td>-</td>
<td>Congested</td>
<td>None, lamina propria edematous and hemorrhagic</td>
</tr>
<tr>
<td>E. coli 0157</td>
<td>Anywhere</td>
<td>Superficial or deep</td>
<td>No</td>
<td>+/-</td>
<td>Congested</td>
<td>Neutrophilic</td>
</tr>
</tbody>
</table>

Spirochetosis does not produce any grossly or endoscopically recognizable lesions, so that it is first diagnosed histologically. Spirochetes adhere to the mucosal surface, where they appear as a luminal blue fringe (Fig. 13.107). They attach to both neoplastic (292) and nonneoplastic epithelia. The surface epithelium appears unremarkable, as does the underlying lamina propria. One can confirm the presence of the spirochetes by staining tissue sections with PAS or Warthin-Starry stains or by using immunohistochemical stains for Treponema pallidum since the antibody cross-reacts with spirochetosis (293). Sometimes the spirochetes are found within epithelial cells or macrophages of the intact mucosa (294).

**Aeromonas**

* Aeromonas hydrophilia causes severe and persistent proctocolitis in children and HIV-infected individuals (295,296) and it superinfects patients with idiopathic IBD. It is easy to confuse this infection with ulcerative colitis (295). *Aeromonas sorbia* may also cause a left-sided segmental colitis (297). *Aeromonas* is an oxidase positive, Gram-negative bacillus. Sigmoidoscopy reveals a friable mucosa with ulcers consistent with an acute colitis. Biopsy or resection specimens show acute and chronic inflammatory cells in the lamina propria together with abscesses (Fig. 13.108). Cultures from the tissues usually yield abundant organisms. The infection is discussed further in Chapter 6.
Infectious Colitis

**Actinomyces**

The appendix and ileocecal regions are the most common sites of infection, whereas colonic and rectal infections are rare (298). Rectal lesions present as areas of induration with or without ulceration, fistulae, or strictures, mimicking Crohn disease. *Actinomyces* can also cause suppurative cecal lesions. The latter may present as a palpable mass with draining sinuses to the abdominal wall. Most cases of invasive abdominal actinomycosis result from appendiceal or colonic perforations following acute appendicitis, diverticulitis, or abdominal trauma. These infections are more common in patients with impaired immune defenses. Granulomas that form at anastomotic lines following colonic resection may contain *Actinomyces* (299).

![Image of Spirochetosis](https://example.com/spirochetosis.jpg)

**FIG. 13.107.** Spirochetosis. *A:* Low-magnification picture showing a prominent blue fringe along the epithelial surface. *B:* Higher magnification shows this apical fringe.

Histologically, the organisms produce rounded masses of faintly discernible branching filaments readily seen on Gram or H&E stains. A radial corona of eosinophilic material called Splendore-Hoepple fibers surrounds the bacterial mass producing the characteristic sulfur granules (Fig. 13.109). The periphery of the Gram-positive bacterial colonies has a club-shaped Gram-negative edge.

**Chlamydial Infections**

The clinical manifestations and histopathologic features of chlamydial infections depend on the organism’s serotype, prior immunity, and the presence or absence of concurrent infections. Both lymphogranuloma venereum (LGV) and non-LGV serotypes cause GI disease. The spectrum of intestinal infection ranges from an asymptomatic infection to severe granulomatous proctocolitis. Infection usually results from direct anal inoculation by infected partners or secondary to lymphatic spread from a penile lesion or from infected vaginal secretions.

*Chlamydia* bacteria are small bacteria that cannot grow outside a living cell because they cannot synthesize their own ATP. Colonization of chlamydia persists at sites that are inaccessible to phagocytes and immune cells. Additionally, the surface of the *Chlamydia* does not contain proteins that are distinctive enough to induce a full immune response, allowing the infection to persist (300). The life cycle has two stages: The elementary body and the reticulate body. The elementary body is analogous to a spore and it germinates into the reticulate body.
Lymphogranuloma Venereum

LGV has a worldwide distribution and its prevalence varies from country to country. The disease develops most commonly in tropical and subtropical countries. It is endemic in Africa, the Indian subcontinent, Southeast Asia, and parts of Central and South America. It occurs sporadically in North America, Europe, and Australia and until recently most cases in these areas were linked to travel in endemic areas (300). The disease is caused by the L1, L2, and L3 serotypes of C. trachomatis. However, in the recent past there have been clustered cases of LGV proctitis in men who have sex with men in an outbreak that appears to be centered in the Netherlands but has spread to other cities in Europe and to the United States (301). The patients characteristically have a high rate of concomitant sexually transmitted diseases and the organism has a predominance of the L2 serotype (302). In countries where the disease is uncommon, it often goes unrecognized (303). Men tend to develop genital lesions followed by suppurative inflammatory reactions, known as buboes, in the inguinal lymph nodes. Women develop rectal disease secondary to lymphatic spread of the organism from the vagina.
Infectious Colitis

Clinically, LGV is divided into three stages. Primary lesions develop 3 to 30 days after the initial infection. In males, the most common lesions involve the penis, often the glans. In women, LGV affects the vaginal wall, labia, or cervix. The primary lesion is transient, often imperceptible, and painless. No specific histopathologic findings identify the early lesion. The primary lesion may heal quite rapidly and scars develop. The second stage begins 10 to 30 days after the primary lesion as the obligate intracellular parasite travels through the lymphatics and into the draining lymph nodes, leading to the development of lymphadenitis. Proctitis is common at this stage. A fluctuant mass in the rectum may lead to the development of abscesses, fistulae, and sinus tracts. If the disease is untreated, it progresses to the third stage, which is marked by fibrosis and the formation of strictures (303) or even the late development of adenocarcinoma or squamous carcinoma (304). The changes may extend proximally as far as to the transverse colon, although the disease tends to remain confined to the distal bowel (Fig. 13.110).

LGV proctitis causes diarrhea, a bloody or mucopurulent discharge, fever, and inguinal and perirectal lymphadenopathy. The disease mimics idiopathic IBD because of the presence of proctitis associated with fibrosis, strictures, deep fissures, ulcers, and granulomas. The disease also mimics herpetic proctitis. However, unlike herpes, the lesions tend to be painless. The diagnosis of LGV is supported by a positive complement fixation test, although 17% of patients have a negative serology. The diagnosis is established by isolation of the organism in culture, direct immunofluorescence testing of biopsies or rectal swabs, or application of gene probes to the tissues.

**FIG. 13.110.** Lymphogranuloma venereum. The bowel wall is irregularly thickened and distorted by the inflammatory process.

The rectal mucosa appears ulcerated, friable, granular, nodular, hemorrhagic, and edematous with fibrosis of the underlying tissues. The degree of each of these reactions depends on the disease stage. Early changes show surface injury with an inflammatory exudate and extensive crypt injury, lamina propria inflammation, and cryptitis. The lamina propria contains lymphocytes, plasma cells, and neutrophils. The neutrophils are especially prominent around the crypts with cryptitis and crypt abscesses, crypt injury, and crypt loss (300). Granulomas are not present early. When the inflammatory response is exuberant, pseudomembranes form. The rectal wall appears thickened, rigid, and severely ulcerated. Rectal strictures are usually tubular in nature, with an abrupt line of demarcation with the noninvolved, more proximal large intestine. The mucosa may also become hypertrophic and granular. Severe rectal LGV shows a complete mucosal loss that becomes replaced by granulation tissue. After a short time, the inflammatory response changes to a mixed and even predominantly mononuclear cell response. Macrophages are particularly common in LGV. The infections often induce lymphoid follicle formation. Late-stage disease associates with granulomas, fistulae, and marked fibrosis. Infections restricted to lymph nodes show marked lymphoid hyperplasia and transformation of the macrophages into epithelioid cells.

**Nonlymphogranuloma Venereum Chlamydial Infections**

Non-LGV strains of *C. trachomatis* occasionally cause mild proctitis (305). The clinical and histologic features resemble anorectal gonorrhea. Endoscopically, one sees a mucopurulent discharge, mucosal friability, and diffuse erythema. Rectal biopsy demonstrates a lamina propria–based pericryptal neutrophilic cell infiltrate. Small erosions, mild inflammation, or
prominent lymphoid follicles affect the distal rectum. The infections may also involve anorectal crypts, but these may be difficult to visualize histologically because of the unwillingness of most clinicians to take deep biopsies in the area near the anal sphincter.

**Anthrax**

*Bacillus anthracis* is a large Gram-positive bacillus that resides as a spore in the soil and causes fatal disease in livestock (306). Humans become incidentally infected when contacting spores on dead animals or their meat, hides hair, or wool. The most common form of the disease is cutaneous, but gastrointestinal disease may develop if raw or undercooked infected meat is consumed. This mostly occurs in tropical Africa and Asia. The other two forms of the disease are oral-oropharyngeal and inhalational (306). Today there is renewed interest in this disease because of possible terrorist use of the organism.

Patients with gastrointestinal anthrax present with fever, anorexia, nausea, vomiting, and later severe abdominal pain (307). The portal of entry for the gastrointestinal form of the disease is believed to be the distal ileum or cecum where the pathologic findings are a solitary hemorrhagic, necrotic, edematous mucosal lesion and hemorrhagic mesenteric lymphadenitis (308). At least 50% of cases are fatal with septicemic toxemia and in some cases hemorrhagic, bacillus-laden ascites or gastrointestinal hemorrhage (306).

**Viral Infections**

**Cytomegalovirus Infections**

CMV infection represents the single most common pathogen identified in autopsy series among AIDS patients. Most patients with GI involvement have disease in the esophagus, stomach, and colon. CMV infections in immunosuppressed and immunocompetent patients fall into primary infections, reactivation infections, and superinfections. CMV is usually not eliminated from the body after a primary infection. Rather, it persists as a low-grade chronic infection or remains in a latent state allowing reactivation at a later time and further viral transmission to new hosts. The macrophage serves as the infection reservoir during latent periods (309).

A number of host and viral factors determine the outcome of a CMV infection. The determinants of CMV infection vary among newborns, organ or bone marrow transplant recipients, HIV-infected persons, or blood transfusion recipients. CMV is transmitted to neonates transplacentally, by passage through a contaminated birth canal, or by ingestion of infected breast milk. In adults, CMV is sexually transmitted or transmitted via infected organs, blood, or needles (310).

Immunocompromised individuals tend to develop CMV viremia, endothelial viral infection (Fig. 13.111) followed by endothelialitis, submucosal ischemia, and secondary ulceration. CMV-associated vasculitis (Fig. 13.112) in the GI tract is especially well documented in the AIDS population, where it preferentially involves the colon in up to 67% of patients. The affected vessels include arteries and veins that undergo segmental necrosis, perivascular hemorrhage, and possible thrombosis (311). Treatment with ganciclovir is capable of reversing many of these effects and hence emphasizes the critical need to diagnose CMV infections in these patients.
FIG. 13.111. Cytomegalovirus (CMV) endothelialitis. This picture represents a dual immunostain for endothelium (brown) and CMV (red) (arrow).
Infectious Colitis

**FIG. 13.112.** Cytomegalovirus (CMV) vasculitis. Often patients with CMV have moderately occlusive vascular lesions without obvious viral inclusions. These cause secondary ischemic necrosis. Careful examination of the tissues, either by histologic examination or by immunostained preparations, demonstrates the presence of CMV in adjacent portions of the mucosa.

The incidence of symptomatic disease differs in the three forms of CMV infection. At least 66%, <20%, and as many as 40% of patients with primary infections, reactivated latent infections, and superinfections become symptomatic, respectively. Clinically evident CMV infections most commonly affect immunosuppressed patients, including renal transplant patients and those with AIDS. CMV colonic infections also complicate ulcerative colitis (see Chapter 11), nonspecific ulcer disease, or adenocarcinomas. CMV infections have a special predilection for pre-existing inflammation (312), explaining in part the enhanced susceptibility of UC patients to CMV infections. The infection may also affect immunocompetent hosts, sometimes developing in a hospital setting.

CMV colitis presents with abdominal pain; watery, bloody diarrhea; colonic hemorrhage; perforation; and peritonitis. Patients may die following a major GI bleed. The organism characteristically causes colonic ulcers, which tend to localize in the ileocecal region. Rare patients develop CMV pancolitis (313). Infection in the myenteric plexus leads to intestinal pseudo-obstruction (314). CMV colitis develops as part of disseminated disease.

Pathologic features of CMV colitis range from discrete ulcers to more diffuse inflammatory changes characterized by edema, erythema, mucosal erosions, pseudomembranous colitis, or perforations (Fig. 13.113). A mildly abnormal intervening mucosa separates discrete ulcers in many patients. In its severest form, multiple ulcers and perforations occur throughout the length of the gut. The gross appearance may resemble ischemic colitis.

The diagnosis of CMV infection in mucosal biopsies is often not difficult. In severely immunosuppressed patients, numerous CMV-infected cells are identified. CMV-infected cells often appear enlarged (cytomegalic) and they contain eosinophilic intranuclear inclusions surrounded by a halo and granular basophilic cytoplasm. Nuclear and cytoplasmic inclusions often
Infectious Colitis

Inclusion-bearing cells are most numerous in areas of ulceration, especially in the ulcer bases and in the endothelium. They also occur in granulation tissue, pseudopolyps, and intervening mucosa. CMV infects epithelium, endothelial cells (Fig. 13.114), smooth muscle cells, fibroblasts, histiocytes, and ganglion cells. CMV exhibits a wide variation in the intensity of inflammation and associated necrosis. It ranges from a relatively bland lesion to extensive acute and chronic inflammation with widespread necrosis and perforation. The number of inclusions generally parallels the severity of the inflammatory response, although occasional cases show numerous inclusions in the absence of significant inflammation. The accompanying inflammatory infiltrate consists of lymphocytes, histiocytes, plasma cells, and polymorphonuclear leukocytes (PMNs). More subtle infections require an awareness of, or high suspicion for, the possibility that the infection might exist so that multiple sections and/or levels should be carefully examined to find the characteristic cells.

In severe infections, ischemia causes many of the gross features. Some intestinal lesions exhibit a severe CMV-related occlusive vasculitis. Cytomegalic inclusions occur within endothelial cells of medium-sized arteries and veins, arterioles, venules, and capillaries. The affected endothelial cells appear markedly enlarged and crowded, leading to partial or complete vascular occlusion with occasional thrombus formation. In addition, a leukocytoclastic vasculitis and lymphoplasmacytic perivascular infiltrate develop, leading to a loss of vascular integrity with complete or segmental necrosis. As a result, the patient develops ischemia, intestinal ulceration, and perforation. The vasculitis may associate with exuberant fibroblastic reactions (315) that are especially prominent in ulcer bases. The lesions may represent a peculiar reaction of the immunologically compromised host to CMV in the intestinal blood vessels (Fig. 13.112). The ischemia causes localized edema, inflammation, thrombosis, necrosis, and frank perforation. Stromal cells surrounding the infected vessels are also commonly infected in patients with vasocentric infections. When the virus localizes to the myenteric plexus, the myenteric plexus becomes inflamed and contains neuronal intranuclear inclusions surrounded by a halo, axonal dilation with pyknotic axons, and glial cell hyperplasia. The absence of viral inclusions does not exclude a diagnosis of CMV. Immunohistochemical stains or genetic probes aid in detecting the infection (Fig. 13.115).

FIG. 13.113. Cytomegalovirus (CMV). A: CMV colitis with chronic inflammation, prominent granulation tissue, and an ulcer. B: Higher magnification of this specimen demonstrating the presence of CMV inclusions in many of the mononuclear cells (arrows).
FIG. 13.114. Cytomegalovirus (CMV) enterocolitis. A: Prominent mononuclear inclusions (arrow) are found in the lamina propria. B: Lower magnification shows a detaching endothelial cell containing a CMV inclusion (arrow.) C: Immunostain demonstrating several immunopositive cells. The infected cells are not all cytomegalic and might have been overlooked in standard hematoxylin–eosin preparations.
Infectious Colitis

FIG. 13.115. Immunostains of cytomegalovirus infection. A: Large numbers of mononuclear cells in the lamina propria. B: A large number of immunoreactive epithelial cells.

Herpes Infections

Large intestinal herpetic infections arise in the same clinical settings as herpes infection affecting other parts of the GI tract (see Chapters 2 and 15). Herpes simplex virus (HSV) infections, usually HSV type II, and herpesvirus hominis type I (HHV-I) affect the anorectum. Disease transmission requires direct contact with infectious lesions or secretions. Anorectal infections usually occur 2 to 7 days following sexual contact (316). The virus penetrates the epithelium, causing cytolysis and a localized inflammatory reaction. Patients present with localized paresthesias, tenesmus, pruritus, anorectal pain, change in bowel habits, and anal discharge (317). Abdominal pain can simulate a bowel obstruction. Herpesviruses usually infect squamous mucosa, although they can infect colonocytes as well. The diagnosis is often made clinically and confirmed by cultures or biopsy of the ulcer. Biopsies of the ulcer edges optimize viral detection. Rectal biopsy in HSV and HHV infection usually shows only nonspecific acute inflammation, but in some cases typical Cowdry type A inclusions and multinucleated cells are present.

Adenovirus Infections

Adenoviruses may cause colitis, particularly in immunosuppressed patients. The histologic features resemble those seen in the appendix or small bowel (see Chapters 6 and 8). The viral inclusions are found in the epithelium of the upper parts of the crypts or along the luminal surface, and are recognizable by smudgy nuclear enlargement.

Fungal Infections

Various fungi infect the large intestine. Candida infections occur relatively commonly (Fig. 13.116), particularly as superinfections involving necrotic tissues. The clinical settings in which Candida infections are found and their pathologic features are discussed further in Chapter 6.

Blastomycosis

Blastomycosis (North American blastomycosis, Gilchrist disease) is a chronic mycosis caused by the dimorphic fungus Blastomyces dermatitidis. It grows in tissues as a thick-walled
Infectious Colitis

round cell measuring 8 to 15 µm in diameter; it reproduces by broad-based budding. The organism spreads in the intestine by invading submucosal lymphoid tissue and by subsequent erosion into the mucosa and lumen. The typical histologic picture consists of granulomatous inflammation with superimposed pyogenic inflammation. Lesions without secondary infections resemble the epithelioid granulomas of sarcoidosis.

**Paracoccidioidomycosis (South American Blastomycosis)**

Paracoccidioidomycosis (South American blastomycosis) is a chronic mycosis caused by the dimorphic fungus *Paracoccidioides brasiliensis*. This fungus is an important public health problem in South America, but it does not usually extend further north than Central America and Mexico. This rare fungal disease usually infects the lungs, but it may disseminate to other organs. In the intestine it simulates idiopathic IBD or it may cause malacoplakia (318). In tissue, the fungus grows to be a large, round, oval cell measuring 5 to 15 µm in diameter. It reproduces by single or multiple budding. The distinctive feature of the fungus in tissue is an occasional large cell that, when hemisected, reveals peripheral buds protruding from a thin-walled, round mother cell that sometimes looks like a ship's wheel. The fungi are often surrounded by a granulomatous reaction combined with pyogenic inflammation (Fig. 13.117).
**FIG. 13.116.** Colonic candidiasis. *A, B:* Various gross appearances of colonic *Candida* infections. The organism typically colonizes already devitalized bowel, which is often ischemic as illustrated here. *C:* Histologic appearance of the infection. The specimen has been stained with a silver stain. Numerous spores are present.
Infectious Colitis
Infectious Colitis

**FIG. 13.117.** South American blastomycosis. *A:* A portion of intestinal mucosa with regenerative features and an intense inflammatory reaction that separates the base of the glands from the muscularis mucosae. *B:* Medium magnification shows mononuclear cells surrounding spherular structures with a prominent clear space. *C:* A large spore with the typical tissue retraction surrounding the spore. (Case courtesy of Dr. Marian Trevisan, Faculdade Medicina Unicamp, Campinas, Brazil.)

**Histoplasmosis**

*Histoplasma* is a dimorphic, facultative intracellular fungus. It grows as a mycelium in the soil and as a yeast within infected cells. It thrives in areas of heavy accumulations of bird or bat excrement. It is endemic in a broad area centered around the Ohio and Mississippi River valleys in the United States, in the Caribbean, and in Central and South America. Skin testing reveals that most people living in endemic areas become infected. Gastrointestinal histoplasmosis affects both immunocompromised and immunocompetent individuals in endemic and nonendemic areas. The skin test for histoplasmosis is often negative in patients with gastrointestinal disease (319). Disseminated histoplasmosis is rare. It affects infants with immature immune systems, persons with defective cellular immunity, AIDS patients, and some patients without an identifiable immunologic defect. It is estimated that disseminated histoplasmosis develops in 55% of infected immunocompromised patients and 4% of immunocompetent patients (320,321). Immunity to histoplasmosis most closely resembles that described for tuberculosis except that the acquired immunity may not be as long-lived so that reinfection occurs more commonly. The course of the infection is mild in most immunocompetent individuals but the organism can produce progressive disseminated infections in individuals compromised by hematologic malignancies, cytotoxic therapy, or HIV infection.

**FIG. 13.118.** Endoscopic features of histoplasmosis. The colon demonstrates elevated, nodular, yellowish, mucosal plaques.

Infections originate in the respiratory tract. Esophageal compression is common. Approximately one third of patients with disseminated disease have small and large bowel intestinal involvement (322). During the early phase of infection macrophages recognize, bind, and ingest the organism, providing it with access to a permissive intracellular environment for replication (323). Exceptional (usually AIDS) patients present with primary gastrointestinal histoplasmosis (324). Intestinal histoplasmosis presents as chronic diarrhea or with symptoms similar to those of IBD. Patients with untreated fatal infections exhibit large collections of organism-containing macrophages, whereas those with localized disease show discrete hyperemia, hemorrhage, mucosal nodules, ulcers that measure up to 4 cm in greatest diameter (319), and inflammation. Endoscopy in patients with disseminated disease reveals the presence of numerous, variably ulcerated, yellowish, submucosal plaques bulging into the intestinal lumen (Fig. 13.118).

A spectrum of gastrointestinal lesions can be found including diffuse lymphohistiocytic infiltration, ulcers, and lymphohistiocytic nodules that usually involve the mucosa and submucosa.
Infectious Colitis

but that can extend into the muscularis propria, serosa, and mesentery (Figs. 13.119 and 13.120). The lesions contain numerous eosinophils, neutrophils, and plasma cells in addition to macrophages and lymphocytes. Giant cells and granulomas are rare. Well-formed granulomas are only present in 8% of patients (319). Superficial mucosal ulceration is often present over the lymphohistiocytic nodules and the ulcers and nodules frequently lie above Peyer patches. (319). The fungus-containing macrophage collections morphologically resemble those seen in various disorders. However, the *Histoplasma* within them have a distinctive appearance. *Histoplasma* spores have rigid cell walls and average approximately 3 µm in diameter. During the process of fixation, the protoplasm retracts from the wall leaving a clear space that gives the impression of an unstained capsule. The tissue may also contain viable budding fungi. Following therapy (with drugs such as amphotericin B), one sees degenerating and dead organisms. Long after remission, one may find fungal cell wall remnants within macrophages.

Cytology preparations made from lesions that present as masses may suggest a diagnosis of a signet ring cell carcinoma due to the presence of large numbers of vacuolated cells (325).

**Aspergillosis**

Patients most at risk for developing *Aspergillus* infections are those undergoing prolonged periods of immunosuppression following transplantation. Risk factors for the infection include the duration of the granulocytopenia and the use of corticosteroids, cytoreductive agents, and broad-spectrum antibiotics (326). Most infections involve the esophagus, but colonic disease occurs. Colonic lesions are characterized by submucosal ulcers with confluent necrosis, which present with lower GI bleeding (327,328). Angioinvasive aspergillosis complicating immune suppression and pancytopenia may present as neutropenic enterocolitis. The angioinvasive fungi cause intravascular thrombosis, ischemic necrosis of the cecum, and a relatively mild lymphocytic and histiocytic infiltrate.

The diagnosis of invasive aspergillosis depends on the presence of typical hyphae in the tissues. The lesion somewhat resembles mucormycosis, which also tends to penetrate blood vessels and disseminate through the vasculature. However, in contrast to *Mucor*, which has irregular branching, *Aspergillus* has a regular dichotomous branching pattern of hyphae, all apparently advancing in the same direction.

**Mucormycosis**

Invasive mucormycosis affects the gut, particularly in malnourished individuals or those on chemotherapy. The large bowel follows the stomach in order of frequency of involvement (329,330). Patients develop mucosal ulcers (330) that lead to bloody diarrhea (329). Characteristic pleomorphic, broad, aseptate, irregularly branched hyphae invade the tissues. The hyphae of *Mucor* measure 3 to 5 µm in diameter.
Cryptococcal Infections

Gastrointestinal cryptococcal infections are rare, occurring either as part of disseminated disease or as an isolated finding. They complicate AIDS, hematologic malignancies, and hyperimmunoglobulinemia, recurrent infection syndrome (331) or occur in patients on corticosteroid therapy (332). They usually present as pulmonary infections but rare cases exist of disease confined to the large bowel (331). The infection produces a granulomatous colitis that mimics Crohn disease.

Trichoderma Infections

*Trichoderma longibrachium* may cause colonic infections in the immunocompromised patient. The fungus is a branching septated organism that has angioinvasive abilities. There is a long main branch that produces shorter side branches terminating in phialides (333). It produces ulcers and ischemic colitis.

Basidiobolomycosis

*Basidiobolus ranarum* typically infects the skin in patients in the tropical climates of Africa and Southeast Asia (334). The organisms are irregularly branched, thin-walled, occasionally septated hyphae typically surrounded by a thick eosinophilic (Splendore-Hoeppli phenomenon). Sporelike spherules measuring 20 to 40 µm may also be present; these contain a central nucleuslike structure (335). Prominent tissue eosinophilic infiltrates and palisading caseating granulomas surround pale fungal hyphae. The granulomas center on the muscularis propria and extend into the subserosa and attached fat and into the submucosa. The organisms cause marked mural thickening with fibrosis. Yellow nodules measuring up to 3 cm in diameter may be seen. The gross appearance of the bowel suggests Crohn disease.

Algal Infections

*Prototheca* species are common, unicellular, achlorophyllous saprophytes that belong to the genus of colorless, eukaryotic algae that grows slowly on conventional bacteriologic media. They occur in wet parts of the environment, such as rivers and wells. Two species, *Prototheca wickerhamii* and *Prototheca zopfi*, cause human infections. They have a characteristic morphology (336). The roughly spherical cysts vary in size from 1.3 to 16.1 µm. Smaller cysts are unicellular; the larger ones are internally divided into 2 to 20 daughter cysts (337). The rectum may become infected. Histologically, chronic inflammatory cells, including eosinophils and histiocytes, surround the organisms (Fig. 13.121). A vaguely granulomatous

---

**FIG. 13.119.** Colonic histoplasmosis. These figures come from the lesion seen endoscopically in Figure 13.118. A: The lamina propria is diffusely infiltrated by foamy histiocytic cells. The epithelium appears normal. B: Gomori stain shows numerous fungal organisms.
Protozoan Infections

Amebiasis

Amebiasis has a worldwide distribution; it is more prevalent in the tropics than in temperate climates where it emerges as a sporadic disease or as epidemic outbreaks. One acquires amebiasis through the ingestion of fecally contaminated food or water. Therefore, the risk of infection is greatest in areas with primitive or nonexistent sanitation or where human feces are used as fertilizer. The disease also spreads via colonic irrigation with infected water, as may occur in chiropractic, homeopathic, naturopathic, or nutritional therapy programs (338). The disorder may also be transmitted via anal intercourse (339). In the United States amebiasis is most commonly seen in immigrants from and travelers to developing countries. The disease is more severe in the very young and the very old (340).
Infectious Colitis

**FIG. 13.120.** Colonic histoplasmosis. *A:* Low-power hematoxylin and eosin–stained section shows a colonic mucosa with nonspecific inflammation. *B:* Higher magnification shows numerous grayish blue, rounded structures corresponding to the fungus in the tissues in the absence of granulomatous inflammation. *C:* Silver stains highlight the fungi.

Four species of the genus *Entamoeba* inhabit humans (Fig. 13.122) but only *Entamoeba histolytica* is pathogenic. *E. histolytica* has two life forms: The invasive motile trophozoite, which measures 12 to 50 µm in size, and the 10- to 20-µm cyst (Fig. 13.123). Trophozoites contain a single nucleus with fine peripheral chromatin and a central karyosome. The karyosome appears as a tiny, darkly stained dot in the center of the nucleus and is often difficult to see (341). Trophozoites have a thin cell membrane and sometimes exhibit fingerlike projections known as pseudopodia. The cytoplasm generally contains vacuoles.

Amoebae propagate through cysts, the resistant form in their life cycle. Cysts frequently contain highly refractile, cigar-shaped structures with rounded ends. *E. histolytica* cysts passed in the stool are immediately infectious. They can survive outside the host for weeks to months in moist environments. Ingested cysts, unlike trophozoites, resist gastric acid, the water chlorine concentrations used in sewage systems, and storage at room temperature. Following ingestion, the organism excysts, usually in the region of the ileocecal valve. The cyst wall dissolves, liberating trophozoites. The trophozoites use the galactose and N-acetyl-D-galactosamine–specific lectin to adhere to colonic mucins and thereby colonize the large intestine (342). The trophozoites also secrete cytolytic enzymes (343), enabling them to pass through the intestinal epithelium, disrupting the tissues and liberating red blood cells that they ingest. Trophozoites digest a small cavity in the mucosal wall where they grow and divide by binary fission. Interaction of the parasite with the intestinal epithelium causes an inflammatory response marked by activation of nuclear factor *kb* and the secretion of lymphokines (344). The infection may remain limited to the GI tract for years or it may extend to the liver and other organs. Specific and sensitive tests for the diagnosis *E. histolytica* in stool are now available and include antigen detection and PCR (340).
Infectious Colitis

**FIG. 13.121.** Protothecosis. A: The rectal biopsy shows mild mucosal regeneration and marked submucosal inflammation. B: Higher magnification of the inflammatory process. C: Higher magnification examination demonstrating the presence of typical spherules (arrow). The patient was an individual who lived in a rural area of Kentucky and bathed regularly in well water.

The disease affects individuals of all ages, including infants (345). The severity of the disease varies considerably. Amebiasis often remains asymptomatic or it may produce severe disease and death. Symptomatic amebiasis presents in three ways: (a) as a localized bowel infection with the typical symptoms of dysentery, including rectal bleeding; (b) as a localized granulomatous lesion that commonly affects the cecum and closely mimics a carcinoma; or (c) with hepatic involvement, causing amebic hepatitis or amebic liver abscesses.
Infectious Colitis

**FIG. 13.122. Entamoeba.** A: *Entamoeba coli* is generally considered nonpathogenic. The trophozoite seen here on stained smear is similar in size to the trophozoite of *Entamoeba histolytica* but is distinguished by its larger irregular karyosome and coarser peripheral chromatin. B: *Entamoeba nana* is also generally considered nonpathogenic. The trophozoite seen here is smaller than the trophozoite of *E. histolytica* and is distinguished by its prominent karyosome. C: On stained smears, the trophozoite of *Entamoeba hartmanni* may be confused with that of *E. histolytica* because of its usually central compact karyosome. The *E. hartmanni* trophozoite is smaller than that of *E. histolytica*, however. D: The *E. histolytica* trophozoite is distinguished on trichrome-stained smears by its size (usually 20 to 50 µm) and its nuclear morphology. The single nucleus has a central compact karyosome and finely granular peripheral chromatin. (A–D courtesy of Dickson Despomier, Ph.D., Department of Parasitology, Columbia University, New York, NY.)

The two most common symptoms of the dysenteric presentation include intermittent bloody diarrhea and lower abdominal cramps. In severe disease, the symptoms simulate ulcerative colitis and toxic megacolon, especially in geographic areas where amebiasis is not endemic. Like IBD, chronic amebic colitis may begin insidiously and exhibit cyclic remissions. Patients experience gradually increasing lower abdominal discomfort, loose stools, malodorous flatus, and recurrent bouts of diarrhea. Intermittent constipation also occurs. Over a period of 3 to 4 days, the number of stools may increase to 25 per day with weakness and prostration. Nausea, vomiting, and right-sided cramps are usual. Amebic colitis often persists for weeks, months, or years. Patients may also show a mild anemia or mildly elevated white blood count. Amebiasis also causes proctitis in children, with the disease often remaining limited to the rectum (346). Individuals particularly at high risk for developing chronic proctitis without diarrhea include immigrants or travelers from endemic areas. Unusual manifestations of amebic colitis include acute necrotizing colitis, toxic megacolon, ameboma, and perianal ulceration with the potential formation of a fistula (340).
Infectious Colitis

Complications of amebiasis result from the migration of the parasite through the bowel wall into adjacent structures (Fig. 13.124). The bowel wall usually becomes severely stenotic due to inflammation with abscess formation and fibrosis. Perforation and fistulae between bowel loops are rare and usually fatal (347). The most serious complication of amebiasis is venous invasion with parasitic migration through the portal system to establish amebic hepatitis or hepatic amebic abscesses, usually involving the right lobe of the liver. Hepatic involvement affects <5% of those with amebic dysentery (348). Hepatic abscesses can perforate into the subphrenic space, right pleural cavity, or right lung. Pericarditis may also occur (349). Colonic carcinoma may follow amebiasis and there is an increased frequency of polyps at the site of amebic ulceration.

Both ova and trophozoites are found in stool specimens or rectal scrapings. Stool examination also often shows the presence of Charcot-Leyden crystals. Stool examination (Figs. 13.122 and 13.123) for motile trophozoites is a simple and easy way to establish the diagnosis. Various immunologic tests help make or confirm the diagnosis, including detection of amebic antigens in stool specimens or serum antibodies by fluorescent antibody techniques (350). Serologic tests may be particularly useful because they show superior sensitivity and predictive value in recognizing invasive disease than do biopsies (351).
Resected specimens often exhibit diffuse mucosal and mural involvement, sometimes producing a pattern grossly resembling IBD, especially Crohn disease (Fig. 13.125). The most extensive lesions affect the cecum, appendix, and rectosigmoid, but they may also be scattered throughout the bowel and be particularly prominent in the hepatic flexure. The earliest amebic lesions appear as small, yellow mucoid elevations containing semifluid, necrotic material infected with the parasite. When the lesions rupture into the lumen, the organisms continue to proliferate, undermining the adjacent intact mucosa to leave discrete, oval-shaped ulcers with overhanging edges extending into the submucosa. The flat, nonindurated ulcers tend to lie on the long axis of the bowel wall, and they exhibit a characteristic hyperemic edge. A ragged, yellowish white membrane covers the ulcer floor, particularly in severe cases. The ulcers may become confluent, leaving isolated patches of intact, hyperemic mucosa among extensive areas of necrosis and extensive inflammatory polyposis.

Although invasive amebiasis is characterized by disruption and invasion of the colonic mucosa by amebic trophozoites (Fig. 13.126), histologic examination of biopsies can be nondiagnostic since often all one sees are inflammation, ulceration, and a fibrinous exudate. Biopsies should be taken from the ulcer edges, especially because this is where the organisms are most numerous. The trophozoites also sometimes lie in the overlying fibrinous exudate. For this reason, enemas should be avoided prior to biopsy, as the luminal mucus and exudate, potentially containing the trophozoites, will be removed in the process.
Infectious Colitis

Few histopathologic changes are pathognomonic except for the presence of the trophozoite. Trophozoites may or may not be seen on the initial examination (Fig. 13.126). The pathologist must be able to recognize *E. histolytica* in its trophozoite form and to distinguish it from nonpathogenic amebas that may inhabit the human large intestine. Typical organisms are large, round to ovoid, varying in diameter from 6 to 40 µm. They contain a voluminous, pinkish purple cytoplasm with a distinctive foamy, vacuolated, or granular appearance. The cytoplasm is PAS positive and, unlike nonpathogenic amoebas, contains ingested red blood cells (352). Erythrophagocytosis is easily demonstrated with Heidenhain iron hematoxylin stains. The organisms must be distinguished from macrophages, which tend to be smaller and less intensely PAS positive, and contain a clearly identified nucleus. *Balantidium coli* infections produce similar histologic changes to those of amebic colitis. However, *B. coli* measure 30 × 150 × 40 µm contrasting with *Entamoeba*, which measure 30 to 40 µm in largest diameter. In tissue sections, the ameba may be surrounded by a clear space, a shrinkage artifact produced by fixation (352). When one suspects the disease, one may wish to perform serologic tests to confirm the presence of the infection. Alternatively, a prophylactic trial of metronidazole may be indicated.

![Image](file:///F|/Gastro/Chapter%2013%20Infectious%20Colitis.htm#fig.13.125.png)

**FIG. 13.125. *Entamoeba histolytica.* A: This colon manifests effects of severe amebiasis due to *E. histolytica*. There are multiple irregular deep ulcers. B, C: Having gained access through the colonic mucosa, the invasive *E. histolytica* spread laterally and deeply through the submucosa, undermining the remaining mucosa.**

Patients who undergo surgical resection are typically those with severe obstructing amebic disease or transmural inflammation. The proximal colon is usually involved, although the rest of the colon, including the rectum, the anal canal, and even the distal ileum, may be affected. Early lesions show mucosal swelling and ulceration. A surface exudate composed of mucin, fibrin, and inflammatory cells develops as the superficial ulceration evolves. Amoebae are most readily detected in this exudate (352).
Infectious Colitis

**FIG. 13.126. Entamoeba histolytica.** A: Typical flask-shaped ulcer of *E. histolytica*. Here much of the mucosa has been spared as the ameba has eroded through submucosa and muscularis. B: Trophozoites of *E. histolytica* are distinguished by their size, nuclear morphology, and phagocytosis of erythrocytes in hematoxylin and eosin–stained sections.

Developing ulcers have irregular, hyperemic mucosal outlines with markedly undermined, overhanging edges, producing a characteristic flasklike shape. The extensive undermining leads to widespread ulceration and even perforation. As the ulcers extend, the organisms may also be found in tissue spaces and small vessels. When amoebae invade tissues, they usually aggregate (Fig. 13.126) and are generally present in areas of necrosis and tissue disruption. In patients with severe disease, trophozoites may extend through the bowel wall to lie freely in the abdominal cavity or in the serosal fat. The mucosa exhibits a chronic inflammatory response characterized by minimal, moderate, or extensive lamina propria infiltrates containing lymphocytes, histiocytes, plasma cells, eosinophils, and prominent lymphoid follicles. Pronounced edema and congestion accompany these changes, along with goblet cell depletion, neutrophil emigration, and early crypt abscesses. Necrosis follows extensive edema.

Amebic ulcers develop slowly, usually allowing cellular proliferation and fibrosis to occur, often protecting against perforation. Some lesions eventually heal without significant scarring, but others progress to chronic fibrosis with persistent or recurrent focal ulceration. Prolonged inflammation leads to the production of inflammatory pseudopolyps and strictures (353). Secondary bacterial infection of the ulcers is common and, if present, complicates the histologic features.

Patients with longstanding infections and exuberant tissue reactions develop tumorous, exophytic, cicatricial, inflammatory masses known as amebomas (Fig. 13.127). Amebomas develop in the cecum, appendix, and rectosigmoid, in decreasing order of frequency. They also develop at the hepatic flexure, transverse colon, and splenic flexure (354). They usually occur in untreated or inadequately treated patients with amebiasis, years after the last recognized dysenteric attack. Amebomas are usually solitary, most commonly affecting men 20 to 60 years of age. Amebomas cause numerous symptoms including alternating diarrhea and constipation, weight loss, and low-grade fever. In endemic areas, cramping, lower abdominal pain, and a palpable mass suggest the diagnosis. In the United States, these symptoms in younger individuals suggest Crohn disease or appendiceal abscesses, whereas in older individuals colon cancer or diverticulitis is suggested.
FIG. 13.127. Ameboma. The patient had chronic amebiasis and the presence of a large necrotic mass, which was resected.

Amebomas result from persistent ulceration and granulation tissue formation, with fibroblastic proliferation and inflammation. The lesions vary in size but may measure up to 15 cm in diameter. They present as localized, often circumferential areas of bowel wall thickening, mucosal excrescences, or large tumor masses. The inflamed mucosa often bulges into the lumen and stricture formation narrows the bowel lumen. Amebomas may extend into the adjacent mesocolon. Biopsy may be required to distinguish the lesion from a carcinoma or large adenoma.

The therapy for invasive infections differs from the therapy for noninvasive disease. Noninvasive infection may be treated with paromomycin. Nitroimidazoles, particularly metronidazole, are the mainstay of therapy for invasive disease (355).

Balantidiasis

Balantidiasis has a cosmopolitan distribution, but most infections occur in tropical and subtropical regions due to ingestion of contaminated water. The disorder may also be transmitted from person to person (356). Pigs and rats serve as reservoirs for the infection (356). B. coli, the largest protozoan, has both a cyst and trophozoite form. It is the only ciliated protozoan known to infect humans. Oval trophozoites, measuring 30 × 150 × 40 µm, contain a characteristic large, kidney-shaped macronucleus and a small or round micronucleus (Fig. 13.128); cilia cover its surface. The cytoplasm contains two contractile vacuoles and numerous food vacuoles. The anterior end is pointed and contains a funnel-shaped cytosome. The oval to spherical cysts measure 40 to 65 µm in diameter. Young cysts are covered by cilia that disappear as they age. Ingested trophozoites are liberated from the cysts in the small intestine and invade the large intestine. They continue to excyst as they descend through the large intestine.

Balantidial infections cause three clinical patterns: Acute, chronic, and fulminating (357). The most common clinical pattern is chronic disease, characterized by alternating diarrhea and constipation. Symptoms can last from days to months. In contrast, patients with acute disease exhibit nausea, vomiting, anorexia, abdominal pain, and up to 30 bloody, mucus-filled bowel movements per day. Endoscopically, shallow ulcers and pseudomembranes are present (357). The fulminant form of the infection affects emaciated or debilitated patients. The stools are bloody, often frankly hemorrhagic, and patients may exsanguinate. If perforation occurs, the infection is fatal.

B. coli invades into and ulcerates the colon (Fig. 13.128), producing severe diarrhea and hemorrhage. The right half of the colon and cecum are most commonly involved, but the rectum and sigmoid can also become infected. The histologic features mimic those of amebiasis, including the presence of

flask-shaped ulcers containing trophozoites (358). The intervening mucosa may appear normal, edematous, or hemorrhagic. Most ulcers are superficial and multiple, but when deep ulcers develop, they perforate, particularly in fulminant disease (357). The tissues become necrotic and infiltrated with neutrophils and erythrocytes. Pseudomembranes containing neutrophils and fibrin cover the ulcers. The diagnosis rests on identifying the parasite.
Infectious Colitis

**FIG. 13.28. Balantidium coli.** *A:* The trophozoite of *B. coli* is relatively large (50 to 70 µm), ovoid shaped, and rimmed by cilia. The trophozoite has two nuclei, the larger of which is kidney bean–shaped and stains red on trichrome stain. *B:* *B. coli* invades the colon to produce ulcers similar to those seen in colonic amebiasis. The ulcers may penetrate through the entire bowel wall, as in this case. (Courtesy of Dickson Despomier, Ph.D., Department of Parasitology, Columbia University, New York, NY.)

**Visceral Leishmaniasis**

Visceral leishmaniasis (kala azar) is a parasitic disease produced by the protozoan *Leishmania donovani*. Patients present with fever, loss of appetite, occasionally diarrhea, and eosinophilia. Patients exhibit splenomegaly, hepatomegaly, anemia, and skin lesions, known as dermal leishmaniasis. The diagnosis requires microscopic identification of characteristic *Leishmania* amastigotes, culture of the organism, or serologic positivity for the protozoan (359). Microscopic diagnosis is usually carried out by bone marrow aspirate or biopsy. However, chronic visceral leishmaniasis may be first diagnosed on a rectal biopsy (359). The rectal mucosa contains well-preserved epithelium, but the intervening lamina propria is obliterated by the presence of large macrophages containing abundant cytoplasmic *Leishmania* amastigotes (Fig. 13.129). The parasitic forms are oval or round, measuring 1.5 to 3 µm in diameter, with two characteristic black dots corresponding to the nucleus and kinetoplast. The organism may also be found in the small intestine.

**Blastocystis (Zierdt-Garavelli Disease)**

*Blastocystis hominis* is a strict anaerobic protozoan that reproduces by binary division or sporulation. It is a single-celled organism found naturally in fresh water. The parasite is directly identifiable by immediate examination of feces. Infected patients present as asymptomatic carriers or with an illness consistent with an acute or chronic gastroenteritis. Organism prevalence ranges from 2% to 18% in the United States (360,361,362), 3% to 13% in Canada, and 3% in Great Britain. The pathogenicity of *Blastocystis* is a topic of debate. In one study, up to 34.7% of patients who are clinically healthy harbor the organism. Symptomatic patients present with abdominal pain, watery diarrhea, constipation, anorexia, vomiting, flatulence, and weight loss. Symptoms may be present for >2 weeks. The colonic mucosa usually appears endoscopically normal, although rarely it appears erythematous and friable. The organism is usually found in the stools in patients with diarrhea, sometimes associated with signs of inflammation. Biopsies from infected persons often appear normal. When abnormal, they may exhibit only mild nonspecific inflammation (360). Rarely, the organism causes colonic mucosal destruction but the parasite does not appear to penetrate and invade the tissues. The presence of large numbers of organisms (more than five organisms per oil immersion field), in the absence of other known bacterial, viral, or parasitic agents, should be treated. The organism may also be diagnosed in colonic cytology brushings.

**Chagas Disease**

Chagas disease results from infection by the parasite *Trypanosoma cruzi*, and the disease is virtually confined to South America. The entire GI tract may become involved. Patients present with achalasia, intractable constipation, megacolon, or intestinal pseudoobstruction. The infection is discussed in detail in Chapter 10.
Infectious Colitis

**FIG. 13.129.** Leishmaniasis. A: Gram section showing portions of the lamina propria infiltrated by the amastigote form. B: Methyl green–pyronine stain showing amastigote. (Pictures courtesy of Miguel Idoate, Faculty of Medicine, Universidad de Navarra, Pamplona, Spain.)

Helminthic Infections

**Schistosomiasis**

Schistosomiasis, also known as bilharziasis, is an infection caused by trematodes in the genus *Schistosoma*. Gastrointestinal disease results from the host's response to the schistosomal eggs and the granulomatous reaction evoked by the antigens they secrete (363). The intensity and duration of the infection determine the amount of antigen released and the severity of the chronic fibro-obstructive disease. Schistosomiasis ranks second to malaria as a cause of serious global morbidity. Schistosomiasis infects about 200 million people worldwide (364). Three schistosomal species cause most human infections: *Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*. *S. mansoni* is endemic throughout Africa and is found in many areas of Latin America and the Middle East. *S. japonicum* occurs in Asia. *S. haematobium* is endemic in Africa and in the Middle East. Rare infections with *Schistosoma intercalatum* and *Schistosoma mekongi* occur in Africa and Indochina, respectively.

Humans become infected when bathing or wading in water infected with cercaria (Fig. 13.130). The cercaria emerge from freshwater snails, penetrate the skin, enter the bloodstream, mature in the liver, and finally settle in the venous system, the intestinal wall, or the mesentery before they develop into adults. Schistosomes are the only flukes that are not hermaphroditic and in which the sexes are separate. Thus, infections by both a male and a female are required to generate ova. The female lies in the gynecophoral canal of the male. Females lay their eggs in the mesenteric veins and GI submucosal vessels. The eggs gain access to the GI lumen and the feces. If the ova reach freshwater, they hatch, releasing motile ciliated miracidia that invade snails. In the snail, the parasites undergo further development before being released again as cercaria to repeat the life cycle. The worm burden of each infected person is relatively constant because schistosomes do not multiply in the vertebrate host (365). Infection intensity increases by repeated exposures or decreases through...
attrition of senescent worms through the host immunity or following chemotherapy. Infected individuals living in endemic areas often remain asymptomatic due to their acquired immunity to the organism (365). This contrasts with visitors to endemic regions who develop acute, and sometimes very severe, symptoms immediately following the first infection (366). So-called Katayama fever consists of fever, chills, eosinophilia, hepatosplenomegaly, generalized lymphadenopathy, and generalized GI symptoms (366). The syndrome develops as the females lay up to 3,500 eggs per day. Proteins in the eggs react with circulating antibodies, thereby producing a serum sickness–like syndrome (366). Other forms of schistosomiasis include hepatosplenic, pulmonary, urogenital, cerebral, and intestinal infections.
Infectious Colitis

**FIG. 13.130. Life cycle of schistosomiasis (see text).**

The intensity of the infection varies from individual to individual. Infected persons complain of abdominal pain, diarrhea, and bloody stools. Intestinal schistosomiasis classically associates with *S. mansoni*, but *S. japonicum* and *S. haematobium* can also produce intestinal infections. Most lesions affect the rectum and left colon. Schistosomiasis also causes duodenitis in places where the parasite is endemic. It can represent a significant cause of upper GI bleeding.

Adult flukes do not cause clinical disease, probably because they incorporate host antigens as they mature. Rather, it is the numerous ova that elicit a granulomatous response (Fig. 13.131) and extensive fibrosis. Intestinal polyps and strictures develop late in the disease. Polyps detected at the time of endoscopy may represent either inflammatory polyps or adenomas. A relationship exists between schistosomiasis and colon cancer (367). Patients with heavy colonic infections do not respond well to chemotherapeutic regimens. They therefore undergo resection to treat the colonic manifestations of the disease.

Patients' tissues tend to be examined only when patients present with intussusception, mass lesions, or strictures that cause intestinal obstruction. Patients with chronic infections exhibit pronounced submucosal thickening due to fibrosis and lymphoid hyperplasia. Minute granulomas resembling tubercles are sometimes visible on the mucosal or peritoneal surfaces. Bilharzial tubercles also accumulate in the submucosa, where ova become trapped in narrow vascular channels. The granulomatous response causes single or multiple areas of focal or diffuse submucosal thickening accompanied by ulceration, hemorrhage, or stenosis, usually involving the rectum and left colon. The disease may grossly mimic CD or carcinoma. Extensive polyp formation may develop, especially in *S. japonicum* infections. Chronic schistosomiasis associated with a high parasitic burden may present as extensive (multiple) large (0.5 to 4.5 cm) serosal, distal mesenteric, and omental nodules (368), producing a lesion also referred to as the bilharzial pseudotumor or retroperitonitis (369). This condition mimics subserosal malignancy or diverticulosis. The cut surface of the lesions has a brown, crusty material reminiscent of fecaliths impacted within diverticula (369).

In the early stages of the infection one sees an acute proctitis and colitis accompanied by edema and hemorrhage as ova are discharged into the bowel lumen. Necrotic areas contain ova without a surrounding granulomatous reaction (370). Eggs in the mucosa and submucosa become surrounded by diffuse cellular infiltrates. In contrast, egg granulomas occur more frequently in the serosa and the muscularis propria (371). One may also encounter eggs in the bowel wall without any inflammation or fibrous reaction around them. Adult worms are sometimes found in mesenteric veins or venules. Morphologic features of chronic infection include localized or diffuse mucosal or serosal ulcers, strictures due to extensive granulomatous or fibrous reactions, pericolic masses, polyposis, and masses of granulation tissue.

The diagnosis rests on finding schistosomal eggs and the colitis they induce. The eggs measure 100 to 180 µm in length and about 70 µm in width. Those of *S. mansoni* are marginally longer than those of *S. japonicum* and exhibit a distinctive subterminal lateral spine. The shell has a light brown, translucent appearance and, in the case of *S. mansoni*, contains acid-fast material. This feature is diagnostically helpful if only the shell fragments are present.

**Anisakiasis and Strongyloidiasis**

Anisakiasis usually involves the stomach and small intestine; only rarely does it involve the colon (372). Colonic involvement is usually right sided, involving an intestinal segment measuring in length from 10 to 15 cm. The outlines of the worms can sometimes be seen, measuring approximately 0.7 mm in width and 12 to 20 mm in length. The intestinal wall surrounding the worms becomes markedly thickened (372). This parasite is discussed further in Chapters 4 and 6. *Strongyloides* infections occasionally involve the large bowel. Their clinical and pathologic features are discussed in Chapter 6.
**Trichuriasis (Whipworm)**

Trichuriasis, an intestinal infection of humans caused by *Trichuris trichuria*, ranks as the third most common intestinal parasite worldwide, infecting approximately 700 million persons. The organism is most prevalent in tropical and subtropical regions. In the United States, trichuriasis is the most common intestinal helminthic infection (373). It also is the most common helminthic infection in Americans returning from tropical areas. In temperate zones, the infection most frequently affects institutionalized, mentally retarded patients (374).

Adult whipworms are found in the large intestine with their anterior ends deeply embedded in the mucosa (Fig. 13.132). They measure 30 to 50 µm in length and possess a threadlike anterior two thirds with a stouter posterior third, producing a whiplike structure. The female lays about 5,000 eggs each day. The bile-stained eggs measure 50 to 54 × 22 to 23 µm and have a bipolar barrel shape with a three-layer shell. *T. trichuria* mature inside the egg. The eggs (Fig. 13.133) must incubate for at least 3 weeks in soil before the infective larvae emerge. *Trichuris* eggs are sensitive to desiccation and a combination of heat and low humidity is detrimental to their survival. Exposure to sunlight kills them. Infection occurs when ova are ingested in fecally contaminated food and water. After ingestion, eggs hatch in the small intestine and the larvae embed themselves in the intestinal villi. They then migrate to the large intestine, where they mature into adults in about 3 months.

The severity and consequences of *Trichuris* infections vary widely. Patients with mild infections usually remain asymptomatic. The parasites have particularly severe adverse health effects in young, malnourished populations. Patients often have infections with multiple organisms. Patients present with abdominal pain, diarrhea, nausea, vomiting, constipation, and...
Infectious Colitis

anorexia. Severe infections associate with mucous and bloody diarrhea, tenesmus, and abdominal pain. Rectal prolapse, volvulus, or intussusception complicates some infections (375). The diagnosis is usually made by finding ova in the stool.

The worms typically inhabit the cecum where they burrow into the mucosa, but they can live anywhere in the colon, appendix, or lower ileum (376). Mechanical injury caused by the adult worms induces atrophy, degeneration, and intestinal necrosis (374,375). If the worms obstruct the mouths of the crypts, they become dilated, containing mucus, fibrin, and acute inflammatory cells. Moderate to severe infections associate with subepithelial hemorrhage and inflammation consisting of lymphocytes, eosinophils, and plasma cells.
Interpretation of Colonic Biopsies

The ability to endoscopically visualize the entire mucosal surface of the large bowel and to biopsy or cytologically sample normal- and abnormal-appearing areas allows clinicians to diagnose and manage colorectal diseases. Biopsies yield information concerning disease patterns, distribution, extent and/or severity, acuity versus chronicity, clinical state of remission or relapse, and complications. In one study, interpretation of mucosal biopsies yielded a positive diagnosis in 31% of patients with chronic diarrhea who did not have a definitive diagnosis prior to the biopsy (85). The most common diagnoses were IBD and microscopic colitis, although cases of ischemia and infection were also first diagnosed on the biopsy (85).

Optimal biopsy evaluation can only occur when careful consideration is given to the clinical, historical, endoscopic, radiographic, microbiologic, and other available patient data. Once tissue has been removed, it may be cultured, examined histologically or ultrastructurally, or submitted for biochemical analysis. Not only can it be examined in routine hematoxylin and eosin (H&E) sections, but it may also be submitted to a battery of histochemical and immunocytochemical stains as well as molecular biologic techniques, many of which can be performed on formalin-fixed, paraffin-embedded materials. One may also re-embed colonic biopsies in which there is a discrepancy between the clinical impression and the histologic findings. In so doing new diagnoses can be made in up to 31% of biopsies (86). In our opinion, this is not likely to be cost effective, especially since in most cases the new diagnosis was that of a small hyperplastic polyp (86), a lesion of little clinical consequence.

P.767

FIG. 13.53. Stercoral ulcers and erosions. A: An isolated erosion only into the superficial submucosa. B: There is acute and chronic inflammation and glandular regeneration. C: Gross appearance of a perforated stercoral ulcer viewed from the outside. Note the serosal adhesions.

One of the most common uses of the colorectal biopsy is to determine the etiology of a colitis or proctitis, which may share overlapping clinical, radiologic, or pathologic features with other disorders (Table 13.2). In the best of circumstances, analysis of the biopsy specimen, in conjunction with an interpretation of the clinical data (Table 13.3), will yield a definitive diagnosis. More often, however, the biopsy does not provide a specific diagnosis, but rather narrows down the differential diagnosis. The histologic features may suggest an inflammatory condition and provide knowledge concerning the severity of the underlying lesion or the extent of disease, allowing one to correlate the clinical impression with the histologic findings. One may also be able to diagnose the presence of specific neoplasms or the presence of a treatable organism.

Mucosal biopsy interpretation can be difficult due to normal architectural variants, effects of the biopsy procedure, and lack of knowledge of the dynamic mucosal events accompanying mucosal repair. Some of the mucosa features that are often unappreciated are the following:
Interpretation of Colonic Biopsies

- Crypt branching is normal in the area of the innominate grooves.
- There is normally a mononuclear cell infiltrate in the upper mucosa that is sometimes referred to as a *physiologic infiltrate*. It is densest in the cecum (a site of bacterial stasis) and least in the rectum.
  The crypts are normal (87).
- In general, the lamina propria cellularity is greatest in the cecum and ascending colon and it decreases distally.
- Mild crypt irregularity in the rectum is not considered to be clinically significant.
- While there are normally five intraepithelial lymphocytes per 100 colonocytes, the number is increased in the cecum (perhaps secondary to the stasis that occurs there) and there are abundant intraepithelial lymphocytes in the epithelium overlying lymphoid follicles.
- A previously inflamed bowel may return to a histologically normal appearance. This is especially important in evaluating biopsies from patients with ulcerative colitis.

It is important to examine mucosal biopsies in a standardized way in order to determine that they are abnormal and to establish a probable diagnosis. A systemic analysis should include evaluation of the features listed in Table 13.4. The most common pattern one sees when evaluating a biopsy for colitis are diffuse and focal active colitis or proctitis without other specific features. The pathology report should indicate whether features are acute, chronic, or chronic active and whether the changes are focal or diffuse. Specific features such as the presence of microorganisms, granulomas, or abnormal infiltrates should be noted. An attempt should be made to establish the etiology of the changes since “diagnoses” such as nonspecific colitis are of little help to the clinicians who already know that the patient has some form of colitis.

### TABLE 13.2 Differential Diagnosis of Colitis

<table>
<thead>
<tr>
<th>Features</th>
<th>Infectious</th>
<th>Antibiotic Associated</th>
<th>Ischemic</th>
<th>Ulcerative Colitis</th>
<th>Crohn Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Acute onset</td>
<td>Recent antibiotic use ± abdominal pain</td>
<td>Concurrent ischemia elsewere; Poor cardiovascular status</td>
<td>Bloody diarrhea</td>
<td>Perianal disease</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>Diarrhea</td>
<td>Segmental distribution of disease</td>
<td>Toxic megacolon</td>
<td>Fistulas</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms</td>
<td>Clostridium difficile organism</td>
<td>Diffusely ulcerated rectal mucosa decreasing in severity as one progresses proximally; extraintestinal disease</td>
<td>Extraintestinal symptoms</td>
<td>Associated small bowel disease</td>
</tr>
<tr>
<td></td>
<td>Watery/bloody diarrhea</td>
<td>or toxin detected</td>
<td></td>
<td></td>
<td>Skip lesions</td>
</tr>
<tr>
<td></td>
<td>Positive cultures and/or serology</td>
<td>Membranes seen at endoscopy</td>
<td></td>
<td></td>
<td>Extraintestinal disease</td>
</tr>
<tr>
<td></td>
<td>Travel to high-risk areas</td>
<td></td>
<td></td>
<td></td>
<td>Rectal sparing</td>
</tr>
<tr>
<td>Radiographic</td>
<td>May resemble ulcerative colitis</td>
<td>Segmental or limited colitis with or without pseudomembranes Edema</td>
<td>Segmental distribution Thumbprinting with reversion to normal or progression to stricture Rectal involvement rare</td>
<td>Backwash ileitis Pseudopolyps Diffuse involvement starting in rectum and progressing proximally with decreasing severity</td>
<td>Segmental disease with skip lesions Small bowel involved Fistulace/fissures Ulcers/cobblestoned appearance Strictures</td>
</tr>
</tbody>
</table>

...
Interpretation of Colonic Biopsies

<table>
<thead>
<tr>
<th>Pathologic</th>
<th>Edema prominent</th>
<th>Polymorphonuclear leukocytes</th>
<th>Crypt inflammation</th>
<th>No crypt distortion</th>
<th>No basal plasmacytosis ± granulomas</th>
<th>Low degree of vascularity</th>
<th>Acute inflammation ± pseudomembranes</th>
<th>Superficial erosions</th>
<th>Focal lesions can resemble ischemia</th>
<th>“Volcanic” eruptions of exudates</th>
<th>Continuous involvement</th>
<th>Edema rare</th>
<th>Inflammation limited to mucosa and submucosa</th>
<th>Crypt abscesses</th>
<th>Basal plasmacytosis</th>
<th>No granulomas</th>
<th>Pseudopolyps</th>
<th>Goblet cell dysplasia</th>
<th>High degree of vascularity</th>
<th>Abnormal mucosal architecture</th>
<th>Segmental disease with skip lesions</th>
<th>Fissures, fistulae</th>
<th>Granulomas</th>
<th>Transmural inflammation</th>
<th>Aphthous ulcers</th>
<th>Pseudopolyp</th>
<th>Gland distortion</th>
<th>Basal plasmacytosis</th>
</tr>
</thead>
</table>

**TABLE 13.3 Information That Aids Pathologists Interpreting Colorectal Biopsies**

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Patient sex</th>
<th>Ethnicity</th>
<th>Endoscopic findings</th>
<th>Country of domicile</th>
<th>Travel history</th>
<th>Reason for the biopsy</th>
<th>Drug use</th>
<th>History of associated diseases</th>
<th>AIDS</th>
<th>Neoplasias</th>
<th>Infections</th>
<th>Metabolic diseases</th>
<th>Immune deficiencies</th>
<th>Prior surgery</th>
<th>Cardiovascular disease</th>
<th>Allergies</th>
<th>Diverticulosis</th>
<th>Polyposis syndromes</th>
</tr>
</thead>
</table>
hyperplasia. **Chronic active colitis** is present when both mononuclear cells (lymphocytes and plasma cells) and neutrophils infiltrate the mucosa (Fig. 13.56). The term **active inflammation** implies acute inflammation. The terms **inactive** or **quiescent** indicate chronic conditions that are in remission.

### TABLE 13.4 Evaluation of the Colonic Mucosal Biopsies

1. **What is the overall architecture?**
   - Is there architectural distortion?
     - Branched crypts
     - Atrophy
     - Loss of parallel arrangement of the crypts
     - Metaplasia
     - Widening between the crypt bases and the muscularis mucosae
   - Are there granulomas?
   - Is there an invasive neoplasm?
   - Is the inflammation acute or chronic?
   - Is the inflammation diffuse or focal?
   - Does the inflammation preferentially affect any part of the mucosa?
     - Surface
     - Basal mucosa
     - Superficial mucosa
     - Lamina propria
     - Crypts

2. **Is there inflammation?**
   - Is there architectural distortion?
     - Branched crypts
     - Atrophy
     - Loss of parallel arrangement of the crypts
     - Metaplasia
     - Widening between the crypt bases and the muscularis mucosae
   - Are there granulomas?
   - Is there an invasive neoplasm?
   - Is the inflammation acute or chronic?
   - Is the inflammation diffuse or focal?
   - Does the inflammation preferentially affect any part of the mucosa?
     - Surface
     - Basal mucosa
     - Superficial mucosa
     - Lamina propria
     - Crypts

3. **What is the appearance of the epithelium?**
   - Is it ulcerated?
   - Are there microorganisms attached to its surface?
   - Does it contain viral inclusions?
   - Is it covered by a pseudomembrane?
   - Is there cryptitis?
   - Is there intraepithelial lymphocytosis?
Interpretation of Colonic Biopsies

- Are there unusual cell types?
  - Paneth cells?
  - Increased endocrine cells?
  - Pyloric metaplasia?
- Is there increased apoptosis?
- Is there macrocytosis?
- Is there separation from the basement membrane?
- Is their subepithelial collagenization?
- Is there dysplasia?
- Is there surface injury?

4. What is the appearance of the lamina propria?
   - Is the cellularity normal? (If not, what cell types are present?)
   - Are there abnormal deposits?
   - Are the vessels normal?
   - Are there viral inclusions?
   - Are there parasites?
   - Are there granulomas or histiocytic collections?
     - Caseating or noncaseating?
     - Any organism present?
     - Is there a storage disease?
   - What is the appearance of the submucosa (if present)?
     - Are the vessels normal?
     - Are there infiltrates?
     - Are there neoplasms or endometriosis?
     - Is there amyloid present?
     - Is there displaced epithelium?
**Interpretation of Colonic Biopsies**

**FIG. 13.54.** Mild versus severe injury. *A:* Biopsy from a patient with toxigenic *Escherichia coli* infection shows only mild edema and mild superficial epithelial loss. These changes contrast with those seen in *B* in *Clostridium difficile* infection with marked epithelial necrosis, acute inflammatory infiltration, and fibrin thrombi.

Other architectural abnormalities include *crypt atrophy* when the crypts appear shortened and more widely spaced (Fig. 13.57) and sometimes at a greater distance from the muscularis mucosae than normal, and when villiform transformation has occurred at the surface. *Branched crypts* are usually defined as the presence of two or more bifurcated crypts in an otherwise well-oriented section (Fig. 13.58). *Superficial inflammation* is defined as inflammation limited to the upper third of the mucosa, whereas *basal plasmacytosis* consists of lymphocytes and plasma cells limited to the lower third of the mucosa (Fig. 13.59). *Nodular lymphoid hyperplasia* is present when there are collections of lymphocytes, with or without germinal centers located between the muscularis mucosae and the crypts (Fig. 13.60). Usually at least two aggregates should be present to be considered abnormal. *Basal lymphoid hyperplasia* is defined as an increased number of lymphocytes at the crypt bases without a nodular configuration (Fig. 13.59). *Isolated giant cells* contain multiple nuclei and homogeneous fine granular cytoplasm. These occur singly without associated epithelioid cells. When a focus of granulomatous inflammation or giant cells is detected, serial sections can be cut to determine whether they are in continuity or proximity with a disrupted crypt and therefore represent a *mucin granuloma*. *Epithelioid granulomas* are defined as discrete collections of epithelioid cells with or without accompanying giant cells and without caseating necrosis or foreign bodies. They should not be in continuity with or proximity to a perforated crypt (Fig. 13.61). A *microgranuloma* is defined as a collection of epithelioid cells small enough to be interposed between two crypts without distorting their architecture, without giant cells (Fig. 13.61). *Goblet cell mucus depletion* is defined as marked reduction or absence of goblet cell mucus (Fig. 13.62). *Reactive epithelial hyperplasia* is defined by the presence of elongated, crowded, stratified nuclei or by markedly enlarged, hyperchromatic, vesicular nuclei. The crypts appear bluer than normal.
FIG. 13.55. Paneth cells in the left colon.

FIG. 13.56. Mixed cell infiltrates in a *Salmonella* infection. **A:** Neutrophils infiltrate the crypts and lamina propria. There are also increased numbers of mononuclear cells in the edematous lamina propria. **B:** Higher magnification showing a crypt abscess and increased mononuclear cells.
Interpretation of Colonic Biopsies

**FIG. 13.57.** Colonic atrophy. The glands are widely spaced and differ in diameter. The distance from the base of the glands to the muscularis mucosae is widened.

_Focal active colitis_ (FAC) is a term used to describe the isolated finding of focal infiltration of the colonic epithelium by neutrophils. This can vary from one focus of cryptitis in a single colonic biopsy to multiple foci of cryptitis scattered throughout multiple colonic biopsies (89). Often there is increased inflammation in the lamina propria surrounding the inflamed crypts. Up to 13% of patients are ultimately found to have Crohn disease. Nearly half the patients have infectious colitis and in about a quarter of cases the finding had no clinical significance (90,91). Those cases without any clinical significance may have focal inflammation secondary to the bowel prep. However, children with FAC have a higher likelihood of subsequently developing Crohn disease (27.6%) compared with adults. FAC in children may also be the result of infectious colitis and rare patients have ulcerative colitis, allergic colitis, or Hirschsprung disease. Patients with FAC that does not correlate with symptoms or the ultimate clinical diagnosis are said to have idiopathic focal active colitis, a finding in 27.6% of patients in one study (89). Unfortunately, one cannot predict which patients will fall into the idiopathic category and which will be ultimately diagnosed with IBD or some other process (89).
**FIG. 13.58.** Chronicity in colitis. The cross sections of the glands show marked variability in their diameters. Several of the crypts have glandular budding (arrows) with smaller cross-sectional lumens lying adjacent to larger ones without intervening lamina propria.

**FIG. 13.59.** Superficial versus basal inflammation. A and B show inflammation that is more prominent in the superficial mucosa. A: The inflammation is acute in nature and is superimposed on branched glands. B: The patient has collagenous colitis with a mild increase in the lamina propria mononuclear cells in the upper one half of the mucosa and an increased collagen table. Inflammatory cells are also present within the epithelium. C: Collections of histiocytes separate the bases of the colonic glands from the underlying muscularis mucosae. D: From a patient with ulcerative colitis. A bandlike infiltrate of mononuclear cells separates the bases of the glands from the underlying muscularis mucosae.
FIG. 13.60. Nodular inflammation. Follicular proctitis. Note the presence of prominent lymphoid follicles both in the mucosa and the underlying submucosa. The epithelium overlying the nodule of lymphoid hyperplasia becomes attenuated and somewhat distorted.

Changes Induced by Bowel Preparations, Instrumentation, and Biopsy

In order to effectively interpret diagnostic large intestinal biopsies, one must be aware of the changes that result from the bowel preparation and/or the biopsy procedure. Preparatory procedures may flatten the surface epithelium, decrease the number of goblet cells, deplete the goblet cell mucus, slightly increase the number of neutrophils in the superficial lamina propria, or cause edema (Figs. 13.63 and 13.64) and focal hemorrhage. Hypertonic phosphate enemas, such as Fleet enemas and bisacodyl laxatives, may mimic mild colitis with surface epithelial vacuolization, subepithelial neutrophilic infiltration (92), sloughing, goblet cell mucin depletion, increased crypt mitoses, margined polymorphonuclear cells, lamina propria edema, and erythrocytic extravasation into the lamina propria (92,93). These changes resolve within a week (94). Crypt abscesses or inflammation rarely extend to more than the superficial zones of the lamina propria.
FIG. 13.61. Granuloma. Mucosal biopsy from a patient with Crohn disease showing the presence of a small, compact, sarcoidlike granuloma (arrows).
FIG. 13.62. Mucin depletion. A regenerating branched gland is present. The epithelium at the base of the gland is hyperchromatic. The mucin droplets are small. The arrow indicates an area of denuded mucosa.

Today most gastroenterologists use osmotic enema preparations, which cause lamina propria edema without inflammation (Fig. 13.64) (95). The crypts appear more widely separated than normal and the distance from the base of the crypts to the muscularis mucosae widens. The endoscopy and biopsy also sometimes cause focal red cell extravasation into the lamina propria.

Artifacts, including crushing, glandular telescoping, and cautery artifacts in biopsy specimens, can interfere with one's ability to interpret certain lesions (Fig. 13.65). Sometimes the cautery artifact may be so severe that it may render the biopsy impossible to read. Conversely, the presence of cautery artifact can be useful in recognizing the resection margin of polypectomy specimens, particularly when the polyps are adenomas containing carcinoma.
**FIG. 13.63.** Enema effects. **A:** Mild changes consist of mucin depletion. **B:** The lamina propria is edematous. **C:** Telangiectasia and mild local mucosal hemorrhage.
Intestinal Changes Associated with Immunologic Injury

HIV Infections

Epidemiology

AIDS results from infection by HIV. It associates with a number of defining abnormalities (Table 13.25). More than 30 million people are infected with HIV-1 worldwide. Epidemiologically, the major risk groups for developing AIDS vary depending on geographic locale. In Africa and Asia, the major risk group is sexually active heterosexuals; women are more often infected than men (472,473). In contrast, in the United States, over 70% of cases affect men having sex with men. Another 15% develop in intravenous drug users. Other high-risk groups include prostitutes, hemophiliacs, children born to HIV-positive mothers, patients transfused with infected blood or blood products, and heterosexual contacts of any of the above groups (474). HIV-infected mothers pass the virus transplacentally, at the time of delivery through the birth canal or through breast milk. AIDS especially affects Hispanics and African Americans (475). The AIDS patient population in the United States is disproportionately male, black, and poor (476). Women represented 18% of all cases in the United States in 1994. Sexual transmission is now the dominant route by which women become infected (477). Substantial declines have occurred in AIDS incidence and death in recent years (475), probably due to an increased awareness in at-risk populations and the introduction of antiretroviral therapies.

Since 1996, profound changes have taken place in the epidemiology, clinical presentation, complications, and management of HIV infections, largely due to the introduction of highly active antiretroviral treatment (HAART). As a result, gastrointestinal complications have dramatically decreased and there has been a substantial decline in the number of opportunistic infections associated with the infection (478). However, while HAART is effective in suppressing opportunistic infections, the antiretroviral medications cause GI side effects in up to 10% of cases (479). Currently, drug-induced side effects and nonopportunistic diseases are among the most common causes of GI symptoms in HIV-positive patients (478,480).

Etiology

Two HIVs exist: HIV-1 and HIV-2; both belong to the lentivirus family of nononcogenic retroviruses. HIV-1 is the predominant virus in the United States, Europe, and eastern Africa. HIV-2 infection predominates in parts of western Africa. Many fewer AIDS cases develop in HIV-2–infected than in HIV-1–infected populations. Viral transmission is similar for both viruses, except that perinatal transmission occurs less frequently in HIV-2 infections. HIV-2 also has a longer latency period before AIDS appears, the course is less aggressive, and the mortality rate is less than in HIV-1 infection. HIV-2–infected patients typically have a lower viral load and higher CD4 counts than HIV-1–infected individuals. HIV easily mutates leading to the emergence of new viral strains that can resist immune attack or drug therapy or alter the clinical or histopathologic features of the disease. The number of active replicating viruses is proportional to the number of CD4+ lymphocytes.

The virion contains two single RNA strands, structural proteins, and the enzymes required for viral replication. HIV genes encode core proteins (GAG), reverse transcriptase, protease, an endonuclease (Pol), and envelope glycoproteins (Env). At least five other genes exert regulatory functions that may affect viral pathogenicity: vif, tat3, rev, nef, and vpr. The viruses use the enzyme reverse transcriptase to transcribe viral RNA into proviral DNA in host cells. The proviral DNA resides in the cells during viral latency. The lipid envelope surrounding the viral core derives from the host cell surface as the virions bud from the infected cell. As a result, this lipid envelope contains host membrane protein remnants as well as the viral envelope glycoprotein gp120 and the transmembrane protein gp41, two proteins involved in viral attachment and entry into host cells (481).

The CD4 protein and its coreceptor, CXCR4, and possibly CD26 on helper T-cell surfaces, serve as high-affinity receptors for the viral envelope gp120, mediating rapid, firm, cellular attachments. T-cell trophic viruses requiring CXCR4 for entry are termed X4 viruses (482).

Some HIV strains (named R5 viruses to reflect their coreceptor requirement) bind to macrophages via the β chemokine...
Intestinal Changes Associated with Immunologic Injury

receptor CCR5 (483,484,485). Genetic polymorphisms in the chemokine receptor genes that mediate HIV disease progression affect disease expression (486). Cells with an absent or reduced CCR5 expression or a CCR5 mutation have a reduced sensitivity to HIV infection (487), and these cells are resistant to HIV infection even in the face of a high risk of infection (487).

Pathophysiology

The most common mode of HIV-1 infection is sexual transmission through the anogenital mucosa. Monocytes, macrophages, dendritic cells, and CD4+ T lymphocytes are the primary viral targets (481). The virus is initially acquired via one of the following: Rectal mucosal tears, M cells overlying lymphoid follicles, direct infection of the rectal epithelium, or infection of lamina propria dendritic cells (488) subjacent to the anorectal epithelium. HIV-1 viruses adhering to the luminal membranes of rectal M cells are endocytosed and delivered to

intraepithelial lymphocytes, macrophages, and the mononuclear cells of the lymphoid follicles (489). The infected cells fuse with CD4+ lymphocytes and spread into deeper tissues. Within 2 days of the initial infection, viruses can be detected in draining internal iliac lymph nodes. Shortly thereafter, systemic dissemination occurs.

The gastrointestinal mucosa serves as an important reservoir for HIV, with lamina propria macrophages frequently harboring the virus (489,490). The gastrointestinal epithelium and lamina propria are also a rich source of CD4+ T cells. There are also abundant CD4+ T cells in the regional lymph nodes. The intestinal mucosa becomes profoundly and selectively depleted of CD4+ cells within days of the infection, even before similar changes occur in peripheral lymphoid tissues. In contrast, CD8+ T cells increase early in the infection and then display increased levels of activation antigens and abnormal MHC-restricted HIV-specific and -nonspecific cytotoxic abilities. A specific increase in apoptotic CD8+ T cells eventually leads to their depletion (490). A nearly complete absence of CD4+ intraepithelial lymphocytes and decreased CD11+ intraepithelial lymphocytes characterize the intestinal mucosa of severely ill AIDS patients (491).

Host factors also play a major role in the pathogenesis of HIV-related disease. A complex network of endogenous cytokines provides a delicate balance between HIV induction and suppression. The β-chemokines RANTES, MIP-1α, and MIP-1β act as suppressors of macrophage-trophic HIV strains (492) and elevated β-chemokine expression levels probably help control HIV load and replication in individuals who do not progress to AIDS (493).

Clinicopathologic Features

Acute HIV-1 infection is a transient symptomatic illness associated with high viral titers and a robust immunologic antiviral response (494). Signs and symptoms of an acute HIV-1 infection occur within days to weeks of the initial viral exposure, and include the first gastrointestinal symptoms. The most common systemic signs and symptoms include fever, fatigue, a rash, headache, lymphadenopathy, pharyngitis, myalgia, arthralgia, aseptic meningitis, retro-orbital pain, weight loss, depression, GI distress, night sweats, and oral or genital ulcers. The acute illness lasts for a few days to more than 10 weeks, but averages <14 days in length (495). Since the early signs and symptoms are nonspecific, acute HIV-1 infections are frequently confused with other viral illnesses. Initial laboratory studies may show lymphopenia and thrombocytopenia, but atypical lymphocytes are infrequent. Standard serologic tests only become positive 3 to 4 weeks after the initial infection (496). Severe and prolonged symptoms correlate with rapid disease progression (497). After the initial infection, there is a rapid viremia with widespread viral dissemination, seeding of lymphoid organs (498), and entrapment by follicular dendritic cells (499). Individuals with the highest viral loads have the highest rates of disease progression (500).

AIDS develops after a long latent period, averaging 7 to 10 years following the initial infection. During the latency period, the immune system remains relatively intact, preventing most secondary infections, but viral replication actively continues in lymphoid tissues. A CD4 count <500/mL heralds the development of clinical AIDS. A drop to <200/mL defines AIDS and indicates a high probability of developing AIDS-related infections, neoplasms, and death.

Diarrhea affects 30% to 50% of North American and European and 90% of African HIV-infected patients (472,501). AIDS patients who present with diarrhea have a greater degree of immunosuppression than those without diarrhea, predisposing the gut to the infections that contribute to morbidity and death. Diarrhea occurred in up to 90% of patients in the pre-HAART era.
More recent data suggest that diarrhea is still a frequent complaint, but is more commonly attributable to drug-induced injury or non–HIV-related pathologic processes. Diarrhea in HIV infected patients results from the presence of (a) enteric pathogenic infections, (b) complications of the drugs used to treat the infection, (c) the presence of AIDS enteropathy or AIDS gastropathy, (d) AIDS-related motility disturbances, and (e) tumor development. Often it is impossible to attribute any AIDS-associated gastrointestinal sign or symptom to a specific underlying cause, since patients usually have numerous intestinal pathologies (Table 13.26). The coccidian parasites Cryptosporidium parvum, Isospora belli, and Cyclospora and the microsporidia account for at least 50% of cases of persistent diarrhea in the industrialized and developing world with major contributions from Mycobacterium avium complex (MAC) and other bacteria, as well as CMV infection (502). These infections are all discussed in Chapter 6.

<table>
<thead>
<tr>
<th>TABLE 13.26 Intestinal Lesions in AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
</tr>
<tr>
<td>Spirochetosis</td>
</tr>
<tr>
<td>Salmonella typhimurium</td>
</tr>
<tr>
<td>Shigella species</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Mycobacterium avium-intracellulare</td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Campylobacter species</td>
</tr>
<tr>
<td>Aeromonas hydrophilia</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Chlamydial species</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td>Ebstein-Barr virus</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Cyclospora species</td>
</tr>
<tr>
<td>Enterobius vermicularis</td>
</tr>
<tr>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Toxoplasma</td>
</tr>
<tr>
<td>Taenia saginata</td>
</tr>
<tr>
<td>Isospora belli</td>
</tr>
<tr>
<td>Microsporidia group</td>
</tr>
<tr>
<td>Leishmania species</td>
</tr>
<tr>
<td>Strongyloides</td>
</tr>
<tr>
<td>Blastocystis hominis</td>
</tr>
</tbody>
</table>
**Fungi**
- *Candida*
- *Histoplasma*
- *Blastocystis hominis*
- *Pneumocystis carinii*
- *Aspergillus fumigatus*
- *Cryptococcus neoformans*

**HIV enteropathy**
**HIV ganglioneuritis**
**Tumors**
- *Kaposi sarcoma*
- *Lymphomas*

**Drug effects**

The gastrointestinal manifestations of HIV change according to the stage of the infection. Early and intermediate gastrointestinal manifestations include diarrhea without detectable pathogens (AIDS enteropathy) and low-grade bacterial overgrowth. Well-established infections, particularly parasitic infections and viral infections, characterize late-stage disease. Severe recurrent systemic and/or gastrointestinal parasitic, viral, fungal, and protozoal infections along with the development of neoplasms and other HIV-associated pathologies often result in a fatal outcome.

Biopsies performed on AIDS patients with gastrointestinal symptoms are done to determine whether the gut is directly affected by the AIDS virus (e.g., AIDS enteropathy) or whether complications such as opportunistic infections or the development of neoplasia (e.g., Kaposi sarcoma, lymphoproliferative disorders) have developed.

**HIV Enteropathy**

*HIV enteropathy*, also known as AIDS enterocolitis or AIDS enteropathy in its broadest sense, refers to gastrointestinal damage resulting from an HIV infection. A more specific definition of AIDS enteropathy is the presence of chronic (≥1 month’s duration) diarrhea, malabsorption, and wasting without evidence of an enteric infection after complete evaluation (503).

Multiple enteric pathogenic bacteria also cause diarrhea in AIDS patients. Patients may have one or more infections, including *C. jejuni* or *Campylobacter fetus*, *C. difficile*, *Enterobacter aerogenes*, *Salmonella*, *S. flexneri*, *Klebsiella*, and other Gram-negative bacilli. The most common infection found in the large bowel is CMV followed by *M. avium*. Patients may also have fungal or parasitic infections (Table 13.26). The degree of inflammation seen in AIDS enteropathy correlates with mucosal levels of p24 antigen and clinical symptoms.

Proposed explanations for HIV-associated enteropathy include any or all of the following: (a) the presence of an occult enteric infection (504), (b) the direct effect of the virus on the gastrointestinal epithelium, (c) the indirect effects of a localized immunologic dysfunction, (d) an immune-mediated enterocolitis, (e) a drug-induced change, or (f) an effect of some of the coexisting nutritional deficiencies. Arguments in favor of a direct HIV-related viral cytopathic effect include the identification of the virus in epithelial cells by in situ hybridization analysis in the absence of other pathogens.

The colonoscopic mucosal pattern shows diffuse abnormalities consisting of contact bleeding, edema, superficial ulcerations, exudates, and/or loss of the normal vascular pattern. The features are nonspecific and diagnosis is by exclusion of other pathologies, especially opportunistic infections.

One often sees nonspecific intestinal inflammation in AIDS-associated enteropathy. It consists of degranulating eosinophils, activated lymphocytes, and plasma cells with increased numbers of intraepithelial and lamina propria T lymphocytes (505). Early in the disease, the lymphocyte density is normal but lymphoid depletion develops in patients suffering from full-blown AIDS. In this latter phase, macrophage and eosinophilic infiltrates are prominent and apoptosis is common. In end-stage disease, opportunistic infections are present together with eosinophilia, neutrophilia, apoptosis, and tissue injury. Either the mucosal T-cell alterations in AIDS or the direct viral infection of the enterocytes may alter mucosal architecture.
Intestinal Changes Associated with Immunologic Injury

producing an enteropathy or colopathy characterized by epithelial damage and crypt hyperplasia. The epithelial mitotic index varies with respect to disease duration and severity; they increase early and then decrease.

Colonic biopsies show a more or less normal architecture with nonspecific inflammatory changes with a mixed cell infiltrate, including intraepithelial lymphocytosis, focal crypt epithelial cell apoptosis, endothelial tubuloreticular bodies, lymphocytes, and monocytes. Colonic biopsies show changes that sometimes resemble microscopic colitis (Fig. 13.155). HIV nucleic acid is identified by in situ hybridization. The degree of inflammation correlates with mucosal levels of p24 antigen and clinical symptoms, suggesting an etiologic role for HIV (506). Other changes include atrophy of single crypts coexisting with crypts that appear regenerative (Fig. 13.156). It is unclear as to whether this results from the infection itself or from a combination of the infection and the medications that the patients receive. The crypts superficially resemble dilated lymphatics. However, lymphatics are not present in the mucosa, and closer examination discloses that the cystic spaces in the lamina propria are lined by variably flattened epithelium; often, the lumens contain apoptotic cells. Vascular calcification with intimal fibrosis, fragmentation of the internal elastic lamina, and fibrosis of the media with luminal narrowing, changes designated as AIDS arteriopathy, develop in the small to medium-sized systemic arteries including those in the gastrointestinal tract and within the mesocolon. This may lead to secondary ischemic changes and mucosal ulceration. Neuromuscular alterations are common (Fig. 13.157).

FIG. 13.155. Colonic biopsy in an AIDS patient with changes superficially resembling those found in patients with microscopic colitis. However, the epithelium appears regenerative and shows increased basophilia. Other specific changes are absent.
FIG. 13.156. Colonic crypt atrophy in an AIDS patient. A: Note the regenerative glands as well as what appear to be cystically dilated spaces (stars). B: One of these spaces seen at higher magnification (star). The left side of the space shows residual epithelium. On the right side of the space one sees flattened cells whose identity might be difficult to interpret in the absence of special stains or in the absence of the more cuboidal epithelium seen on the left side. The glandular lumen contains apoptotic debris.

One may also see small xanthomas that superficially may suggest the presence of MAC or Whipple disease, but these are negative for microorganisms. Small xanthomatous lesions are relatively common in the colon and probably represent nonspecific responses to mucosal damage resulting from many etiologies. In our experience, it is always wise to stain biopsies containing these xanthomas for the presence of mycobacteria and fungi, especially if the xanthomatous foci are prominent.
Intestinal Changes Associated with Immunologic Injury

FIG. 13.157. Neuromuscular changes in AIDS. A: The myenteric ganglia often demonstrate mild nonspecific vacuolar degeneration. B: The external muscle coat often shows marked atrophy of individual myofibers. This may result either from the viral infection itself or from treatment.

The changes of AIDS enteropathy may resemble microscopic colitis, celiac disease, or GVHD. The clinical setting, HIV testing, and antigliadin or antiendomysial antibody status serve to distinguish among these possibilities.

Treatment

A recent panel of experts recommended that immediate therapy be considered for persons with acute HIV infections (507). Early treatment restores the virus-specific cellular immune responses required to control the early viremia (508) so that they may limit the extent of viral dissemination, restrict damage to the immune system, protect antigen-presenting cells, and reduce the chance of disease progression. However, there are drawbacks to the institution of such therapy, and recent trends are leaning toward more conservative treatment with HAART. Recent recommendations are that HAART be instituted at a time when CD4 counts suggest an immediate risk of progression to AIDS, or in patients at risk of dying (509). Risks of early therapy include the adverse effects of these drugs on the quality of the patient's life as well as potential serious side effects that may result from drug toxicity. In addition, the duration of the beneficial effects of HAART is currently unknown. Previously treated patients are known to experience a poorer response to reinstitution of HAART, perhaps as a result of acquisition of some degree of drug resistance (510). Updates for treatment guidelines are available from the World Wide Web site of the HIV/AIDS Treatment Information Service (ATIS) at http://www.hivatis.org.

Graft-Versus-Host Disease

GVHD most commonly follows bone marrow or solid organ transplantation, and represents the response of immunocompetent donor cells to the histocompatibility antigens of the recipient. Less commonly, it complicates maternal–fetal cell transfer in immunodeficient children (511) or transfusion of nonirradiated cells and blood products (512,513). Although GVHD may affect any organ, intestinal GVHD is particularly important because of its frequency, severity, and impact on the general condition of the patient. The incidence of GVHD is possibly higher in African Americans than in other individuals (514).

Acute GVHD occurs in three phases: Epithelial cell injury caused by the conditioning regimen; activation of donor T cells by antigens presented by the recipient's dendritic cells; and apoptosis induced by activated T cells, cytokines, and cells of the innate immune system (520). HLA disparities between donor and recipient are the major predisposing factor. Other factors include the ages of the donor and the recipient, sex mismatch (female donor and male recipient), mismatched minor histocompatibility antigens in HLA-matched transplants, the source and dose of the transplanted hematopoietic stem cells, the intensity of the preparative regimen, and prophylaxis against GVHD or T-cell deletion of the graft (521,522).

CD8+, CD3+, and TiA1+ cytotoxic T cells mediate epithelial cell death (515,516). CD8 cells recognize class II MHC-restricted antigens producing the lymphokines that lead to the development of the enteropathy associated with GVHD (517). Apoptosis may occur through the Fas/Fas ligand pathway (518). Patients who are homozygous for a common variant in the promoter region of the interleukin-10 gene are at a low risk for GVHD after stem cell transplantation (519).

The endoscopic appearance of the mucosa in acute GVHD ranges from edema and erythema to ulcers and mucosal sloughing (523). Mucosal biopsy provides a sensitive test for detecting GVHD. Apoptotic bodies are the sine qua non of the diagnosis. However, the biopsy should not be done during the first 3 weeks of immunosuppressive therapy because all patients will show some inflammation in the immediate posttransplant period. The lesions of acute GVHD range from necrosis of individual crypt cells to total mucosal loss (Table 13.27). Apoptotic bodies collect at the crypt bases in the intestine, and in the neck region of the gastric glands (Fig. 13.158). The crypt bases contain vacuolated cells with karyolytic debris in cellular lacunae, producing "popcorn lesions." The cells are also sometimes called "exploding crypt cells." As a result, the base of the glands may appear dilated and contain apoptotic debris. As the lesions evolve, an entire crypt may drop out, creating single crypt loss. Acute
Intestinal Changes Associated with Immunologic Injury

Inflammatory bowel disease and neutrophilic infiltrates accompany the apoptosis and crypt dropout. The mucosal architecture is progressively lost with ulceration, mucosal denudation, and submucosal edema. The epithelium may appear degenerated and cuboidal. In some cases, the epithelium appears as a flattened monolayer. Ulcer healing leads to fibrosis and stricture formation. The lamina propria contains a relatively sparse mononuclear cell infiltrate.

### TABLE 13.27 Histologic Grading of Graft Versus Host Disease

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild necrosis of individual crypts</td>
</tr>
<tr>
<td>2</td>
<td>Crypt abscesses and crypt cell flattening</td>
</tr>
<tr>
<td>3</td>
<td>Crypt dropout</td>
</tr>
<tr>
<td>4</td>
<td>Flat mucosa</td>
</tr>
</tbody>
</table>

In chronic GVHD, one sees segmental lamina propria fibrosis and submucosal fibrosis extending to the serosa. These lesions occur throughout the entire length of the gut from the esophagus to the colon. Occasional patients pass ropy, tan material resembling strands of sloughed mucosal tissue, known as mucosal casts, per rectum. The composition of the material is rarely clear-cut. It usually contains fibrin, neutrophils, cellular debris, bacteria, or fungi, and very little identifiable tissue (524). The presence of free intestinal epithelium may be confirmed by immunostaining for cytokeratin (524). *C. difficile* infection may associate with gastrointestinal GVHD and a high mortality rate. It is postulated that the toxins produced by the bacteria increase the severity of the GVHD (525).

The changes of GVHD mimic certain infections, particularly *Salmonella* with its neutrophilic collections in the bases of the crypts (Fig. 13.158). Histologic changes resembling GVHD in the colon may develop in patients with CMV infections (526, 527), malignant thymomas (Fig. 13.159) (528), severe T-cell deficiencies (529), and common variable immunodeficiency (530). Some patients have autoimmune diseases. This entity probably overlaps with autoimmune enteropathy. Histologic features similar to those of GVHD may also be due to drug injury particularly due to mycophenolate mofetil, a drug used to reduce acute graft rejection in solid organ transplant patients (526).

The surrounding mucosa may show changes that mimic IBD. The mucosa may demonstrate mild to moderate architectural distortion (villiform surface with crypt branching and atrophy). However, the lamina propria is typically hypocellular with prominent small blood vessels. The lamina propria may appear to be focally fibrotic. It is unclear whether these changes are part of the GVHD or complicate the superimposed infections that may develop (531).
Intestinal Changes Associated with Immunologic Injury

**FIG. 13.158.** Graft-versus-host disease (GVHD). *A:* Gross appearance of the bowel in a patient with severe GVHD demonstrates the presence of atrophy and numerous petechiae. *B:* Segmental crypt loss and necrosis are typical in marked GVHD. In the area to the right, one sees a few intact glands. *C:* Higher power magnification of the intact glands demonstrates the presence of single-cell necrosis (arrow). *D:* Inflammation extends through the bowel wall to involve the serosa, which is markedly thickened. (Courtesy of Drs. Meyerson, Sale, and Schulman, Fred Hutchinson Cancer Center, Seattle, WA.)
Omenn Syndrome

Omenn syndrome is an autosomal recessive severe combined immunodeficiency syndrome that clinically and pathologically resembles GVHD. It is characterized by an expansion of an oligoclonal T-cell population (532). Hypereosinophilia and hypogammaglobulinemia are present.

Autoimmune Colitis

Autoimmune colitis complicates autoimmune enteropathy. The colitis presents as a mild intraepithelial lymphocytosis producing a pattern resembling lymphocytic colitis, or the epithelium contains large numbers of degranulating eosinophils and mast cells superimposed on a background of mucosal atrophy (Fig. 13.160). These changes often associate with endoscopic evidence of colitis and the changes are not restricted to the large bowel. The patients lack the clinical stigmata of celiac disease. The patients often have evidence of other autoimmune diseases, such as juvenile diabetes, autoimmune hepatitis, or autoimmune thyroiditis. This disorder is discussed further in Chapter 6.
Ischemic Colitis

General Comments

Acute ischemia results from an acute reduction in the blood flow resulting from an acute occlusive event or as a result of a decreased blood flow. It can result from either arterial or venous impairment. Ischemic colitis affects patients of all ages including infants, but it preferentially affects elderly patients with a history of arteriosclerosis, diabetes, hypertension, renal insufficiency, and/or cardiovascular disease. The mesenteric arteries become atherosclerotic with either gradual arterial occlusion or acute blockage by a thrombus. It is also more common in patients with a thrombophilic state including the presence of factor V Leiden mutations (96). Ischemia developing in a younger person without a history of drug use and in a patient without apparent predisposing factors, such as cardiac failure or arrhythmia, should be investigated for one of the vascular lesions listed in Table 6.8 or for a primary clotting abnormality. In women, the use of hormones or oral contraceptives should be investigated. Ischemia also complicates many other disorders, including some infections, especially cytomegalovirus (CMV). Common causes of low flow states include cardiac failure, arrhythmias, digitalis toxicity, shock resulting from a marked reduction in left ventricular output, and sepsis. Occlusive causes of acute ischemia include arteriolar or venous obstruction

P.775

(Table 13.5) as the consequence of thromboembolism (Fig. 13.66), dissecting aneurysm, vascular spasm, or vascular compression during prolapse, intussusception, etc. Colonic ischemia also complicates major surgery, infections, drug use (see below), retroperitoneal fibrosis (97), and cocaine abuse. Marathon runners may also develop colonic ischemia (98). Large intestinal ischemia exhibits a spectrum of changes ranging from fatal infarctions with gangrene (Fig. 13.67) to reversible ischemia.

Clinical Features

The clinical signs and symptoms vary according to the underlying etiology, duration and linear extent, and depth of mural involvement. In elderly individuals with generalized cardiovascular disease, a rapidly developing syndrome that starts with mild to moderate abdominal pain and quickly evolves with nausea, vomiting, diarrhea, rectal bleeding, and abdominal distention suggests the presence of ischemia (99). Such patients often have a predisposing hypotensive period. Reversible colonic ischemia manifests as crampy, usually left-sided, lower abdominal pain, associated with tenesmus, fever, and leukocytosis. Severe pain, fever, leukocytosis, peritoneal irritation, and/or profound ileus indicates extensive, and probably irreversible, ischemic damage (100). Anorexia, nausea or vomiting, abdominal distention from ileus, an altered sensorium, and clinical signs or symptoms of sepsis or shock can also develop. When ischemia extends to the muscularis propria, motility problems develop.
Ischemic Colitis

FIG. 13.65. Biopsy artifact. The glands have intussuscepted into one another, appearing as glands lying within the lumen of other glands.

### TABLE 13.5 Causes of Intestinal Venous Compromise

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric venous thrombosis</td>
</tr>
<tr>
<td>Venulitis associated with systemic diseases</td>
</tr>
<tr>
<td>Behçet disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Necrotizing giant cell granulomatous phlebitis</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Enterocolic lymphocytic phlebitis (mesenteric inflammatory veno-occlusive disease)</td>
</tr>
<tr>
<td>Idiopathic myointimal hyperplasia of mesenteric veins</td>
</tr>
</tbody>
</table>

Three types of colonic ischemia develop: (a) a transient reversible form that usually remains confined to the mucosa or submucosa; (b) a chronic form that extends into the bowel wall and lasts for months; and (c) an acute fulminating form that progressively destroys all layers of the bowel wall, usually with catastrophic consequences, including transmural necrosis and perforation. Complete recovery often follows mild ischemia. More severe disease undergoes partial resolution complicated by fibrosis and stricture formation. P.776

The most severe form of injury, transmural infarction, requires resection of the affected segment; otherwise, perforation or death will ensue. Almost half of patients with colonic ischemia have a transient, reversible form of the disease; 20% to 25% have chronic colitis or deep colonic infarction; and more than 10% to 15% develop late ischemic strictures (100,101,102). Approximately 15% to 20% of patients develop gangrene or perforation, either as an initial presentation of the disease or within a variable time following symptom onset. Sigmoidoscopic
Ischemic Colitis

findings can include striking mucosal edema, ulceration, nodularity, hypervascularity, friability, and pseudomembranes. Ulcers may or may not be present. These features evolve rapidly from one examination to the next.

FIG. 13.66. A recanalized thrombus is present in a submucosal vessel. The overlying mucosa is neoplastic.
Ischemic Colitis

FIG. 13.67. Massive infarction of the small and large intestine.

Pathophysiology of Ischemic Injury

As in the small intestine, the physiology of the circulation is such that a countercurrent exchange mechanism shunts oxygen into the lower mucosa at the expense of its upper portion (103). Consequently, the normally relatively hypoxic upper mucosa, which is particularly vulnerable to the effects of hypoperfusion, becomes necrotic, while the lower mucosa remains intact (Fig. 13.68). The degree of ischemic damage depends on the adequacy of the collateral circulation, on vascular autoregulatory mechanisms, and on tissue resistance to hypoxia. The extent and pattern of disease also depends on the anatomy of the blood supply, duration of the hypoxic episode, and bacterial population within the bowel lumen. The mildest lesions affect only the mucosa, and one sees superficial necrosis and hemorrhage. If reflow occurs, neutrophils infiltrate the tissues (see Chapter 6). There are three phases in the colonic reaction to ischemia: (a) acute with hemorrhage and necrosis, (b) repair with the formation of granulation tissue and fibrosis, and (c) the formation of structures and other complications. A number of disorders and damaging agents cause colonic injury via an ischemic mechanism (Table 13.6).

Large Vessel Occlusion Versus Small Vessel Occlusion

The severity of the lesions varies from microscopic focal damage to involvement of the entire colon. The size of the lesion correlates directly with the size of the affected vessels. Colonic ischemia results from occlusion of large vessels such as the mesenteric arteries or diseases or thromboemboli, which affect the intramural circulation with its smaller vasculature. Obstruction or diffuse vasospasm involving the major arterial supply of the large intestine results in severe ischemia to extensive regions of the colon or rectum. More distal obstruction of the colonic blood supply results in segmental ischemia or infarction. Only rarely does one see complete vascular occlusion. The superior branch of the mesenteric artery is more prone to undergo embolization than the inferior mesenteric artery due to the smaller caliber and more acute angle of takeoff of the inferior mesenteric artery (103). The ostium may undergo thrombosis at its origin from the aorta due to aortic atherosclerosis, but the presence of a collateral circulation often maintains an adequate perfusion (104). Small vessel disease results from
Ischemic Colitis

microangiopathies as seen in patients with hypertension, arteriolosclerosis, diabetes, vasculitis, radiation injury, or coagulation diatheses. Vascular obstruction also results from nonocclusive factors or obstruction of the vessels by external forces, as discussed in Chapter 6.

Sites of Injury

Ischemia affects the colon more commonly than it affects the small bowel, probably because of the vast collateral vascular network that exists in the small bowel (105). Colonic regions with poor collateral circulation, particularly around the splenic flexure and the rectosigmoid, are especially vulnerable (106). The superior and inferior mesenteric arteries communicate via the left branch of the middle colic artery and the ascending branch of the left colic artery at the arc of Riolan (marginal artery of Drummond). Approximately 5% of individuals have underdeveloped or absent connections between the two arterial systems at the splenic flexure, making them susceptible to ischemic damage (107).

Gross Features

The gross features of large intestinal ischemia resemble those of small intestinal ischemia. The changes vary depending on the severity and depth of the ischemic process, whether the event is acute or chronic, and the stage of healing that may have occurred (Figs. 13.69, 13.70, and 13.71). In early ischemia (usually seen during endoscopic procedures), the mucosa appears paler than normal but an increased vascular pattern with patchy, granular, swollen areas may be present. Bowels with transmural infarction may either appear pale or hemorrhagic depending on the circumstances. If hemorrhage has occurred, the bowel appears darkish blue or purple with blood in the bowel lumen. The wall may appear thinner than normal. As the disease becomes more severe, it extends into the submucosa causing edema and hemorrhage. Eventually, the mucosa sloughs and areas of grayish green necrosis develop, producing pseudomembranes. Ulcers may be present. These may be only superficial or they may be deep and linear. Occasionally the ulceration is extensive and confluent. Perforation may occur. The features may mimic fulminant UC or toxic megacolon. The ischemic changes exhibit a geographic distribution, often with a sharp line of demarcation between the involved and uninvolved mucosa (Fig. 13.70).
Ischemic Colitis

**FIG. 13.68.** Ischemic colitis. A: Early change with edema and separation of the surface epithelium from the underlying basement membrane. B: Epithelial regeneration and mucin depletion are present. The intervening lamina propria is hemorrhagic and edematous. C: High-power magnification of the mucin depletion. The lamina propria is hypocellular in this particular area. D: Active regeneration from the crypt bases in a patient with repeated ischemic episodes. The lamina propria is fibrotic. E: Surface re-epithelialization. A pseudomembrane overlies the surface epithelium.

**TABLE 13.6 Disorders with an Ischemic Basis**
In patients who survive the acute event, the wall will appear thickened, fibrotic, and contracted. Strictures covered either by an ulcerated granular-appearing mucosa or by a re-epithelialized mucosa may be present. The gross features of chronic disease may mimic Crohn disease or a neoplasm. Resection specimens for ischemia should be handled in a regular way so as to evaluate the extent of the ischemic damage, the viability of the margins, and, if possible, the etiology. The vessels should be examined both macroscopically and microscopically to detect evidence of thrombosis or vascular occlusion. Handling an intestinal resection specimen is discussed in detail in Chapter 6.
**Ischemic Colitis**

There is a form of ischemia that is transient and reversible. Usually the patients present with mild GI complaints and no obvious cardiovascular event precedes or appears to precipitate the ischemia. The patients may also have crampy abdominal pain and rectal bleeding. The diagnosis is usually a clinical one. Therefore, the lesion is not typically resected or biopsied because the bowel will heal if the damage is minimal. However, sometimes biopsies are performed to elucidate the cause of the pain or the bleeding. The biopsies may show the acute ischemic changes described below or they may show evidence of mucosal regeneration.

![Image of ischemic colitis](image)

**FIG. 13.69.** Numerous mucosal petechial hemorrhages are present in this early area of ischemia.

**Acute Ischemia**

The earliest ischemic lesions vary in their histologic appearance depending on the size of the occluded vessel. If the vessel is small and the degree of ischemia is minimal, the first changes affect the superficial parts of crypts and spare all but the superficial lamina propria. With continuing injury the damage progressively involves more of the crypts, eventually reaching the base. Biopsies in the acute stage show variable mucosal necrosis with loss of surface epithelium (Figs. 13.68 and 13.72, 13.73, 13.74), dilated capillaries and lymphatics, mucosal edema with hemorrhage and fibrin deposition (Fig. 13.72), and crypt dropout. In severe cases, the crypts appear to be bursting, dilated, and lined by an attenuated epithelium (Fig. 13.73). The crypts become filled with mucus and inflammatory debris. One may also see crypt abscesses. The epithelial loss leaves dilated, ghostlike, bare crypts supported by a congested lamina propria (Fig. 13.73). Goblet cells become mucin depleted and neutrophils infiltrate the mucosa. The muscularis mucosae becomes frayed. Early in the process neutrophils are relatively sparse. In patients with more extensive lesions, the submucosa becomes markedly edematous with concomitant capillary and lymphatic dilation. The submucosa contains inflammatory cells and it appears edematous, congested, and hemorrhagic (Fig. 13.74). Red cells sludge in the vessels, causing further thrombosis and hemorrhage. The mucosa becomes necrotic. Ulcers develop. The depth of the ulcers varies depending on the extent of the anoxic injury. They may be mucosal, extend into the submucosa or muscularis propria, or be transmural (Fig. 13.75). Transmural ulcers lead to perforation and these perforation sites may appear well demarcated and punched-out.

FIG. 13.71. Stricture complicating ischemic colitis.

Once the mucosa breaks down, bacteria may invade, eliciting a neutrophilic infiltration. Neutrophils also infiltrate the bowel as a result of reperfusion injury. At this stage, fibrin thrombi are frequently present, both in the submucosa and mucosa. Because the damage is typically patchy, normal mucosa is present between the involved areas. As the disease becomes more severe and the duration of the ischemia continues, the anoxia causes deeper injury to the bowel wall, possibly with transmural necrosis. Often there is an endophlebitis beneath the ulcers. This is present in the mucosa and submucosa and in severe cases it may extend along the veins, involving the extramural vessels. In this situation it may be difficult to tell whether the phlebitis is the cause or the effect of the ischemia.
Ischemic Colitis

**Reparative Phase**

If the patient survives the acute injury, a reparative phase will follow. The ulcer bases are replaced by granulation tissue and fibrosis. The granulation tissue response may be quite extensive. Large numbers of infiltrating neutrophils are present initially; these are gradually replaced by chronic inflammatory cells, including lymphocytes, plasma cells, and histiocytes. Fibroblasts proliferate in the lamina propria, obliterating the normal cell population and leading to mucosal fibrosis. If the hypoxic damage remains superficial and spares the crypt bases, regeneration ensues with increased mitotic activity in the crypt bases. If the injury was minor with only mild crypt dropout, the epithelium will regenerate using the pericryptal myofibroblast sheath as a scaffold and the architecture may return to a completely normal state (Fig. 13.76). Ulcers re-epithelialize from residual viable cells at the base of the crypts and from ingrowth of surface epithelium. The regenerating epithelium forms crypts, but a normal mucosal pattern may not be restored. Glandular distortion persists and the new lamina propria consists of fibrous tissue containing hemosiderin-filled histiocytes. At this time, very prominent submucosal collections of chronic inflammatory cells may be present. These may present as band-like infiltrates that are populated by large numbers of plasma cells, and the changes may mimic CD. The resemblance to CD is enhanced if mild acute injury continues. Large ulcers may heal, leaving only an area of re-epithelialized flat surface without crypts. Patients with resolved ischemic injury may develop strictures, glandular irregularities, architectural distortions, and areas of pyloric gland; Paneth cell metaplasia; or colitis cystica profunda. Additionally, endocrine cell hyperplasia may develop. Acute changes may persist with continuing ischemia or resolve with fibrosis, scarring, and stricture formation (Fig. 13.71).
FIG. 13.73. Ischemic colitis. A: Crypt dropout is present in the left side of the picture. B: Ischemic colitis is a patchy process that affects some areas and leaves adjacent ones more or less normal. C: An ischemic ulcer.
FIG. 13.74. Ischemic colitis. A: The superficial colonic mucosa shows epithelial loss. Only the bottoms of the crypts are left. The submucosa is markedly edematous. B: Higher magnification of the damaged crypts with residual epithelium at the crypt base (left). The mucosa is infiltrated with acute and chronic inflammatory cells. The submucosa is congested, edematous, and inflamed.
FIG. 13.75. Severe acute ischemia. A: Low-magnification photograph demonstrating the transmural coagulative necrosis with marked vascular congestion and no inflammation. B: Higher magnification showing the details of the mucosal necrosis. C: Portion of another case showing a marked mucosal hemorrhage.
Ischemic Colitis

**FIG. 13.76.** Regeneration following ischemia. There are two regenerative crypts surrounded by a more normal mucosa.

Regenerating crypts often appear hyperchromatic and disorganized and the hyperchromatic epithelium may mimic dysplasia. However, because the hyperchromasia occurs in the setting of other histologic features of ischemia, including lamina propria fibrosis, inflammation, and sometimes hemosiderin deposits, a misdiagnosis of dysplasia is seldom made.

**Fibrosis and Stricture Formation**

The features of the strictures involve all layers of the bowel wall. The mucosa architecture is typically distorted and may show any of the features typically associated with chronic colitis. It may exhibit a range of changes that include continuing acute inflammation, ulceration, granulation tissue, variable degrees of repair, and fibrosis. The muscularis mucosae is often hyperplastic, frayed, and fibrotic. Initially the submucosa is chronically inflamed and edematous. This is replaced by increasing fibrosis that extends into the muscularis propria.

**Biopsy Findings of Ischemia**

The major clinical differential diagnosis in patients presenting with colitis is IBD, infection, ischemia, and microscopic colitis. The biopsy features of ischemic colitis may overlap those seen in other diseases, particularly clostridial and enterohemorrhagic Escherichia coli infections. Clues to the diagnosis of ischemia are listed in Table 13.7. The biopsy features reflect the stage in the evolution of the injury. Early ischemic lesions consist of mucosal necrosis and hemorrhage with minimal or no inflammation if reperfusion injury has not occurred. These changes are usually restricted to the superficial mucosa. The more severe the ischemia, the more severe the changes are. The epithelium appears flattened with mild crypt dropout. As the lesions evolve, one may see erosions and areas of acute inflammation (Figs. 13.77 and 13.78) and reactive epithelial hyperplasia. The lamina propria appears variably cellular and there may be eosinophils in addition to mononuclear cells and neutrophils. The crypts may appear distorted with variable atrophy and fibrosis of the lamina propria. A pseudomembrane may cover the mucosal surface and the lesions may resemble those seen in Clostridium difficile–associated colitis described later in this chapter. Biopsies in individuals with clinically evident disease may have injury extending into the underlying submucosa or deeper portions of the wall.
Ischemic Colitis

FIG. 13.77. Mucosal biopsies in ischemic colitis. A: Three tissue fragments are present. These are labeled 1, 2, and 3. Number 1 shows mild inflammation in the lamina propria and mild glandular irregularity. Specimen 2 is a portion of a pseudomembrane or ulcer bed, and specimen 3 is a piece of mucosa demonstrating severe damage with focal glandular loss and regeneration as seen by fused glands and glands of differing sizes. Such features are typical of ischemia, which is a focal disease. B: Patchy chronic inflammation in an otherwise more or less normal-appearing mucosa. There is crypt dropout at the surface (arrow). This patient had known circulatory disturbances and previous documented ischemic bowel. C: A portion of colonic mucosa with focal fibrosis and glandular loss. The mucosa appears fibrotic. D: A biopsy from a patient who had significant rectal bleeding. The biopsy shows severe ischemic injury with marked hemorrhage and dilation of the vasculature, loss of the individual crypts, and dropout at the superficial portion. These acute changes are superimposed on chronic damage as evidenced by the presence of the branched crypt bases. The inflammation extends to the underlying submucosa.

| TABLE 13.7 Clues to the Biopsy Diagnosis of Ischemia |
**Features present**
- Glandular dropout
- Injury preferentially affecting the glands
- Injury preferentially affecting the superficial parts of the glands
- Presence of thrombi
- Presence of a vasculitis
- Hemosiderin in the lamina propria
- Presence of abnormal vessels

**Features absent**
- Granulomas

---

**FIG. 13.78.** Mucosal biopsies in ischemia. **A:** Acute ischemia with hemorrhagic necrosis. The *arrows* indicate three crypts that have dropped out of the mucosa. The *right-hand arrow* shows where an entire crypt has been lost. The *middle arrow* indicates a crypt with a small amount of residual basal epithelium in the base of the crypt. The *left-hand arrow* shows another crypt in which the base has a larger number of cells. **B:** Multiple irregularly shaped glands and focal chronic inflammation are present. This patient had known multiple past episodes of ischemia.

The changes may also overlap with Crohn disease because of the focal nature of the inflammation (Fig. 13.78). However, unlike CD, some patients lack features of chronicity as evidenced by architectural distortion. In contrast, patients with severe chronic ischemic disease may develop chronic damage, with marked architectural distortion, fibrosis, and strictures. In this setting, the presence of hemosiderin-laden macrophages in the lamina propria helps to establish a diagnosis of ischemia rather than CD. The presence of what appears to be a transmural infiltrate in a biopsy may also mimic CD. However, in ischemia, cryptitis and crypt abscesses are usually absent and the adjacent colonic epithelium does not usually appear mucus depleted. Additionally, in ischemia one does not have the compact granulomas typical of CD.

The biopsy features also overlap with pseudomembranous colitis. Both *C. difficile* enterocolitis and ischemic enterocolitis produce pseudomembranes. Hyalinization of the lamina propria is highly predictive of the presence of ischemic injury, as are atrophic microcrypts. Additionally, lamina propria hemorrhage, full-thickness mucosal necrosis, and diffuse microscopic distribution of the pseudomembranes are more common in ischemia than in *C. difficile* colitis. In contrast, endoscopic identification of diffuse pseudomembranes favors the diagnosis of *C. difficile* (108).
Ischemic Enterocolitis (Necrotizing Enterocolitis)

Necrotizing enterocolitis represents a type of ischemic injury. Ischemic enterocolitis, also known as pseudomembranous enterocolitis, usually produces massive necrosis of the small intestine and colon, often as a terminal event following an episode of shock. The disease also affects newborns (see Chapter 6). Some patients develop toxic megacolon (109). The severity of the lesion depends on (a) the severity of the ischemia, (b) the virulence of the luminal microbial flora, and (c) the overall general health of the patient at the time of the episode. It differs from segmental forms of ischemia, which remain localized to a small area of the colon. Perforation, peritonitis, and sepsis contribute to its high mortality rate.

In the acute stage, the infarcted area shows mucosal necrosis, submucosal hemorrhage, and edema with congested capillaries often containing fibrin plugs. As the mucosa sloughs, ulcers develop and their bases become covered by fibrin, neutrophils, and necrotic debris. Bacterial and fungal invasion occur as a result of the loss of the mucosal integrity. The ulcer margins and the edges of the ulcer base show ischemic injury and vascular congestion. The adjacent nonulcerated mucosa appears erythematous. A pseudomembrane containing fibrin and white blood cells covers the surface. As the lesions evolve, plasma cells, lymphocytes, and macrophages infiltrate the area and the capillaries proliferate, forming granulation tissue. The macrophages may contain hemosiderin. Capillary endothelium may become swollen and appear atypical. The nerves and muscle cells may become vacuolated and degenerate. As these lesions evolve, they are replaced by granulation tissue and then fibrosis. Often, a well-demarcated zone of neutrophilic infiltration forms between the necrotic and viable bowel wall. Pneumatosis intestinalis may also develop. The differential diagnosis of pseudomembranous colitis is listed in Table 13.8. If the patient recovers, prominent submucosal fibrosis may develop, leading to stricture formation. Morphologically, one may see all stages of injury and repair in the specimen. When a stricture develops, the lesion may mimic colonic carcinoma.

### Table 13.8 Diseases Associated with Formation of Pseudomembranes

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic-associated colitis</td>
</tr>
<tr>
<td>Ischemia</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Heavy metal toxicity</td>
</tr>
<tr>
<td>Chemotherapy-induced intestinal damage</td>
</tr>
<tr>
<td>Neutropenic enterocolitis</td>
</tr>
<tr>
<td>Shigellosis</td>
</tr>
<tr>
<td>Colitis complicating obstruction</td>
</tr>
<tr>
<td>Amebiasis</td>
</tr>
<tr>
<td>Mucosal prolapse</td>
</tr>
<tr>
<td>Microscopic colitis (rare)</td>
</tr>
</tbody>
</table>

**Enterocolitis in Hirschsprung Disease**

Enterocolitis is the most severe, potentially life-threatening complication of Hirschsprung disease. It is estimated that 5% of patients with Hirschsprung disease will die of enterocolitis. The enterocolitis develops any time during the disease course irrespective of age, sex, or method of management. It is characterized by abdominal distention, diarrhea, fever, and hypovolemic shock. The diagnosis is made clinically and confirmed radiologically. Radiography demonstrates colonic dilation, mucosal ulceration, GI hypomotility, and sometimes pneumatosis coli. Several factors contribute to its pathogenesis, including proximal colonic dilation with resultant mucosal ischemia and bacterial invasion, and hypersensitivity to bacterial antigens. More recently, *C. difficile* and its toxin have been implicated in its development (110).

**Tropical Enterocolitis**

Tropical enterocolitis, a distinct form of necrotizing enterocolitis, differs from neonatal enterocolitis discussed in Chapter 6. It presents as an acute abdomen with pain, bilious vomiting, constipation, or bloody diarrhea due to the presence of a segmental jejunitis, ileitis, or colitis and, rarely, duodenitis. The pathology appears to involve a local hyperimmune reaction in the affected bowel segment. Changes range from punctate hemorrhages in the muscular layer of the bowel to a generalized fiery red appearance and possible perforation secondary to mucosal inflammation.
ulceration. Whatever the causative agent, the pathogenesis involves a local vasculitis leading to variable ischemic damage (111).

**Obstructive Colitis**

The term *obstructive colitis* refers to ulceroinflammatory lesions measuring 0.5 to 2.5 cm in length that occur proximal to obstructing lesions including tumors, diverticular disease, volvulus, torsion, hernias, strictures, or atresias (112). The diseased bowel is separated from the obstruction by a variable length (2.5 to 35 cm) of normal mucosa. The patients are typically female and elderly with a mean age of 73 years. They usually have coexisting hypertension, diabetes, or other prior chronic illnesses. This lesion likely results from vascular compromise by the obstructing lesion. An altered intestinal flora may exert a synergistic effect (112).

The changes vary depending on whether the obstruction developed over a long time or acutely. Slowly developing lesions result in chronic superficial ulceration with evidence of both acute and chronic injury. Ulcers and pseudopolyps may be present and the overall architecture may appear cobblestoned. The changes are patchy in nature, distinguishing the lesion from ulcerative colitis, which it grossly resembles. In contrast, rapidly developing lesions resemble necrotizing enterocolitis. Loss of individual muscle fibers in the muscularis propria results in "vanishing muscle." This disorder often develops in the right colon.

The lesions range in severity from discrete ulcers to extensive areas of fulminant colitis with necrosis, diffuse ulceration, and fibrosis (113). Endoscopically, the involved colon usually appears mildly to massively dilated and exhibits moderate intramural thickening with a granular luminal surface accentuated by deeper longitudinal transverse ulcers. Perforation and peritonitis may develop. Because the biopsy features of obstructive colitis are nonspecific, it may be impossible to distinguish this entity from other disorders, particularly ischemia, due to other causes. The mucosa distal to the obstructing lesion usually appears normal, but this may not allow one to make a diagnosis of obstructive colitis unless one has been informed that an obstruction was present. These histologic changes are those of ischemic colitis.

**Ischemic Colitis Complicating Chronic Renal Disease**

Renal transplant patients develop various gastrointestinal complications. Half of posttransplant deaths result from GI complications (114). Large doses of corticosteroids, azathioprine, and other immunosuppressive drugs deplete the gut of its lymphoid tissue and depress cellular immune responses to noxious agents, predisposing the bowel to infection. Additionally, epithelial cell turnover is delayed, impeding mucosal repair. Several drugs, especially cyclosporine, induce vascular damage. Systemic calciphylaxis is an uncommon complication of chronic renal failure characterized by disseminated intravascular calcification and progressive vascular compromise that may involve many parts of the body including the GI tract. Mural calcification of medium and large vessels leads to severe ischemic necrosis (115). Parathyroidectomy may lead to clinical improvement.
Ischemic Colitis

**FIG. 13.79.** Biopsy from a renal transplant patient with hemolytic uremic syndrome. The changes show features typical of ischemia with loss of the superficial epithelium, focal glandular dropout, mucosal congestion, and a pseudomembrane overlying the surface.

**Hemolytic Uremia Syndrome**

Hemolytic uremic syndrome (HUS) usually affects children under 7 years of age following a prodromal period of bloody diarrhea caused by the Shiga toxin from *E. coli* 0157:H or renal transplant patients of any age. It consists of the triad of microangiopathic hemolytic anemia, thrombocytopenia, and oliguric renal failure. Neurologic manifestations may also occur. GI involvement is seen in 75% of children with HUS (116). GI symptoms include bloody diarrhea, vomiting, abdominal pain and tenderness, peritonitis, and hepatomegaly. Proctoscopy demonstrates a friable rectal mucosa with rectal ulcers and mucosal pseudomembranes (Fig. 13.79). Patients may present with segmental colonic gangrene (117). The illness may be clinically misdiagnosed as ulcerative colitis, pseudomembranous colitis, or intussusception. Endoscopic appearances vary and include normal, mild patchy colitis with edema, focal mucosal hemorrhage, aphthous ulcers, and erythema anywhere from the ileocecal valve to the rectum.

In most cases no causative agent is identified but a genetic predisposition (118); certain viruses, especially enteroviruses (119); Shiga toxin–producing, Gram-negative enteric bacteria (120); estrogens; and postpartum and postrenal transplant oliguria all associate with HUS. Endothelial damage underlies the injury. Bacterial enzymes, endotoxins, and immune injury mediate the endothelial damage initiating the coagulation cascade (121). Patients develop localized Schwartzman-type reactions with fibrin and platelet thrombi formation.

Histologically, colonic submucosal vessels show perivascular mononuclear infiltrates, focal mural necrosis, and thrombi in various stages of organization. The latter cause secondary ischemic necrosis. Neutrophils infiltrate the lamina propria and crypts. The inflammatory changes vary from mild and patchy to a more widespread diffuse cryptitis with crypt abscesses. The focal nature of the infiltrate and absence of chronic damage distinguish the disorder from ulcerative colitis. Apoptoses are present in the superficial epithelium and lamina propria. Pseudomembranes develop as the ischemia progresses.
Ischemic Colitis

**Vasculitis**

The diagnosis of vasculitis involving the colon is more easily made in a resection specimen than in a biopsy. Vasculitis may affect both the small and large intestines and causes either localized or more widespread ischemic disease that may appear as areas of ulceration, hemorrhage, or wider gastrointestinal infarction. In order to make a diagnosis of vasculitis, the tissue specimen must include the submucosa. In its absence, all one can say is that ischemic damage is present. Some of the vasculitides are discussed below. The remainder are discussed in Chapter 6.

**Phlebosclerotic Colitis**

Colonic phlebosclerosis is a rare disease characterized by a thickening of the colonic wall with fibrosis, hyalinization, and calcification of the affected veins (122,123). These cause a unique form of ischemic colitis. The lesion occurs sporadically or in association with colonic adenomas (122). Radiographic studies demonstrate linear calcifications in the intestinal wall. The right colon is preferentially affected and there are no skip lesions. Grossly the mucosa may appear discolored with ulcers. Histologically there is a mucosal fibrosis, hyalinization, and calcification diffusely involving the colon. The mucosa shows architectural distortion and mild lymphoplasmacytic infiltrates, all features of chronic ischemia. The fibrosis often centers around the veins. The mesenteric vasculature appears calcified.

The differential diagnosis includes amyloidosis, but a negative Congo red stain rules out this as an etiology of the histologic alterations. Diabetic colonopathy, also in the differential diagnosis, is unlikely given the fibrosis that affects the veins and randomly involves the lamina propria. Collagenous colitis involves superficial fibrosis and it does not center around the veins.

**Idiopathic Myointimal Hyperplasia of Mesenteric Veins**

Idiopathic myointimal hyperplasia of mesenteric veins (IMHMV) is a rare cause of intestinal ischemia secondary to venous compromise that typically affects the sigmoid area. The disorder affects males who present with lower abdominal pain, diarrhea, and rectal bleeding (124). Colonoscopic mucosal biopsies may show the presence of many dilated thick-walled, eosinophilic, hyalinized blood vessels lined by plump endothelial cells. Depending on the stage of the disease, the mucosa exhibits varying degrees of ischemic damage. Some vessels may contain fibrin thrombi. In resection specimens similar vessels are present in the submucosa, adventitia, and mesocolon. There is a marked myointimal hyperplasia of the vessels, reducing their luminal caliber to small slitlike spaces. The abnormal veins appear more prominent than the arteries. The veins also show increased deposition of Alcian blue material and collagen type IV. There is no inflammation of the veins (124). Patients do well following surgical resection of the affected segment.

**Mesenteric Inflammatory Veno-occlusive Disorder (Enterocolic Lymphocytic Phlebitis)**

Mesenteric inflammatory veno-occlusive disease, also known as enterocolic lymphocytic phlebitis, is a rare disease involving small veins of the large and less frequently the small intestine. The colon, distal ileum, and appendix may be affected (125). The disease occurs twice as frequently in males than in females and patients range in age from 24 to 78 years (126). It results from an isolated vasculitis involving mesenteric veins and their intramural tributaries that leads to intestinal ischemia and produces changes that may mimic IBD (127). It presents with the insidious onset of abdominal pain, bloody or nonbloody diarrhea, nausea, and a tumorlike mass. The pathogenesis of this disorder is unknown, although it has been suggested that there may be an etiologic relationship with the drugs rutoside or flutamide (125). A predominantly lymphocytic infiltration surrounds intramural tributaries of the mesenteric veins, sometimes with the formation of perivenous lymphocytic cuffs. Giant cells may be present (128). In some areas the phlebitis does not compromise the vascular lumens, but in others there are subintimal fibroproliferative lesions that are focally occlusive (129). It is thought that the myointimal hyperplasia is a reactive vasculopathy secondary to chronic vasculitis, perhaps related to mesenteric thrombosis from hypercoagulable states, trauma, or sepsis. The vascular changes lead to the typical features of colonic ischemia

The lymphocytic infiltrate consists of both B and T cells. Some have shown a zonal arrangement of the T and B cells, but this has not been found by all (129). The T cells are of a cytotoxic lineage and express TIA-1 (T cell–restricted intracellular antigen-1) (129), a protein found in cytotoxic granules of T cells. These findings suggest that the vascular damage is lymphocyte mediated.

At the present time it is unclear whether myointimal hyperplasia of mesenteric veins and enterocolic lymphocytic phlebitis are different stages of the same disease or two separate but interrelated diseases (128). The other disease that may be interrelated with both myointimal hyperplasia of mesenteric veins and enterocolic lymphocytic phlebitis is necrotizing giant cell granulomatosis. The rarity of all of these disorders makes it impossible to sort out these possibilities at the present time. These patients do well after surgical resection.

**Collagen Vascular Diseases**

Colonic ischemia may complicate collagen vascular diseases such as systemic lupus erythematosus. Patients may develop massive intestinal hemorrhage, total colonic necrosis, or limited infarctions and perforations (130,131). Patients often have concurrent renal failure. They develop a vasculitis involving smaller arteries and veins due to deposition of circulating immune complexes in the vessel walls (131). The vascular changes are worsened by the presence of uremia, coagulopathy, and medications.
**Behçet Syndrome**

Behçet syndrome and its associated vasculitis typically affect the terminal ileum and cecum. Its histologic features are discussed in Chapter 6.
Lesions Associated with Increased Numbers of Eosinophils

Occasionally one encounters biopsies in which the most striking change is a marked increase in the number of eosinophils. Their presence can suggest a drug or allergic reaction (Fig. 13.144) (442,443) or the presence of a parasitic infection. However, in the colon they also commonly associate with chronic disorders. The number of lamina propria eosinophils varies significantly, differing by a factor of 40 in different regions of the country (444). Their numbers may also differ seasonally. In children, the cecum and appendix appear to have the highest concentrations of eosinophils in comparison with the distal intestine.

**FIG. 13.144.** Allergic enteritis. The lamina propria of this portion of the colon is intensely infiltrated by eosinophils.

Food Allergies

Up to 45% of the population report adverse reactions to food (445). The incidence appears to be increasing, although this may reflect increased patient and physician reporting of allergic symptoms (446). Food sensitivity occurs particularly commonly in infants and young children. Definitive diagnosis of a food allergy requires the demonstration of an unequivocal clinical reaction after a controlled food challenge and elimination of the symptom complex subsequent to removal of the offending food. The increased susceptibility of young infants to food allergic reactions results from their general immunologic immaturity and the overall immaturity of their gastrointestinal tracts (447,448). The majority of allergic reactions to food are IgE-mediated, mast cell–dependent, immediate hypersensitivity-type reactions. The interaction of an antigen with an antibody or immunocyte triggers the allergic reaction. It is mediated by soluble factors from activated neutrophils, mast cells, and macrophages, or by direct membrane interactions between immune cells and antigens on their cell surfaces. Cytokine and inflammatory mediators...
Lesions Associated with Increased Numbers of Eosinophils

are released that act directly on the epithelium, endothelium, or muscle, or indirectly through nerves and mesenchymal cells. The immediate consequences of these mediators include a local change in vascular permeability, stimulation of mucus production, increased muscle contraction, stimulation of pain fibers, recruitment of inflammatory cells, edema of mucosal epithelial villi, increased protein loss from the gut, and increased absorption of foreign antigens. Also, as a result, eosinophils, lymphocytes, and monocytes are attracted to the reaction site, where they release additional inflammatory mediators and cytokines. Repeated ingestion of an allergen stimulates mononuclear cells to secrete histamine-releasing factors, some of which interact with IgE molecules bound to basophils and mast cell surfaces (449). If significant mast cell degranulation occurs, mast cell mediators may provoke potentially fatal systemic anaphylaxis.

Cow's Milk and Soy Intolerance

A common form of allergic colitis is cow's milk and soy formula intolerance (450). It may also develop in breastfed infants, probably as the result of transfer of potentially immunogenic substances (especially cow-milk–derived β-lactoglobulin) from the maternal diet into the breast milk (451). Food allergy, whether IgE or non-IgE mediated, affects males and females equally and at any age, but occurs more often in infants and young children with a prevalence of 0.5% to 3%. Allergic proctitis commonly affects young infants who present with rectal bleeding, with or without associated diarrhea (452). Common symptoms include vomiting, pain, weight loss, an allergic history, anemia, and peripheral eosinophilia. Patients may also present with constipation (453).

The fact that food hypersensitivity reactions occur more commonly in the pediatric population and tend to decrease in incidence with increasing age suggests that immaturity of the intestinal barrier function, immaturity of the mucosal immune system, or both are important in the pathogenesis of the disorder (454,455). This is supported by the fact that as the infants age, the allergy disappears due to the development of IgG antibodies, which prevent the allergic reaction.

The degranulating eosinophils release a number of biologically active mediators, including major basic protein, eosinophil-derived neurotoxin, eosinophilic cationic protein, and eosinophilic peroxidase, all of which may be cytotoxic and lead to epithelial injury. They also produce platelet-activating factor, a substance shown to cause intestinal injury in experimental animals (456). The eosinophils have surface receptors for complement components and leukotrienes. Eosinophils also express surface receptors for IgG and a low affinity receptor for IgE and IgA (457). The fact that eosinophils can bind IgA and then degranulate is important because the gut is the major site of IgA production.

Allergic colitis involves any colonic segment, but the rectosigmoid is preferentially affected (458,459). Endoscopic features include focal erythema, a friable-appearing mucosa, and increased mucosal nodularity suggestive of lymphoid hyperplasia. Zones of entirely normal mucosa separate the abnormal areas. Severe cases may show decreased mucosal vascularity, multiple superficial aphthous erosions, or ulcers covered by a surface exudate.

Histologically, one sees increased numbers of eosinophils populating the lamina propria, epithelium, and muscularis mucosae (Fig. 13.144). A particularly characteristic feature is the presence of large numbers of eosinophils in the lamina propria (>60 eosinophils/10 high-powered field [hpf]), as well as numerous intact or degranulated eosinophils located in the base of the mucosa and interspersed among muscle fibers of the muscularis mucosae (450,458,459). The eosinophils are the major cell type in cryptitis and crypt abscesses (Fig. 13.145). Often the eosinophilic aggregates closely associate with lymphoid nodules. The intensity of the eosinophilic infiltrates varies, not only between biopsies at different sites but within individual biopsy specimens. Although the eosinophils are thought to mediate the injury, no significant correlation exists between the number of mucosal eosinophils, patient age, illness duration, endoscopic appearance, or type of inciting formula.

The overall mucosal architecture is maintained in allergic proctocolitis without histologic features of chronicity, such as distorted, branched, or atrophic crypts; Paneth cell metaplasia; basally located lymphoid aggregates; or diffuse plasmacytosis. The eosinophilia represents an excellent marker for infantile allergic proctocolitis, but given the focal distribution of the lesion, multiple mucosal biopsy specimens must be obtained, and several levels of each should be examined (450,458,459).

Recognition of the disease is important because pediatric patients with allergic proctitis generally respond promptly to dietary
Lesions Associated with Increased Numbers of Eosinophils

Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis tends to affect older children and young adults, and predominantly involves the proximal gut, especially the esophagus, stomach, and small intestine. The colon is one of the least commonly affected sites (450). Rare patients with colonic disease also have biliary tract involvement (460). Symptoms include diarrhea, rectal bleeding, abdominal pain, and fever. Barium enema and colonoscopy disclose changes indistinguishable from CD, usually confined to the right colon. Some patients also have coexisting IBD and/or cholangitis (460). Histologically, the mucosa, submucosa, or muscularis propria is infiltrated by eosinophils (Fig. 13.146). Eosinophilic gastroenteritis is discussed in detail in Chapter 6.

FIG. 13.145. Eosinophilic colitis. A crypt abscess is present that consists almost entirely of eosinophils. There are also increased numbers of eosinophils in the lamina propria.

FIG. 13.146. Eosinophilic gastroenteritis. The photograph shows an intense infiltration of the muscularis propria by eosinophils.
Lesions Associated with Increased Numbers of Eosinophils

Pericryptal Eosinophilic Enterocolitis

Some patients who present with chronic watery diarrhea have connective tissue diseases and eosinophilic infiltrates around the intestinal crypts. The infiltrates localize to the deep mucosa, separating the crypt bases from the muscularis mucosae and penetrating into the superficial submucosa. Patients with these findings exhibit chronic diarrhea that resolves with steroid therapy (461). The patients lack gross structural abnormalities.

![FIG. 13.147. Mucosal histiocytic infiltrates. A: Superficial cluster of pale histiocytic cells lies under the free surface. B: A group of histiocytic cells separates the base of the glands from the muscularis mucosae.](image)

“Eosinophilic Colitis”

We make a diagnosis of eosinophilic colitis if we see eosinophils infiltrating the crypts or if there are focal collections of 10 or more eosinophils per hpf, in the absence of other identifiable abnormalities such as collagenous colitis, lymphocytic colitis, IBD, infection, diverticular disease, or neoplasia. We make an effort to determine if these changes occur alone or, more importantly, if there are associated increased apoptoses in the crypt bases. If these are present then we interpret the changes as most likely representing a drug reaction. In some cases, the patients will eventually be diagnosed with Crohn disease. However, in other patients the cause of the changes is never determined. It is our anecdotal experience that we make this diagnosis more often when the general public is suffering from bouts of hay fever or other seasonal allergies.
Lesions Presenting as Polyps

Normally, the dynamic process of cell division is balanced by exfoliation from the luminal surface. If an imbalance occurs, either because of increased replication or decreased exfoliation, a polyp results. Broadly speaking, the word *polyp* simply denotes any mucosal elevation. Polyps may consist of benign or malignant epithelial proliferations, inflammatory infiltrates localized in the lamina propria, or deeper, submucosal or intramural mesenchymal proliferations, malformations, or even metastatic tumors. The three most common colorectal polyps are inflammatory, hyperplastic, and adenomatous (see Chapter 14).
Lesions Presenting as Polyps

**Amyloidosis.** A: The amyloid affects not only the small blood vessels, but also the muscularis mucosae. B: Congo red stain (left) of amyloidosis involving the smooth muscle fibers. The specimen is seen by polarized light on the right demonstrating the typical apple-green birefringence. C: Crystal violet stain in patient with amyloidosis in a rectal biopsy involving the submucosal vessel. An area of smudgy purplish discoloration is seen at about 2 o'clock in the blood vessel.

**Hyperplastic Polyps**

Hyperplastic polyps are one of the most common polyp types seen in the adult colon. They share risk factors with adenomas and colon cancer including dietary fiber, calcium, and total fat intake; smoking; body mass index; and alcohol consumption. They often arise in a colon harboring adenomatous polyps or carcinomas (576,577). They often cluster in large numbers around colon carcinomas. Hyperplastic polyps increase in frequency with age in some populations, but not all studies confirm this (578,579). The hyperplastic polyp:adenoma ratio is highest in those parts of the world with the highest incidences of colorectal carcinoma and it falls to unity in low-risk regions (580). These lesions remain asymptomatic and are found incidentally at the time of colonoscopy or resection.

The relationship between hyperplastic polyps and the subsequent development of adenomas and carcinomas remains controversial. Hyperplastic polyps have been regarded by most observers as innocuous and nonneoplastic and unrelated to colorectal neoplasia (581). This issue has been clouded by the recognition of mixed hyperplastic–adenomatous polyps. Mixed polyps combine the features of both hyperplastic and adenomatous polyps without intermediate forms between them. This may be explained by the engulfment of a pre-existing hyperplastic polyp by a spreading adenoma, by stimulation of the mucosa at the advancing edge of an adenoma, or by the development of an adenoma in a hyperplastic polyp. The hyperplastic component alone does not predispose to carcinoma, but the presence of a coexisting adenomatous component does have malignant potential. It is also clouded by the inclusion of the serrated adenomas and the polyps of the hyperplastic polyposis syndrome, which are different entities that somewhat resemble hyperplastic polyps. These lesions are discussed in Chapters 12 and 14. Hyperplastic polyps are generally not regarded as having a direct relationship to colonic cancers (582,583).

The fact that the vast majority of hyperplastic polyps arise in the colons of patients with concomitant adenomas (584) has prompted speculation that hyperplastic polyps are biomarkers of colorectal neoplasia and that the associations are causally related. Some suggest that hyperplastic polyps may be a marker for an environmental factor implicated in the progression of adenomas to carcinomas (585). Alternatively, individuals may be constitutionally prone to the development of both the adenomas and hyperplastic polyps, and they may require similar environmental conditions for their development. The lesions, or at least some of the lesions, may not be as innocuous as once believed since they contain a variety of genetic abnormalities.

There is evidence of dysregulated cell proliferation and apoptosis (582,586,587). The presence of clonal genetic alterations, including K-ras (588,589,590), BRAF (590), and TGFβRII mutations; DNA microsatellite instability; and loss of the APC, p53, p16 genes and a tumor suppressor gene on chromosome 1p has led to the suggestion that hyperplastic polyps are “neoplastic” but lack malignant potential (591). There is also methylation of the DNA repair gene O6methylguanine DNA methyltransferase (MGMT) (592). It appears that a subset of “hyperplastic polyps” may be a biomarker of increased risk or even represent a subtype carrying a significant malignant potential (592). These are now commonly referred to as sessile serrated polyps or sessile serrated adenomas as discussed further in Chapter 14. Identical DNA microsatellite alterations can be found in the hyperplastic and adenomatous regions of mixed hyperplastic–adenomatous polyps, suggesting that the two lesions are sequentially related (591). Features that might suggest the presence of a hyperplastic polyp with malignant potential include those listed in Table 13.29 (591).

Hyperplastic polyps are pale, sessile nodules usually developing on the crest of mucosal folds. The lesions are often multiple and appear as small mucosal elevations (Fig. 13.164), usually
Lesions Presenting as Polyps

measuring <5 mm in diameter and rarely measuring >1 cm; most arise in the sigmoid and rectum. Their surfaces appear smooth and glistening, and the lesions are usually slightly paler than the surrounding mucosa. Hyperplastic polyps are significantly smaller and lighter in color than adenomas. Endoscopically, it is not possible to distinguish between small adenomas and hyperplastic polyps, so the lesions tend to be biopsied.

Hyperplastic polyps consist of groups of elongated hyperplastic colonic crypts. The upper half of the crypt contains characteristic intraluminal papillary infoldings. These infoldings result from an expanded replication zone and a slower rate of maturation that give the crypt a serrated or saw-toothed appearance (593). While the proliferative zone is lengthened, it is still restricted to the bottom of the crypt. Epithelium lining the crypts contains a mixture of absorptive, goblet, and endocrine cells (594). Absorptive columnar cells predominate over goblet cells. The upper part of the crypts appears crowded by a population of hypermature goblet cells, which are usually larger than normal due to intracellular mucin accumulations. The nuclei remain in a basal location and are typically enlarged and vesicular with a prominent nucleolus. Atypical mitoses are rare. The bases of the crypts appear hyperchromatic and immature, resembling adenomatous epithelium. However, unlike adenomas, the epithelium matures as one progresses up the crypt toward the lumen. A large proportion of hyperplastic polyps also contain a hybrid epithelium with bidirectional differentiation toward both gastric foveolar and colonic epithelium in the same crypt (595). The replicative zone of the crypt, which contains mitotically active cells, is expanded and may comprise its lower half (Fig. 13.164). A hyperplastic pericryptal myofibroblast sheath associates with the hyperplastic epithelium. It produces an increased amount of collagen, a feature best appreciated under the free surface where there is a thickened collagen table. These lesions may become inflamed and when they do they may appear mucin depleted.

<table>
<thead>
<tr>
<th>TABLE 13.29 Features that May Indicate “Hyperplastic Polyps” with a Malignant Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Unusual numbers (more than 20)</td>
</tr>
<tr>
<td>● Unusual size (.10 mm)</td>
</tr>
<tr>
<td>● Location in the proximal colon</td>
</tr>
<tr>
<td>● Presence of high-grade dysplasia</td>
</tr>
<tr>
<td>● Coincidental adenomas</td>
</tr>
<tr>
<td>● First-degree relatives with high-risk hyperplastic polyps</td>
</tr>
<tr>
<td>● First-degree relatives with colon cancer</td>
</tr>
</tbody>
</table>
Lesions Presenting as Polyps

FIG. 13.164. Hyperplastic polyp. A: The hyperplastic polyps usually occur on mucosal folds and have the same color as the surrounding mucosa (arrowhead). B: Low-power view of a hyperplastic polyp. C: Higher power magnification demonstrates the stellate lumens and thickened collagen table. D: Higher power magnification of the thickened collagen table stained with antibodies to collagen IV.

Serrated crypts, a hallmark of the hyperplastic polyp, may be seen in the regenerative mucosa in a number of settings including IBD, mucosal prolapse, and juvenile polyps. The major entity in the differential diagnosis of the hyperplastic polyp is the serrated adenoma discussed in Chapter 14. The two lesions are compared in Table 13.30.

Inverted Hyperplastic Polyp

A variant of the hyperplastic polyp, the so-called inverted hyperplastic polyp, may simulate a carcinoma and may appear to invade the underlying submucosa. The lesions affect both sexes and patients are generally older than 50 years. The lesions tend to develop in the rectum or sigmoid and range in size from 0.2 to 1 cm with a mean size of 0.5 (596). These lesions resemble hyperplastic polyps, but instead of being solely exophytic, groups of glands lie beneath the level of the mucosa, forming one or more lobulated submucosal nodules (Fig. 13.165). There may also be a mixed pattern of lobules and distorted crypts. The overlying mucosa contains glands typical of hyperplastic polyps arranged as a sessile nodule or in a flat patch. Pedunculation is absent. The endophytic nodules show a peripheral hyperbasophilic proliferative zone and a central area of pale, more mature cells with characteristic serrated tubular profiles seen in hyperplastic polyps. In contrast to the usual exophytic hyperplastic polyp, the endophytic elements exhibit a more complex growth pattern, sometimes demonstrating back-to-back glandular arrangements and intraluminal budding. The epithelial lining lacks dysplasia. Occasionally, lymphoid nodules intermingle with the lesions. Multiple endophytic lesions may be present. The muscularis mucosae appears to stretch thinly around the deep aspect of smaller lesions and is incomplete around larger nodules (596,597). When cut tangentially, one may see splaying and dissociation of the muscularis mucosae. Downward extension of hyperplastic tubules projecting into the submucosal lymphatics when sectioned obliquely simulates invasion. Fresh
Lesions Presenting as Polyps

hemorrhage, vascular congestion, or hemosiderin may be present around the glands. The lesions arise secondary to trauma-induced protrusion of the glands through breaks in the muscularis mucosae, often near lymphoid aggregates.

**TABLE 13.30 Hyperplastic Polyp Versus Serrated Adenoma**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyperplastic Polyp</th>
<th>Serrated Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Generally &lt;0.5</td>
<td>Generally &gt;0.5</td>
</tr>
<tr>
<td>Mitoses</td>
<td>A few at the crypt base</td>
<td>Abundant, the length of the crypt</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>Mild at base</td>
<td>Mild to marked, the length of the crypt</td>
</tr>
<tr>
<td>Surface maturation</td>
<td>Hypermature</td>
<td>Immature</td>
</tr>
<tr>
<td>Crypt dilation</td>
<td>Surface</td>
<td>Base</td>
</tr>
<tr>
<td>Cytoplasmic eosinophilia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Surface nuclear stratification</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Horizontal crypts</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Collagen table</td>
<td>Thicker than normal</td>
<td>Thinner than normal</td>
</tr>
</tbody>
</table>
Lesions Presenting as Polyps

**FIG. 13.165.** Inverted hyperplastic polyp. *A:* Low magnification showing the presence of a prominent mucosal fold that contains an area of epithelium within the submucosa. This is seen better at higher magnification in *B.* The epithelium appears hyperplastic with a gradient of differentiation extending from the periphery of the lesion to its center. The crypt bases lie radially arranged at the periphery of this lesion. *C:* Higher magnification showing the edge of the lesion with the crypt bases and the serrated lumen as one approaches the center of the lesion. The absence of cytologic atypia distinguishes this from an invasive carcinoma. The presence of the glandular infoldings and prominent goblet cells distinguishes this lesion from colitis cystica profunda. Cytologically, the cells appear histologically identical to those seen in hyperplastic polyps.

**Inflammatory Fibroid Polyp**

Inflammatory fibroid polyps are uncommon tumorlike lesions arising in the submucosa. They are most common in the stomach and small intestine (see Chapters 2 and 4), but they occasionally develop in the rectum. Rectal lesions demonstrate the same histology as those occurring more proximally. The histology of these lesions is discussed further in Chapter 6.
Fibroblastic Polyps

Fibroblastic polyps are a recently described distinctive type of colorectal mesenchymal polyp (598, 599). The lesions develop in individuals ranging in age from 37 to 84 with a mean of 60 years and with a moderate female predominance. They occur almost exclusively in the left and distal colon and generally measure <10 mm in size. They are solitary lesions that occur alone or coexist with hyperplastic polyps. They contain a mucosal proliferation of bland, monomorphic spindled cells with oval nuclei arranged as bundles parallel to the surface or as haphazardly arranged sheets with focal periglandular or perivascular arrangements. Some polyps display a vague zoning arrangement with superficial bundles of spindled cells arranged parallel to the surface changing to deeper haphazardly arranged sheets of cells. There may be a thin rim of uninvolved, mildly inflamed lamina propria separating the fibroblastic cells from the superficial lining. The proliferating spindled cells can lead to a wide separation and disorganization of the crypts. The muscularis mucosae may appear slightly disorganized. There may also be a subset of lesions that contain serrated crypts that are referred to as mixed fibroblastic–hyperplastic polyps. The spindle cell areas in fibroblastic polyps are positive for vimentin and negative for S100 protein, c-kit, epithelial membrane antigen, cytokeratin, CD34, CD68, COX-2, and factor XIIIa. Ultrastructurally they exhibit the features of fibroblastic cells (598, 599).

Inflammatory Pseudopolyps

Inflammatory pseudopolyps are not true mucosal proliferations. Rather, they are areas of inflamed regenerating mucosa that project into the colonic lumen. As a result they may grossly resemble pedunculated or sessile adenomas (Fig. 13.166). Exceptionally, they may be very large, owing principally to an expansion of the stromal fibrous tissue. Such polyps often have an irregular surface. They have no malignant potential but their presence does not rule out other lesions in the colon. Inflammatory polyps occur most frequently in patients with colitis and sites of mucosal injury, including ulcers and anastomoses. They often appear as multiple, small sessile, sometimes ulcerated polyps. The ulcerated mucosa is partially replaced by exuberant, edematous granulation tissue admixed with an intense inflammatory cell infiltrate. The lamina propria contains dilated crypts with both epithelial degeneration and regeneration and variable surface erosion. The crypts typically appear irregularly branched, dilated, and regenerative. Cryptitis and crypt abscesses may be prominent. Occasionally, hyperchromatic mucin-depleted regenerative epithelium simulates adenomatous epithelium. However, in contrast to adenomatous tissue, the epithelium usually shows evidence of maturation toward the surface. In patients with ulcerative colitis the changes mimic dysplasia, but the inflammatory background should alert one to not overdiagnose the lesions as dysplasia. The lesions may also contain marked atypia as described below. The lesions may also mimic juvenile polyps and the polyps of some of the rare polyposis syndromes discussed in Chapter 12. A knowledge of the clinical features (the presence of a polyposis syndrome or a colitis) helps distinguish between these possibilities.

Inflammatory Polyps with Bizarre Stromal Cells

A small group of inflammatory polyps contain bizarre stromal cells that may be mistaken for a malignancy. Most lesions occur in middle-aged or elderly patients (600, 601). Large, bizarre, mesenchymal cells are present. These appear as atypical, spindled, stellate, epithelioid, or large round cells within the lamina propria or in granulation tissue. They have abundant amphophilic cytoplasm, vesicular nuclei, and large eosinophilic inclusionlike nucleoli. Because of the inclusionlike nature of the nuclei, the cells may be confused with CMV infections, but immunohistochemical stains for CMV are negative. They are usually dispersed in a zone under the ulcerated or regenerated mucosa without infiltrating the deeper stroma (Fig 13.167). Sometimes the atypical cells blend into the granulation tissue. Multinucleated and giant cell forms are also present. Rarely, atypical pale epithelioid cells form round, cohesive clusters resembling acini or vascular structures (600, 601). Lack of staining with cytokeratin rules out a carcinoma. Mitotic figures are uncommon and atypical mitoses are absent. The cells do not contain mucin or glycogen. These cells lie within the inflammatory exudate and any associated epithelial elements usually appear benign or reactive in nature. They stain strongly for vimentin and sometimes for muscle-specific actin, a phenotype that is consistent with reactive fibroblasts or myofibroblasts (601).
Lesions Presenting as Polyps

FIG. 13.166. Inflammatory polyp. A: Endoscopic appearance. A small fibrin cap is present on top of the lesion. B: Endoscopic polypectomy of a bosselated inflammatory polyp. C: Histologic section demonstrates an exophytic lesion that is intensely congested. The architecture is distorted with crypt loss and prominent inflammation. D: Higher power magnification of the inflammatory process demonstrates the presence of intense vascular engorgement, loss of surface glands, and fibrosis of the lamina propria.
Lesions Presenting as Polyps

Misinterpretation of these reactive changes can result in unnecessary radical surgery. These lesions can be particularly confusing when encountered in small biopsies in which the entire tissue context is lost. However, immunostains should resolve their true nature, but in case of doubt the area can be rebiopsied.

P.874

FIG. 13.167. Inflammatory polyp with stromal atypia. A: This low-magnification picture shows that there is significant disruption of the colonic mucosal architecture. B: Higher magnification shows the regenerative glands and a lamina propria filled with a proliferation of very atypical epithelioidlike spindle cells. These cells were cytokeratin, actin, S100, CD34, and CD117 negative. C: The usual mononuclear cells of the lamina propria are replaced by a spindle cell proliferation. D: Section from a different polyp with atypia that centers around the capillaries.

Inflammatory Cap Polyps

Inflammatory cap polyps develop in the setting of anorectal mucosal prolapse, affecting patients of all ages. The patients present with diarrhea, mucoid stools, gastrointestinal bleeding, and/or tenesmus. The lesions usually arise in the rectosigmoid and are often multiple, measuring in size from a few millimeters to 2 cm (602). The lesions lie on the crests of the mucosal folds separated by normal or edematous mucosa. They likely arise secondary to transitory mild ischemia that occurs when the mucosa and submucosa prolapse. These nonneoplastic lesions consist of elongated, tortuous hyperplastic crypts. These are frequently dilated and inflamed. There is acute and chronic inflammation in the lamina propria and a characteristic cap of inflamed granulation tissue and fibrin covers the mouths of adjacent crypts (Fig. 13.168). The polyps may mimic hyperplastic polyps or adenomas, except for the distinctive covering cap. The stroma frequently contains hyperplastic frayed smooth muscle bundles extending up from the muscularis mucosae, a feature commonly seen in anorectal mucosal prolapse.

Lymphoid Polyps and Lymphonodular Hyperplasia

Large intestinal lymphoid polyps and focal lymphoid hyperplasia most commonly arise in the rectum. They may reflect a reactive change to a prior inflammatory episode. Most patients are children, adolescents, or adults under the age of 50. Prolapse of a rectal mass, rectal bleeding, constipation, diarrhea, and discomfort may be presenting symptoms. The lesion presents as
Lesions Presenting as Polyps

single or multiple sessile polyps or as a cobblestoned Mucosa. The “polyps” measure from 0.5 to 5 cm in diameter and have an intact mucosal surface. Some lesions appear to result from a hypersensitivity reaction to food because the patients have high IgE levels and increased intestinal permeability (603). Histologically the lesions are well circumscribed and they often have prominent germinal centers. The lymphocytes are well differentiated without atypia or mitoses.

**FIG. 13.168.** Inflammatory cap polyp. The regenerative glands at the bases are covered by a cap of granulation tissue that spans the surface of many glands. (Photograph courtesy of Dr. Geraint Williams, University of Wales, Cardiff, Wales.)

**Bilharzial Polyp**

An interesting inflammatory polyp that is rare in the United States but common in Egypt and other tropical countries is the bilharzial polyp. It results from schistosomal infections. Grossly, the polyps are hard and as they develop they become polypoid. They are covered by a layer of normal mucosa but their inner core consists of a mass of granulomatous tissue, ova, and, occasionally, female worms (Fig. 13.131). A true stalk gradually develops.

**Juvenile Polyps**

Juvenile (or retention) polyps develop most commonly in children, but they may occur in persons of any age. They present as single or multiple lesions. They invariably have a smooth, lobulated surface. The histologic features are predominantly inflammatory with a variable but usually prominent degree of cystic dilation of the glands admixed with inflammation and
Lesions Presenting as Polyps

regeneration. These lesions are discussed further in Chapter 12.

**Peutz-Jeghers Polyps**

Peutz-Jeghers polyps contain a mature epithelium lining arborizing proliferations of the muscularis mucosae. They occur as part of an autosomal dominant syndrome that includes polyps in the stomach and intestines, as well as mucocutaneous pigmentation and genital tumors. The polyps tend to involve the small bowel but they may also involve the colon, either as solitary lesions or as part of PJS. This syndrome is discussed further in Chapter 12.

**Isolated Colonic Hamartomas**

Colonic hamartomas are localized, nonneoplastic growths usually consisting of disorganized overgrown normal mature tissues whose cellular elements are similar to those of the organ in which the lesion is found. GI hamartomas are usually thought of as belonging to patients with PJS. However, other rare hamartomas occur. Hamartomas identical to those found in PJS affect patients with tuberous sclerosis (604,605). Rare lesions consist of a mixture of mature adipose tissue lying between simple benign glands (605). Other lesions consist of a proliferation of smooth muscle cells lying between the glands (Fig. 13.169). These lack the typical arborizing pattern of Peutz-Jeghers polyps.

**Inflammatory Myoglandular Polyps**

Inflammatory myoglandular polyps (IMGs) are a unique subset of colorectal polyps (606). Patients range in age from 15 to 78 years, and they lack evidence of IBD or other inflammatory colitides. Endoscopic examination reveals solitary pedunculated, smooth-surfaced, red polyps. The pedunculated polyps occur in the left colon, particularly in the sigmoid, and often have a long stalk. They may be asymptomatic and found at the time of screening colonoscopy or they may cause rectal bleeding. They measure up to 2.5 cm in diameter and their cut surface reveals the presence of mucin-filled cysts. The spherical head of the polyps consists of hyperplastic glands, often with a serrated appearance or with occasional cystic dilation. The surface of the polyp appears eroded, without a fibrinous exudate. It is also covered by regenerating epithelium. Acute and chronically inflamed granulation tissue with engorged capillaries is present in the lamina propria. Many neutrophils populate the eroded areas at the periphery of the lesion. Hemosiderin deposition in the lamina propria is common. The polyps superficially resemble juvenile polyps, inflammatory polyps, and Peutz-Jeghers polyps. However, their unique feature is the presence of radially arranged smooth muscle in the central lamina propria. Smooth muscle bundles are unusual in inflammatory and juvenile polyps. The presence of the inflammation and the cystically dilated glands are unusual for Peutz-Jeghers polyps.
Lesions Presenting as Polyps

FIG. 13.169. Colonic hamartoma. A: Cross section through a “polyp” that demonstrates an intermingling between bands of smooth muscle and the glands. There is no clear demarcation between the smooth muscle proliferation and the muscularis mucosae. The lack of clear demarcation of the smooth muscle bundles from the intimately admixed glands distinguishes the lesion from a leiomyoma arising from the muscularis mucosae. The lesion arose in the transverse colon, distinguishing it from an area of prolapse. B: The lesion at higher magnification with the intermingling of smooth muscle bundles and glands. C: Specimen from another lesion cut in cross section showing the intermingled mixture of the smooth muscle bundles and glands.

Polyps due to Atheromatous Emboli

Rare atheromatous emboli-associated polyps have been described in the colon (607,608). The polyps are multiple, ranging from 0.3 to 1.9 cm in greatest dimension, and they usually localize to a specific colonic segment. They have an edematous submucosa and a superficially ulcerated mucosa. Microscopically, arterioles within the submucosa contain organized atheroemboli. The overlying mucosa is largely replaced by granulation tissue with focal coagulative necrosis present in the residual mucosa. The remainder of the bowel is unremarkable (608).

Granuloma Pyogenicum
Lesions Presenting as Polyps

The intestinal counterpart of pyogenic granuloma presents as an ulcerated, polypoid growth with either a sessile or pedunculated configuration. Histologically, it consists of lobular proliferations of variably sized capillaries in an edematous stroma. The capillaries are lined by a single layer of flattened or rounded endothelial cells supported by sparse spindle cells and a delicate collagenous stroma. Endothelial swelling may be prominent. Capillary endothelial hyperplasia is absent. The stroma contains variable numbers of inflammatory cells and varying degrees of edema (Fig. 13.170). This angiomatous lesion has an unclear pathogenesis.

FIG. 13.170. Pyogenic granuloma. A: Typical configuration of the pyogenic granuloma arising from the mucosal surface. B: Higher power magnification showing the granulation tissue components.

Filiform Polyposis

Filiform polyposis usually accompanies IBD. However, it occasionally is seen in the absence of known CD or UC. It presents as localized clusters of multiple fingerlike mucosal extensions, which can reach several centimeters in length (Fig. 13.171). Histologic sections demonstrate the presence of mucosal extensions supported by submucosa. The overlying mucosa generally appears relatively normal except in the case of IBD. These lesions may be received as biopsy specimens, in which case all one gets are long, fingerlike extensions of mucosa with a central submucosal core containing variable smooth muscle fibers. Often the thin structures show mucosa on both sides of the specimen.
Lesions Presenting as Polyps

FIG. 13.171. Filiform polyposis. A: Gross specimen illustrating the presence of a cluster of fingerlike mucosal extensions. B: Biopsy from this patient showing the presence of tissue lined on both sides by colonic epithelium. It is relatively normal and supported by a submucosa containing strands of smooth muscle.

FIG. 13.172. Lipomatous hypertrophy of the ileocecal valve. A: Pedunculated polyp from the cecum that has a short, narrow stalk. The muscularis propria (MP) extends to the middle of the lesion. The majority of the lesion consists of fatty tissue. It is not well demarcated and contained within a fibrous capsule, as would be expected for a lipoma. B: A similar lesion that was less obviously pedunculated. The muscularis mucosae extends into the center of the lesion and nonencapsulated fatty tissue lies on either side.

Lipomatous Hypertrophy of the Ileocecal Valve

The ileocecal valve sometimes presents as a cecal polyp, usually as the result of lipomatous hypertrophy. This lesion is easily identified because it consists of an expansion of the submucosal fatty tissues. These do not form a well-rounded mass. Generally, the muscularis propria is thrown up into this polypoid projection and is usually seen in the center of the lesion (Fig. 13.172).

Prominent Mucosal Folds

Prominent mucosal folds may appear to the endoscopist as a polypoid lesion and may therefore be biopsied. These are usually areas of mucosal prolapse and they occur most frequently in patients with an underlying motility disorder including diverticular disease. They are discussed further in Chapter 10.
Reactive Fibromuscular Proliferations

Reactive fibromuscular proliferations consist of mucosal and submucosal proliferating mature smooth muscle cells often admixed with vessels, neural tissue, and even ganglion cells. These lesions usually complicate other disorders such as IBD. They vary in size from several millimeters to 3 or 4 cm in diameter. The mucosa generally appears regenerative with branched crypts. Evidence of active inflammation is absent. However, there may be mild chronic inflammation both in the mucosa and in the submucosa. The underlying submucosa is variably obliterated by a proliferation of smooth muscle cells, vessels, and neural tissue. Immunostains of such lesions generally show a mixture of actin-positive cells intermingled with S100- or synaptophysin-positive cells corresponding to neural tissue. The demarcation between the muscularis mucosae and the underlying submucosa is lost. These lesions may progress on to a more mature and densely cellular stromal core that consists almost exclusively of smooth muscle tissue intermingled with other normal elements. The submucosa becomes completely obliterated. The etiology of these lesions is obscure, but they appear to represent reparative responses (Fig. 13.173).
Lysosomal Storage Diseases

The lysosomal storage disorders result from various enzymatic defects, which include the absence of an enzyme activator or a protective protein, lack of a substrate activator protein, lack of a transport protein required for egress from the lysosome, defects in posttranslational processing, or synthesis of catalytically inactive proteins (552). The sites that are affected are those where the specific substrates need to be metabolized. Lysosomal storage diseases are usually classified into three categories: (a) sphingolipidoses (Gaucher disease); (b) mucopolysaccharidoses (Hurler and Hunter diseases); and (c) glycogen storage disease (Pompe disease) (Table 13.28). All three categories show variable severity and time of onset. The lysosomal disorders are usually diagnosed by enzymatic assay of white blood cells or fibroblasts or by rectal biopsies. Acid phosphatase stains highlight the intracellular inclusions present in lysosomal storage diseases. The tissues may also be examined by PAS, Luxol fast blue, and Sudan black stains, and for acid phosphatase activity, as well as examined under ultraviolet light to show accumulations of autofluorescent material (553). Most individuals advocate use of both histologic and ultrastructural examination to document the disease (553). Because the stored substances are often lipids, frozen sections are necessary to demonstrate the abnormal accumulations. Thus, when such a disease is suspected, a piece of unfixed tissue must be snap-frozen for further analysis.

Batten Disease (Neuronal Ceroid Lipofuscinosis)

Batten disease is the most common neuronal storage disease of children. It is classified into congenital, infantile, late infantile, early juvenile, and juvenile based on its pathology and age of onset. The abnormal nerves stain with Luxol fast blue (554). Patients with infantile Batten disease exhibit delayed development, including microcephaly, hyperkinesis, and neurologic problems. Neurophysiologic examinations are abnormal. In order to make the diagnosis on rectal biopsy, one needs to see neurons that can be highlighted by Sudan black or acid phosphatase staining. The patients develop seizures and dementia. Vacuolated lymphocytes are absent.

| TABLE 13.28 Examples of Lysosomal Storage Diseases Affecting the Gastrointestinal Tract |
|---------------------------------|---------------------------------|---------------------------------|
| **Disease**                     | **Enzyme Deficiency**           | **Major Stored Substance**      |
| Glycogen storage disease        |                                 |                                 |
| Type 2-Pompe disease            | α-1,4-Glucosidase (lysosomal glucosidase) | Glycogen                        |
| Sphingolipidoses                |                                 |                                 |
| GM1-gangliosidosis              | GM1-ganglioside β-galactosidase  | GM1-ganglioside, galactose-containing oligosaccharides |
| GM2-gangliosidosis              | Hexosaminidase A                | GM2-ganglioside                  |
| Tay-Sachs disease               | Hexosaminidase A and B          | GM2-ganglioside, globaside       |
| Sandhoff disease                | Ganglioside activator protein   | GM2-ganglioside                  |
| GM2-gangliosidosis, AB variant  |                                 |                                 |
| Fabry disease                   | α-Galactosidase A               | Ceramide trihexoside             |
| Gaucher disease                 | Glucocerebrosidase              | Glucocerebroside                 |
Lysosomal Storage Diseases

<table>
<thead>
<tr>
<th>Niemann-Pick disease</th>
<th>Sphingomyelinase</th>
<th>Sphingomyelin</th>
</tr>
</thead>
</table>

**Mucopolysaccharidoses**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Enzyme</th>
<th>Sulfate/Sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler syndrome</td>
<td>α-L-Iduronidase</td>
<td>Heparan sulfate</td>
</tr>
<tr>
<td>Hunter syndrome</td>
<td>L-Iduronosulfate sulfatase</td>
<td>Dermatan sulfate</td>
</tr>
</tbody>
</table>

**Lipid storage diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme</th>
<th>Lipid Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolman disease</td>
<td>Acid lipase</td>
<td>Cholesterol esters, triglycerides</td>
</tr>
</tbody>
</table>

**Hurler and Hunter Syndromes**

The mucopolysaccharidoses include Hurler and Hunter syndromes. Patients with these syndromes have genetically determined deficiencies of the lysosomal enzymes involved in the degradation of mucopolysaccharides leading to their accumulation in the cell. Patients with Hurler syndrome accumulate heparin sulfate and dermatan sulfate, as do patients with Hunter syndrome. Hurler syndrome is inherited in an autosomal recessive manner, whereas Hunter syndrome is inherited as an X-linked recessive disorder. The patients present with involvement of many organs, including the GI tract (555). Ultrastructurally, the intracellular, membrane-bound lysosomes contain variable amounts of opaque, flocculent lamellae representing mucopolysaccharides. Fibroblasts, endothelium, and smooth muscle cells may appear vacuolated (556).

**Niemann-Pick Disease**

Niemann-Pick disease results from absence of sphingomyelinase, so that sphingomyelin accumulates in many organs throughout the body, including the viscera. In severe cases, extreme visceral accumulations are present along with progressive wasting, and patients often die in the first few years of life. Macrophages accumulate sphingomyelin in many tissues, including the lamina propria. They can be highlighted with the use of special stains for lipids, including Sudan black and oil red O. Ultrastructurally, macrophages contain membranous cytoplasmic bodies that resemble concentric lamellated myelin figures. Parallel palisaded lamellae impart an appearance of zebra bodies (557).

**Gangliosidoses**

Tay-Sachs disease is the prototype of the gangliosidoses. It results from a deficiency of the enzyme hexosaminidase A. This disease is particularly prevalent among Ashkenazi Jews. Hexosaminidase A catalyzes the degradation of GM2 ganglioside and because of the absence of the enzyme, this material accumulates within the cells, particularly of the nervous system (558). Patients also develop diarrhea and autonomic dysfunction, including motility disturbances. Adult GM1 gangliosidosis is a recently identified rare form of hereditary neuronal storage disease. It has a benign clinical course and cerebral lesions are restricted to the basal ganglia (559).

Rectal biopsies play a role in the diagnosis of gangliosidosis by demonstrating characteristic changes in the autonomic neurons (560). The biopsies need to be deep enough to include the submucosal plexus. Ultrastructurally, ganglion, Schwann, perithelial, and endothelial cells and histiocytes all contain characteristic electron-dense bodies, zebra bodies, and membranous cytoplasmic bodies (556). Patients with Tay-Sachs disease have these bodies in neural tissue. In contrast, patients with Sandhoff disease (hexosaminidase AB deficiency) exhibit similar structures in nerves as well as mesenchymal tissues, such as endothelial cells and fibroblasts (556). Membrane-bound clear vacuoles are also occasionally seen in the cytoplasm of rectal and cutaneous fibroblasts. The axons of the
unmyelinated nerves appear normal (560).

**Glycogen Storage Diseases**

Glycogen storage disease IA and 1B result from a deficiency or defective transport of the microsomal enzyme glucose-6-phosphatase in liver, kidney, and intestinal mucosa. Impaired gluconeogenesis, fasting hypoglycemia, hepatomegaly, lactic acidosis, hyperlipidemia, hyperuricemia, impaired platelet function, and bleeding diathesis are common to both diseases. Glycogen storage disease 1B is additionally complicated by recurrent pyogenic infections caused by apparent neutropenia and neutrophil dysfunction (561). Patients with these disorders demonstrate changes indistinguishable from Crohn disease, including ileal mucosal irregularities, colitis, granulomas, and stenosis involving the right side of the colon (562). Perianal abscesses are common. The bowel lesions may result from neutrophil deficiencies. Because a similar enteritis develops in patients with neutrophil deficiency states, treatment of the patients with colony-stimulating factors results in decreased bowel inflammation (563).

**Lipid Storage Diseases**

**Fabry Disease**

Fabry disease, an X-linked disorder of lipid metabolism, results from a deficiency of the enzyme α-galactosidase A that leads to ceramide trihexosidase accumulation. Malabsorption sometimes affects patients with small intestinal involvement. Patients with Fabry disease also present with enterovesical fistulae and lymphadenopathy. Foamy, lipid-containing, vacuolated neurons and nerve fibers of Meissner plexus, vascular endothelial cells, muscularis mucosae, and histiocytes are all strongly positive with Sudan black, Luxol fast blue, PAS, and oil red O stains on frozen sections. Ultrastructural examination shows the presence of zebralike, lamellar, lysosomal inclusions (564).

**Tangier Disease**

Patients with Tangier disease have abnormal apolipoprotein metabolism (565), hemolytic anemia, and lipid-containing macrophage accumulation in many tissues, including the gastrointestinal lamina propria. These accumulations most commonly affect the large intestine, but they can occur anywhere in the gut. They present as yellow to orange nodules and streaks. Histologically, these streaks and nodules contain collections of foamy, lipid-containing histiocytes.

**Wolman Disease**

Wolman disease (lysosomal acid esterase deficiency) is a lethal heritable disorder affecting children. It is characterized by hepatosplenomegaly, enlarged calcified adrenals, and a generalized visceral infiltration by foamy histiocytes containing neutral fats and cholesterol. Affected individuals develop persistent diarrhea and they rarely survive for more than 1 year. Fat-laden histiocytes containing cholesterol and triglycerides infiltrate the superficial lamina propria. The mucosal accumulations are most marked in the jejunum (553).

**Cholesterol Ester Storage Disease**

Cholesterol ester storage disease is a rare inherited disorder of lipid metabolism also due to a deficiency of lysosomal acid esterase, but it exhibits a much more benign clinical course than Wolman disease. The liver and spleen enlarge and serum cholesterol becomes elevated. Numerous foamy macrophages filled with cholesterol esters populate the muscularis mucosae and submucosa. Lipid droplets accumulate due to a block in the transport of cholesterol into lacteals. They are found in macrophages in the lamina propria of both the large and small intestine, alongside the lacteal endothelium, in the smooth muscle, and in vascular pericytes. The mucosal histiocytes containing the cholesterol...
esters and carotenes impart an orange tinge to the mucosal surface. The myenteric plexus appears vacuolated secondary to cholesterol ester deposits. The epithelium appears normal.

**Peroxisomal Disorders**

The normal intestinal epithelium contains numerous elliptical peroxisomes filled with coarsely granular material. These are absent in Zellweger syndrome (a lethal condition), and as a result, patients accumulate very-long-chain fatty acids. Other peroxisomal defects include neonatal adrenoleukodystrophy and infantile Refsum disease. The diagnosis is usually made by a combination of detecting metabolic abnormalities in very-long-chain fatty acids, bile acids, pipecolic acid, and phytanic acid, and demonstration of the absence of peroxisomes in intestinal biopsies (566,567).
Microscopic Colitis

General Comments

Some patients with chronic idiopathic diarrhea have histologic evidence of colitis even though their colons appear normal by 
barium enema and by colonoscopy; such patients have the entity known as microscopic colitis (380). The term microscopic 
colitis has been used to include several distinct but probably related diseases, including collagenous colitis and lymphocytic 
colitis, although more accurately it is lymphocytic colitis that has been traditionally called microscopic colitis. The term 
microscopic colitis has also been used more broadly to include the finding of colitis in the absence of endoscopic 
abnormalities. As a result, the diagnosis could include IBD, especially Crohn disease and eosinophilic colitis and potentially 
other mild forms of colitis. This leads to confusion and we prefer to not make a diagnosis of microscopic colitis but to use more 
specific diagnoses of either lymphocytic colitis or collagenous colitis since these entities are well characterized. 
Reports showing a progression of lymphocytic colitis to collagenous colitis have led to the suggestion that the formation of the 
subepithelial collagen band develops at a later stage in the disease process as a result of continued inflammation and 
subsequent fibrosis and that the two disorders are variations of the same disease (381). 
Since patients with lymphocytic and collagenous colitis present with a history of watery, nonbloody, persistent or intermittent 
diarrhea, often lasting several years, it is reasonable to consider these two disorders as part of the watery diarrhea–colitis 
syndrome (WDCS), a distinct form of chronic colitis (382). 
It is likely that similar immune abnormalities affect both groups of patients. They both have a significant increase in mean 
numbers of intraepithelial lymphocytes (IELs) with significantly more CD8+ than CD4+ IELs. Most IELs bear the TCRαβ; 
TCRγδ–bearing cells are not increased. CD4+ helper T cells predominate in the lamina propria. The colonic epithelium 
abnormally expresses human leukocyte antigen (HLA)-DR antigens. These findings suggest that a major histocompatibility 
complex (MHC)-restricted immune mechanism can be involved in the pathogenesis of both diseases (383). There is also an 
association with various gastrointestinal and autoimmune disorders. Two associations are particularly prominent: 
Degenerative osteoarticular disease and celiac disease (381,384,385). There are also reports of patients with these diseases 
who subsequently develop either autoimmune thyroid diseases, ulcerative colitis or Crohn disease (386), primary biliary 
cirrhosis, and the CREST syndrome (387). Lymphocytic colitis is more common than collagenous colitis in patients who 
develop Crohn disease (388). A family has been reported in which different family members had ulcerative colitis, Crohn 
disease, and collagenous colitis (389). 
There is also a relationship between both diseases and the uses of some drugs, especially aspirin, NSAIDs, ticlopidine, 
lansoprazole, and flutamide. There may also be a relationship with smoking (390). Overall, the natural history of both 
collagenous colitis and lymphocytic colitis is benign and in some patients the disease resolves spontaneously.

Collagenous Colitis

The diagnosis collagenous colitis describes patients who suffer from chronic, watery diarrhea and who have subluminal 
deposits of a collagenous ground substance beneath the surface epithelium at the lamina propria interface (391). The female-
to-male ratio is 10:1, with an age range of 23 to 86 and a mean of 54 to 66 years (385). The incidence of the disease in 
individuals who suffer from chronic diarrhea ranges from 0.3% to 5%. The incidence is reported to be about 16 cases per 
100,000 population (384). The disorder sometimes affects children (392) and families (393). 
Postulated etiologies include immune dysregulation leading to colonic inflammation, abnormalities in collagen synthesis, 
abnormalities in the pericryptal myofibroblasts, mast cell or eosinophil abnormalities, “plasmatic vasculosus,” drugs, and 
bacterial toxins (394,395,396,397,398,399). Plasmacytic vasculosus is a theory that proposed leakage of plasma proteins and 
fibrinogen through the subepithelial capillary walls and their subsequent replacement by collagen. Surface epithelial damage 
appears to cause the secretory diarrhea, whereas the thickened subepithelial collagen table appears to represent a variable 
response to the surface damage. The injury may result from bile acid malabsorption (400), mast cell infiltrates (395), 
prostaglandin effects (401), or drug exposures. A significant percentage of patients with collagenous colitis have a history of 
using NSAIDs or antibiotics (402). Yersinia infections may also trigger the development of collagenous colitis (403).
The symptoms vary in duration and intensity and long periods of remission have been described. Symptoms include watery, nonbloody diarrhea with up to 20 stools per day. The diarrhea can last for months or decades. Colicky abdominal pain occurs frequently. Nausea, vomiting, flatulence, incontinence, and weight loss vary in frequency. Patients may also present with protein-losing enteropathy (404). Rarely, collagenous colitis associates with chronic constipation (405) in the absence of watery diarrhea. The disorder typically involves the colon, although the small bowel and stomach may be involved, particularly in patients with celiac disease or other autoimmune disorders. Collagenous colitis exhibits spontaneous remissions and relapses; occasionally the disease resolves spontaneously (406,407). In some patients it resolves following treatment with drugs or by diverting the fecal stream.

The histologic hallmark of collagenous colitis is mucosal colonic inflammation associated with a broad, continuous, hypocellular, eosinophilic, linear, subepithelial, fibrous band immediately subjacent to the surface epithelium (Fig. 13.139). This collagen band measures 10 to 70 µm in thickness, with a mean of 12 to 30 µm (408), and it surrounds subluminal capillaries and myofibroblasts. A thickness of at least 30 mm provides the greatest consistency in establishing the diagnosis (409). There is little if any extension of the thickened collagen table around the crypts, except in cases demonstrating marked intercryptal subepithelial thickening. In addition to its thickness, the relative inhomogeneity and irregularity of the collagen layer at its lower borders helps distinguish it from the normal subepithelial basement membrane (Figs. 13.139 and 13.140). The thickened subepithelial layer stains light pink with PAS and green with Masson trichrome stains. Congo red stains are negative. The thickened collagen table predominantly contains collagen IV and tenascin (410,411,412). Plasma cells, mast cells, and multinucleated giant cells may be underneath, or embedded within, the thickened collagen table. The changes are most marked in the proximal colon and the distal bowel may be spared. In one study biopsies from the transverse colon were more likely to be diagnostic of the disorder than biopsies from the rectosigmoid or right colon (409). The lesion is often continuous, but it may also exhibit a patchy distribution, particularly early in the disease course or as it resolves (413,414). As the disease is treated, the basement membrane thickening disappears (407).
**FIG. 13.139.** Collagenous colitis. *A:* A dense, irregular, eosinophilic band lies below the luminal surface. *B:* Higher magnification showing the acellular dense band underneath an epithelium that is beginning to lift off the surface. *C:* The subepithelial band is relatively inhomogeneous and there is chronic inflammation in the lamina propria.

**FIG. 13.140.** Collagenous colitis. *A:* Medium magnification showing the band underlying the surface epithelium. *B:* High magnification demonstrating the presence of numerous cells within this thickened band (*A, B:* trichrome stain).
The diagnosis of collagenous colitis not only requires a thickened collagen table, but also the presence of changes characteristic of colitis, including epithelial damage and intraepithelial lymphocytosis. Damaged epithelial cells appear flattened, mucin depleted, vacuolated, and irregularly oriented. Focally, small strips of interglandular surface epithelium lift off their basement membrane and a subepithelial cleft filled with neutrophils and eosinophils forms. Rarely, subepithelial multinucleated giant cells are present (Fig. 13.141) (415,416). Epithelial nuclei may appear slightly enlarged and minimally pseudostratified, but mitotic figures are not prominent. The glands sometimes appear slightly more basophilic than normal due to mild regeneration. Paneth cell metaplasia, which is usually a marker of IBD, may occasionally be seen and may predict the severity of the disease (385). In one study Paneth cell metaplasia was present in up to 44% of biopsies from patients with
Microscopic Colitis

Collagenous colitis (417). Pseudomembranes have also been described in collagenous colitis (402). The intraepithelial lymphocytosis in collagenous colitis is not as dramatic as that seen in lymphocytic colitis (382). IELs are seen in the colon and may also be present in the terminal ileum (418). Focally, the superficial lamina propria contains slightly to moderately increased numbers of lymphocytes, plasma cells, and mast cells admixed with variable numbers of eosinophils and neutrophils. Eosinophils can be focally prominent and degranulating (396). The subepithelial tissues may show prominent vascularity. Neutrophilic cryptitis is often focally present (381), perhaps reflecting the exposure to NSAIDs or other drugs. The mucosal thickness remains normal and the glandular architecture is maintained without crypt elongation, atrophy, irregularity, or branching.

Patients with collagenous colitis may also have collagenous gastritis (419) and/or collagenous duodenitis or enteritis (420). We recently encountered a patient with extensive subepithelial collagen deposits throughout the gastrointestinal tract without evidence of celiac disease and NSAID or other drug use in whom there was no obvious etiology for the extensive changes that were present. The patient became extremely malnourished and eventually required total parenteral nutritional support. Subepithelial collagen thickening occurs in various diseases, so that one must make the diagnosis of collagenous colitis in the proper clinical and histologic settings (421). Tangential sectioning of normal colon results in artifactually thickened basement membranes and such cases can be wrongly interpreted as collagenous colitis. If biopsies lack the characteristic inflammation, a thick basement membrane should be ignored. The differential diagnosis of collagenous colitis also includes lymphocytic colitis, UC, ischemic colitis, radiation colitis, amyloidosis, progressive systemic sclerosis and infectious colitis, colonic mucosal prolapse syndrome, fecal stream diversion, and diverticular disease (Fig. 13.142). Biopsies with increased subepithelial collagen deposits from patients without microscopic colitis generally come from the rectum or rectosigmoid. Features that distinguish the diseases that mimic collagenous colitis are listed in Table 13.22.

Patients may spontaneously recover from their disease or they may require treatment with antidiarrheal agents or even steroids. Mesalazine and budesonide are effective treatments for the disease and the drugs are well tolerated (422). However, there is a high risk of relapse after stopping 8 weeks of treatment (423). Patients who appear to have NSAID-related collagenous colitis or those with increased inflammation in the lamina propria tend to require steroids to treat the disease (424).

Lymphocytic Colitis

Lymphocytic colitis typically presents in elderly patients with chronic diarrhea. Patients with lymphocytic colitis exhibit a more variable age range than those with collagenous colitis; it occurs at all ages and it may be a more heterogeneous disease than collagenous colitis. The disorder affects both men and women almost equally (390,425). In one study the incidence of lymphocytic colitis was three times higher than that of collagenous colitis (426). Patients with lymphocytic colitis present with chronic watery diarrhea that can be intermittent or continuous, ranging in duration from 2 months to 25 years. The watery diarrhea results from markedly decreased water absorption (425). Related symptoms may include mild crampy abdominal pain, moderate weight loss, and an essentially normal physical examination (382). Up to one third of patients with celiac disease have lymphocytic colitis (427). An association also exists between lymphocytic colitis and tropical sprue (428) and collagenous gastritis or enterocolic lymphocytic phlebitis (429) as well as with various autoimmune diseases. These include rheumatoid arthritis, sicca syndrome, uveitis, idiopathic pulmonary fibrosis, diabetes, pernicious anemia, autoimmune thyroid disease (430), and idiopathic thrombocytopenic purpura (384). Some patients have increased antinuclear antibodies, antiparietal cell antibodies, and antimicrosomal titers. Lymphocytic colitis patients have an increased frequency of HLA A1 and a decreased frequency of HLA A3 compared to control populations (402). There is also an association with the use of some drugs including NSAIDs, ranitidine, flutamide, Cyclo-FORT, gold salts, bentazepam and ticlopidine, carbamazepine, cimetidine, simvastin, and vinburnine (385,426,431,432). In addition, some patients develop lymphocytic colitis following infections. The lymphocytic colitis in such patients may represent either a resolving bacterial or viral infection or a persistent immune response following the infection.
### TABLE 13.22 Distinguishing Characteristics of Diseases that May Mimic Collagenous Colitis on Biopsy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenous colitis</td>
<td>Subluminal collagen thickening; intraepithelial lymphocytosis; inflammation in upper mucosa</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Diffuse continuous process with numerous crypt abscesses, cryptitis, glandular destruction, and signs of chronicity; no subluminal collagen thickening</td>
</tr>
<tr>
<td>Radiation colitis</td>
<td>Mucosal telangiectasia, submucosal vascular changes, atypical fibroblasts, fibrosis</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>Diffuse lamina propria inflammation, significant neutrophils in lamina propria; usually no subluminal collagen thickening</td>
</tr>
<tr>
<td>Mucosal prolapse syndrome</td>
<td>Glandular distortion, mucosal ulceration, mucosal hyperplasia, mucosal fibrosis, perpendicular smooth muscle fibers in lamina propria</td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>Coagulative necrosis, fibrin thrombi, architectural distortion if disease chronic, mucosal fibrosis, glandular dropout</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Perivascular, muscular, or lamina propria eosinophilic deposits; positivity with Congo red stains</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td>Fibrosis along all basement membranes, including crypts</td>
</tr>
<tr>
<td>Diverticulosis</td>
<td>Chronic inflammation, thickened basement membranes</td>
</tr>
<tr>
<td>Diversion colitis</td>
<td>Prominent nodular lymphoid hyperplasia, ulceration, acute inflammation, aphthous ulcers, cryptitis</td>
</tr>
</tbody>
</table>

The most distinctive feature of lymphocytic colitis is the presence of increased intraepithelial lymphocytes, particularly at the luminal surface (Fig. 13.143). Significantly increased numbers of intraepithelial cytotoxic T lymphocytes populate the surface epithelium (433). To be of diagnostic significance, the increased lymphocytes must number at least 15 per 100 epithelial cells (434). This threshold compares an average of 4 to 5 lymphocytes per 100 epithelial cells in the normal colon, inflammatory bowel disease, and infectious colitis (425); a mean of 8.4 in patients with celiac disease without colonic epithelial lymphocytosis; and a mean of 25 to 32.4 in patients with lymphocytic colitis without concurrent celiac disease. Sometimes the lymphocytes stack up in a vertical array between the enterocytes. Increased IELs may also be seen in the terminal ileum (418). The lamina propria contains increased numbers of lymphocytes, eosinophils, or neutrophils, although the lamina propria inflammation tends to be less than that seen in collagenous colitis and there tend to be few numbers of eosinophils. Occasionally, subepithelial multinucleated giant cells are present (415). Paneth cell metaplasia and an increased number of mast cells can also be seen. Goblet cell mucin may be reduced. Other prominent features include surface epithelial damage with cellular loss and epithelial detachment, infiltration of the surface epithelium with eosinophils and neutrophils, and minimal crypt distortion or active cryptitis (425). Increased apoptosis may be present in some patients. The increased number of eosinophils and apoptotic activity may warrant questioning the patient concerning drug use so that one can determine if the changes disappear following drug cessation. Unlike collagenous colitis, the histologic features of lymphocytic colitis are usually uniform throughout the large bowel.

Increased intraepithelial lymphocytes are common to several diseases (Table 13.23), but when diffusely present they are more likely to be associated with lymphocytic colitis. Focal lesions, sometimes taking the form of lymphoid aggregates, are more likely to be seen associated with polyps.
Microscopic Colitis

diverticula, or Crohn disease (433). Intraepithelial lymphocytosis may also be encountered in proximal biopsies of patients with ulcerative colitis and distally in patients with Crohn disease (91).

**FIG. 13.143.** Lymphocytic colitis. *A:* The photograph shows a hypercellular colonic biopsy. The hypercellularity is due to a lymphocytic infiltrate in the lamina propria and the epithelium. There is no architectural distortion. *B:* Higher magnification showing the intraepithelial lymphocytosis and the infiltration of the lamina propria by lymphocytes.

**Atypical Lymphocytic Colitis**

Lymphocytic colitis consists of the classic triad of nonbloody watery diarrhea, normal endoscopic features, and colonic epithelial lymphocytosis. Recently a group of patients has been recognized as having atypical lymphocytic colitis. These patients have the classic histologic features but they lack either the appropriate clinical or endoscopic findings (434). The patients may present with constipation rather than diarrhea, as well as hematochezia, or have macroscopic evidence of colitis at endoscopy. The histologic abnormality may also be an incidental finding. Thus, atypical lymphocytic colitis appears to be a heterogeneous group of diseases and includes patients with idiopathic constipation, coexisting lymphocytic colitis, IBD, or possibly infectious colitis (434).

**TABLE 13.23 Large Intestinal Disorders Associated with Increased Intraepithelial Lymphocytes**

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic colitis</td>
</tr>
<tr>
<td>Collagenous colitis</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy</td>
</tr>
<tr>
<td>Brainerd diarrhea</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Graft vs. host disease</td>
</tr>
<tr>
<td>AIDS enteropathy</td>
</tr>
</tbody>
</table>

Some patients who have what appears to be focal lymphocytic colitis subsequently develop Crohn disease. However,
endoscopic abnormalities are present and there are moderate numbers of neutrophils in the tissue alerting one to the possibility that the disease is not lymphocytic colitis but Crohn disease (388).

**Large Intestinal Changes in Celiac Disease**

Patients with celiac disease may show histologic abnormalities in the rectal mucosa. These consist of increased populations of mucosal plasma cells, lymphocytes, and mast cells, especially in untreated patients or in patients rechallenged with gluten. CD3+ lymphocytes and activated CD25 lymphocytes expressing IL-2 receptors increase in the lamina propria, usually subjacent to the basal lamina. CD8+ IELs are also present. The inflammatory cells disappear (except for the mast cells) on dietary gluten restriction. The absence of neutrophils suggests that the lesion is not a conventional inflammatory-type proctitis but one induced by the gluten in the fecal stream and represents a cell-mediated form of response (435).

The changes in celiac disease may be identical to those seen in lymphocytic colitis. However, the colonic mucosa in patients with untreated celiac disease tends to lack surface epithelial abnormalities and an increased cellularity of the lamina propria, and there is lack of watery diarrhea when gluten is removed from the diet. In contrast, patients with refractory celiac disease may show colonic abnormalities indistinguishable from lymphocytic colitis. However, there may be differences in the number of CD8+ IELs in the two diseases, with more being present in lymphocytic colitis. (436).

**Brainerd Diarrhea**

The term *Brainerd diarrhea* is applied to the syndrome of chronic watery diarrhea characterized by abrupt onset, marked urgency to defecate, frequent fecal incontinence, abdominal cramps, weight loss, and fatigue in the absence of other systemic symptoms. The diarrhea typically lasts from 1 month to 3 years with a median duration of about 16 months (437,438,439,440,441). Most cases occur among patient cohorts following epidemic exposures to an unknown agent. The disease was named after Brainerd, Minnesota, where more than 100 residents developed watery diarrhea after drinking unpasteurized milk from a local dairy.

Colonic biopsies reveal surface epithelial lymphocytosis without mucosal architectural distortion, surface degenerative changes, or thickened subepithelial collagen. There is usually not an increase in the mononuclear cells of the lamina propria. The degree of surface epithelial lymphocytosis is greater than that seen in control specimens, similar to that seen in collagenous colitis, and less than that seen in lymphocytic colitis. Acute focal colitis similar to that seen in acute infectious colitis may also be seen in addition to the epithelial lymphocytosis (437). The disorder can only be diagnosed in conjunction with epidemiologic data that indicate that the patient is part of an epidemic colitis with a common point source.
Neutropenic enterocolitis, also known as typhlitis, agranulocytic colitis, neutropenic enteropathy, and ileocecal syndrome, traditionally affects children treated for leukemia and other conditions. It may complicate chemotherapy for solid tumors (377). However, the disorder also affects healthier, nonterminal, neutropenic children and adults with solid tumors and other conditions including AIDS. The incidence of neutropenic colitis is increasing, particularly in patients with acute myelogenous leukemia undergoing high-dose cytosine arabinoside chemotherapy. Although direct mucosal cytotoxicity from cytotoxic drugs may contribute to the disorder, it is not a prerequisite for neutropenic enterocolitis to occur.

Most patients are profoundly granulocytopenic, with their neutrophil count measuring <500 to 1,000 cells/mm³. Patients are typically neutropenic for at least a week before symptom onset (378). Patients usually present with a dramatic onset of fever, watery or bloody diarrhea, right abdominal quadrant pain, abdominal distention, rebound tenderness, nausea, and vomiting (378). The presence of fever, rigors, and shock suggest the development of sepsis or colonic perforation. The disorder is often fatal unless aggressively treated, usually with resection of the involved bowel segment. Mortality rates range between 5% and 100% and average 40% to 50%. Death results from cecal perforation, bowel necrosis, and sepsis.

The pathogenesis of the syndrome is illustrated in Figure 13.134. The chemotherapy damages the GI mucosa by destroying the rapidly dividing epithelium. Alternatively, mucosal neoplastic infiltrates may cause breaks in the mucosal barrier. Loss of mucosal integrity coupled with the neutropenia allows bacteria to invade the bowel wall and sepsis to develop. In children, the infections usually result from Pseudomonas or E. coli, whereas in adults C. septicum is the most common infecting organism. Ischemia also plays a role in the genesis of the lesion. The ischemia likely results from vascular invasion by bacteria or the production of bacterial toxins followed by the development of a disseminated intravascular coagulopathy. One often sees small thrombi within the mucosal and submucosal capillaries. Other causes of ischemia include perivascular neoplastic infiltrates, episodes of hypotension following sepsis, or mucosal hemorrhage complicating severe thrombocytopenia or the presence of angioinvasive fungi. The process preferentially involves the cecum due to the luminal stasis that occurs at this site. The relatively poor vascular supply of the cecum further predisposes to ischemic injury. Rarely, other bowel segments become involved.
The gross features of neutropenic enterocolitis vary due to the influence of its multiple etiologic factors. The changes range from mucosal erythema and localized areas of hemorrhagic necrosis with moderate degrees of edema to severe transmural edema and diffuse transmural hemorrhagic necrosis (Figs. 13.135 and 13.136). Usually, the bowel appears markedly thickened, edematous, and dusky, with scattered serosal ecchymoses (Fig. 13.135). The mucosa often appears beefy red, eroded, and ulcerated. Pseudomembranes develop. The edema gives the bowel wall a boggy or myxoid appearance. The submucosal edema is so severe that fluid oozes from the cut surfaces of the specimen. When the process is transmural, perforation may occur.

A severe necrotizing colitis is present with marked transmural submucosal edema, vasculitis, stromal hemorrhage, and patchy to complete epithelial necrosis (Figs. 13.136, 13.137, and 13.138). Degenerated epithelial cells detach from the basement membrane and lie within dilated glandular lumens. This process starts superficially (Fig. 13.137) and progressively involves the remainder of the crypt, frequently reaching its base (Fig. 13.138) and producing the glandular dropout typical of ischemia. The mucosa becomes variably ulcerated and a pseudomembrane containing fibrin and necrotic cellular debris covers the luminal surface (Fig. 13.137). In severe cases, the bowel exhibits transmural necrosis and degeneration of the muscularis propria. Vascular damage produces subtle or profuse intramural and intraluminal hemorrhage, and fibrin thrombi are often present in the submucosal vessels. Additionally, changes characteristic of chemotherapeutic injury (Fig. 13.137), including prominent apoptosis in the crypts, focal crypt dropout, and glandular regeneration, are often present. Numerous bacteria often are present in the pseudomembrane overlying the damaged epithelium. One may also occasionally see bacteria invading the mucosa and submucosa or lying within macrophages or the interstitial spaces (Fig. 13.138). One may also find evidence of the pre-existing neoplastic condition in the form of leukemic infiltrates within the bowel wall. There is a striking paucity of inflammation, given the degree of mucosal damage, and neutrophils are absent. The absence of neutrophils in the face of significant cell injury allows one to make the diagnosis of neutropenic enterocolitis. Patients may develop secondary infections that may complicate the histologic pattern. These most commonly are Candida or CMV infections.
Neutropenic Enterocolitis (Typhlitis)

FIG. 13.135. Gross appearance of neutropenic enterocolitis. A and B are from the same specimen. A: A dilated bowel with an erythematous serosal surface. Early adhesions are beginning to form. B: Opened specimen showing a boggy mucosa without ulceration due to marked submucosal edema. C: Another specimen that has much more mucosal erythema. The ileocecal valve bulges into the cecal lumen. The marked submucosal edema can be seen where the bowel wall is cut in cross section (arrow).

The histologic features overlap with *C. difficile*–associated pseudomembranous colitis. However, *C. difficile*–associated
Neutropenic enterocolitis (typhlitis) differs from pseudomembranous colitis in that pseudomembranous colitis has large numbers of neutrophils present in the exudate, while patients with neutropenic enterocolitis lack a neutrophilic infiltrate. The features also overlap with ischemic enterocolitis and infectious enterocolitis, but the absolute lack of neutrophilic infiltrates only occurs in ischemia prior to reperfusion injury and neutropenic enterocolitis.

**FIG. 13.136.** Neutropenic enterocolitis. Whole mount section showing the marked submucosal and subserosal edema. The muscularis propria is the eosinophilic band that has somewhat of a V shape between the two lighter areas. The mucosa is variably ulcerated.
Neutropenic Enterocolitis (Typhlitis)

**FIG. 13.137.** Neutropenic enterocolitis. *A:* Low-magnification photograph showing prominent submucosal edema (*SM*). The mucosa is also edematous, but not as severely as the submucosa. There appear to be dilated vessels in the mucosa, but these in fact represent attenuated crypts. The surface is variably ulcerated. *B:* Portion of mucosa with focal ulceration and a densely adherent pseudomembrane (*arrow*). The pseudomembrane appears slightly basophilic due to the presence of numerous bacteria. The lamina propria underlying this is congested. *C:* Higher magnification showing the submucosal edema and focal erosions. The glands in the mucosa appear hyperchromatic or attenuated. Some crypts have died and are lined by flattened, atrophic cells (*stars*). Other crypts appear regenerative. *D:* Higher magnification showing an atrophic crypt (*star*) among several regenerating crypts. Note the absence of acute inflammation in all of the figures.
Phlegmonous Colitis

Phlegmonous colitis is a very rare disorder that presents as submucosal cellulitis. It is rarer than its gastric counterpart, discussed in Chapter 4 (379). The bowel appears thickened and congested with submucosal edema and expansion. The mucosa is intact but the folds are thickened due to the submucosal edema. An intense neutrophilic infiltrate is present in the submucosa, which variably spreads into the muscularis propria. It associates with various bacterial infections, but often an organism is not identified.
FIG. 13.138. Neutropenic enterocolitis. This case differs from that shown in Figure 13.137 by having a much more hemorrhagic mucosa. 

A: The submucosa (SM) is congested and the vessels are markedly dilated. 

B: Higher magnification showing marked hemorrhagic necrosis and several residual crypt bases. Vascular congestion is also present. These changes are consistent with ischemic damage that occurs in neutropenic enterocolitis. Note the absence of neutrophils. 

C: Another area of a third specimen showing early damage of the superficial portion of the crypt. The changes mimic those seen in *Clostridium difficile* colitis. 

D: Numerous bacteria are present in the tissues. They are also present in a capillary. No neutrophils are present.
Pneumatosis Coli

Pneumatosis coli consists of gas-filled cysts within the bowel wall. Pneumatosis is asymptomatic or accompanied by constipation or diarrhea. The lesion may also be detected endoscopically or radiographically. Most often colonic disease follows mucosal ulceration due to ischemia, necrotizing enterocolitis, infection, and other causes. In the colon it may present endoscopically as a small mucosal elevation or polyp. It may also present as an intussusception (547). The cysts are found in all bowel layers. They are lined by epithelioid macrophages, multinucleated giant cells, and a variable chronic inflammatory cell infiltrate. An exceptional example of cysts containing spirochetes in a patient with coexisting spirochetosis was recently reported.
Radiation Injuries

Radiation injury causes two types of gastrointestinal damage. The first is the radiation damage itself; the second is the long-term consequence of radiation (i.e., ischemic changes or cancer development). Even though the colon and rectum are relatively radioresistant, they have a high incidence of radiation damage due to both the large radiation doses used to treat tumors arising in the pelvic area and the fixed position of the sigmoid colon. Many patients receiving radiotherapy also receive drugs with radiosensitizing effects. These drugs are directly toxic to the mucosa, predisposing it to further radiation damage. Between 75% and 90% of all intestinal complications affect the distal colon (177), with the rectum being most commonly involved (178,179).

Recent evidence suggests that microvascular endothelial apoptosis represents the primary lesion in gastrointestinal radiation damage (180,181). A single large dose of radiation preferentially damages the endothelial cells and epithelial cells die following the endothelial damage. The pathophysiology of radiation injury is discussed in detail in Chapter 6.

About 75% of patients develop clinical symptoms, usually by the middle of the second week of therapy. These include diarrhea, a mucoid discharge, tenesmus, abdominal distention, and abdominal pain. Mucosal edema, dusking, and loss of the normal vascular pattern develop. Severe proctosigmoiditis follows radiation therapy in 2.4% to 5% of patients; it is more common in patients treated with >6,000 rads over 6 weeks. Diffuse pancolitis may develop, as may ulcerations, stenosis, necrosis, and fistulas, all caused by progressive intramural vasculitis with submucosal and subserosal fibrosis. Delayed lesions include strictures, perforation, intestinal pseudo-obstruction, vascular obliteration, and mural fibrosis. Delayed proctosigmoiditis with intermittent bleeding of mild to moderate severity occurs 6 months to 5 years following therapy but can be delayed for as many as 30 years.
Radiation Injury

FIG. 13.89. Barium granuloma. A: Multiple small barium granulomas are present within this bowel, causing mural inflammation and luminal narrowing. B: Barium particles in macrophages. C: Histologic section through a barium granuloma demonstrates the presence of numerous epithelioid cells as well as multinucleated giant cells containing birefringent foreign material as seen under polarized light. D: Histiocytic cells containing refractile material.

Early colorectal changes include mucosal edema (Fig. 13.91), mucosal discoloration or duskiness, and loss of the normal mucosal vascular patterns. Pallor, loss of mucosal folds, and irregular shallow ulcers, fistulae, and abscesses may also be present. Chronic radiation-induced colitis often manifests as strictures that may be long or short and generally have tapered and smooth margins.

During acute injury, characteristic changes usually remain confined to the mucosa. They include crypt cell damage, crypt abscesses, inflammatory cell infiltrates, nuclear P.797
atypia, reduced mitotic activity, loss of nuclear polarity, crypt loss, and mucosal sloughing. Eosinophils are often prominent (Fig. 13.92). Other acute effects consist of prominent submucosal edema often with a myxoid appearance, ulcers, inflammatory polyps, mucosal telangiectasia, and sometimes ischemia. There may be glandular proliferation with mild cellular atypia. The changes may simulate dysplasia. Most of the changes resolve within a month, although mild atrophy and inflammatory cells may remain and be present at 3 months following treatment cessation (182), but they eventually regress.

FIG. 13.91. Acute radiation damage. The image in A demonstrates the focality of the damage. The mucosa is edematous, and the crypts are separated by edema. At higher power magnification (B), one sees the presence of hemosiderin-laden macrophages.
Radiation Injury

**FIG. 13.92.** Acute radiation colitis. A: High-power magnification demonstrating the presence of degenerating glands lying within an edematous stroma and surrounded by acute inflammatory cells, including eosinophils. B: Mucosal vessels demonstrate mild vascular fibrosis.

Mucosal lesions that develop in the delayed period include erosions, ulcers, perforations, fistulas, atypia, and neoplasia. Carcinomas, sarcomas, and malakoplakia develop in previous radiation fields. The neoplasms follow exposure to both low and medium radiation doses, and they develop after a long latency period (183). Vascular changes include petechiae, hemorrhages, hyalinized arterioles, areas of healed necrosis in the vessels, thrombi, and fibrous intimal plaques. Stromal changes include strictures, submucosal fibrosis, interstitial fibrosis of the muscularis propria, serosal fibrosis, and loss of sphincter control. The strictures and fibrosis result from up-regulation of the multifunctional cytokine transforming growth factor-β, which is a major regulator of epithelial and mesenchymal proliferation, inflammation, extracellular matrix deposition, and angiogenesis (184,185).

More chronic features include architectural distortion with variable atrophy; goblet cell loss; shortened crypts; a thickened, distorted muscularis mucosa; epithelial atypia; intestinal wall fibrosis; serosal thickening; vascular sclerosis (Figs. 13.93 and 13.94); lymphangiectasia; and thickening of the collagen layer beneath the surface and crypt epithelium (186), which may mimic collagenous colitis. The large intestine may show Paneth cell metaplasia. Marked hyalinization of the submucosal vessels may mimic amyloidosis. Variable distortion of the intestinal wall results in glandular entrapment deep in the bowel wall, causing colitis cystica profunda, focal discontinuity of the muscularis mucosa, mucosal erosions, deep ulcers, vascular ectasia, and serosal thickening (186). The atypical nuclei in the displaced glands may simulate an invasive carcinoma. Submucosal neuronal proliferations and muscular degeneration also develop.

Biopsy features that suggest a diagnosis of radiation damage include the patchy nature of the process, marked telangiectasia, enlarged nuclei in either the epithelium or the stroma, and, if one is lucky enough to have submucosa in the biopsy, typical vascular changes sometimes associated with characteristic radiation fibroblasts. In other cases, the tissue appears nonspecifically chronically damaged. The lamina propria also contains excessive numbers of chronic inflammatory cells. The fibroblasts have enlarged nuclei and the cytoplasm tends to become basophilic. The cells may acquire a swallow-tailed appearance. The arterioles often show intimal proliferation, sometimes with foamy endothelial cells, particularly earlier in the disease. Biopsies of the strictures typically show portions of distorted colorectal mucosa with fibrosis in the lamina propria and vascular dilation.
The gross appearance of chronic radiation damage may resemble that of Crohn disease but without fissures and without the creeping growth of the mesenteric fat. The gross appearance can also mimic a carcinoma. Microscopically, radiation colitis mimics other large intestinal colitides, including infectious, microscopic, ischemic, drug-induced colitis, allergic/eosinophilic, and IBD, particularly if only a superficial biopsy is examined. The presence of eosinophilic crypt abscesses is highly suggestive of radiation injury (187).

The vascular damage with myointimal hyperplasia and subintimal collections of foamy macrophages may be seen in radiation damage, chronic allograft cellular rejection with medial sclerosis, fibrinoid necrosis, and thrombosis in varying degrees and combinations (186). Because the mechanisms of radiation injury resemble those seen in ischemia and reperfusion injury, it is not surprising that the histologic features of both ischemia and acute radiation injury resemble one another and overlap.

Increasingly neoadjuvant therapies are used to treat rectal cancer, including preoperative chemotherapy, radiation therapy, or chemoradiation. This is followed by the resection of the tumor a few days or weeks later. Short-term preoperative irradiation induces severe diffuse, transmural inflammation and increased cellularity of the lamina propria. The inflammation consists of a mixture of eosinophils, lymphocytes, and plasma cells. The eosinophils are present in the lamina propria and/or crypts and/or surface epithelium and within crypt abscesses. Some patients have collections of muciphages in the lower mucosa. Neutrophils are present in proximity to ulcers and erosions, but they do not contribute to the crypt abscesses (188).
Radiation Injury

Disarray, surface and crypt epithelial damage, nuclear abnormalities, and apoptotic bodies in the crypt epithelium all develop (188). The crypts show a slitlike or dilated lumen lined by flattened epithelium mimicking the changes induced by chemotherapy. The epithelium may appear intensely eosinophilic and may contain bizarre nuclear atypia. The crypts appear elongated and the distance between the base of the crypts and the muscularis mucosae is increased. Decreased crypt numbers or small residual crypts may be present in severely inflamed areas. In less inflamed areas there is mild crypt distortion. It is important to recognize that the changes induced by the short-term irradiation can spontaneously completely resolve (188).

Sometimes one receives tissues that have had radon needles inserted into them to deliver localized radiation therapy. In such cases, an abscesslike inflammatory infiltrate surrounds a central empty cavity that corresponds to the site where the needle was. The vessels in proximity to the abscesses often show degenerative and fibrinoid changes.

Perirectal seeds used for brachytherapy of prostate cancer may cause localized gastrointestinal toxicity, although this is usually mild in nature (189).

Trauma

Most severe colonic trauma results from surgical or endoscopic interventions, accidents, and penetrating wounds. More than 95% of colonic injuries are penetrating (190) due to gunshot and stab wounds, iatrogenic injuries, automobile accidents, war wounds, and miscellaneous sexual injuries, in decreasing order of incidence. Trauma may also result from the insertion of enema tubes. The extent of the damage varies with the cause. The pathologic spectrum ranges from hematomas to full-thickness lacerations that, if not repaired, lead to perforation and peritonitis. Intramural hematomas complicate blunt abdominal trauma and bleeding diatheses, such as hemophilia. Blunt abdominal trauma in child abuse syndromes associates with significant morbidity and mortality. The midabdomen is particularly vulnerable to the direct blows and results in compression injuries to anatomically fixed viscera against the spine (191). Colonic trauma accounts for only 3% to 5% of blunt abdominal injuries (192) and most affect the descending colon, ascending colon, or cecum (192,193). The clinical features depend on the size of the hematoma and can include acute or chronic pain, obstruction, rectal bleeding, anemia, and hemoperitoneum (194,195).

Histologic changes associated with trauma depend on whether the mucosa is examined during an acute phase or whether a biopsy is taken after repeated traumatic episodes. Acutely, one sees acute inflammation and hemorrhage. If repeated trauma has occurred, mucosal distortion and chronic inflammation may be present. Hemosiderin deposits may be present in the tissues. The tissue along the path of bullet wounds demonstrates coagulation necrosis.
Vascular Lesions

A number of vascular lesions affect the large intestine. In this chapter we will deal with nonneoplastic vascular abnormalities. Vascular tumors are covered in Chapter 19.

Portal Colopathy

Patients with portal hypertension often develop hematochezia, Hemoccult-positive stools, and anemia. Some patients develop hemorrhoids (533); most patients have esophageal varices. Seventy percent of patients have a mosaic mucosal vascular pattern or multiple vascular ectasias. The ectasias cause both acute and chronic gastrointestinal bleeding (534). Other endoscopic mucosal abnormalities include edema, erythema, granularity, and friability, features often seen in colitis (535). Histologically, increased numbers of small vessels with prominent branching lie in the upper and midmucosa. The dilated, tortuous mucosal capillaries may show irregular thickening and arterIALIZATION of their walls. Vascular diameters can measure 20 ± 2 micra in the ascending colon and 30 ± micra in the rectum (536). These findings associate with edema of the lamina propria and mild chronic inflammatory changes (537). The typical signs of portal hypertension are present, including dilation and tortuosity of the mesenteric veins. Neither signs of chronic liver disease nor stigmata suggestive of severe portal hypertension correlate with the endoscopic findings. The colonic lesions resemble those found in portal gastropathy, an entity discussed in Chapter 4.

Varices

Esophageal varices are well known, but it is not generally appreciated that varices can involve the rest of the GI tract (538). Adhesions or enterostomies favor the formation of intestinal varices if portal hypertension is present. Patients with pancreatitis and splenic vein thrombosis also develop colonic varices (539). Colonic varices may also occur on a familial basis in the absence of portal hypertension (540). Mean patient age is 50 and there is a slight male predominance. Sites where varices form reflect the embryonic juxtaposition of visceral and systemic vascular plexuses. Portal hypertension not only causes dilation of the pre-existing natural shunts with creation of collateral vessels, but also reopens embryonic vessels, particularly the periumbilical veins, producing the caput medusae.
FIG. 13.160. Autoimmune colitis in a 9-month-old child. A: A rectal biopsy demonstrating the presence of severe glandular atrophy. B: This specimen is from another area and demonstrates regenerating mucosa on the upper right-hand surface. The mucosa has become simplified without glands. Several glands are being destroyed by an eosinophilic infiltrate. This is seen better at higher magnification in C.
In patients with portal hypertension, the coronary azygous system is the primary portal–systemic channel in 50% of cases; in 25% the inferior mesenteric and internal iliac systems represent the primary portal–systemic channel. Portal–systemic communications also exist in the rectum. Prominent dilated vessels are present in the submucosa (Fig. 13.161). The histology of the varices resembles that of esophageal varices (see Chapter 2).

Dieulafoy Vascular Malformations

Dieulafoy vascular malformations, also known as caliber-persistent submucosal arteries, are rare but well-known causes of upper GI bleeding. They also affect the colon, although they rarely (541) lead to massive bleeding. A large submucosal artery lies in close contact with the mucosa, often attached to the muscularis mucosae; the vessel is oversized for the site. In the colon, the lesions arise in the ascending colon or cecum, and the preferential involvement of this site may be the result of the vascular architecture. Their histology resembles their gastric counterpart (see Chapter 4).

Angiodysplasia

The most common type of colonic vascular dysplasia is angiodysplasia, which usually involves the right colon, although it does affect other sites as well. Most regard angiodysplasia as a degenerative disease of the elderly in which malformed vessels present in the submucosa extend into the overlying mucosa. Numerous studies show an association between bleeding from angiodysplasias and the presence of aortic stenosis (542). Valve replacement causes cessation of the recurrent bleeding. This suggests that the aortic stenosis does not cause the lesion but contributes to bleeding from it. Arteriovenous malformations (AVMs) also associate with chronic renal failure, coagulation disorders, defective platelet aggregation, and warfarin therapy for artificial heart valves and diverticular disease (61). Coagulation abnormalities contribute to episodic bleeding. Most patients with bleeding have a deficiency of the largest multimers of von Willebrand factor induced by a latent acquired von Willebrand disease (543). Bleeding from angiodysplasia can be massive and recurrent.

The true incidence of angiodysplasia is unknown because the lesion is difficult to demonstrate surgically and pathologically. Angiodysplasias are an incidental finding in 3% to 6% of individuals undergoing colonoscopy and affect up to 25% of the elderly. They usually occur in persons older than 50 years of age, although they can affect individuals of any age. Average patient age is 70 years. The lesions are frequently multiple and primarily involve the cecum and right colon.

Selective mesenteric arteriography has been the preferred way to diagnose angiodysplasia. The hallmarks of the lesion include (a) an early filling vein that visualizes within 4 to 5 seconds after contrast material is injected; (b) a vascular tuft that represents an abnormal vascular structure, best seen in the arterial phase and usually located at the termination of a branch in the ileocolic artery; and (c) a slowly emptying, densely opacified, intramural vein that remains visualized after the other mesenteric veins have emptied. However, recent studies suggest that helical computed tomography (CT) angiography is a sensitive, specific, well-tolerated, and minimally invasive tool for diagnosing colonic angiodysplasia (544).

Most angiodysplasias are mucosal and submucosal lesions (Fig. 13.162) that are not always visible externally to the surgeon or the pathologist. A helpful way to identify the vascular abnormality is to have the surgeon cannulate the major vessels at the time of the resection, leaving the cannulas in place. When the specimen is received in the laboratory, the pathologist can inject a combination of India ink and a radiopaque dye into the specimen and then x-ray it. The specimen can then be fixed and sections taken in the area of the abnormal vasculature. The India ink will remain visible within the abnormal vessels (Fig. 13.162).

Grossly, the lesions usually consist of small (1 to 2 mm or less) or larger (>5 mm), cherry-red, fan-shaped mucosal lesions with a tense central vessel and radiating foot processes (545). Mucosal erosions may be present. The lesions are often multiple and flat. If the lesion is examined under the dissecting microscope, one sees multiple, often coalescent vascular channels with adjacent arteries and veins standing out as “coral reefs” against the normal capillary “honeycomb” pattern of the colonic mucosa. Sometimes a gross specimen is received in which the angiodysplasia has been cauterized, in which case the lesion may appear as a heaped-up ulcer.

Histologically, angiodysplasia consists of dilated, distorted vessels lined by endothelium and rarely by a small amount of smooth muscle. Enlarged arteries are also present (Fig. 13.162).
The lesions are ectasias of the normal vasculature rather than true malformations. The pattern of involvement points to dilation of submucosal veins as the initial morphologic change, lending credibility to the notion that recurrent obstruction plays a role in its etiology. Repeated obstructions during the muscular contraction and distention of the colon result in dilation and tortuosity of submucosal veins and retrograde involvement of the venules of the arteriolar capillary venular units. Ultimately, the capillary rings surrounding the crypts dilate and the competency of the precapillary sphincters is lost, producing a small arteriovenous communication.
Vascular Lesions

**FIG. 13.162.** Cecal angiodysplasia in a patient who bled 45 units of blood in a 36-hour time period. A: Endoscopic view of irregular angiodysplastic lesion with characteristic hyperemic “blush.” B: Composite picture of specimen radiograph with ectatic vascular area appearing like a medusa (left panel, lower left at 8:00); transilluminated specimen with central vascular ectatic area (right). C: Specimen with a prominent vascular ectasia in central area of hemorrhage. The specimen was injected with a combination of radiopaque dye and India ink, accounting for the pronounced vascular pattern. D: Low-power micrograph of colonic erosion and fibrin plug in dysplastic vessel. E: India ink injection demonstrating ectatic vasculature in mucosa and submucosa.

The earliest abnormality is the presence of dilated (twice the normal diameter), thin-walled, submucosal veins that may occur in the absence of mucosal involvement. The dilated, thin-walled vessels are not sclerotic. An occasional venous tributary pierces the muscularis mucosae and joins dilated venules and capillaries of the mucosa. The architecture of the colonic crypts is not altered and the lamina propria is not significantly inflamed.

More extensive involvement leads to increased numbers of dilated and deformed mucosal and submucosal vessels, eventually distorting the mucosal architecture. Late-stage lesions show a mixture of the early lesions and dilated and tortuous mucosal capillaries and venules. As the lesions advance, the proliferating blood vessels displace the crypts. Only a layer of endothelial cells may separate the vascular channels from the intestinal lumen. Arterialization of the veins, which is recognized as hypertrophy of both the intima and smooth muscle, only occurs in advanced stages of the disease (545). Submucosal arteries are normal or moderately dilated. Occasionally, they reveal mild to moderate sclerotic changes sometimes associated with atheromatous emboli. Organized and recanalized thrombi may be present in larger submucosal veins. Some vascular ectasias extend full thickness from the serosa through the muscularis propria to the submucosa and mucosa. The presence of distorted and dysplastic vessels distinguishes this lesion from hemangiomas.

**Arterial Dysplasia of the Colonic Arteries**

In arterial dysplasia, the arterial vasculature varies significantly from one intestinal area to another. In some areas, the vessels appear dysplastic due to the irregularity of their walls and adventitia. They exhibit fibrous, annular thickening with medial destruction. The internal elastic layer is variably absent. The absence of the elastica allows aneurysmal dilation and subsequent rupture (546). In some segments, the vascular lumen may be completely obliterated by thrombi or variable degrees of fibrosis. Previous bleeding sites organize and are recognized by an abundance of iron-containing histiocytes and chronic inflammatory cells. In other segments, the arterial wall appears relatively normal, although mild abnormalities of the inner elastic membrane and moderate disorganization of the media and muscular layer are present. The etiology of arterial dysplasia is unknown and many factors have been postulated, including embryologic variations, hormonal influences, autoimmune mechanisms, and trauma (546). Clinical signs and symptoms usually develop secondary to ischemic complications.

**Vascular Changes in Homocystinuria**

Homocystinuria causes changes in the vasculature simulating fibromuscular dysplasia. The vascular changes consist of fibroblastic intimal proliferations and narrowing of the vascular lumen, in the absence of inflammation and fibrinoid necrosis. The changes resemble those seen in atherosclerosis and may lead to intestinal ischemia.
Aberrant Crypt Foci

Aberrant crypt foci (ACF) constitute putative preneoplastic lesions originally described in experimental animal models of colorectal cancer (253,254,255). ACF have been proposed as intermediate biomarkers in carcinogenesis studies (253,254,255,256,257). Their detection involves examining colons cleaned with Krebs-Ringers solution. The colons are cut open along their longitudinal axis, fixed flat in buffered formalin, and then placed in a Krebs-Ringers solution containing 0.2% methylene blue for approximately 30 minutes. This preparation is then placed on a glass slide, mucosal side up, and examined under a light microscope at a magnification of 40× with transillumination (253). ACF consist of clusters of abnormally large, darkly staining, slightly elevated mucosal crypts (Fig. 14.69).

FIG. 14.62. High-grade dysplasia is characterized by increased nuclear:cytoplasmic ratios, nuclear irregularity, and true nuclear stratification.
Aberrant Crypt Foci

FIG. 14.63. In intramucosal carcinoma, cells extend through the basement membrane into the lamina propria. Often the glands develop a cribriform or back-to-back architecture. ACF vary from single altered glands to plaques of 412 abnormal crypts/focus (258). Aberrant crypts are three times larger in diameter than normal crypts and have oval or slit-shaped lumina rather than the usual circular lumina of the normal mucosa. They are slightly elevated above the mucosal surface when viewed microscopically (258). They consist of histologically diverse lesions.

### TABLE 14.12 Guidelines for Colonoscopic Surveillance after Polypectomy

<table>
<thead>
<tr>
<th><strong>Guideline</strong></th>
<th><strong>Details</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>1 year after polypectomy, then every 3 years.</td>
</tr>
<tr>
<td><strong>Polyp Size</strong></td>
<td>&gt;10 mm in size requires endoscopic resection.</td>
</tr>
<tr>
<td><strong>High-Risk Features</strong></td>
<td>Presence of capillary loops, vascular pedicle, or stalk.</td>
</tr>
<tr>
<td><strong>Follow-Up</strong></td>
<td>If no polyps at 1 year, surveillance can be stopped.</td>
</tr>
<tr>
<td><strong>Special Considerations</strong></td>
<td>Women with a personal or family history of colorectal cancer should be monitored more frequently.</td>
</tr>
<tr>
<td>Colonscopic and Pathologic Findings</td>
<td>Recommended Interval to Next Colonoscopy</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Small, rectal, hyperplastic polyps</td>
<td>10 years</td>
</tr>
<tr>
<td>Other interval determined by patient's colorectal cancer risk</td>
<td></td>
</tr>
<tr>
<td>1–2 low-risk adenomas</td>
<td>5–10 years</td>
</tr>
<tr>
<td>3–10 low risk adenomas</td>
<td>3 years</td>
</tr>
<tr>
<td>Any high-risk adenomas</td>
<td>3 years</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3 years</td>
</tr>
<tr>
<td>Inadequately removed adenomas</td>
<td>2–6 months</td>
</tr>
</tbody>
</table>

\[a\]Low grade dysplasia

\[b\]High grade dysplasia

The mean proportion of the altered colonic mucosa and the number of foci with aberrant crypts/cm² colonic mucosa is higher in patients with colon cancer than in patients without colon cancer or predisposing conditions and is highest in patients with polyposis syndromes (256,258,259,260). ACF from patients with FAP appear dysplastic (256), whereas those from patients with colon cancer range from almost normal to hyperplastic to dysplastic. ACF may play a role in the early steps of human colon cancer development, particularly since dysplasia is often present.
FIG. 14.64. Carcinoma arising in the head of a polyp that was later shown to have metastasized. A: Polypectomy specimen demonstrating the presence of an adenomatous polyp. A small area of carcinoma is present within the lesion and invades only the superficial portion of the submucosa of the head of the polyp. B: High-power magnification demonstrating the tumor invading the submucosa. C: There are well-differentiated and poorly differentiated glands. D: Tumor cells are present in the lymphatics of the polyp stalk.
Adenomas

Adenomas, the benign glandular neoplasms that precede colon cancer development, originate from the intestinal epithelium. They occur singly or multiply. When multiple, the patients may have a genitic syndrome (see Chapter 12).

Biologic Alterations in Adenomas

Despite their differing structure, all adenomas share two basic features of neoplasia, dysregulated proliferation and the failure to fully differentiate. The dysregulated proliferation is evidenced by an upward shift in the proliferative compartment (Fig. 14.5). This shift can be highlighted with the use of proliferation markers, such as with the antibody MIB-1 (Fig. 14.6) or by other labeling techniques. Mitotic figures, including abnormal ones, are present throughout the entire length of the hyperchromatic, adenomatous epithelium.

It has always been believed that adenomas form because the rate of cellular proliferation exceeds that of cellular exfoliation. However, today we know that cellular exfoliation is not the only mechanism for removing cells from the crypt. Cells also undergo apoptosis. In the normal colon, most apoptosis occurs near the luminal surface (159) consistent with a model of colorectal cell differentiation and senescence, which culminates in physiologic cell death as the cells migrate upward from the proliferative compartment in the basal crypt. This process is under the influence of the autocrine growth inhibitory apoptosis-inducing effect of transforming growth factor-β (TGF-β) (160). In contrast to the normal crypt, adenomas contain numerous apoptotic cells (Fig. 14.7), which often lie at the adenoma base, a reversal of the normal distribution. This observation led Moss et al (161) to suggest that adenomas exhibit a reversed epithelial cell migration and an inward growth pattern directed toward the crypt base rather than toward the lumen. The shift in the location of the apoptotic figures is accompanied by a shift in TGF-β-immunoreactive cells from the adenoma surface to the base. The apoptosis-related bcl-2 family of proteins also exhibit altered expression in adenomas (162,163,164).

FIG. 14.6. Proliferation in adenomatous polyps. A: Multiple adenomas are present in the colonic mucosa from this patient with familial polyposis. B: Immunohistochemical staining for the proliferation marker Ki-67 using the MIB-1 antibody demonstrates a prominent band of proliferating cells at the luminal surface of the polyps. C: Higher magnification demonstrating the shift of the proliferation zone to the mucosal surface in an adenomatous polyp. In contrast, the adjacent nonneoplastic mucosa demonstrates the normal proliferation pattern with MIB-1-positive cells restricted to the base of the glands. D: Higher-power view showing numerous proliferating neoplastic cells in the superficial mucosa of the adenoma.
FIG. 14.7. Apoptosis in adenomatous polyps. An adenomatous gland contains scattered apoptotic cells (arrows). Apoptosis is commonly seen at the bases of the neoplastic glands.

Adenoma Growth

Small adenomas represent neoplastic clonal populations of colonic epithelial cells, suggesting that they arise from a single abnormal precursor stem cell. Adenomas begin in a single crypt (Fig. 14.11) and then grow by replacing normal epithelium in a centrifugal manner. Unicryptal adenomas are rare and most typically affect patients with FAP (see Chapter 12). New adenomatous glands result from infolding of the neoplastic surface epithelium. The neoplastic cells appear to cluster at the luminal aspect of the mucosa without extending to the base of the glands (Fig. 14.12). Normal-appearing mucosa lies below the adenomatous glands (Fig. 14.12). In 80% of early tubular adenomas, the number of gland openings along the polypl surface is larger than the number of gland bases; this difference increases with polyp size (165). Additionally, gland proliferation predominates in the upper crypts and along the surface of the lesions (Fig. 14.6). Early adenomas present as small growths with a very benign tubular histology.

A small proportion of tubular adenomas increases in size and develop villous features and cytologic characteristics of high-grade dysplasia. The progression of most small adenomas is slow and occurs over several years. On average, small adenomas double their diameter in 10 years (166). In one study, small adenomas doubled during a 2-year observation period, but none of the adenomas observed over time exceeded 5 mm in size at the time of resection, nor did any show high-grade dysplasia or carcinoma (166). Another estimate of the projected increased growth relates to lesional volume. There is a 52% mean volume increase after 2 years (166).

Some adenomas ultimately progress to invasive cancers. However, it should be remembered that not all adenomas progress, and that some stay stable or may even regress and disappear while new ones form in the same colon (167).

Incidence

Incidence rates of adenomas vary considerably throughout the world. Geographic areas exhibiting a high risk for colon cancer also exhibit a high risk for adenoma development and vice versa. The incidence in the general population varies from 0% to 69% depending on the country of origin (168,169,170) and on how the adenomas are detected (171). The incidence of adenomas depends on several other factors, including (a) whether one is examining data from an autopsy study versus an endoscopic screening study, (b) the age of the patient, and (c) whether or not the patient has a hereditary colon cancer syndrome.

FIG. 14.8. Comparison of epithelium in normal crypts and crypts from hyperplastic and adenomatous polyps. A: Cross section of an adenomatous gland (A) and a normal gland (N). The adenomatous gland is lined by hyperchromatic cells, which demonstrate prominent crowding. The epithelium appears somewhat mucin depleted. In contrast, the normal epithelium to the left is lined by cells with small, round, basally located nuclei without evidence of crowding. Numerous goblet cells are present. B: Hyperplastic polyps are lined by cells with very small, round nuclei and abundant eosinophilic cytoplasm. Note the serrated architecture of the gland. C: Horizontal section of an adenomatous crypt demonstrating immature cells that fail to mature as they reach the luminal surface. The nuclei are crowded and, in some areas, appear pseudostratified.
FIG. 14.9. Typical picket fence appearance of an adenomatous polyp.

FIG. 14.10. Comparison of differentiation in adenomatous and nonneoplastic glands. The nonneoplastic gland in the center of the photograph demonstrates the normal pattern of progressive differentiation. Goblet cells and absorptive cells line the gland. The colonic crypt nuclei are small, round, and basally placed. No mitotic figures are seen. In contrast, the adenomatous glands on either side show no evidence of differentiation toward the luminal surface. All of the cells appear similar and demonstrate crowded, pseudostratified, hyperchromatic nuclei.
Some patient populations have an extremely low adenoma incidence. For example, no adenomas were found among 14,000 autopsies performed on the South African Bantu (172), and Medellin, Colombia, which has a low incidence of colorectal cancer, also has a low incidence of adenomas (173). In Western populations, the average prevalence rate for adenomas from flexible sigmoidoscopy screening is 10%, and colonoscopic screening prevalence averages 25% (174). Adenomas accounted for 68% of all polyps removed by colonoscopy in the National Polyp Study (175). In the 50- to 59-year age group, population screening studies and autopsy studies show an adenoma prevalence rate of 41.3% to 69% (176), increasing in advancing years up to 88% in centenarians (177). Arminsky and McLean (178) documented a 7.5% increase in adenoma incidence per decade. These data contrast with incidences of only 2.8% to 50% and a mean of 10% among autopsied patients (179,180). Low prevalence rates from autopsy series reflect geographic variations and various methodologic biases, including the fact that usually the autopsies are performed by numerous individuals with colorectal examinations ranging from a casual inspection to examinations with a hand lens. The most reliable autopsy data derive from those studies performed by a single, experienced investigator. Another confounding variable is whether the data include autopsies on children as well as on adults. Autopsy series containing large numbers of children would be expected to have lower prevalence rates due to the fact that adenomas are age-related lesions. In carefully performed studies, 46.9% to 69% of cases have at least one adenoma (178,181).

Frequency of Multiple Polyps

Individuals with one adenoma have a 40% to 55% likelihood of having additional synchronous lesions (184,187,188). The additional adenomas are detected at the same time as the initial adenoma (synchronous adenomas) or at a different time (metachronous adenomas). The prevalence of multiple adenomas increases with age. Nineteen percent of individuals younger than 60 years, 17% of people between 60 and 74 years, and 28% of people older than 75 years have three or more adenomas. Multiple adenomas also arise with increased frequency at ureterosigmoidostomy sites and in patients with hereditary colon cancer syndromes and FAP. Sometimes a single sessile adenoma may appear as multiple adenomas. It may be difficult to separate a single lesion from multiple lesions if one is unaware of the gross appearance of the lesion (Fig. 14.14). The incidence of synchronous neoplasms in patients with an index resectosigmoid adenoma measuring <5 mm in diameter, with an index rectosigmoid adenoma measuring >5 mm, or with a rectosigmoid carcinoma is 34%, 53%, and 73%, respectively (188). The synchronous neoplasm is an adenoma measuring >5 mm in diameter is 13%, 40%, and 64%, respectively (188). The incidence of large intestinal adenomas occurring synchronously with carcinomas is approximately double that of adenomas occurring alone. Metachronous adenomas, compared to index adenomas, tend to be smaller, tubular, only mildly dysplastic, and more uniformly distributed (189). The substantial prevalence of proximal colonic neoplasms, including advanced lesions, in asymptomatic, average-risk patients with rectosigmoid adenomas measuring <5 mm in diameter warrants colonoscopy in these patients in order to detect them (189).

Patient Age and Sex

Age and male sex correlate with adenoma development (170,175,182). Adenomas show a sharp rise in incidence in patients without hereditary adenomatous polyposis syndromes at about age 40, and adenoma incidence peaks at age 60 or 70 years. In the National Polyp Study, adenomas occurred more frequently in men than women, 61.6% versus 38.4%. Patient mean age was 62.6 ± 11.9 years. Of these, 21% reported a family history of colon cancer and 12% had a family history of colonic polyposis. Forty-three percent had a family history of another cancer. Thirty-nine percent had more than one adenoma (175). These authors found that the prevalence of adenomas increased 21% in the 6th to the 8th decades (53%). The prevalence of polyps in patients aged 50 to 70 years is 30% to 50%, and the likelihood of cancer developing is 6% (183).

Lesion Location

Based on endoscopic studies, most sporadic adenomas arise in the rectosigmoid (66% to 77%), where 97% are amenable to endoscopic removal (184). However, following endoscopic removal of all adenomas from the colon, adenomas have a higher incidence on the right side of the bowel in the initial follow-up period and then become more evenly distributed with time (184). Adenomas also shift from a distal to a proximal location as patients age (168,169,170,171,185). Thus, left-sided adenomas occur more commonly in younger age groups and right-sided lesions increase in frequency in individuals older than 65 years of age. HNPCC patients have a predominance of right-sided adenomas at all ages. FAP patients have predominantly left-sided lesions and, since patients undergo prophylactic colectomy, it is unknown whether the adenoma distribution would shift toward right-sided lesions with age. Some adenomas cluster (Fig. 14.13). This means that multiple adenomas tend to occur closer together than would be expected from the general distribution of adenomas. This phenomenon occurs in all colonic segments but is less pronounced in the rectum than in other parts of the large intestine (186).

Lesion Location

Based on endoscopic studies, most sporadic adenomas arise in the rectosigmoid (66% to 77%), where 97% are amenable to endoscopic removal (184). However, following endoscopic removal of all adenomas from the colon, adenomas have a higher incidence on the right side of the bowel in the initial follow-up period and then become more evenly distributed with time (184). Adenomas also shift from a distal to a proximal location as patients age (168,169,170,171,185). Thus, left-sided adenomas occur more commonly in younger age groups and right-sided lesions increase in frequency in individuals older than 65 years of age. HNPCC patients have a predominance of right-sided adenomas at all ages. FAP patients have predominantly left-sided lesions and, since patients undergo prophylactic colectomy, it is unknown whether the adenoma distribution would shift toward right-sided lesions with age. Some adenomas cluster (Fig. 14.13). This means that multiple adenomas tend to occur closer together than would be expected from the general distribution of adenomas. This phenomenon occurs in all colonic segments but is less pronounced in the rectum than in other parts of the large intestine (186).
Adenomas

FIG. 14.14. Comparison of the appearance of multiple adenomas and a large lesion simulating multiple adenomas. A: Patient with familial polyposis and multiple adenomas (arrows). B: Gross specimen demonstrating a large sessile adenoma straddling the ileocecal valve and extending into the ileum. C: Histologic appearance of the lesion shown in B. If one had not seen the gross specimen, the multiple polypoid excrescences (arrows) might suggest the presence of multiple adenomas.

Recurrent Adenomas

"Recurrent" adenomas result from the appearance of new adenomas, continued growth of an incompletely resected adenoma, or detection of a previously undetected but pre-existing adenoma. The overall recurrence rates for new adenomas are estimated at 20% to 60% with average follow-up times of 3 to 10 years after index polypectomy (171,183,184,191). Most recurrences occur in the first 2 years following polypectomy. The estimated time to finding new adenomas is 58 months for patients clear on the first colonoscopy and 16 months for patients who had adenomas on the first examination. In 18% of patients, the adenomas arise proximal to the splenic flexure (192,193). Vitilous tumors, particularly broadly sessile ones, usually have a less well-defined border than do tubular adenomas and, therefore, have a greater tendency to recur after local resection than smaller, pedunculated adenomas.

Endoscopic follow-up studies to evaluate new adenomas are hampered by the fact that as many as 25% to 27% of adenomas measuring <5 mm in diameter and up to 6% of adenomas measuring 1 cm in diameter are missed during one endoscopic examination (194,195). Right-sided adenomas are missed more often (27%) than left-sided adenomas (21%) (194). Lesions measuring up to 6 cm in diameter may be missed, and some of these may contain areas of malignancy (196).

Adenoma Incidence in Hereditary Colon Cancer Syndromes

Relatives of individuals with colorectal cancer have an adenoma prevalence rate of 39%. Patients with FAP or its variants (see Chapter 12) have an increased incidence of colon adenomas. These are multiple and occur at a younger age than they do in the general population. FAP patients have the largest number of adenomas, although some patients have the attenuated form of the disease. Thirty percent of HNPCC patients have at least one adenoma and 20% have multiple adenomas. It is unusual to find more than five adenomas in HNPCC patients (197,198). Table 14.7 compares polyp numbers in the HNPCC and FAP hereditary syndromes.

Clinical Features and Diagnosis

Adenomas develop in diverse clinical settings. They either occur sporadically or arise in the setting of a hereditary syndrome such as a polyposis syndrome (FAP) or HNPCC. Sometimes the clinical features result from associated diseases such as diverticulosis (diverticulitis). Small adenomas, ranging up to 1.0 cm in maximum diameter, usually remain asymptomatic unless they are located in the rectosigmoid, in which case they may bleed when their surfaces become traumatized by the passage of well-formed, hardened stool. Larger lesions become symptomatic, with the symptoms depending on polyp size and location. Bleeding is the most frequent symptom, followed by a profuse, watery, or mucoid rectal discharge. Bleeding occurs more often in left-sided lesions than right-sided ones (199). At most, the patient may notice a slight reddish discoloration of the stool after defecating. The bleeding is seldom severe. Factors correlating with severe hemorrhage include adenoma size, pedunculation, and a villous growth pattern (199). The incidence of bleeding increases with increasing adenoma size and once a carcinoma develops within the adenoma. Villous tumors are more likely to bleed than tubular ones, since they tend to be larger and have a statistically higher incidence of coexisting carcinoma. The most common symptoms of villous lesions include bleeding, mucous diarrhea, constipation, and tenesmus (200). Some adenomas lead to incontinence, prolapse, and anemia. If the adenomas are large enough, they may cause changes in bowel habits or intussusception. Cecal lesions that block the appendiceal orifice may produce symptoms mimicking acute appendicitis. Ominous signs and symptoms associated with adenomas include obstruction and abdominal pain.

TABLE 14.7 Comparison of Hereditary Nonpolyposis Colon Cancer (HNPCC) and Familial Adenomatous Polyposis (FAP)

<table>
<thead>
<tr>
<th></th>
<th>HNPCC</th>
<th>FAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Early</td>
<td>Early</td>
</tr>
<tr>
<td>Adenoma, number</td>
<td>&lt;10</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Adenoma histology</td>
<td>Tubular adenomas</td>
<td>Tubular adenomas</td>
</tr>
<tr>
<td>Polyp distribution</td>
<td>Mainly right side</td>
<td>Left or total</td>
</tr>
<tr>
<td>Degree of dysplasia in adenoma</td>
<td>High grade</td>
<td>Low grade</td>
</tr>
<tr>
<td>Cancer distribution</td>
<td>Mainly right side</td>
<td>Random or mostly rectal</td>
</tr>
<tr>
<td>Other cancers</td>
<td>See Figure 20.3</td>
<td>See Figure 17.15</td>
</tr>
<tr>
<td>Proportion of adenomas becoming malignant</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Types of polyps</td>
<td>Adenomas, hyperplastic polyps, mixed hyperplastic-adenomatous polyps</td>
<td>Adenomas</td>
</tr>
</tbody>
</table>

Other clinical features develop in individuals with distinctive polyposis syndromes in whom extraintestinal manifestations may herald the presence of intestinal lesions. These are discussed in Chapter 12.

Endoscopic Features

Small (<5 mm) colorectal polyps commonly affect individuals older than 50 years of age (201) and adenomas account for 60% to 66% of these small lesions (167,202,203,204). The gross endoscopic appearance may suggest the correct diagnosis. However, the endoscopic diagnosis is only correct in 82% of smaller polyps (Fig. 14.15), so histologic examination is required for confirmation (205). The current wisdom is that distal small adenomas represent biomarkers of risk for colorectal neoplasia, warranting a complete colonoscopy in the patient and lifetime surveillance for colon cancer (167). Recently, attention has focused on the development of fluorescence endoscopic imaging and high-resolution chromoendoscopy, which might provide morphologic detail of diminutive colorectal polyps that might correlate with polyp histology and eliminate the need for a biopsy and/or subsequent colonoscopy.

Gross Features
Adenomas

Grossly, adenomas assume one of three major growth patterns: (a) pedunculated, (b) sessile, or (c) flat or depressed (Fig. 14.16).

**Pedunculated and Sessile Adenomas**

Most sporadic colorectal adenomas appear as exophytic, mucosal protrusions. They range in size from invisible unicryptal lesions to large sessile adenomas sometimes measuring >20 cm in greatest dimension. Adenoma size generally correlates with gross growth pattern.

---

**FIG. 14.15.** A diminutive adenomatous polyp is present in the lower center of the photograph. The endoscopic features of such small lesions are not distinctive and require biopsy and histologic examination to confirm their neoplastic nature.


**FIG. 14.17.** Gross appearance of a pedunculated adenoma with the typical lobulated head and a stalk covered by normal mucosa.

Adenomas measuring only 1 or 2 mm grossly resemble hyperplastic polyps. These minute adenomas have smooth surfaces and lack lobulations, and their color often resembles that of the normal mucosa. However, when such lesions are examined under a dissecting microscope, they exhibit characteristic pit patterns that differ from those seen in either small carcinomas or hyperplastic polyps.

Polyp architecture depends in part on whether the adenoma has a tubular, villous, or tubulovillous histologic pattern. The typical tubular adenoma presents as a small, spherical, and variably pedunculated lesion, with its surface broken into lobules by intercommunicating clefts in larger lesions (Figs. 14.16 and 14.17).
Larger lesions appear redder than the surrounding mucosa (Fig. 14.17), unless the patient has melanosis coli, in which case the lesions may appear lighter. Larger lesions exhibit a lobulated, bosselated or villous, raspberrylike, friable surface. In surgical material, approximately 90% of adenomas appear variably pedunculated and normal mucosa lines their stalks. The stalk ranges in length from several millimeters to a few centimeters. Tubulovillous adenomas tend to be larger than tubular adenomas, with a mean diameter of 19.0 mm (178).

Villous adenomas fall into three types: (a) flat, carpetlike masses; (b) lobulated, bulky, sessile masses; and (c) pedunculated lesions with short, broad pedicles. Sessile adenomas tend to be large, shaggy lesions covered by fingerlike fronds (Figs. 14.18 and 14.19). Generally, adenomas appear as grossly homogeneous, soft lesions without induration, ulceration, or fixation. Areas of pigmentation may indicate previous hemorrhage, fibrosis, pseudoinvasion, or previous fulguration (Fig. 14.20). Areas of ulceration, depression, or firmness suggest the possibility of a coexisting carcinoma (Fig. 14.21). Villous adenomas can be multiple and often associate with other adenomas, polyps, or separate carcinomas.

Villous adenomas often have ill-defined edges and attach to the mucosa by a broad base, often extending over wide mucosal areas. Because villous adenomas are less well circumscribed than tubular adenomas, with less well-defined edges than pedunculated adenomas, villous adenomas have a greater tendency to recur after local excision. Large, circumferential, carpeting, benign villous rectal adenomas are rare (Fig. 14.22) but problematic. They recur after the initial excision and may require repeated excision or diathermy to control the recurrences. Adenomas tend to be larger in males and to be largest in the rectum, followed by the ascending colon, cecum, and sigmoid colon. Adenomas also tend to be larger in individuals with multiple adenomas (206).

**FIG. 14.18.** Villous adenomas are composed of many fingerlike fronds that give them a shaggy appearance.

**FIG. 14.19.** Villous adenoma composed of long fingerlike fronds.

**FIG. 14.20.** Hemorrhage within polyps. **A:** The entire surface of these two polyps is markedly reddened due to hemorrhage. **B:** Cut surface of a polyp with hemorrhage and secondary fibrosis.

**FIG. 14.21.** Hemorrhage within polyps.
**FIG. 14.21.** Adenomatous polyp with a central depression representing carcinomatous transformation within the lesion. Additionally, the bowel is affected by melanosis coli but the polyp is not.

**FIG. 14.22.** Large, carpetlike, sessile rectal adenoma.

**Adenomas Containing Carcinoma**

The incidence of cancer in an adenoma increases as the size of the adenoma increases. Thirty percent of villous adenomas >5 cm contain an invasive carcinoma (207). However, even a 4-mm adenoma may contain an invasive cancer (208). Conversely, we have encountered exceptionally large sessile adenomas measuring >20 cm in greatest diameter without malignant change.

**Flat (Depressed) Adenomas**

Flat adenomas constitute a special subgroup of adenomas with a greater potential for malignant transformation while still small than is exhibited by exophytic adenomas Fig. 14.23).

The terms superficial, flat, and depressed adenoma are all used synonymously to describe this entity. Flat adenomas can be single or multiple (209). Because flat or depressed adenomas display little or no mucosal elevation, they can be very difficult to see endoscopically and pathologically, especially in the proximal colon (210). They are often more clearly delineated endoscopically after spraying the mucosa with methylene blue or indigo carmine (211,212,213,214).
Adenomas

**FIG. 14.23.** Depressed adenoma. A: Low-power photomicrograph demonstrating a depressed lesion, which contains crowded glands lined by a hyperchromatic and mucin-depleted epithelium. B: At slightly higher power, the epithelium appears adenomatous with crowded, hyperchromatic nuclei. C: On higher power, there is evidence of high-grade dysplasia, and a focus of early invasion into the muscularis mucosae is seen. D: Immunohistochemical staining with antibodies to p53 demonstrate p53 overexpression, suggesting that the p53 gene may be mutated in this case.

Endoscopically, flat adenomas are recognized as plaquelike lesions with vague redness or discoloration. They tend to be small, usually not exceeding 1 to 2 cm in diameter (Fig. 14.24). Flat adenomas are much more readily identified in colectomy specimens following fixation than they are at the time of endoscopy, presumably because the gross features become highlighted following formalin fixation (209). The failure to recognize these flat lesions may account for the lingering concept of de novo colorectal carcinoma (215). Depressed adenomas tend to arise more commonly in the right colon than elsewhere (215). They occur in the HNPCC syndrome, sporadically, or in patients with FAP (216). The frequency of flat adenoma is 50.7% in HNPCC patients. Flat adenomas have a high incidence of high-grade dysplasia and a high association with synchronous and metachronous invasive colorectal carcinomas.

**Histologic Features**

Histologically, adenomas fall into four categories: Tubular, tubulovillous, villosus, and flat or depressed lesions. Large or sessile adenomas are generally predominantly villous lesions, whereas smaller, pedunculated adenomas usually display a tubular or tubulovillous architecture (Fig. 14.25). Although most villous adenomas are large, small villous adenomas do exist. Some tubular adenomas may become large and sessile, and some pedunculated adenomas exhibit villous features. Many adenomas histologically show a mixture of both tubular and villous growth patterns.

**FIG. 14.24.** Grossly flat adenomas appear plaquelike and slightly redder than the surrounding mucosa.
Adenomas

FIG. 14.25. Spectrum of pure tubular to pure villous adenomas. A through H show the transition of the pure tubular to the pure villous lesion. A–C: Pure tubular lesions. D: Early villous change is apparent by the elongation and crowding of the glands. E: Mixed tubular villous lesion, although it is predominantly tubular. F: Tubular villous adenoma, predominantly villous, showing some tubular glands within the villous fronds. G: Pure villous adenoma. H: Delicate fronds of the pure villous adenoma.

Tubular Adenomas

The most common adenoma is tubular, accounting for 68% to 87.1% of adenomas in several studies (175,217,218), depending on whether or not one allows for up to a 25% villous component in tubular lesions (217). Tubular adenomas maintain their original crypt architecture, but adenomatous epithelium replaces the normal colonic epithelium in lining the crypts (Fig. 14.26). Small tubular adenomas always have dysplastic (adenomatous) surface epithelium overlying nondysplastic epithelium in the crypt base. Lamina propria separates the closely packed adenomatous crypts (Fig. 14.27). The lamina propria may contain increased numbers of lymphocytes, plasma cells, and eosinophils. When the adenomatous tubules grow, they may branch, sometimes producing an irregular architecture. In pedunculated polyps, adenomatous epithelium remains confined to the mucosa of the head of the polyp. The stalk consists of normal mucosa, including the muscularis mucosae and submucosal tissue, in continuity with the major part of the bowel wall (Fig. 14.28). Focal cystic tubular dilation (Fig. 14.29), inflammation, hemorrhage, or erosion can all secondarily affect adenomas, especially at their surface. Small superficial tubular adenomas composed of an adenomatous epithelium that produces some mucin are occasionally overlooked. Their neoplastic nature can be confirmed using an antibody to Ki-67. The strongly immunoreactive cells will be confined to the surface, and more weakly positive cells will be at the crypt bases (Fig. 14.6).

FIG. 14.26. In this small adenoma, the normal architecture of the mucosa is preserved. However, the epithelium lining the crypts has been replaced by neoplastic cells. The neoplastic glands are hyperchromatic, and the cells are crowded and pseudostratified.

FIG. 14.27. Tubular adenoma. A: The lamina propria separating the adenomatous glands contains numerous lymphocytes, plasma cells, and eosinophils. B: The adenoma depicted in this photograph demonstrates more dysplasia than that in A. The nuclei lining the glands are stratified and have lost much of their polarity. The surrounding lamina propria contains scattered mononuclear cells and eosinophils.

FIG. 14.28. Cross section through a pedunculated adenomatous polyp. The stalk is lined by normal colonic epithelium, while the adenomatous epithelium of the polyp head thickens the mucosa.

Villous Adenomas

Approximately 20% of asymptomatic persons screened by colonoscopy have villous adenomas, a third of which contain high-grade dysplasia. Slightly <2% contain invasive carcinoma (219). Villous adenomas consist of elongated fingerlike nonbranching fronds of dysplastic epithelium extending outward from the muscularis mucosae to the colonic lumen (Fig. 14.30).

P.922

The villi contain cores of lamina propria covered by a single layer of adenomatous epithelium (220). Konishi and Morson (217) defined villous lesions as those that contain >80% of a villous component.
Adenomas


Tubulovillous Adenomas

Tubulovillous adenomas contain a mixture of both tubular and villous growth patterns or have broad villi containing tubular structures (Fig. 14.31). The villi may be blunt and short. Kornishi and Morson (217) define tubulovillous lesions as those that contain from 20% to 79% villous components. Fung and Goldman (221) estimated that a villous component is present in 35% to 75% of all adenomas measuring >1 cm in greatest diameter.

Cell Types in Adenomas

Adenomas contain a mixture of variably differentiated absorptive cells, goblet cells, intermediate cells, endocrine cells, and Paneth cells. An abrupt transition between adenomatous and normal colonic epithelial cells is often seen, with the adenomatous cells displacing the nonneoplastic cells of the crypt creating a “snowplow” effect (Fig. 14.32). Most adenomas show some ability to partially differentiate into immature mucus-producing cells called oligomucous cells (222,223). However, the mucus content of the adenomatous epithelium varies (Fig. 14.33). Adenomas may demonstrate true goblet cell formation, although these cells often have an eccentric nucleus and are referred to as dystrophic goblet cells (Fig. 14.33). Occasionally, large numbers of mucin-producing cells are present in villous adenomas, especially those associated with potassium loss. Endocrine cells are discernible in 59% to 85% of adenomas if special stains are used to detect them (Fig. 14.34). Paneth cells are present in approximately 10% (Fig. 14.35), and squamous differentiation (Fig. 14.36) occurs in approximately 4% of lesions. Paneth cells are easily recognized in hematoxylin and eosin–stained sections due to their prominent supranuclear, eosinophilic, cytoplasmic granules. The Paneth cells are neoplastic, as evidenced by their cytologic features (Fig. 14.35). Some cells exhibit both mucinous and Paneth cell differentiation. Adenomas that contain squamous epithelium probably act as the precursor lesions for adenosquamous carcinomas, adenoacanthomas, or pure squamous cell carcinomas. Adenomas may also contain foci of osteoclastic metaplasia, melanocytes (224), or areas of gastric mucosa (Fig. 14.37). The presence of these various cell types reflects stem cell potential to differentiate along several cell lineages (220). The presence of these various cell types in adenomas has no clinical significance.

FIG. 14.30. Villous adenomas are characterized by long fingerlike fronds lined by neoplastic epithelium.
Adenomas

**FIG. 14.31.** Tubulovillous adenoma. *A:* Whole mount section of a tubulovillous adenoma demonstrating a mixture of tubular and villous architectures. *B:* On higher power, villous fronds and tubular glands are identifiable.

**FIG. 14.32.** Adenomatous cells grow downward from the surface, undermining the nonneoplastic mucosa like a snow plow. The resulting abrupt transition from neoplastic and nonneoplastic epithelium is evident in the photograph.

**Muscle Fibers in Adenomas**

When adenomas form, the underlying muscularis mucosae frays, sending small fingerlike muscular extensions short distances into the overlying interglandular stroma (Fig. 14.38). The muscular component is most evident at the junction of the head and stalk of the adenoma, where it may form a broad muscular zone. The muscularis mucosae of the stalk merges with the muscular zone of the adenoma. The deeper border of the muscular zone is not as distinct in pedunculated lesions as in sessile ones. The thick muscular zone disappears when invasive cancer develops in the adenoma (225).
Adenomas

**FIG. 14.33.** Mucin production in adenomatous epithelium. *A:* Adenoma with almost no intracytoplasmic mucin. *B–F:* Increasing degrees of mucin content in adenomatous cells. Note the presence of dystrophic goblet cells in *E* and *F.* Dystrophic goblet cells demonstrate a loss of polarity and, as a result, are not basally located. They often contain an eccentric nucleus, giving them a signet ring cell–like appearance.

**Vasculature in Adenomas**

The lymphatic plexus begins in the area of the muscularis mucosae, and it may accompany the distorted fibers of the muscularis into the overlying mucosa. However, lymphatics never extend higher than the bases of the crypts (Fig. 14.39).

The microvasculature of adenomas has an organization similar to that of the normal colon, but the capillaries and venules appear elongated and have increased diameters compared to the vessels present in the normal lamina propria. Microvessel density increases in the spaces between the neoplastic cells. It also increases as the severity of the dysplasia increases (226).
FIG. 14.34. Endocrine differentiation in adenomas. A: Grimelius stain demonstrating the presence of endocrine cells. B: Chromogranin immunoreactivity in adenoma demonstrating focal collections of endocrine cells within the adenomatous glands. C: Higher-power magnification of one of these glands demonstrating the large numbers of endocrine cells within the adenomatous crypt.

FIG. 14.35. Paneth cell differentiation in adenomas. A: Neoplastic Paneth cells are intermingled with other cells in the adenoma. B: Immunohistochemical localization of lysozyme within the Paneth cells of a villous adenoma.


Pseudocarcinomatous Entrapment (Pseudo-invasion)

A recognized histologic pitfall in diagnosing adenomas is the presence of pseudo-invasive foci surrounded by areas of hemosiderin deposition and fibrosis. Its significance is its resemblance to invasive carcinoma and its potential to be misdiagnosed, thereby leading to needless colonic resections. Pseudocarcinomatous entrapment, variously termed colitis cystica profunda, submucosal cysts, pseudocarcinomatous invasion, or epithelial misplacement, affects a small proportion of pedunculated adenomas. Affected adenomas usually measure >1 cm in diameter, have at least a 1-cm stalk, and originate in the sigmoid colon (64% to 85%) (227).
Adenomas

FIG. 14.38. Smooth muscle in adenomas. A: Low-power view of a pedunculated adenoma demonstrating abundant smooth muscle within the stalk of the polyp. The muscle is highlighted with immunohistochemical stains to actin. B: The muscularis mucosae of this adenomatous polyp is frayed and somewhat thickened. Thick bundles of muscle fibers surround the adenomatous epithelium. The actin stain also highlights the submucosal vessels within the stalk. C: Muscle fibers often extend upward from the muscularis mucosae into the lamina propria between the adenomatous glands. D: Adenoma with pseudocarcinomatous entrapment. Low magnification highlights the thick muscle bundles separating the lobules of adenomatous epithelium. These are not irregular and infiltrated, as could be seen in the case of an invasive carcinoma.

FIG. 14.39. Lymphatics in adenomas. A: The bases of the crypts are seen overlying a somewhat disorganized muscularis mucosae. The dilated lymphatics are present in the space between the muscularis mucosae and the base of the crypts. B: Higher-power magnification of this region demonstrating dilated lymphatics (open spaces) and congested capillaries. Fibers of the muscularis mucosae are also seen. C: Illustration of lymphatic distribution (yellow) in normal colonic mucosa (top) and in an adenomatous polyp (bottom). The lymphatics start as a plexus around the muscularis mucosae.

Repeated episodes of torsion lead to hemorrhage, inflammation, and ulceration of the adenoma. As a result, the adenomatous epithelium herniates through the muscularis mucosae into the underlying submucosa. The presence of thick-walled and occasionally thrombosed submucosal blood vessels supports the concept of torsion and subsequent ischemia as the initiating event. Forceps biopsies may also cause epithelial displacement into the underlying submucosa (Figs. 14.40 and 14.41). The adenomatous tissue may be pulled further into the stalk by contraction of fibrous tissue as the biopsy site heals. The changes reflect the time elapsed from the biopsy procedure and the polyp resection. Displaced cells become embedded within capillary-rich granulation tissue during the first week following the biopsy. Subsequent submucosal fibrosis results in persistent submucosal mucin pools (228).

Histologically, one recognizes areas of pseudoinvasion by the presence of adenomatous epithelium in a submucosa without cytologic evidence of malignancy (Figs. 14.40 and 14.41). The displaced glands often resemble that of the glands immediately underlying it. The displaced glands may also coexist with nonneoplastic glands that were displaced along with the neoplastic ones, providing assurance that the submucosal glands are displaced rather than invasive (Fig. 14.41). Normal lamina propria surrounds displaced adenomatous glands (as opposed to a desmoplastic response surrounding an invasive carcinoma) (Figs. 14.42 and 14.43). If the epithelial displacement occurs immediately prior to the polypectomy, the glands may be surrounded by a narrow rim of granulation tissue. Fresh or old hemorrhage with hemosiderin deposits in the fibrotic stroma surrounding the displaced glands is known as siderogenous desmoplasia (Figs. 14.44 and 14.45). Hemosiderin also deposits in the lamina propria and in the fibrotic stroma surrounding the glands and thick-walled blood vessels. This contrasts with the lack of hemosiderin deposition in areas of true invasive carcinoma.

Rarely, areas of high-grade dysplastic mucosa become entrapped in the submucosa, a change that represents an even greater diagnostic challenge to the pathologist (Fig. 14.46). Features suggesting pseudoinvasion are listed in Table 14.8.
Adenomas

FIG. 14.40. Comparison of pseudocarcinomatous entrainment and invasive cancer. A: Pedunculated adenomatous polyp without pseudoinvasion or invasive cancer. The stalk consists of fibrous tissue, smooth muscle, vessels, and nerves. No glandular structures are present. B: In pseudoinvasion, glands that are cytologically benign are entrapped within the stalk. These glands are surrounded by normal lamina propria, and a desmoplastic response is absent. The glands exhibit a lobulated arrangement. C: In invasive carcinoma, cytologically malignant glands are present in the submucosa. These glands are surrounded by desmoplastic stroma and lack the lobulated arrangement seen in pseudoinvasion. Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

TABLE 14.8 Features Suggesting Pseudoinvasion in Adenomas

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.

Occasionally, the displaced glands undergo cystic dilation with rupture and epithelial lining loss or atrophy (Fig. 14.47). Sometimes, the mucinous material within the submucosa calcifies. The distinction between a mucin-secreting invasive adenocarcinoma and cystically dilated pseudoinvasive glands may also be difficult. Pseudoinvasive glands usually appear regular, sometimes exhibiting a lobular distribution in the submucosa. In contrast, mucinous carcinomas display an irregular distribution of angular glands or nests of atypical cells. No lamina propria surrounds the cysts or glands; instead, a desmoplastic stroma usually lacking hemosiderin deposits is present. Focal stromal desmoplasia may be present.
Direct continuity of submucosal glands with surface adenoma
Presence of lamina propria surrounding the neoplastic glands
Presence of hemosiderin
Lack of desmoplasia
Lack of cytologic features of malignancy
Presence of an admixture of adenomatous glands with normal colonic epithelium in the submucosa
Presence of an admixture of benign adenomatous glands with frankly malignant glands
Marked disorganization of the muscularis mucosae

Differentiating pseudocarcinomatous entrapment in adenomas from localized colitis cystica profunda or the mucosal prolapse syndromes (see Chapter 13) is also usually not difficult, since in the latter, the submucosal cysts are covered by an ulcerated, normal, or hyperplastic-appearing epithelium. The overlying epithelium is not adenomatous in prolapse or colitis cystica profunda. These lesions are compared in Table 14.9

**Flat Adenomas**

Flat or depressed adenomas are a variant of tubular adenoma with little or no mucosal elevation. By definition, the thickness of the adenomatous mucosa does not exceed twice that of the nonadenomatous mucosa in flat adenomas (Fig. 14.48). The adenomatous changes concentrate near the luminal surface. A disproportionate number of flat adenomas contain high-grade dysplasia (41% to 42%) as determined by a higher nuclear:cytoplasmic ratio and degree of cellular atypia than typically seen in polypoid adenomas (209,216). They are also more likely to harbor an invasive carcinoma than their polypoid counterparts (229).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Surface</th>
<th>Submucosa</th>
<th>Lamina Propria in the Sub-Mucosa</th>
<th>Desmoplasia</th>
<th>Muscular Zone</th>
<th>Nonneoplastic Glands the Sub-Mucosa</th>
<th>Architecture of Displaced Glands</th>
<th>Sidero Genous Desmo-Plasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis cystica profunda</td>
<td>Nonneoplastic nonneoplastic glands</td>
<td>Displaced</td>
<td>Often</td>
<td>No</td>
<td>Thickened</td>
<td>Yes</td>
<td>Often</td>
<td>Lobular</td>
</tr>
<tr>
<td>Adenoma with pseudo-invasion</td>
<td>Adenoma with variable degrees of dysplasia</td>
<td>Displaced glands with variable degrees of dysplasia</td>
<td>Yes</td>
<td>No</td>
<td>Thickened bands</td>
<td>Often</td>
<td>Often</td>
<td>Lobular</td>
</tr>
<tr>
<td>Adenoma with invasive cancer</td>
<td>Neoplastic with variable degrees of dysplasia</td>
<td>Irregular malignant glands</td>
<td>No</td>
<td>Yes</td>
<td>Invaded by tumor</td>
<td>No</td>
<td>Not usually</td>
<td>Irregular infiltration</td>
</tr>
</tbody>
</table>

**FIG. 14.42.** Invasive carcinoma arising in a villous adenoma. In contrast to the lesion shown in Figure 14.41, the glands within the stroma are associated with a prominent desmoplastic response.

Flat adenomas contain crowded adenomatosus tubules with diameters that are smaller than those seen in the more common polypoid, tubular adenomas. This feature increases the glandular density when compared to elevated tubular adenomas. The adenomatous tubules tend to occupy the full thickness of the lamina propria at the center of the lesion with superficial growth to the periphery. Depressed adenomas measuring <1 mm in diameter show horizontal growth between the normal adjacent crypts, often leaving normal crypts entrapped as residual islands (Fig. 14.48), whereas polypoid adenomas tend to grow expansively without including remnants of the normal crypts.

The mean labeling index for proliferating cells is higher in depressed adenomas than in nondepressed adenomas, but lower than seen in intramuscular carcinomas (215). Flat lesions are also more commonly aneuploid, and demonstrate differential expression of many genes compared with normal mucosa or polypoid...
Adenomas are classified into different types based on their histological features. For example, Ras gene mutations are significantly more common in flat than polypoid adenomas, and epigenetic changes occur less frequently (231).

**Hypersecretory Adenomas**

Hypersecretory adenomas are characterized by their ability to produce excessive fluid and electrolyte-rich mucus. These abnormalities are often seen in the rectum, leading to symptoms such as profuse watery diarrhea, severe fluid and electrolyte loss, elevated blood urea nitrogen, reduced serum sodium, and hypokalemia.

Due to hypersecretion, patients may experience a normal return of these abnormalities once the adenoma is excised. Typically, the diaphoretic diarrhea is most severe in the morning after the stool has accumulated during sleeping hours. The secretion is often mediated by cyclic nucleotides (233). Histologically, pale, mucus-filled cells line the villi of hypersecretory adenomas (Fig. 14.49).

**Clear Cell Adenomas**

Clear cell adenomas are rare and contain clear cells. They often exhibit areas of clear cell differentiation intermingled with areas of more traditional adenoma (Fig. 14.50). Clear cell adenomas often contain basal nuclei and appear minimally pseudostatified. In another variant of clear cell adenoma, the pseudostratified nuclei exhibit clear cytoplasmic contents above and below the nuclei, a pattern somewhat reminiscent of endometrium. These areas of clear cell adenoma presumably give rise to the clear cell carcinomas that are sometimes encountered in the colon. There is no known clinical significance to the presence of the clear cells in the adenoma.

---

**FIG. 14.43.** Adenoma with pseudocarcinomatous entrapment compared with invasive carcinoma. A: Low-power photomicrograph demonstrating the presence of pseudoinvasion. The displaced pseudoinvasive glands appear lobulated and are surrounded by lamina propria. Thick muscle bundles surround the glands and stroma. B: Higher-power view of the area of pseudoinvasion. The glands demonstrate low-grade dysplasia and are surrounded by lamina propria. C: Invasive carcinoma. Malignant glands infiltrate the submucosa. These glands are surrounded by a desmoplastic stroma. D: Higher magnification of the invasive carcinoma. The irregular glands are lined by disorganized cells with hyperchromatic, irregular nuclei. A prominent desmoplastic response surrounds the malignant glands.
Adenomas constitute the obligate precursor lesion for most colorectal carcinomas (Fig. 14.51). The earliest lesions consist of pseudostratified immature, mildly dysplastic, adenomatous cells. The adenoma may be of any of the types discussed in previous sections. In some cases, one may see a continuous histologic spectrum of increasing degrees of dysplasia culminating in the development of an invasive carcinoma (Figs. 14.52, 14.53, and 14.54). This neoplastic continuum can be diagrammed schematically (Fig. 14.55) and can also be shown histologically (Fig. 14.52). Carcinomas are more likely to arise in larger adenomas than smaller ones. Observations supporting the concept that most colorectal cancers develop from adenomas are listed in Table 14.10.

**Adenoma–Carcinoma Sequence**

The histologic features of adenomas may be defined as low- and high-grade dysplasia, carcinoma in situ, intramucosal carcinoma, and invasive carcinoma. Low-grade dysplasia and high-grade dysplasia are defined in the following section. High-grade dysplasia consists of cytologically malignant cells that remain confined within the basement membrane of the original colonic crypt. It is recognizable by the presence of marked cytologic atypia, the loss of cellular polarity, and the occasional formation of solid nests of dysplastic cells, sometimes including dystrophic goblet cells (Fig. 14.52). Extension of the neoplastic cells through the basement membrane of the crypt into the surrounding lamina propria can be designated an intramucosal carcinoma (Fig. 14.53) (169). Areas of intramucosal carcinoma show greater glandular irregularity and greater glandular density than carcinoma in situ. Intramucosal carcinoma may occupy the entire mucosal thickness, or it may represent a small focal area within the adenoma. Once intramucosal carcinomas reach the deep mucosa, the neoplastic cells may mingle with frayed fibers of the muscularis mucosae and may gain access to lymphatics and may theoretically metastasize (Fig. 14.58). This is extraordinarily rare. Invasion into, but not through, the muscularis mucosae is still intramucosal carcinoma.
Adenomas

FIG. 14.46. Glands demonstrating high-grade dysplasia are present in the submucosa of this adenoma. These glands represent pseudocarcinomatous entrapment because they are surrounded by lamina propria, and there is no associated desmoplastic response.

Since neither intraepithelial neoplasia nor intramucosal carcinoma has a clinically significant potential for metastasis (if all neoplastic tissue is removed), the lesions do not require additional treatment. In fact, we rarely use the term intramucosal carcinoma because of the clinical misinterpretation of the significance of the lesion that can occur as a result of the word carcinoma. A carcinoma of the large bowel is not considered to be invasive and clinically significant until it invades through the muscularis mucosae into the underlying submucosa (Fig. 14.57). Submucosal invasion is most easily recognized by the intermingling of the malignant glands with normal submucosal structures, including medium-sized blood vessels, fat, nerves and ganglia, and larger lymphatics (Fig. 14.58). A prominent desmoplastic response often accompanies even early invasion (Fig. 14.59).

TABLE 14.10 Adenoma–Carcinoma Sequence

Arguments Cited in Support of the Concept

1. Similar distribution of adenoma and carcinomas
2. Colorectal carcinoma frequently coexists with adenoma in the same lesion
3. Prevalence rates of adenomas and carcinomas in countries at various magnitudes of colon carcinoma risk show correlation between the two
4. A similar anatomic distribution exists for adenomas and carcinomas
5. Increased frequency of carcinoma in patients with adenomas
6. Adenomas present in patients who develop metachronous carcinomas show a significant excess of severe dysplasia compared to adenomas present in patients in whom second cancer did not develop
7. Adenomas occur with increased frequency in colons containing carcinomas
8. Increasing age of patients with increasing degrees of atypia and areas of invasive cancer (age succession adenoma–carcinoma)
9. Residual adenomas can be found in some patients with cancer
10. Production of both adenomas and carcinomas in laboratory animals
11. Endoscopic removal of adenomas reduces the expected incidence of carcinoma by 85%
12. All patients with familial adenomatous polyposis syndrome develop cancer if adenoma-bearing colons are not removed
13. Absence of carcinoma in situ outside the area of adenoma
14. Areas of direct transition are identifiable
15. Patients who have adenomas identified endoscopically refuse therapy and eventually return with an invasive carcinoma at the same site
16. De novo carcinoma extremely rare
17. Failure to demonstrate carcinoma in normal mucosa despite the countless thousands of polyps and colon sections examined histologically each year
18. Presence of an adenoma places a patient at increased lifetime risk for developing colon cancer
19. Growth of adenomatous cells in vitro results in cell populations that acquire the features of carcinoma in situ or invasive carcinoma
20. Chromosomal constitution in adenomatous and carcinomatous tissue similar
21. Antigenic relatedness between adenomas and carcinomas
22. DNA content of benign adenomas is intermediate between normal colon and cancer
23. Enzyme patterns similar in adenomas and carcinomas. Adenomas differ from hyperplastic polyps and normal mucosa
24. Similar oncogenes found in some adenomas and carcinomas

Arguments Cited Against the Concept

1. Different distribution of adenomas and carcinomas in some studies
2. Same incidence of carcinoma developing in patients with and without polyps
3. Failure to demonstrate areas of adenoma in “small” carcinomas
4. Failure to demonstrate carcinomas in adenomas

Low-grade Dysplasia

By definition, all adenomas contain at least low-grade dysplasia. Low-grade dysplasia consists of stratified dysplastic epithelium that retains its columnar shape. The nuclei are spindle or oval shaped. The stratified nuclei tend to remain in the basal epithelium extending no more than three quarters of the height of the epithelium. There is minimal nuclear hyperchromasia. Minor cytologic variations, such as variations in mucin content, nuclear pleomorphism, differences in chromatin distribution, and variations in cell size and shape, frequently occur in adenomatous epithelium, especially in larger lesions (Fig. 14.60). These findings represent features of the underlying neoplastic process and, in the absence of significant atypia or architectural alterations, have no clinical significance. Such changes are insufficient to warrant a diagnosis of high-grade dysplasia. Occasionally, it is difficult to distinguish a small tubular adenoma from reactive epithelium present in an inflamed mucosa. One approach that we find works well is to examine the degree of differentiation of the epithelium along the length of the tubular crypt. Reactive glands appear more basophilic than normal, and the nuclei may exhibit pseudostratification.

These changes extend from the crypt base toward the luminal surface. Mitotic activity is present in the basophilic regenerating cells. If the entire gland is not replaced by basophilic epithelium, then its restriction to the bottom portion of the crypt serves to identify the epithelium as regenerative (Fig. 14.61). Conversely, in small adenomas the adenomatous glands appear more basophilic at the surface of the lesion and nonneoplastic epithelium lies below it. The mitotic activity is at the surface. Ki-67 immunostains help highlight the proliferating compartments. When the entire crypt appears immature, the epithelium may be either regenerative or adenomatous. Then one must rely on the histologic context in which the glands are found to distinguish between these two possibilities. In a setting of active inflammation, the glands are most likely to be regenerative. The one disorder in which these distinctions are particularly difficult is ulcerative colitis, as discussed in Chapter 11.
Adenomas

FIG. 14.47. Pseudocarcinomatous entrapment. A: Sometimes entrapped glands undergo cystic dilation, resulting in large mucin-filled pools within the submucosa underlying the adenoma. B: Higher magnification demonstrating cystically dilated mucin-filled glands, which are partially lined by adenomatous epithelium. C: In some cases, the epithelial lining atrophies or is lost, leaving only pools of mucin within the submucosa. In such cases, careful scrutiny for irregular, atypical glands or nests of cells is warranted to rule out the presence of a mucinous carcinoma.

FIG. 14.48. Flat adenoma. A: Low-power photomicrograph of a flat adenoma. The adenoma is approximately the same thickness or thinner than the adjacent nonneoplastic colonic mucosa indicated by the arrow. B: The adenomatous epithelium is concentrated at the surface in this flat adenoma and is overgrowing some residual nonneoplastic glands seen on the right-hand side of the photograph. C: Higher-power magnification demonstrating adenomatous glands admixed with nonneoplastic glands at the edge of a flat adenoma. The neoplastic epithelium shows high-grade dysplasia characterized by nuclear stratification and loss of cell polarity.
Adenomas

FIG. 14.49. Hypersecretory villous adenoma. A: Pale clear epithelium lines villous fronds. B: X-ray diffraction study of the lesion. Bar lines represent the elements found in the adenomatous tissue. Dotted lines represent the elements found in the surrounding normal mucosa. The single vertical line indicates a peak present only in the adenomatous tissue. Its energy level measures 3,300 electron-volts corresponding to the Ka show of potassium. C: Using the window indicated in B, the potassium was mapped to the lesion. No localization was found on the normal mucosa (not shown). However, the villous fronds showed the presence of large amounts of potassium (white dots).

High-grade Dysplasia

High-grade dysplasia is present when the nuclei consistently come to the surface of the epithelium (Fig. 14.60). High-grade dysplasia also includes loss of the columnar shape with cellular rounding, increasing nuclear:cytoplasmic ratios, nuclear irregularity, loss of polarity, development of cellular pleomorphism, and heaping up of cells (Fig. 14.62). The cells may remain confined to the basement membrane of the original crypt, or they may extend into the surrounding lamina propria, assuming a dense cribiform pattern (Fig. 14.63) that obliterates the intervening stroma. Glandular density increases (506). It is not uncommon for the surface of adenomas to exhibit focal loss of nuclear polarity. These changes probably reflect the passage of intestinal contents over their surface stimulating reactive changes. Very reactive changes may exaggerate the cytoplastic features of the epithelium, causing it to resemble high-grade dysplasia, particularly if papillary tufting forms. However, the presence of associated inflammation should alert one to the possibility that the changes are reactive in nature. If the changes are minor, they should be disregarded and not used to diagnose high-grade dysplasia.
Adenomas

FIG. 14.50. Clear cell change in an adenoma. A: Some of the glands within this tubular adenoma appear pale, while others contain more typically eosinophilic cytoplasm. B: On higher magnification, the pale-staining glands are lined by cells with clear, vacuolated cytoplasm. The nuclei are smaller and rounder than those of the adjacent adenomatous glands, and they contain small nucleoli. C: The clear cells appear mildly stratified in some areas. These cells contain abundant glycogen.

High-grade dysplasia represents the extreme end of the spectrum of abnormal histologic changes short of invasive carcinoma in the adenoma–carcinoma continuum. The presence of high-grade dysplasia strongly correlates with a contiguous invasive carcinoma. Overall, approximately 5% of adenomas contain high-grade dysplasia or carcinoma in situ at the time of presentation (175). Individual adenomas may contain transitions between high-grade and low-grade dysplasia. The percentage of adenomas containing high-grade dysplasia increases significantly with increasing adenoma size, villous architecture, multiplicity of adenomas, and age older than 60 years (189,234). The odds ratio for high-grade dysplasia is 20 for adenomas >1 cm and for adenomas containing a >75% villous component (189). Patients with multiple adenomas are more likely to have at least one adenoma with high-grade dysplasia (13.8%) than patients with a single adenoma (7.8%). The incidence of high-grade dysplasia in patients with a single tubular adenoma, multiple tubular adenomas, a single villous adenoma, and multiple villous adenomas is 2.8%, 4.6%, 16%, and 22%, respectively.

FIG. 14.51. Serial barium enema examination of descending colon shows transformation of pedunculated polyp (A) becoming wider at base (B) then sessile with malignant change (C) and obvious malignant tumor (D).

Adenomas Containing Cancer

The diagnosis of invasive carcinoma is made when the carcinoma extends into and through the muscularis mucosae, and one can demonstrate the tumor in the submucosa of the bowel wall or in the submucosa of the stalk of an adenoma. The stroma of both the head of the polyp and the underlying submucosa of the bowel wall appears much looser than the lamina propria, and lacks the large population of lymphocytes and histiocytes typically seen in the lamina propria. This diagnosis is made either on a polypectomy specimen or on a biopsy of sessile lesions. Diagnosing areas of invasive carcinoma on a midsagittal section of a pedunculated adenoma is often easier than making a diagnosis of invasion on a small forceps biopsy of a larger lesion. Biopsy fragments in which the neoplastic cells mingle with the fat, medium-sized blood vessels, nerve trunks, ganglia, or large lymphatics can be diagnosed as invasive lesions. Desmoplasia often surrounds the invading glands. The glands themselves have irregular, angulated contours and show cytologic features of malignancy. Areas of invasion must be distinguished from areas of pseudo-invasion as discussed previously. Invasive cancer is present in 2.5% of adenomas at the time of presentation (175). Carcinomas develop in the geographic centers of adenomas and spread centripetally, replacing the pre-existing adenomatous epithelium. Several factors predispose to carcinoma development, including adenoma size, growth pattern, dysplasia grade, and patient age (169,189). Both growth pattern and dysplasia grade correlate with lesional size. Small adenomas have the lowest risk of malignant transformation, but this risk is not completely negligible. Most adenomas <1 cm in diameter usually show low-grade dysplasia and have a very low malignant potential. The risk of cancer developing in such adenomas is only 5% at 15 years. When high-grade dysplasia is present, the rate of malignancy rises to 27%. The larger the adenoma, the more likely one is to encounter a villous architecture and high-grade dysplasia. Actuarial analysis reveals a cumulative risk of developing cancer in adenomas that are not removed at 5, 10, and 20 years of 2.5%, 8%, and 24%, respectively. Additional cancers occur at a site remote from the initial polyp, yielding a 35% risk for the development of cancer at any site over 20 years (193). It is estimated that the conversion rate of adenomas to cancer is 0.25% per year (235).
Even though adenomas clearly constitute the precursor lesion for most carcinomas, a vast gap exists in the prevalence rates of adenomas and carcinomas, indicating that some 90% to 95% of adenomas will never become malignant during a person’s lifetime (168). This fact offers the challenge of developing markers for identification of those adenomas that have a high probability of progressing to an invasive carcinoma.

**Prognosticators of Metastatic Risk of Cancers Present in Adenomas**

Patients who have a carcinoma diagnosed following endoscopic polypectomy present a therapeutic challenge, since invasive carcinomas arising in an adenoma are at risk for developing metastases. The clinician faces the therapeutic decision as to whether or not polypectomy alone is adequate therapy or whether the patient requires a definitive surgical resection. Therefore, the metastatic risk must be determined (Table 14.11) to plan future therapy. The presence or absence of invasion into the submucosa of the bowel wall is the most critical prognostic factor (236). The metastatic risk is low if only the submucosa of the head of a
Carcinomas arising in sessile and semi-sessile adenomas with invasion into the submucosa of the bowel wall should be regarded as any other invasive colorectal carcinomas.

FIG. 14.54. Invasive carcinoma arising in a sessile adenoma. A: Whole mount section of a sessile adenoma demonstrating an area of invasive carcinoma within the central portion of the specimen. B: Another polyp containing infiltrating glands within the submucosa. Almost no residual adenomatous glands are present.

Carcinomas arising in pedunculated adenomas cause the biggest clinical question with regard to further management. Some of these lesions require further therapy; others do not (217,237,238,239,240,241,242). The incidence of nodal metastasis in colon resections following polypectomies is extremely small in most series. The highest reported incidence was 25% in the series reported by Collacchio et al (241). However, many of these polyps were pathologically not early carcinomas. Most patients who develop nodal metastases are individuals with unfavorable histologic features, including adenomas that contain poorly differentiated carcinomas and exhibit lymphatic or vascular invasion and/or have positive resection margins (Table 14.11) (242,243). If these parameters are present, 35.7% of patients have lymph node metastasis (242). In contrast, adenomas containing well-differentiated or moderately differentiated cancers that are completely excised have a probability of having residual or metastatic cancer of <1% (Fig. 14.64) (236,240,241,242,244,245). In one large, multi-institutional study, an adverse outcome was present in 19.7% of individuals with an unfavorable histology, 8.6% with indefinite unfavorable histology, and 21% to 33% of patients with cancer at or near (within 1 mm) the cautery margin (244). The presence of cancer at or near the margin significantly associates with an adverse outcome, even in the absence of other unfavorable parameters.

FIG. 14.55. Diagram of the continuum that exists in the neoplastic progression from adenoma to carcinoma.

Adenomas Containing Carcinoid Tumors

Adenomas containing carcinoid tumors are rare. They fall within a general category of composite tumors and arise either from a common stem cell exhibiting multidirectional differentiation or from multiple cellular events affecting several cell lineages. Adenomas often contain endocrine cells, but, despite the frequency of endocrine cells, they are seldom associated with synchronous carcinoid tumors. Carcinoid tumors in adenomas may arise via several mechanisms (246). Such lesions may arise from a common stem cell, or alternatively, the adenoma and the carcinoid tumor may arise from separate cell lineages, with their appearance in the same lesion representing collision of two separate tumors. Patients with carcinoid tumors have an increased incidence of additional malignancies, many of which arise in the gastrointestinal tract. One could postulate that substances produced by the carcinoid tumor stimulate the adjacent colonic mucosa to proliferate, ultimately leading to neoplastic transformation. Additionally, growth-regulating substances produced by carcinoid tumors could also play a role (247,248,249).

TABLE 14.11 Risk Factors for Metastases from Cancer Arising in a Pedunculated Adenoma

| Poorly differentiated carcinoma | Presence of lymphatic invasion | Tumor present at the resection margin | Presence of submucosal invasion of bowel wall |

Pathologic Evaluation of Polyps

When one receives polyp biopsies or polypectomy specimens, it is important to record all of the pathologic features, including the number of tissue fragments received, their size, their gross morphology (i.e., pedunculated or sessile), and their locations. This is especially important in today's world of cost containment, in which one may receive multiple polyps from different sites in a single specimen container. Endoscopists should be careful to limit handling of specimens to polyps in the same colorectal subsite. The presence of unsuspected invasive tumor among one of several polyps derived from different segments of the bowel would not allow identification of the segment requiring further resection. Under this circumstance, it is important to diagnose each tissue piece, if one can determine that each represents a separate polyp. It helps to interpret the number of lesions if the endoscopist indicates the number of polypoid lesions biopsied and/or removed on the requisition. This facilitates a diagnosis of each lesion.
All lesions should be submitted for pathologic examination to (a) adequately classify the lesions histologically, (b) determine the degree of dysplasia, and (c) detect foci of invasive malignancy. Adenomas should be fixed prior to cutting. Small specimens often contract into balls once they are removed from the endoscope due to contraction of the muscularis mucosae. Tissue fixation ensures retention of the ball shape, making identification of the resection site difficult. This artifact can be avoided by having the endoscopist place sessile polyps on a firm matrix, such as a piece of paper or Gelfoam, before placing the specimen in the fixative.

FIG. 14.56. Clusters of neoplastic cells lie within lymphatic channels in the muscularis mucosae of an adenomatous polyp. The adenoma did not contain invasive carcinoma, but did harbor an intramucosal carcinoma that abutted the muscularis mucosae.

If the lesion is pedunculated and received in a fresh state, it can be fixed in such a way that the stalk is pinned to a piece of cork and the specimen is floated upside down in the fixative so as to straighten out the stalk, thereby facilitating examination of the relationship between the head and the underlying stalk. Ideally, the endoscopist should indicate the stalk of larger adenomas by placing a needle at its base when the polyp is removed from the endoscope. In this way, the polypectomy margin can be identified later (Fig. 14.65). Realistically, this almost never happens. Occasionally, the pathologist and the endoscopist disagree as to whether a stalk is present or how long the stalk is, since the stalk often retracts into the head of the adenoma. In many lesions, it is possible to identify the excision edge of the specimen due to the presence of prominent cautery effect. However, some specimens defy accurate orientation so that the assessment of margins may be impossible. In this case, the margins are reported as not evaluable.

FIG. 14.57. Determination of depth of invasion is a critical pathologic assessment. Levels of invasion in a pedunculated adenoma (left) versus a sessile adenoma (right). The green areas are zones of carcinoma. Invasion below the muscularis mucosae in a sessile lesion places the level of invasion into the submucosa of the bowel wall, increasing the risk of metastasis. This contrasts with the invasive carcinoma in a pedunculated polyp, where the invasion is limited to the polyp head.
If an adenoma containing high-grade dysplasia is only biopsied or removed in a piecemeal fashion, one may not be able to determine whether an invasive carcinoma is present or not. The histologic classification of fractional biopsies of smaller adenomas (<1.7 cm) are in 88.9% agreement with the final diagnosis in the polypectomy specimen, whereas the reliability of the biopsies in accurately diagnosing adenomas >1.7 cm is only 27.6%. Invasive carcinomas are frequently missed in biopsies taken of larger lesions (251). Reasons for the poor predictability of the biopsy relate to the fact that larger adenomas tend to be villous, with invasive carcinoma developing in the center of the lesion. These centrally invasive foci tend to retract due to the tumor-associated desmoplasia. As a result, the villous fronds fall into the center of the lesion, covering the invasive component. Also, villous fronds at the periphery of the lesion are more accessible for biopsy than the cells in the central scarred carcinoma. Cytologic evaluation of adenomas can augment the diagnostic yield of malignancy (Fig. 14.67), particularly if the brush dislodges malignant cells from the center of the lesion where cancer is likely to be present. However, as with superficial biopsies, it is usually not possible to cytologically distinguish between invasive and noninvasive foci.

**Pathology Report**

The pathologist must carefully word pathology reports of colorectal adenomas to facilitate clear communication with the clinician and appropriate therapy. The pathology report should state the highest degree of dysplasia present in the adenoma, whether or not it has villous features, the completeness of its removal, and the presence or absence of invasive tumor. If invasive cancer is present, it should be reported in terms of the depth of its invasion, involvement of the stalk or cautery margin, the presence or absence of lymphatic and vascular involvement, and the degree of differentiation. It is also sometimes helpful to estimate the volume of adenoma replaced by the carcinoma.

**FIG. 14.58.** Invasive adenocarcinoma within the submucosa. The submucosa is easily identified by the presence of a large submucosal blood vessel.

**FIG. 14.59.** Invasive carcinoma. A: Irregular glands infiltrate the submucosa creating a ragged invasive margin, especially prominent in the area marked by the arrows. B: Desmoplastic response surrounding an invasive cancer.
Adenomas

FIG. 14.60. Dysplasia in adenomas. A: This adenomatous polyp contains cells with little or no atypia and, therefore, represents only low-grade dysplasia. B: Adenomatous polyp with minor cytologic alterations including numerous mitoses and mild nuclear pleomorphism. The changes in this polyp are common in larger polyps and do not warrant a diagnosis of high-grade dysplasia. C: High-grade dysplasia characterized by cellular disorganization and more marked cytologic atypia. The degree of nuclear pleomorphism is sufficient in this area so that it might be called intraepithelial carcinoma. In many areas the cells are truly stratified. D: Stratification of cells to the luminal surface of the glands is a feature of high-grade dysplasia.

FIG. 14.61. Proliferation in normal and regenerative colonic mucosa versus adenomas. A: Ki-67 immunostain using the monoclonal antibody MIB-1. This section was taken from an area of active mucosal regeneration in a patient with inflammatory bowel disease. Large numbers of proliferating cells are identifiable in the regenerating crypts. Note the restriction of the proliferative zone to the base of the glands. B: In adenomas, cell proliferation is dysregulated, and the proliferating cells appear in the superficial portion of the mucosa. The normal pattern of proliferation in the basal crypts is present in the adjacent nonneoplastic mucosa (right). Note that fewer proliferating cells are present in this area than in A.

Treatment

Most experienced endoscopists recommend complete removal of polyps and their submission for histologic analysis (203,218). Small polyps may be either hyperplastic polyps or adenomas, and the size of a polyp does not predict its histologic features (205). It is important to note, however, that even small polyps may have advanced histologic features and, therefore, should be carefully examined histologically. Larger polyps may be removed with cautery snare, while small sessile polyps may be biopsied and ablated with hot biopsy forceps, laser ablation, or photodynamic therapy. Pedunculated polyps and sessile polyps with small mucosal attachment areas can be completely removed. However, endoscopic excision may not be possible when the lesion lies in an inaccessible site or if the polyp measures more than 2 cm in diameter and is sessile, especially if it has a broad attachment area to the colonic wall. Large sessile lesions usually undergo multiple forceps biopsies to determine if they contain a carcinoma. Incompletely removed, wide-based, sessile polyps may require endoscopic mucosal resection to remove the remaining neoplasm. If complete endoscopic resection cannot be performed, surgical resection may be required. Following complete removal of a pedunculated adenoma containing an invasive cancer, most endoscopists perform a colonoscopy 2 to 6 months and 1 year later before reverting to a general follow-up scheme (252). The endoscopist may sometimes place a tattoo at the polypectomy site in order to identify it later (Fig. 14.68). Guidelines for clinical follow-up of patients with adenomas are summarized in Table 14.12.
Colon Cancer Prevention

Colon cancer prevention strategies fall into three major categories: (a) identification and removal of precursor and early lesions, (b) dietary alterations, and (c) chemoprevention. Disease prevention falls into primary and secondary modalities. Primary prevention is defined as prevention of disease by some active intervention before the disease occurs. The second form of disease prevention is called secondary prevention, which involves detecting a disease before it is symptomatic and implementing an intervention to prevent the clinical manifestations of the disease, such as by removing a colonic adenoma thereby preventing its progression to adenocarcinoma.

If an improvement in colon cancer survival is to occur, increased efforts need to focus on primary prevention as well as on early detection and removal of premalignant and malignant lesions. Since epidemiologic, animal, and biochemical studies suggest that diets high in total calories and fat and low in various dietary fibers, vegetables, and micronutrients associate with an increased incidence of colorectal cancer, one primary means of prevention would be dietary education and diet modification. There are no data on the efficacy of this approach; therefore, most attention has focused on early detection of colonic neoplasms and chemoprevention.

<table>
<thead>
<tr>
<th>Screening Method</th>
<th>Interval</th>
<th>Consequences of a Positive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood testing</td>
<td>Annual</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>Every 5 years</td>
<td>Polypectomy for distal polyps; possibly colonoscopy</td>
</tr>
<tr>
<td>Combined FOBT and sigmoidoscopy</td>
<td>FOBT annually, sigmoidoscopy every 5 years</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 10 years</td>
<td>Polypectomy; surgery for cancers or lesions that are not endoscopically resectable</td>
</tr>
<tr>
<td>Double-contrast barium enema</td>
<td>Every 5 years</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>FOBT, fecal occult blood testing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Screening for Colorectal Adenomas and Carcinomas

Early Detection of Colorectal Cancer

The beneficial effects of early adenoma detection and removal were initially reported by Gilbertson in 1974 (122). Several more recent trials based on sigmoidoscopy or colonoscopy have reported a significant reduction in mortality as a result of screening (123,124,125). Case control studies indicate a reduction in the mortality rate from distal colorectal cancers in the magnitude of 60% to 85% (126). All studies indicate that the cancers detected have a more favorable stage when the patients are in a screening program (127). The reduction in cancer mortality results from (a) identification of early curable cancers, (b) identification and removal of premalignant polyps, and (c) the benefits of subsequent surveillance.

Screening recommendations vary depending on whether a patient falls into a high- or average-risk category. Therefore, asymptomatic individuals should have their risk evaluated to include an analysis of inherited syndromes,
personal history of adenomas, or colorectal cancer and IBD (126,127).

**Screening of Average-risk Populations**

In 1995, an expert panel was assembled by the U.S. Agency for Health Care Policy and a consortium of gastroenterological societies to prepare clinical guidelines for colorectal cancer screening. The panel's initial report was published in 1997 (128) and later updated in 2003 (128). Screening for colorectal carcinoma is recommended for all persons aged 50 and older using one of several possible strategies: fecal occult blood testing (FOBT), flexible sigmoidoscopy, a combination of FOBT and sigmoidoscopy, colonoscopy, and double-contrast barium enema (Table 14.5). The rationale for presenting patients with a number of screening options lies in the fact that no single test is of unequivocal superiority to the others, and giving patients a choice of methodologies may increase the likelihood that screening will occur.

**Screening for High-risk Patients**

Individuals with one or more relatives with colon cancer or adenomatous polyps or those with known colorectal cancer syndromes should undergo screening beginning at an earlier age and at shorter intervals than are recommended for those at average risk for colorectal cancer (Table 14.6) (128).

**Chemoprevention**

Cancer chemoprevention is defined as the prevention of cancer by the administration of one or more chemical entities either as individual drugs or naturally occurring dietary constituents. The three major types of chemopreventive agents are (a) inhibitors of carcinogen formation, (b) blocking agents, and (c) suppressing agents. Blocking agents inhibit tumor initiation, while suppressing agents act as inhibitors of tumor promotion and progression. An individual agent may belong to more than one class.

Significant interest lies in decreasing the incidence of both adenomas and carcinomas in patients enrolled in chemoprevention trials. Substances of current interest include antioxidants, nonsteroidal anti-inflammatory drugs (NSAIDs), and calcium, vitamin D, and other micronutrients.

**Aspirin and Other Nonsteroidal Anti-inflammatory Drugs**

Evidence strongly supports the notion that aspirin and other NSAIDs prevent the development and progression of gastrointestinal adenomas and carcinomas. Three separate lines of investigation indicate a correlation between NSAID use and a reduction in colorectal cancer: (a) some epidemiologic studies show a 40% to 60% decrease in the relative risk of colorectal carcinoma and an approximately 70% risk reduction in adenoma incidence in individuals taking NSAIDs compared with those not taking them (129,130,131,132,133,134,135,136); (b) NSAIDs alter the biology of FAP, since sulindac administration results in a striking reduction in adenoma size and number (137,138,139,140); (c) experimental models show their chemopreventive effects as judged by a reduction in the frequency and number of premalignant/malignant lesions (141,142,143). Several recent clinical trials involving patients at high risk for colorectal cancer development have shown a significant reduction in adenoma development in those patients receiving daily aspirin (144,145).

**TABLE 14.6 Screening Recommendations for Patients at High Risk for Colorectal Cancer**
<table>
<thead>
<tr>
<th>Familial Risk Category</th>
<th>Screening Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative with colorectal cancer or an adenoma diagnosed at an age ≤60 years, or two second-degree relatives with colorectal cancer</td>
<td>Same as average risk, but beginning at age 40</td>
</tr>
<tr>
<td>Two or more first-degree relatives with colon cancer, or one first-degree relative with colorectal cancer or an adenoma diagnosed at age ≥60 years</td>
<td>Colonoscopy every 5 years, beginning at age 40, or 10 years younger than the youngest affected relative, whichever comes first</td>
</tr>
<tr>
<td>One second- or third-degree relative with colorectal cancer</td>
<td>Same as average risk</td>
</tr>
<tr>
<td>Gene carrier or at risk for familial adenomatous polyposis</td>
<td>Sigmoidoscopy annually beginning at age 10–12</td>
</tr>
<tr>
<td>Gene carrier or at risk for attenuated familial adenomatous polyposis</td>
<td>Colonoscopy annually beginning in the late teens or early 20s because of the preponderance of proximal polyps in this group</td>
</tr>
<tr>
<td>Gene carrier or at risk for hereditary nonpolyposis colorectal cancer syndrome</td>
<td>Colonoscopy every 1–2 years, beginning at age 20–25, or 10 years younger than the youngest affected relative, whichever comes first</td>
</tr>
</tbody>
</table>

**NSAIDs** exert their effects through inhibition of two enzymes involved in prostaglandin synthesis, cyclooxygenase (COX)-1 and COX-2. Both enzymes play key roles in the biosynthetic pathway by which arachidonic acid is converted into prostaglandin (PG) E₂, PGD₂, PGF₂α, PGI₂, and thromboxane A₂. COX-1 is normally expressed in most tissues, while COX-2 expression is normally low. However, COX-2 is rapidly up-regulated by proinflammatory cytokines and many tumor regulators (146). In addition, COX-2, but not COX-1, is commonly overexpressed in colorectal adenomas and carcinomas (147). Evidence suggests that the COX-2-derived prostaglandin PGE₂ may play a direct role in malignant progression in colon cancer (148,149). PGE₂ appears to promote transactivation of the epidermal growth factor receptor, and may, through a complex series of steps, stabilize β-catenin within colonic epithelial cells leading to cell proliferation (150).

**Calcium Supplementation**

Calcium supplementation reduces intestinal proliferation (151,152,153) and alters the composition of intestinal bile acids, increasing the concentration of cholic acid, decreasing chenodeoxycholic acid, and increasing total fecal bile acid excretion. Calcium counteracts the effects of fatty and bile acids by binding them, making them insoluble and harmless (154). Several randomized trials have demonstrated reduction in colorectal adenoma development in patients receiving daily calcium supplementation (155,156,157). Consumption of dairy products containing calcium and vitamin D also reduces colorectal cancer risk in a dose-dependent fashion (158). The beneficial effects of calcium supplementation may extend for years following cessation of calcium supplements (157).
Introduction

The large intestine gives rise to a host of neoplasms. In this chapter we will focus on epithelial neoplasms. Neuroendocrine tumors are covered in Chapter 17, hematologic malignancies in Chapter 18, and mesenchymal tumors in Chapter 19.

Colonic Adenomas and Carcinomas

Colorectal carcinoma is one of the most common neoplasms affecting individuals living in industrialized nations. Colorectal cancer is the fourth ranking cancer worldwide, accounting for approximately 9% of all cancers (1). The lifetime risk of developing colorectal carcinoma in the United States is approximately 5.5% for both men and women, with an approximately 2% chance of dying from the disease (2). Most carcinomas develop from adenomas, their precursor lesion. These adenomas occur sporadically or as part of a polyposis syndrome (see Chapter 12). Adenomas are benign by definition, although they are neoplastic and may harbor an invasive carcinoma. Carcinomas also arise in areas of dysplasia in patients with idiopathic inflammatory bowel disease (IBD) (see Chapter 11).

Considerable advances have occurred in our understanding of the molecular events associated with the progression of colorectal carcinoma since the publication of the first edition of this book. Complex interactions between inherited and acquired genomic and other biologic changes associate with both benign and malignant large bowel neoplasia. Colon cancer is highly curable if it is diagnosed in its early stages.

Incidence

Colorectal cancer exhibits at least a 25-fold variation in occurrence worldwide (1,3). It is most common in the industrialized countries of Western and Eastern Europe, North America, New Zealand, and Australia (Fig. 14.1), while its incidence is low in Africa and Asia (1,4). These large geographic differences in colorectal cancer incidence are most likely explained by different environmental and dietary exposures. Migrants from countries where colon cancer risk is low to high-risk countries show a rapid increase in their colon cancer rates (1,5). A rapid increase in colorectal cancer frequency occurring in Japan parallels its increasing prosperity and westernization (4). This phenomenon is equivalent to a migration in time rather than space and suggests that indigenous Japanese, like those who have migrated to the United States, will acquire levels of colorectal cancer risk equivalent to, or higher than, those of U.S. whites. In fact, colorectal cancer rates for Japanese individuals born in the United States are now higher than those for U.S. whites (6).

The overall and subsite frequency of colorectal cancer also shows considerable intranational ethnic variation, a phenomenon best documented in the United States and New Zealand. It is difficult to determine whether these differences have a genetic or environmental basis, given the different cultural and socioeconomic backgrounds of the ethnic groups within these countries. In the United States, the highest incidence rates in the Surveillance, Epidemiology, and End Results (SEER) registries for the years 2000 to 2003 were in Black males (72.9 of 100,000) followed by White males (61.4 of 100,000), Black females (56.1 of 100,000), Asian males (51.2 of 100,000), Hispanic males (47.3 of 100,000), White females (44.7 of 100,000), Asian females (35.7 of 100,000), and Hispanic females (32.7 of 100,000) (2).

Mortality

In 2006, an estimated 55,170 people died of colorectal cancer in the United States (2). Overall, the age-adjusted mortality rate for colorectal cancer among all ethnic groups in the United States has declined since 1975 (2). However, SEER mortality data for the years 2000 to 2003 show a significantly higher mortality for black Americans with colorectal cancer than their white compatriots (2). Mortality rates are lowest for Asian and Hispanic colorectal cancer patients in the United States.

Etiology

It is important to recognize that colon cancers and rectal cancers associate with different risk factors. This is consistent with the observation that colon cancers rise in frequency among migrants from low- to high-risk areas, while rectal cancers exhibit a fairly stable incidence (4). Moreover, the colonic subsites also show considerable variation in cancer incidence and in cancer-associated risk factors. Thus, right-sided
cancers generally constitute a larger proportion of colorectal cancers in low-risk populations than in high-risk groups and show smaller postmigration increases than do left-sided cancers. That said, it should be noted that the progression of the neoplastic process from adenoma to carcinoma is similar throughout all segments of the large bowel, and that the risk factors for carcinoma and adenoma are similar (7).

**FIG. 14.1.** Map showing the geographic variation in colon cancer incidence worldwide. Countries indicated in *red* represent areas of high incidence, those in *green* intermediate incidence, and those in *yellow* a low incidence of the disease.

Environmental and genetic influences probably play roles at different points in the neoplastic progression. Several well-characterized colon cancer syndromes indicate that inherited susceptibility plays an important role in the pathogenesis of colorectal cancer (see Chapter 12). Conversely, epidemiologic, experimental, and migrant studies clearly indicate environmental influences in the genesis of the disease. Diet may alter endogenous characteristics, such as the bowel flora, which in turn influence the conversion of ingested foods into potential carcinogens. Other environmental factors, such as physical activity, occupational exposures, or ethanol, may further influence these interactions. The interaction of environmental factors with genetic factors is complex and currently under intense scrutiny.

**Genetic Factors**

Familial forms of colon cancer fall into several categories: (a) patients with a polyposis syndrome, (b) patients with defined colon cancer family syndromes, and (c) patients who appear to have sporadic cancers but who have other family members with colon cancer. Genetic influences are best defined in two autosomal dominant syndromes: Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer syndrome (HNPCC) (see Chapter 12). Hereditary polyposes account for approximately 1% of all colorectal carcinomas, HNPCC accounts for another approximately 5%, and perhaps 30% or more of sporadic carcinomas may be inherited (8).

**Neoplasia in Asymptomatic First-degree Relatives of Persons with Colon**
Cancer

The presence of a colorectal cancer in a first-degree relative (sibling or parent) represents an important colon cancer risk factor. It may increase a person's lifetime risk from 1.8-fold to as high as eightfold that of the general population (9). The effect of family history is greatest for younger individuals (i.e., those younger than 45 years of age). Asymptomatic patients with one first-degree relative with colorectal cancer have nearly double the risk of developing adenomas or cancers than asymptomatic individuals without a family history; the cancer often affects younger persons (9,10,11,12). The incidence of colonic neoplasms among first-degree relatives of colorectal cancer patients ranges from 15% to 20% (13). These trends are even more pronounced in those having more than one affected relative (14,15). Familial clusters of colorectal cancer could arise on the basis of a shared gene pool, a shared environment, or a combination of both.

Relationship between Colon Cancer and Energy Balance

Reduced physical activity and obesity have emerged as consistent epidemiologic associations with colon cancer risk (7,16,17,18,19,20,21,22,23) and probably account for the association of this cancer with sedentary occupations, weight gain since age 25, body mass index, family income, and the rural/urban gradient in colon cancer frequency. Colon cancer is also associated with central adiposity independent of body mass index (22). Excess energy intake over energy expenditure may also account, at least in part, for the association of colon cancer with fat intake, since fat is a major source of energy (16). It is of interest that rectal cancer does not share these risks (7). The mechanism that accounts for the association between a positive energy balance and colon cancer has not been identified, but it has been proposed that physical activity may stimulate hormonal release, activating neural reflex mechanisms that enhance propagative peristalsis and increased colonic motility. This, in turn, leads to decreased mucosal contact with intraluminal carcinogens.

In addition, the insulin resistance that commonly affects obese individuals may also play a role (24). Type 2 diabetes associates with a threefold increase in colorectal cancer risk compared with the nondiabetic population (25). In addition, colon cancer patients exhibit greater degrees of glucose intolerance and insulin resistance than patients without colorectal cancer (26). Insulin has growth and metabolic effects that could impact the colonic epithelium predisposing to cancer development. Insulin stimulates proliferation and inhibits apoptosis in colorectal cancer cell lines, and promotes growth of colon tumors in experimental animals (27,28,29). The metabolic effects of insulin lead to increased concentrations of glucose and triglycerides that may additionally result in an environment in which transformed colonocytes have greater available energy sources. Insulin may also affect cell-signaling pathways by activating insulinlike growth factor, protein kinase C, and mitogen-activated protein (MAP) kinase, leading to increased mitotic activity and potential carcinogenesis (30).

Nongenetic Host Factors

Intestinal epithelium is exposed to a complex luminal environment that plays an etiologic role in colorectal tumorigenesis. Variably digested food passes into the colonic lumen from the small bowel and mixes with bile acids and other luminal constituents (Fig. 14.2). The luminal contents vary with the diet. Millions of bacteria are present in the gut lumen, and many of these generate energy by degrading and fermenting plant cell material (31). The effects of the bacterial flora are noted in Table 14.1. One byproduct, butyrate, slows cell proliferation and facilitates access of DNA repair enzymes.
Introduction

FIG. 14.2. Nongenetic factors involved in colon carcinogenesis. Dietary substances, including fruits, vegetables, and meats, influence the composition of the luminal contents of the gut. Ingested substances such as fat, fiber, vitamins, and minerals interact with bile acids and the luminal anaerobic bacterial population, producing some carcinogenic and mutagenic molecules, as well as cytoprotective substances. The level of production of each of these molecules varies depending on the composition of the luminal contents.

Dietary Factors

The vast literature associated with the relation of diet to colorectal cancer continues to generate controversy. This is due, in part, to differences in the methods employed to measure dietary variables and to the comparatively small increases in risk that can be demonstrated with even the strongest dietary associations. The three methods for dietary studies are ecologic studies that relate cancer incidence to per capita food consumption, and two analytic methods—the case control method, which assesses dietary practices of patients who have been diagnosed with cancer, and prospective cohort studies, which measure dietary exposures in healthy subjects who are followed until cancer develops. Each method has built-in flaws. Ecologic studies do not identify the dietary patterns of specific cancer patients, which may actually differ from those of the general population. Dietary data collected prospectively in cohort studies may not hold true for the future, and dietary measurements taken at the time of cancer diagnosis may reflect the influence of disease upon food preferences rather than past experience. Moreover, complex interrelationships exist between energy balance, fat and meat consumption, fiber, alcohol intake, and micronutrients, making it difficult to tease out the relative impact of any one variable upon the risk of colon cancer. The following discussion summarizes the pertinent trends in this field of study.

<table>
<thead>
<tr>
<th>TABLE 14.1 Effects of Colonic Bacterial Flora</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deconjugate bile acid to form secondary bile acids</td>
</tr>
<tr>
<td>Produce butyrate and other short-chain fatty acids</td>
</tr>
<tr>
<td>Activate procarcinogens</td>
</tr>
<tr>
<td>Form diacylglycerol</td>
</tr>
<tr>
<td>Ferment polysaccharides, protein, and glycoproteins</td>
</tr>
<tr>
<td>Synthesize fecapentaene</td>
</tr>
<tr>
<td>Adsorb hydrophobic molecules</td>
</tr>
</tbody>
</table>

Fat and Animal Protein

These two items are combined because they are highly correlated in dietary intake studies. In many of the published dietary analyses, fat intake is inferred from meat consumption, so that it is not possible to assess their individual impact on colon cancer risk. The origin of the hypothesis that a high-fat diet favors the development of colon cancer dates from the early correlation studies of Burkitt (32) that showed that colon cancer and coronary heart disease (CHD), as well as their precursors adenomatous polyps and atherosclerosis, were seldom encountered in black Africans who consume very low levels of dietary fat (33). Subsequent studies in other populations showed a strong correlation between national per capita fat consumption and both colon cancer and CHD. It has been well established that a high fat intake favors CHD, and it is therefore reasonable to...
suggest that this also holds true for colon cancer. Furthermore, there is a strong international correlation between the mortality rates from colon cancer and CHD (34), although France (low CHD and high colon cancer rates) and Finland (high CHD and low colon cancer rates) are exceptions. Kolonel (35) reviewed 14 correlational studies and found that six favored a fat–colon cancer connection and eight did not. In spite of these inconsistencies, he pointed out that dietary variability in fat intake in homogenous populations may not be great, and that intergroup correlational studies may be more likely to show true associations than case control or cohort studies, which show similar interstudy inconsistencies (35). The mechanisms by which a high-fat diet could associate with an increased risk of colon cancer are as follows:

- As a source of calories. In sedentary males, even the small excess of energy intake over expenditure that is provided by a diet with 30% of calories derived from fat has resulted in quite impressive long-term weight gain, an identified risk factor for colon cancer (36).
- As a surrogate marker for protein intake. Animal protein in the form of red meat appears to have a strong, consistent, independent association with colon cancers, while the association of fat with colon cancer disappears after controlling for red meat (7).
- Diets high in fat and meat and poor in fiber associate with formation of hydroxyl radicals in feces, a factor that could lead to oxidative injury to DNA of colonic epithelial cells and subsequent neoplastic transformation (37).

**Fibers, Fruits, and Vegetables**

Many of the existing and proposed intervention studies designed to lower the frequency of colon cancer have been justified by epidemiologic studies that have shown that an inverse relationship exists between this cancer and the intake of fruits, vegetables, and selected micronutrients. This inverse association shows considerable interstudy consistency. As in the case of fat and red meat consumption, there is a strong correlation among these food items, so it is difficult to weigh the contribution of any one variable toward the decrease in large bowel cancer risk. The mechanisms by which fiber may protect against colon cancer are summarized in Table 14.2. In addition to fiber, green leafy vegetables and fruits are sources of antioxidant vitamins and substances that inhibit carcinogenesis (Table 14.3).

**Micronutrients**

The role of dietary vegetables in colorectal cancer prevention is more complex than just their fiber effects (Table 14.4). Vegetables contain numerous other substances, including antioxidants, folate, micronutrients such as carotenoids and ascorbate, and nonnutrients such as phenols, flavonoids, isothiocyanates, and indoles that possess potent anticarcinogenic properties (38,39,40,41). An abundant plant constituent, inositol hexaphosphate (phytic acid), is a powerful inhibitor of iron-mediated production of hydroxyl radicals, and it suppresses hydroxyl radical generation and lipid peroxidation. Consumption of vitamins D, A, C, and E and the micronutrients calcium, selenium, and diallyl sulfide or almethyl trisulfide (substances found in garlic) also reduces colorectal cancer risk. Garlic is the vegetable with the strongest inverse association with colon cancer risk (40,42). The anticarcinogenic effects of garlic and other allium vegetables result from the induction of detoxifying enzymes, a reduction in tumor proliferation, or antibacterial activity (40).

<table>
<thead>
<tr>
<th>TABLE 14.2 Potential Benefits of Fiber in the Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>As a source of calories. In sedentary males, even the small excess of energy intake over expenditure that is provided by a diet with 30% of calories derived from fat has resulted in quite impressive long-term weight gain, an identified risk factor for colon cancer (36).</td>
</tr>
<tr>
<td>As a surrogate marker for protein intake. Animal protein in the form of red meat appears to have a strong, consistent, independent association with colon cancers, while the association of fat with colon cancer disappears after controlling for red meat (7).</td>
</tr>
<tr>
<td>Diets high in fat and meat and poor in fiber associate with formation of hydroxyl radicals in feces, a factor that could lead to oxidative injury to DNA of colonic epithelial cells and subsequent neoplastic transformation (37).</td>
</tr>
</tbody>
</table>
Introduction

Increases fecal mass
Decreases mucosal contact time with potential carcinogens
Increases intestinal transit time
Increases defecation frequency
Binds various reactive compounds
Dilutes intestinal contents
Has direct antitoxic effects against carcinogens and cocarcinogens
Blocks free radical formation
Substitutes for dietary fat
Reduces time for bacterial conversion of bile acids
Increases production of hydrogen, methane, and short-chain fatty acids
Adsorbs organic and inorganic substances, including bile salts
Decreases dehydroxylation of bile acids

Vitamin C, an antioxidant abundant in fruits and vegetables, may inhibit the formation of fecal mutagens, thus protecting against colon cancer development. Vitamin C and E supplementation decreases the number of recurrent rectal adenomas following polypectomy (43,44). Vitamin E and selenium function as antioxidants and could protect against carcinogenesis by neutralizing the toxic effects of free radicals, particularly those originating from fat metabolism.

Alterations in calcium and vitamin D metabolism may explain the geographic variation in colon cancer death rates, which tend to increase with increasing latitude and decreasing sunlight intensity, since sunlight exposure profoundly affects vitamin D metabolism. Mortality rates from colorectal cancer in the American northeast are nearly three times those found in the American south for both urban and rural populations. Colon cancer is uncommon at low latitudes and almost disappears within 10 degrees of the equator (45). An exception to this is Japan. However, the Japanese consume a diet rich in fish containing large amounts of vitamin D (46).

### TABLE 14.3 Dietary Influences in Colon Cancer

Normal colon bacteria convert bile acids to carcinogenic compounds, especially in individuals who consume high-fat, low-fiber diets.
Oxygen radicals and lipid peroxidation products form by diet-induced metabolic activation of procarcinogens.
Heterocyclic amines form due to cooking of meats.
Nutrient antioxidants, minerals, and trace elements in fruits and vegetables inhibit toxicity of luminal carcinogenic compounds by (a) quenching free radicals, (b) enhancing cell repair mechanisms, (c) increasing cellular immunity, and (d) regulating proliferation.

### TABLE 14.4 Beneficial Properties of Certain Micronutrients in Possible Risk Lowering in Colorectal Cancer
**Micronutrient** | **Mechanism of Action**
--- | ---
**Calcium** | Increases cellular adhesion, decreases cellular proliferation
**Vitamin D** | Retards in vitro growth of human cancer cells, lowers level of ornithine decarboxylase in rats
**Vitamin C** | Prevents formation of N-nitro-nitrosamines, has antioxidant properties, decreases tumor development after carcinogen administration
**Vitamin E** | Free-radical scavengers shown both to inhibit and to promote colon tumor growth in carcinogenesis models
**Selenium** | Cofactor for the anticarcinogen glutathione peroxidase
**Diallyl sulfide (garlic compound)** | Inhibits carcinogen-induced nuclear injury
**Allyl methyltrisulfide (garlic compound)** | Increases activity of glutathione-S-transferase, which may inactivate carcinogens

In some studies (45) but not others (47,48), increased dietary calcium consumption inversely correlates with colon cancer incidence and mortality. Calcium reduces colonic epithelial cell proliferation (49,50) and decreases the effects of bile acids and fatty acids on the colonic epithelium by converting them to insoluble calcium soaps. Calcium effects are modulated in part by interactions with 1,25-dihydroxy-vitamin D₃ and fatty acids (51).

An inverse relationship also exists between selenium levels and colorectal cancer risk (52). Selenium serves as a cofactor for glutathione peroxidase, which protects cells from oxidative damage. It is also probably involved in prostaglandin and antibody synthesis. A number of other micronutrients may play a role in lowering colorectal cancer incidence (Table 14.4) (53).

**Alcohol Consumption**

Alcohol significantly increases the risk of developing rectal cancer, whether assessed on the basis of total amount consumed or as percent of total calories (54,55,56,57,58). Alcohol shows a weaker association with colon cancer, exhibiting a dose response only when assessed on the basis of presence of total calories (54). This may reflect the contribution of alcohol to a positive energy balance among heavy consumers. Additionally, substantial alcohol consumption increases the risk of adenomas and cancers due to abnormal DNA methylation (59). Cirrhosis itself may represent an independent risk factor for adenoma development; alcohol may increase the risk (60).

**Smoking**

Both rectal cancer and adenoma incidence is significantly elevated among users of chewing tobacco, snuff, pipes, and cigars and among current and former cigarette smokers. Cancer risk significantly increases with pack years and an earlier age of first use (61,62). It is estimated that tobacco use causes 16% of colon cancer deaths and 22% of rectal cancer deaths in a study conducted among U.S. veterans (61). The induction period for colorectal cancers is at least 35 years. Smoking may act as a tumor initiator (61). In addition, recent studies have linked smoking to microsatellite instability, CpG island methylator phenotype (CIMP), and *BRAF* mutations in colon cancers (63,64).

**Occupational Factors**

Rectal cancer, and to a lesser extent sigmoid cancer, associates with occupations in which dusts or fumes are inhaled, especially if the jobs are held for long time periods and when a person is young. An increased cancer risk exists among workers exposed to wood and metal dusts, plastics, fumes, organic solvents (65,66), cement, and fiberglass. Cancer risk also increases with exposure to asbestos (67). Both asbestos fibers and ferruginous bodies may be found in the tumor tissue of...
such patients (68). Thus, occupations associated with increased colon cancer risk include asbestos workers, pattern makers, carpet workers, steel workers, railway employees, those in the auto building or housing industry, and dry cleaners (69). Finally, individuals with sedentary jobs are more likely to develop colorectal cancer than those with active jobs.

**Relationship to Atherosclerosis and Cholesterol and Lipoprotein Levels**

A high fat intake over a long period of time increases serum cholesterol and β-lipoprotein levels (70). Data on the relationship between cholesterol levels and the development of colorectal adenomas and carcinomas are contradictory. Several cohort studies (71,72,73) have shown an inverse association between cholesterol levels and colon cancer risk. This inverse relation is strongest with right-sided cancers and attenuates with increasing time between testing and diagnosis, so that by 10 years the association is no longer apparent (72). This suggests that the effect is a marker for undiagnosed colon cancer, since it is not observed with gastric or rectal carcinoma (71,72,73). Other studies have established a positive association between serum cholesterol levels and cancer risk (74). Of interest is the occasional association of Muir-Torre syndrome with familial hyperlipidemia (75). The e4 allele of apolipoprotein E may protect an individual from developing proximal colonic adenomas and carcinomas (76).

**Association with Diverticulosis**

There is an increased incidence of left-sided colon cancer in patients with diverticular disease, and it was Burkitt who first suggested that adenomas or cancers were likely to coexist in the same population (77). The coexistence of adenomas and diverticule (Fig. 14.3) is especially true in Western populations, but it occurs less commonly in Asian populations where the incidence of diverticulosis is lower and the diverticula tend to be right sided (78). Stemmermann and Yatani (79) showed that adenomas and diverticula both increase in migrant populations, presumably due to dietary influences. It is unlikely that the diverticula themselves predispose to neoplastic development or vice versa.
FIG. 14.3. Diverticulosis and adenoma. A: This bowel contains several polypoid mucosal structures. The straight arrows indicate an adenomatous polyp. The curved arrows highlight the prolapsing folds that create the accordion pleated mucosal pattern characteristic of diverticular disease. B: An adenoma arises from the epithelium lining the diverticulum and projects into the lumen. The normal colonic mucosa is seen on the right.

Relationship to Idiopathic Inflammatory Bowel Disease

Patients with both ulcerative colitis and Crohn disease exhibit an increased risk of developing colorectal cancer, as extensively discussed in Chapter 11.

Socioeconomic Factors and Urbanization

In most countries, colorectal cancer incidence is higher among urban residents than among rural ones (80), perhaps due to dietary influences. Some patient populations also exhibit a significant association between social standing, as measured by highest level of education, and colon cancer risk (81,82).

Hormonal Factors

Sex Hormones

Several observations suggest a role for sex hormones in colon cancer development. Women have an excess of right-sided colon cancers at all ages and a relationship may also exist with parity, which may protect against the development of colorectal cancer (83). Exogenous hormones may significantly reduce the risk of large bowel cancer, especially rectal cancers.
Introduction

(84,85), although this is controversial (86,87). Reproductive or hormonal factors may influence bile acid metabolism, physical activity, or other variables. Up to 70% of colonic tumors are estrogen receptor (ER) positive (88). The clinical significance of ER positivity in colon cancer remains unclear.

**Gastrin**

Gastrin is usually made by gastric antral G cells where it stimulates gastric acid secretion, thereby facilitating protein digestion and preventing bacterial overgrowth. It also functions as a gastrointestinal growth-promoting hormone, sometimes leading to the development of colonic tumors. Total plasma gastrin levels are significantly elevated in some colon cancer patients (89). The tumors contain gastrin mRNA, progastrin, and gastrin (89,90,91). It remains unclear whether gastrin from the tumors acts as an autocrine growth factor and what the contribution of the serum gastrin is to colorectal carcinoma growth. However, Seitz et al (92) followed serum gastrin levels following colon cancer treatment and found that tumor recurrences associated with increasing serum gastrin levels. This led the authors to suggest autocrine secretion of gastrin by the tumor (92).

**Growth Hormone**

Acromegaly, a clinical syndrome characterized by growth of bones, soft tissues, and visceral organs, results from excessive growth hormone secretion. Acromegalic patients exhibit an increased adenoma and colon cancer risk (93,94). This risk is higher in males than in females. Acromegalic patients with colonic neoplasia tend to be young and display aggressive disease. The colons of such patients also exhibit increased cell proliferation (95).

**Radiation**

Radiation plays an etiologic role in a minority of colorectal carcinomas. Rectal tumors are most likely to develop in patients treated with radiotherapy for cervical, uterine, or prostatic carcinomas. Women irradiated for gynecologic cancers have a relative risk for subsequent colorectal cancer of 2.0 to 3.6 (96). Some tumors arise in radiation-induced strictures, sometimes associated with areas of colitis cystica profunda.

**Schistosomiasis**

Patients infested by *Schistosoma japonicum* have an increased incidence of colorectal neoplasms (97). Carcinomas arising in this setting occur at an earlier age and are often multicentric. The adenomas and carcinomas arise on a background of schistosomal colitis, often with preceding areas of dysplasia. The dysplasia can be either focal or diffuse and occurs in flat mucosa, in pseudopolyps, or at the edge of ulcers. The histologic appearance of the tumors resembles that occurring in noninfected individuals, except that the parasitic ova are admixed with the neoplasm (Fig. 14.4).

**Relationship to Gallstones and Cholecystectomy**

The role of cholecystectomy as a risk factor for colorectal cancer is controversial. Individuals who are older than 60 years of age and who have undergone cholecystectomy >10 years previously may exhibit a mildly increased risk of developing colorectal adenomas (98) and cancers, especially in the right colon (99,100,101). Cholecystectomy alters the proportion of secondary bile acids, including deoxycholic acid, in the bile by increasing enterohepatic cycling and allowing greater exposure to intestinal bacteria. Part of the association between colon cancer and cholelithiasis may relate to the identification of asymptomatic cholelithiasis in patients who undergo imaging of the liver as part of their clinical workup for potential metastatic colon cancer. Alternatively, common risk factors for gallstones and colon cancer may explain the apparent association (102).

**Role of Ureterosigmoidostomy, Ileal Conduits, Ileostomy, and Anastomoses**

A number of polypoid lesions complicate ureteral implantation into the bowel. Ureterosigmoidostomy increases colon cancer risk by as much as 500 times in patients who have undergone the procedure (103). Adenomas develop up to 10 to 20 years following the ureterosigmoidostomy (103,104); carcinomas can arise as late as 53 years later (105,106). Experimental data suggest that activation of fecal carcinogens by the diverted urine may increase cell proliferation and cause chronic inflammation (107). Ileal conduits are less prone to develop neoplasms (108). Colon cancer also develops at other
anastomotic sites and in colostomies (109,110). Increased proliferative activity around anastomoses may explain some of the increased cancer risk (111).

**FIG. 14.4.** Schistosomiasis and colon cancer. *A:* Adenomatous polyp with early invasive carcinoma arising in a patient with schistosomiasis. Clusters of *Schistosoma* ova are identifiable in the region of the muscularis mucosae on the left. *B:* Higher magnification of the calcified ova in the submucosa (arrows).

### Role of Gastric Surgery

Some studies suggest that patients who have undergone remote peptic ulcer surgery have an increased risk of developing colorectal cancer (112). It is postulated that increased levels of both carcinogens and unconjugated and secondary bile acids in the gastric juice after the peptic ulcer surgery increase the colon cancer risk (112), and truncal vagotomy may alter bile acid metabolism (113). However, other studies have not found an increased incidence of large bowel cancer following gastric surgery for benign disease (114).

### Relationship to Skin Tags

Skin tags may constitute a marker for the presence of colonic neoplasia, since they occur more frequently in patients with colorectal cancer. It is likely that the patients have inherited a gene with pleiotropic effects involving both the skin and gut epithelium (115).

### Other Factors

Tumors sometimes arise in malformations, and such tumors may exhibit unusual histologies, such as adenosquamous carcinomas (116). Patients with congenital anomalies of the urinary tract may also exhibit an increased colorectal cancer risk (117). Patients with pernicious anemia (118), diabetes mellitus (119), celiac disease (120), or AIDS (121) may have an increased risk of developing colorectal adenocarcinoma.
Gastrointestinal Neuroendocrine Lesions

General Organization of the Gastrointestinal System

The gastrointestinal neuroendocrine system (GNES) is the largest and most complex endocrine organ in the body (1). The gut contains numerous neuroendocrine (NE) cells that produce many peptide hormones. Since NE cells exhibit endocrine, paracrine, and neurotransmitter functions (Fig. 17.1), they are best termed NE cells rather than endocrine cells. They constitute a complex system that regulates many gastrointestinal (GI) functions. Some NE secretions act as true peptide hormones. Gastrin, secretin, and cholecystokinin (CCK) are secreted into the blood to reach their target organs (stomach, pancreas, and gallbladder); soon thereafter they are metabolized and eliminated. Other peptides, such as somatostatin, are released into the local subepithelial connective tissue or directly onto other cell types via long basal cytoplasmic processes in a paracrine fashion. Neurons interact with gastrointestinal endocrine cells, endocrine cells interact with other endocrine cells, and endocrine cells may influence neurons (1,2). In addition, many GI hormones interact with the hypothalamic-pituitary axis to orchestrate the secretory activity and motility necessary for effective digestion (1), including acid, bicarbonate, and enzyme secretion and local blood flow. The GNES also interacts with the immune system (1). Immune responses alter neural and endocrine function, and in turn, neural and endocrine activity modifies immunologic functions. Finally, some GI hormones enhance metabolic levels and promote GI growth.

NE cells are widely distributed throughout the epithelia of the stomach, intestines, distal esophagus, and anus. Their overall density, contents, and structure differ in various parts of the gut. Most NE cells lie within the epithelium, but some are also present in the lamina propria of the stomach and the appendix. Endocrine cells are sensitive to chemical and mechanical stimuli, to which they respond by releasing extracellular mediators. At least 14 types of NE cells populate the GI mucosa (Table 17.1) (2). Some peptides are produced solely in the upper GI tract and are stimulated only for a short time following meals; others are scattered throughout the gut and are exposed to prolonged stimulation. Gastrin is primarily a gastric antral hormone; CCK, secretin, gastric inhibitory polypeptide, and motilin are mainly upper small intestinal hormones; and enteroglucagon and neurotensin are lower intestinal peptides. In contrast, vasoactive intestinal polypeptide (VIP), substance P, enkephalins, bombesin, somatostatin, and other substances are produced more diffusely throughout the gut. NE cells may be open or closed, depending on whether or not they reach the gastrointestinal lumen (Fig. 17.2). Closed endocrine cells fail to reach the lumen, suggesting that they do not react to luminal stimuli. Instead, they probably react to other stimulants, such as distension, temperature, and neural or hormonal factors. “Open” cells extend from the basal lamina to the lumen. Most open endocrine cells reach the lumen in a narrow specialized area containing tufts of microvilli and a centriole that acts as a sensor of the luminal contents.

Identification of Neuroendocrine Cells

NE cells can sometimes be recognized in routinely stained sections by the presence of pyramidally shaped eosinophilic or clear cells lying along the basement membrane. Eosinophilic granules, which generally are smaller than those seen in Paneth cells, may be visible and lie diffusely distributed throughout the cell or in a subnuclear location (Fig. 17.3). Since not all NE cells are immediately recognizable in hematoxylin and eosin (H&E)-stained sections, numerous techniques have been devised to detect their presence. The earliest techniques involved reactions with various heavy metals, especially silver (Table 17.2), and ultrastructural evaluation. In this country, these techniques have largely been abandoned due to their expense, the difficulty in performing them well, and the more recent development of a number of immunostains that reliably detect endocrine cells. Immunologic markers of neuroendocrine differentiation include antibodies to neuron-specific enolase (NSE), protein gene product (PGP) 9.5, synaptophysin, and chromogranin (CgA). Of these, NSE is the least specific. CgA is a secretory granule that is located alongside specific hormones in large dense-core vesicles of neuronal and NE cells (3). It is secreted in tumors; the amount present in the blood correlates with the tumor burden. NE cells containing amines (histamine and serotonin) regularly exhibit CgA immunoreactivity.

Other peptide-containing endocrine cells are heterogeneous in their CgA immunoreactivity. We prefer synaptophysin immunostains since they reliably detect a wide variety of gastrointestinal NE cells. These antibodies and the silver-based techniques allow the identification of endocrine cells but do not provide information with respect to their hormonal products. Specific cell types can be identified immunohistochemically using antibodies directed against the specific hormone that the cells are known to produce.
FIG. 17.1. Endocrine cells have endocrine functions whereby the contents of their secretory granules are released into the circulation to have an effect at a location distant from the site of production. They also have neurocrine effects influencing neuronal functions. Long basal extensions of endocrine cells that touch other endocrine cells or nearby epithelial cells mediate paracrine effects.

In this chapter, we will first discuss normal gastrointestinal NE cell populations. This will be followed by a discussion of gastrointestinal NE cell proliferations. These include hyperplastic lesions as well as NE tumors.

Normal Gastrointestinal Neuroendocrine Cell Populations

Esophagus

NE cells lie scattered among the basal cells in approximately 25% of normal individuals (4). They are also present in the mucous glands (5).

Stomach

There are at least eight distinct gastric endocrine cell types, including enterochromaffin (EC), enterochromaffinlike (ECL), D, D1, P, G, X, and ghrelin-producing cells (Table 17.1) (6). Three cell types (ECL, G, and D) account for >75% of the gastric NE cell mass. NE cells appear as cuboidal or short columnar cells scattered among the gastric epithelia, usually in the glands (Fig. 17.4). Less commonly they occur in the glandular neck. NE cells rarely reach the foveolae; they are absent from the surface. Their composition and distribution differ in the oxyntic and antral mucosa. Approximately 50% of antral NE cells are G cells (gastrin producing), 30% are serotonin-producing EC cells, and 15% are somatostatin-producing D cells. The remaining 5% consist of other cell types. The predominant NE cell in the fundus is the histamine-producing ECL cell. There are also a few X cells with an unknown secretory product, ghrelin-producing cells, and EC cells. Most gastric NE cells are closed. They lie along the basement membrane and are covered by nonendocrine epithelium that prevents their contact with the glandular lumen.

They contain numerous basally located hormone-containing granules. The NE cells secrete their hormones into the intercellular space, where they diffuse into capillaries. Scattered endocrine cells are occasionally found in the lamina propria near the base of glands apparently unattached to epithelium. They exist singly (Fig. 17.5) or in clusters and are seen in the antrum or antrocorpus junction. Lamina propria endocrine cells occur predominantly in the stomach of patients with gastritis, but they can also be found in the normal stomach.

| TABLE 17.1 Gastrointestinal Endocrine Cells |

P.1101

D, D1, P, G, X, and ghrelin-producing cells (Table 17.1) (6). Three cell types (ECL, G, and D) account for >75% of the gastric NE cell mass. NE cells appear as cuboidal or short columnar cells scattered among the gastric epithelia, usually in the glands (Fig. 17.4). Less commonly they occur in the glandular neck. NE cells rarely reach the foveolae; they are absent from the surface. Their composition and distribution differ in the oxyntic and antral mucosa. Approximately 50% of antral NE cells are G cells (gastrin producing), 30% are serotonin-producing EC cells, and 15% are somatostatin-producing D cells. The remaining 5% consist of other cell types. The predominant NE cell in the fundus is the histamine-producing ECL cell. There are also a few X cells with an unknown secretory product, ghrelin-producing cells, and EC cells. Most gastric NE cells are closed. They lie along the basement membrane and are covered by nonendocrine epithelium that prevents their contact with the glandular lumen.

P.1102

They contain numerous basally located hormone-containing granules. The NE cells secrete their hormones into the intercellular space, where they diffuse into capillaries. Scattered endocrine cells are occasionally found in the lamina propria near the base of glands apparently unattached to epithelium. They exist singly (Fig. 17.5) or in clusters and are seen in the antrum or antrocorpus junction. Lamina propria endocrine cells occur predominantly in the stomach of patients with gastritis, but they can also be found in the normal stomach.
<table>
<thead>
<tr>
<th>Cell Name</th>
<th>Location</th>
<th>Main Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Stomach</td>
<td>Somatostatin</td>
</tr>
<tr>
<td></td>
<td>Small intestine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large intestine</td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>Stomach</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Small intestine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large intestine</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>Stomach</td>
<td>Serotonin</td>
</tr>
<tr>
<td></td>
<td>Intestines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Submucosal glands</td>
<td></td>
</tr>
<tr>
<td>ECL</td>
<td>Stomach</td>
<td>Histamine</td>
</tr>
<tr>
<td></td>
<td>Intestines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Submucosal glands</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Pylorus</td>
<td>Gastrin</td>
</tr>
<tr>
<td></td>
<td>Duodenum</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Small intestine</td>
<td>Cholecystokinin</td>
</tr>
<tr>
<td>K</td>
<td>Small intestine</td>
<td>Gastrin-releasing peptide</td>
</tr>
<tr>
<td>L</td>
<td>Intestine</td>
<td>Enteroglucagon, pancreatic polypeptidelike peptide</td>
</tr>
<tr>
<td>M</td>
<td>Small intestine</td>
<td>Motilin</td>
</tr>
<tr>
<td>N</td>
<td>Small intestine</td>
<td>Neurotensin</td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>Stomach</td>
<td>? Gastrin-releasing peptide</td>
</tr>
<tr>
<td></td>
<td>Small intestine</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>Small intestine</td>
<td>Pancreatic polypeptide</td>
</tr>
<tr>
<td>S</td>
<td>Small intestine</td>
<td>Secretin</td>
</tr>
<tr>
<td>X</td>
<td>Gastric antrum</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
FIG. 17.2. Open and closed endocrine cells in normal colonic mucosa stained with an antibody to chromogranin.

FIG. 17.3. Cross section of several crypt bases showing a mixture of cell types. The endocrine cell highlighted by the *arrow* lies beneath other cell types.

<table>
<thead>
<tr>
<th>TABLE 17.2 Special Stains Used to Detect Neuroendocrine Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentaffin cells</td>
</tr>
<tr>
<td>Enterochromaffin cells</td>
</tr>
<tr>
<td>Argyrophilic cells</td>
</tr>
</tbody>
</table>
FIG. 17.4. Argyrophilic endocrine cells in the normal fundus stain with Grimelius stain (A). Corresponding hematoxylin and eosin stain (B).

FIG. 17.5. Widely scattered endocrine cells (arrow) within the lamina propria. Chromogranin immunostain.
G Cells

G cells are large, round or oval cells (7) that produce gastrin. They mainly lie in the neck region of the antral glands trailing off toward the gland base. G cells normally have an irregular and random spatial distribution that ranges between one and three to four cells per gland. They contain variably dense cytoplasmic granules measuring 150 to 200 in µm diameter. Argyrophilic and argentaffinic stains fail to detect most G cells (7), but they are easily identified by CgA or synaptophysin stains. They are also identifiable using gastrin-specific immunohistochemical stains (Fig. 17.6).

The number of antral G cells varies, depending on the acid content of the stomach, the presence of proliferative stimuli, and gastric location. G cells are most numerous on the greater curvature. Gastrin promotes acid and pepsinogen secretion (Fig 17.7), gastric motility, and gastric oxyntic mucosal proliferation. In sustained hypergastrinemia, parietal cells, ECL cells, and surface mucosal cells increase in number. The trophic effect of gastrin is most marked on ECL cells (8). Parietal cell mass and G-cell density are interrelated.

P.1103

Hypochlorhydria causes G-cell proliferation and increased gastrin transcription.
Enterochromaffin Cells

EC cells are the most numerous NE cell populations in the gut and they are widely found in many sites including the stomach. They are sparse in the mucous neck portion but are quite numerous in the lower half of the gland. Their overall distribution is patchy; areas with numerous EC cells alternate with areas containing few or none. They are especially numerous in areas of intestinal metaplasia (9). These cells are described further below.

D Cells

D cells secrete somatostatin and are uniformly distributed throughout the antral and oxyntic mucosa (Fig. 17.8). Approximately 20% of gastric D cells have basal axonal-like cytoplasmic processes with terminal expansions that allow D cells to function in a paracrine fashion (10). Most antral D cells are open cells that act as receptors, interacting with luminal contents. A feedback mechanism exists in which intraluminal acid stimulates somatostatin secretion. In the fundus, D cells are closed. Somatostatin secretion from D cells inhibits gastric acid, gastrin and intrinsic factor secretion, and acetylcholine release.

Enterochromaffinlike Cells

ECL cells are confined to the oxyntic mucosa, where they represent the dominant NE cell type, constituting 40% to 45% of oxyntic NE cells (6). ECL cells express CCK-2 (gastrin) receptors, which mediate histamine secretion and ECL cell growth (11,12). ECL cells decrease in number after antrectomy due to reduced gastrin levels. The pyramidally shaped ECL cells are closed with a broad base that directly abuts the basement membrane of oxyntic glands. They are randomly scattered throughout the lower and middle thirds of the glands (11). Their lateral processes extend to, and terminate on, parietal cell surfaces, allowing them to act in a paracrine fashion. They also act in an endocrine fashion. ECL cells can be identified by silver stains, or more specifically, by antibodies against histamine, histidine decarboxylase, and vesicular monoamine transporter 1 and 2 (VMAT 1 and 2) (13). ECL cells are a self-renewing population.

Ghrelin-producing Cells

Ghrelin is a recently discovered peptide that is produced by about 20% of endocrine cells in the oxyntic mucosa. These cells appear to differ from the ECL, EC, D, and probably X cells also present in this area (14). Ghrelin stimulates release of growth hormone (15), stimulates food intake, and modulates sleep (16). It also has an antiproliferative effect in neoplastic tissues (17) and stimulates gastric contractility (18). The hormone localizes to polygonal or flask-shaped endocrine cells in the oxyntic mucosa. These cells appear larger than the adjacent cells (19).

Small Intestine

While NE cells constitute <1% of all intestinal epithelial cells, numerous subpopulations of NE cells are present in this site (20). NE cells lie interspersed among absorptive cells and goblet cells in the crypts (Fig 17.9) and on the villi (Fig. 17.10), and some are found within Brunner glands. They share a common origin from the crypt epithelial stem cell (21). Each subpopulation has a distinct distribution along the cranial–caudal axis and along the crypt–villus axis, thereby producing an integrated response to various stimuli and facilitating normal secretory, absorptive, and motor functions.
**FIG. 17.8.** Somatostatin-containing cells are quite numerous in the antrum.

**FIG. 17.9.** Small intestinal enterochromaffin (EC) cells stained with an antibody to serotonin.
EC cells have an almost exclusively intraepithelial location resting on the basement membrane and projecting into the lumen with their apical portions. They are evenly distributed between crypts and villi. They are recognizable by their bright red granules. Others appear clear. Their cytoplasm is occupied by a large number of secretory granules. The major secretory product is serotonin, but subsets of EC cells also produce minor amounts of tachykinins, enkephalins, and motilin (7). Serotonin is synthesized from the amino acid tryptophan by hydroxylation and decarboxylation in the EC cell cytoplasm and subsequently transported into secretory granules by an active transport mechanism. Upon specific membrane simulation, granules are translocated to the cell membrane and released by exocytosis. Serotonin may influence adjacent cells by paracrine mechanisms or reach distant cells via the circulation. Release of serotonin in response to an acid pH, hypertonic glucose, amino acids, and noxious stimuli affects nerve endings that evoke mucosal hyperemia, secretion, and peristalsis (22).

The duodenum and jejunum harbor a large number of different NE cell types; the spectrum gradually narrows as one proceeds distally (23). The duodenum contains EC cells, D cells, and cells immunoreactive for CCK and gastrin. Gastric inhibitory polypeptide–containing cells occur in the midzone of the duodenal glands and to a lesser extent in the jejunum (24). Motilin-immunoreactive cells populate the duodenum and upper jejunum. Substance P cells in the proximal small intestine occur mainly in the crypts and lower villi, whereas secretin-containing cells are found nearly exclusively on villi. Brunner glands also contain NE cells producing and storing somatostatin, gastrin, CCK, and peptide YY (25).

Appendix

The appendix contains two populations of EC cells: Those in the crypts and those in the lamina propria (Fig. 17.11). They occur singly or in small clusters, and are more common in adults than in children. Lamina propria NE cells lie scattered near the base of the crypts, apparently unattached to crypt epithelium. They are invariably part of a structure termed the enterochromaffin cell–nerve fiber complex (26) that contains a mixture of endocrine...
cells, neurons, Schwann cells, and unmyelinated nerve processes all surrounded by an external lamina that is continuous with that of adjacent peptidergic nerve fibers. The EC cell–nerve fiber complex facilitates integration between intestinal endocrine cells and the enteric nervous system. Crypt endocrine cells tend to lie near the base of the crypts. Both crypt and lamina propria endocrine cells contain serotonin, somatostatin, enteroglucagon, vasoactive intestinal polypeptide, and substance P. More endocrine cells populate the distal appendix than the proximal appendix. ECL cells, D cells, L cells, and N cells are also present.

Large Intestine, Rectum, and Anus
The colon has the largest number of NE cells of any region of the GI tract, except the esophagus. The endocrine cell population in this region is heterogeneous in nature (Table 17.1). NE cells appear as small round or pyramidal cells lying on the basement membrane and scattered among the nonendocrine epithelial cells. They are most numerous in the base of the crypts and appear clear or they contain prominent eosinophilic basal granules. The latter are released by pinocytosis from the basal and lateral surfaces of the cells. Secretory products of these cells exert a paracrine modulating effect on neighboring eocrine and endocrine cells. When these products cross the basal membrane, they enter the bloodstream reaching target organs, where they exert endocrine effects. The neural effects of these cells are ex-erted as the hormones diffuse to synapses. Anal endocrine cells lie above the dentate line in the colorectal mucosa, in the transitional mucosa, in anal ducts and glands, in crypts, and in perianal sweat glands. Like endocrine
cells elsewhere, they lie close to the basement membrane. Endocrine cells are absent in the pectineal folds and perianal skin.

Molecular Features of Gastrointestinal Endocrine Tumors
Neuroendocrine tumors (NETs) exhibit a series of genetic aberrations, including point mutations, gene deletions, DNA methylation, chromosomal losses, and chromosomal gains involving both oncogenes and tumor suppressor genes. Several genetic syndromes with mutations in tumor suppressor genes, including multiple endocrine neoplasia type 1 ( MEN-1) and neurofibromatosis type I (NF1), associate with the development of gastrointestinal NE tumors. MEN-1, an autosomal dominant disorder, associates with mutations in the *MEN1* gene on chromosome 11q13. *MEN1* encodes the protein menin, which binds Jun1, inhibiting Jun1-activated transcription (27,28). Mutations and/or loss of heterozygosity (LOH) at the *MEN1* locus occur in 40% to 75% of gastrointestinal NE tumors (27,29). The frequency of this event differs depending on tumor site and whether the tumors are sporadic or arise as part of the MEN-1 syndrome. For example, foregut and some midgut NETs have frequent deletions and mutations in the *MEN1* gene (30). *MEN1* LOH is present in 33% of midgut carcinoid tumors (31). Type II gastric carcinoids show LOH at the *MEN1* locus in 75% of tumors as compared to 16% of type I gastric carcinoids (32). LOH at the *MEN1* locus appears to be an important prerequisite to switch hypergastrinemia-induced ECL proliferations from a hyperplastic to a neoplastic state (31). Further, the presence of 11q13 LOH in gastric carcinoid tumors of patients without hypergastrinemia suggests that inactivation of the *MEN1* gene alone can cause ECL cell tumors (33). *Reg-a* gene alterations may be important in gastric ECL carcinoids (34). Mutation of the *Reg-a* gene could contribute to the development of ECL cell carcinoid tumors by allowing unrestrained stimulating effects of gastrin (34). Alterations in the *MEN1* gene also occur in 25% to 40% of sporadic gastrinomas (35).

LOH at locations distal to 11q13 at the location of the *succinate ubiquinone oxidoreductase subunit D* (SDHD) tumor suppressor gene is also implicated in the development of midgut (rather than foregut) carcinoids (36). Twenty-two percent of duodenal and ileal carcinoids show alterations at the *SDHD* locus (36). A number of other chromosomal gains and losses develop in NETs, but losses at 18qter, 11q22-24, and 16q are the most common genetic defects in midgut carcinoids (37,38). LOH at chromosome 18q is seen in 67% of midgut tumors (37). Fifteen percent of midgut tumors show abnormalities of the X chromosome (39). Inactivation of the *p16*^{INK4A}/CDKN2A tumor suppressor gene on chromosome 9p21 is also common in NE tumors. *p16*^{INK4A} inactivation occurs by either gene deletion or methylation of CpG islands (40) and is observed in 50% to 52% of sporadic gastrinomas (35). Other abnormalities found in gastrinomas include aneuploidy, mismatch repair defects, amplification of the HER2/neu protooncogene (41), and other genetic changes. Almost 80% of gastrointestinal NE tumors demonstrate nuclear and cytoplasmic β-catenin expression and 37.5% contain an exon 3 mutation (42). Another gene that may be important in the development of NETs is the *PDCD4* (programmed cell death protein 4) gene (43). *PDCD4* is a newly described tumor suppressor gene that suppresses cell proliferation and lies close to the *MEN1* gene on chromosome 11q13. Sporadic endocrine tumors arising in several sites frequently show loss of its expression.

NF1 is an autosomal dominant disorder resulting from mutations in the *NF1* gene located at 17q11. These mutations lead to premature truncation of neurofibromin, the tumor suppressor gene product. Some NF1 patients develop duodenal somatostatinomas (44) or gangliocytic paragangliomas. Several genes are frequently methylated in GI NETs including *p14*, *p16*, *MGMT*, *THBS1*, *RAR*, *ER*, and *COX2* (37,45). p16 methylation is more frequent in older patients and associates with metastasis (45). The *Ras association domain family 1, isofrom A* (*RASSF1A*) gene is also frequently methylated in these neoplasms and associates with lymph node metastasis (45). Allelic losses of chromosomes 11q, 16q, and 1q may be important in the pathogenesis of goblet cell carcinoids and ileal carcinoids (46).

Immunohistochemical studies describe overexpression of the antiapoptotic bc22 protein in gastric endocrine cell hyperplasia (47) and loss of E-cadherin expression in two thirds of malignant rectal carcinoid tumors (48). p53 expression is rare in small intestinal NETs (49) but occurs in up to 16% of carcinoid tumors (50). Inactivation of the *p53* gene could contribute to the development of ECL cell carcinoid tumors by allowing unrestrained stimulating effects of gastrin (34). Alterations in the *MEN1* gene also occur in 25% to 40% of sporadic gastrinomas (35).

LOH at locations distal to 11q13 at the location of the *succinate ubiquinone oxidoreductase subunit D* (SDHD) tumor suppressor gene is also implicated in the development of midgut (rather than foregut) carcinoids (36). Twenty-two percent of duodenal and ileal carcinoids show alterations at the *SDHD* locus (36). A number of other chromosomal gains and losses develop in NETs, but losses at 18qter, 11q22-24, and 16q are the most common genetic defects in midgut carcinoids (37,38). LOH at chromosome 18q is seen in 67% of midgut tumors (37). Fifteen percent of midgut tumors show abnormalities of the X chromosome (39). Inactivation of the *p16*^{INK4A}/CDKN2A tumor suppressor gene on chromosome 9p21 is also common in NE tumors. *p16*^{INK4A} inactivation occurs by either gene deletion or methylation of CpG islands (40) and is observed in 50% to 52% of sporadic gastrinomas (35). Other abnormalities found in gastrinomas include aneuploidy, mismatch repair defects, amplification of the HER2/neu protooncogene (41), and other genetic changes. Almost 80% of gastrointestinal NE tumors demonstrate nuclear and cytoplasmic β-catenin expression and 37.5% contain an exon 3 mutation (42). Another gene that may be important in the development of NETs is the *PDCD4* (programmed cell death protein 4) gene (43). *PDCD4* is a newly described tumor suppressor gene that suppresses cell proliferation and lies close to the *MEN1* gene on chromosome 11q13. Sporadic endocrine tumors arising in several sites frequently show loss of its expression.

NF1 is an autosomal dominant disorder resulting from mutations in the *NF1* gene located at 17q11. These mutations lead to premature truncation of neurofibromin, the tumor suppressor gene product. Some NF1 patients develop duodenal somatostatinomas (44) or gangliocytic paragangliomas. Several genes are frequently methylated in GI NETs including *p14*, *p16*, *MGMT*, *THBS1*, *RAR*, *ER*, and *COX2* (37,45). p16 methylation is more frequent in older patients and associates with metastasis (45). The *Ras association domain family 1, isofrom A* (*RASSF1A*) gene is also frequently methylated in these neoplasms and associates with lymph node metastasis (45). Allelic losses of chromosomes 11q, 16q, and 1q may be important in the pathogenesis of goblet cell carcinoids and ileal carcinoids (46).

Immunohistochemical studies describe overexpression of the antiapoptotic bc22 protein in gastric endocrine cell hyperplasia (47) and loss of E-cadherin expression in two thirds of malignant rectal carcinoid tumors (48). p53 expression is rare in small intestinal NETs (49) but occurs in up to 16% of carcinoid tumors (50). *p53* mutations are found in up to 25% of appendiceal goblet cell carcinoids as well as in some conventional appendiceal carcinoids (51). Ki-67 staining and p53 staining may serve as prognostic factors in some tumors (52,53).

Transforming growth factor-α (TGF-α) is expressed in 72% of gastrointestinal carcinoid tumors and most tumors also express its receptor, epidermal growth factor receptor (EGFR) (37). Gastrin-releasing peptide (GRP) is expressed in a proportion of NETs and gastrin-releasing peptide receptor (GRPR) is expressed in the majority of such tumors. Both GRP and GRPR are coexpressed in some gastrointestinal NETs, although GRP is not expressed by normal gastrointestinal neuroendocrine cells (54). Other proteins that are frequently expressed include c-myc, c-erbB2, and c-jun (55). These tumors also frequently express the somatostatin receptor subtype 2, a factor that may help select patients suitable for somatostatin analog treatment (56).
TABLE 17.3 Proliferative Endocrine Cell Lesion

<table>
<thead>
<tr>
<th>Histologic Pattern</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple hyperplasia</td>
<td>Increase in single cells in glands</td>
</tr>
<tr>
<td>Linear hyperplasia</td>
<td>Forms of chains of five or more endocrine cells and equals two chains per millimeter</td>
</tr>
<tr>
<td>Micronodular hyperplasia</td>
<td>Nodules of endocrine cells with more than five endocrine cells in glands or crypts that do not exceed the diameter of the gastric glands</td>
</tr>
<tr>
<td>Adenomatoid hyperplasia</td>
<td>The presence of five or more coalescing nodules</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Enlargement and fusion of enterochromaffinlike nodules measuring &lt;0.5 mm in diameter. These contain relatively atypical cells and may have microinvasion or newly formed stroma</td>
</tr>
<tr>
<td>Intramucosal or invasive carcinoids</td>
<td>Endocrine cell growths measuring &gt;0.5 mm or invading the submucosa</td>
</tr>
</tbody>
</table>

NE cell hyperplasia results from a combination of a prolonged cell half-life, augmented replication of mature cells, and/or differentiation of a larger fraction of uncommitted stem cells into specific NE cell types. Each of these mechanisms may be triggered by loss of normal inhibitory influences on NE cell proliferation, a lack of normal negative feedback mechanisms, or the trophic action of stimulating substances. Additionally, autocrine mechanisms may stimulate a cell's own proliferation. The local tissue microenvironment may also play a significant role in inducing the hyperplasia.

The stages in the progression of hyperplastic neuroendocrine lesions are shown in Table 17.3. Simple or diffuse hyperplasia, the earliest hyperplastic stage, is characterized by a diffuse increase in NE cells scattered singly or in clusters of up to three cells per gland. The cells may appear enlarged, especially in the lower third of the mucosa. Linear hyperplasia is diagnosed when linear, semi-linear, or daisy-chain–like ECL cell configurations are present. The next stage, micronodular hyperplasia, consists of solid micronodular NE cell nests measuring 100 to 150 µm in size (the average diameter of a gastric gland) (57,59,60). These may be bounded by an intact basement membrane continuous with that of the rest of the gland or lie in the basal glandular portion of the mucosa dissociated from the glands lying free in the lamina propria abutting the muscular mucosae. Adenomatoid hyperplasia consists of a close aggregation of five or more interglandular micronodular lesions, each with an intact basement membrane. As each micronodule enlarges, it breaks down its basement membrane and the cells develop cytologic atypia with an increased nuclear:cytoplasmic ratio, thereby qualifying for a diagnosis of a dysplasia. This dysplastic stage marks the borderline between the hyperplastic stages preceding it and the neoplastic stage of a fully developed carcinoid tumor following it. It is the earliest “point of no return” in the hyperplasia–neoplasia sequence of ECL proliferation (57). These lesions include enlarging micronodules, fusing micronodules, microinvasive lesions, and nodules with newly formed stroma. The carcinoid stage is characterized by nodular infiltrating growths measuring >0.5 mm in diameter. These steps may be seen in proliferative NE cell lesions involving many cell types including G, ECL, EC, D, and L cells.

Often, gastrointestinal NE cell hyperplasia is unsuspected (61), since most lesions do not release enough hormones or other secretory products to produce significant biochemical abnormalities or to give rise to specific clinical syndromes. Furthermore, even though hyperplasia may be present, the lesions may not be visible endoscopically or grossly. Additionally, NE cell hyperplasias often remain unrecognized even when standard H&E-stained sections are examined due to their rarity and the difficulty in recognizing increased numbers of endocrine cells among the other epithelial cells present in the glands. Sometimes, it is only when suspicions of the gastroenterologist and/or pathologist cause the specimen to be stained a neuroendocrine marker that the increased number of endocrine cells becomes apparent.

**Neuroendocrine Cell Hyperplasia in the Esophagus**

NE cell hyperplasia in the esophagus usually develops in the setting of Barrett esophagus (BE). It is a common event affecting up to 90% of cases of BE. The majority of the cells are EC cells (62).

**Neuroendocrine Cell Hyperplasia in the Stomach**

G-cell Hyperplasia

G cells become hyperplastic in any condition that lowers gastric acid concentrations, including extensive multifocal gastritis.

pernicious anemia, vagotomy, and prolonged treatment with proton pump inhibitors (Table 17.4; Figs. 17.12, 17.13, and 17.14). G-cell hyperplasia following vagotomy results from a combination of chronic antral distention, decreased acid secretion, and release from vagally mediated inhibitors of G-cell proliferation. G-cell hyperplasia in acromegaly results either from the patients also having the MEN-1 syndrome or from unidentified trophic factors secreted by the pituitary.

**TABLE 17.4 Conditions Associated with Hypergastrinemia and G-cell Hyperplasia**
Primary antral G-cell hyperplasia and hyperfunction is a rare pediatric disorder in which G-cell hyperplasia, hyperfunction, or both occur without a clear cause (63). This entity, also known as pseudo-Zollinger-Ellison syndrome, causes clinical and biochemical features resembling those seen in Zollinger-Ellison syndrome (ZES) but the patients lack a gastrin-producing tumor. The hypergastrinemia reverts to normal following antrectomy. Most familial cases result from a genetic defect in normal regulation of G-cell function or proliferation. Patients with nonfamilial forms of the disease have increased antral G-cell sensitivity to intragastric food stimulation (64). The distribution of hyperplastic G-cell populations in primary and secondary antral G-cell hyperplasia is similar with increased G-cell numbers in the lower and middle thirds of the antral glands. Occasionally, longstanding diffuse antral G-cell hyperplasia progresses to multiple small micronodular G-cell clusters (Fig. 17.14) that eventually give rise to G-cell tumors (gastrinomas). Gastrin also stimulates oxyntic mucosal growth and increases the progenitor cell labeling index in this area.

FIG. 17.12. Progression of autoimmune gastritis to carcinoid tumors and intestinal-type carcinomas. Patients with autoimmune gastritis develop G-cell hyperplasia in response to an antibody-mediated attack on the parietal cells that subsequently leads to decreased acid production. The hyperplastic G cells produce increased amounts of gastrin, leading to both foveolar hyperplasia as well as ECL cell hyperplasia. The ECL cell hyperplasia progresses further to the development of ECL micronests and eventually carcinoid tumors. At the same time, the gastric epithelium may become intestinalized in response to epithelial loss from the immunologic attack. This intestinal epithelium becomes dysplastic and can progress to intestinal-type carcinomas.
Enterochromaffinlike Cell Hyperplasia

ECL cells are extremely sensitive to the stimulatory effects of gastrin, undergoing secondary hyperplasia in chronic hypergastrinemic states (65). Hypergastrinemia results in increased proliferation of both pluripotential stem cells and mature ECL cells (66). Gastrin also stimulates ECL function, as reflected by an increase in histamine decarboxylase activity and histamine release (67). The ECL hyperplasia is reversible if the hypergastrinemia is removed. ECL lesions develop exclusively in the oxyntic mucosa. In CAG, the hyperplastic cells are present only in the atrophic fundic glands and pyloric metaplastic glands but not in the intestinal metaplastic glands. Hyperplastic ECL lesions range from a diffuse ECL cell hyperplasia through linear and nodular aggregates to intramucosal and frankly invasive carcinoid tumors (Figs. 17.15 and 17.16). Patients with hypergastrinemia due to *H. pylori* infections or the chronic use of proton pump inhibitors (68) develop ECL cell hyperplasia, but carcinoid tumors are rare.
FIG. 17.15. Chromogranin immunostain showing linear hyperplasia.

The most frequent histologic change in ECL cells in ZES patients is a diffuse hyperplasia, affecting more than half of ZES patients. Linear hyperplasia affects approximately 18% of patients, whereas micronodular hyperplasia is infrequent (59). Dysplastic ECL lesions can also develop. The topographic distribution of linear hyperplasia often localizes to the greater curvature and does not correspond to that of the ECL cell micronodular hyperplasia, dysplasia, and ECL tumor, changes that are more uniformly distributed between the lesser and greater curvatures. This observation led Bordi to suggest that the linear hyperplasia occurring in the setting of ZES may not be a step in the micronodular hyperplasia–dysplasia–NET (carcinoid) sequence. Rather, linear hyperplasia may represent a self-limited lesion (59). Antrectomy as well as some pharmacologic treatments may reverse the ECL cell hyperplasia.

D-cell Hyperplasia

Antral D-cell hyperplasia develops in patients with duodenal ulcer disease (69). Extensive gastric D-cell hyperplasia was reported in a 37-year-old woman with dwarfism, obesity, dryness of the mouth, and goiter. The D-cell density in this patient was increased 39-fold in the gastric fundus and 25-fold in the antrum. Antral G cells were increased 2.3-fold and they showed pronounced hypertrophy (69). The hypersomatostatinemia may have interfered with pituitary hormone release at an early age, thereby resulting in the dwarfism.

Hyperplasia of Ghrelin-producing Cells

Pericarcinoidal oxyntic mucosal ghrelin cell hyperplasia consistently occurs in patients with CAG. The ghrelin-producing cells are larger than their normal counterparts and appear polygonal or flask shaped. Diffuse, linear, and nodular forms of hyperplasia occur (19).
Chapter 17

**FIG. 17.16.** Enterochromaffinlike (ECL) cell hyperplasia. A: Linear hyperplasia with micronests. B: Dysplastic ECL cell nodules with newly formed stroma. C: Fully developed ECL cell carcinoid tumor infiltrating the mucosa and submucosa. Chromogranin immunostain.

**Neuroendocrine Cell Hyperplasia in the Intestines**

EC cell hyperplasia occurs in the intestines in three major settings: Celiac disease, inflammatory bowel disease, and adjacent to carcinoid tumors. D-cell hyperplasia may be present in patients with somatostatinomas and MEN-1. In the setting of celiac disease, hyperplastic NE cells are irregularly distributed within the crypts, often associated with increased numbers of Paneth cells. Goblet cells are normal or occasionally increased in number. The subepithelial basement membrane may appear normal or thickened (Fig. 17.17) (70). These changes progress with increased mucosal flattening and expansion of the crypt cells. Pyloric metaplasia may develop. The abnormalities are most marked on the crests of mucosal folds.

**FILE:** Gastro/Chapter%2017%20neuroendocrine%20CA.htm (16 of 78) 2/4/2009 2:04:22 PM

---

**TABLE 17.5 World Health Organization Classification of Endocrine Tumors**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated endocrine tumors (carcinoid tumors)—benign or low-grade malignancy</td>
<td></td>
</tr>
<tr>
<td>Well-differentiated endocrine carcinomas (malignant carcinoids)</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated endocrine carcinomas (small cell carcinoma)</td>
<td></td>
</tr>
<tr>
<td>Mixed endocrine–exocrine tumors (such as adenocarcinoids)</td>
<td></td>
</tr>
<tr>
<td>Rare neuroendocrine-like lesions</td>
<td></td>
</tr>
</tbody>
</table>

Endocrine cell hyperplasia affects as many as 40% of IBD patients (71). Paneth cell metaplasia distal to the hepatic flexure, pyloric metaplasia, and endocrine cell hyperplasia often indicate a long history of colitis (72). IBD patients may also develop very small NE tumors, called microcarcinoids. They are not grossly evident and are typically detected in biopsy specimens performed for other reasons or in resection specimens. When present, these lesions lie in the muscularis mucosae and upper submucosa (73). The cells are arranged in a trabecular fashion and consist of multiple small islands of large, pale, eosinophilic cells. Endocrine cell micronests (ECMs) occur in the minor and major duodenal papillae and are usually immunoreactive for somatostatin and pancreatic polypeptide (74). Some of the lesions break off the ductules of the pancreatic duct or represent atrophic or degenerating islets. Some patients exhibit rectal endocrine cell hyperplasia or focal NE micronests, often surrounding rectal carcinoid tumors (Fig. 17.18) (75). Microcarcinoids may...
develop in areas of diversion colitis (76).

Terminology of Neuroendocrine Tumors

NE tumors range from classic carcinoid tumors to small cell carcinomas. They may be classified according to their location, the normal cell counterpart toward which differentiation is occurring, and whether they are benign, of borderline malignancy, of low-grade malignancy, or of high-grade malignancy (77,78). Tumors of mixed endocrine and glandular lineage are classified separately. Carcinoid tumors are classically defined as low-grade, potentially malignant, epithelial neoplasms showing NE differentiation. They most frequently develop in the gastrointestinal system. The term carcinoid tumor, as commonly used by pathologists, encompasses a wide spectrum of neoplasms that originate from various NE cells. However, it has become clear that not all gastrointestinal carcinoid tumors are the same. Rather, they reflect the products they secrete and the cells from which they arise. Thus, gastric carcinoids differ substantially from ileal carcinoids, which differ significantly from appendiceal lesions. Current estimates indicate that the various gastrointestinal carcinoid tumors produce as many as 40 different secretory products (79). These tumors may be referred to by the name of the cell population from which they arise (such as ECL tumors), by the hormones they produce (such as gastrinoma), or by their location in the gut (such as midgut carcinoid). It has recently been suggested that these tumors be called well-differentiated neuroendocrine tumors (78), terminology adopted by the latest World Health Organization (WHO) classification (Table 17.5) (77). However, to avoid confusion, the term carcinoid was not entirely abandoned in the revised classification.

Well-Differentiated Neuroendocrine Tumors (Carcinoid Tumors)

Fifty-four to eighty-five percent of all carcinoid tumors arise in the GI tract (80). They develop anywhere, from the esophagus to the anus, but they are decidedly unusual in the esophagus and anus. The widespread use of endoscopy, ultrasonography, computerized tomography, magnetic resonance imaging, and other imaging techniques have significantly enhanced the detection of previously undetectable lesions. For this reason, there appears to have been an increase in the incidence of gastrointestinal carcinoid tumors as well as a shift in the relative proportions of tumors arising in various sites (81). In a recent population-based cancer registry study, the gastrointestinal tract accounted for 54% of NETs. Within the gut, the small intestine was the most common site (44.7%), followed by the rectum (19.6%), appendix (16.7%), colon (10.6%), and stomach (7.2%) (81).

Some NETs develop in unusual locations, such as in Meckel diverticula (Fig. 17.19) (82), cystic duplications (83), and the mesentery (84). These neoplasms often arise on a background of NE cell hyperplasia.
Chapter 17

FIG. 17.18. Rectal endocrine cell hyperplasia and carcinoid tumors. A: Endocrine cell hyperplasia adjacent to a carcinoid tumor (chromogranin immunostain). Note that the carcinoid tumor (left) is chromogranin negative. B: A carcinoid tumor lies in the superficial submucosa. The overlying rectal mucosa shows endocrine cell hyperplasia. C: Small rectal carcinoid found incidentally at the time of histologic examination. D: Synaptophysin-stained adenocarcinoid tumor. E: Microcarcinoid straddling the muscularis mucosae. This was one of multiple small carcinoid tumors present in the rectum of this patient. There is overlying endocrine hyperplasia in the colonic mucosa.

Foregut NETs include esophageal, gastric, and proximal duodenal tumors. Midgut lesions include distal duodenal, small intestinal, ascending colon, and proximal transverse colon tumors. Hindgut NETs include distal transverse colon, descending colon, and rectal tumors. While this concept is probably outdated today, it has historical value since tumors derived from these embryologic origins differ clinically, histochemically, and immunohistochemically. Foregut and hindgut tumors are typically argentaffin negative in contrast with midgut tumors, which are argentaffinic.

FIG. 17.19. Incidental carcinoid arising in Meckel diverticulum. A: The lesion is not readily visible in the gross specimen unless one looks carefully for it (arrows). B: The tumor (arrow) is well demarcated but unencapsulated.

NETs are usually easily diagnosed because of their distinctive histologic appearance. They exhibit five histologic patterns (Table 17.6) (85). The tumors contain cytoplasmic secretory granules identifiable by the techniques previously discussed. A tumor should only be diagnosed as a carcinoid tumor if it displays the classic histologic architecture of trabecular, insular, or ribbonlike cell clusters with little or no cellular pleomorphism and sparse mitoses. The presence of focal endocrine differentiation in a tumor lacking classic histologic features should not be diagnosed as a NET.

The clinical behavior of this group of tumors is often unpredictable and the traditional morphologic criteria of malignancy have limited applicability to NETs. Tumor biology is influenced by tumor size, location, stage, evidence of metastasis, and histologic features (78). Thus, tumors arising in the appendix are often found incidentally and are usually small and seldom metastasize (86). In contrast, ileal and jejunal tumors are frequently already metastatic to the regional lymph nodes and liver when they are first diagnosed (87). Patient prognosis may also be influenced by the clinical setting in which the tumors arise, the presence or absence of the carcinoid syndrome, and the underlying molecular abnormalities. These features are discussed further in the context of the site-specific NETs.

Some NETs may present early when there is an overt syndrome such as that related to a gastrinoma, but other tumors present at a late stage with liver metastases and the carcinoid syndrome and metastatic tumor in the liver. The measurement of tumor markers in the circulation of patients with NETs may be useful and is of threefold importance. It often establishes the diagnosis, it is useful in monitoring disease progression and response to treatment, and it may serve as a prognostic marker. For example, circulating CgA is elevated in approximately 90% of malignant gastrointestinal NETs (88). In addition, many neoplastic NE cell proliferations express somatostatin receptors (SSTRs), allowing new diagnostic and therapeutic strategies to be developed. Somatostatin analogs reduce secretion via inhibitory G proteins and therefore may lead to marked symptom relief. By using radiolabeled somatostatin analogs, tumors can be localized scintigraphically or during surgery with the aid of scintillation detection (radioguided surgery). Residual tumors may be treated with radionuclide therapy since radionuclides are internalized into tumor cells after SSTR binding (89).

| TABLE 17.6 Histologic Patterns of Carcinoid Tumors |

- Trabecular
- Insular
- Ribbonlike
- Mixed
- Oncocytic
Chapter 17

Type I Solid, nodular, and insular cords
Type II Trabeculae or ribbons with frequent anastomosing patterns
Type III Tubules and glands or rosettelike patterns
Type IV Poor differentiation or atypical patterns
Type V Mixed tumors

One problem that arises in the diagnosis of NETs is distinguishing a gastrointestinal carcinoid tumor from a pulmonary carcinoid tumor. The panel of cytokeratin (CK)-20/CK-7 and thyroid transcription factor (TTF)-1 antibodies may distinguish among these lesions, since pulmonary tumors do not express CK-20 and GI tumors usually do not express TTF-1 or CK-7 (90).

Esophageal Carcinoid Tumors

Esophageal NETs are very rare, accounting for 0.05% of all gastrointestinal carcinoids and 0.02% of all esophageal carcinomas. The majority of patients are males with an age range of 30 to 82 and a mean age of 56 to 63 years (91,92). The tumors usually develop in the lower esophagus, are typically solitary lesions, and may arise in association with adenocarcinoma in the setting of Barrett esophagus (92). Patients present with dysphagia. The development of the carcinoid syndrome is extremely rare (93). The tumors tend to be large, measuring up to 12 cm in diameter, and they may be restricted to the lamina propria or deeply infiltrate the esophageal wall (92,94,95). Some tumors appear polypoid. Metastases are present in approximately 50% of cases (95). Histologically, foregut NETs contain anastomosing ribbons, solid nests, trabeculae, acini, or rosettes. The cells are usually round or polygonal but they may appear oval or cylindrical and may have a high mitotic rate (4 mitoses/10 high-powered field [hpf]) (94,95). Carcinoid tumors that arise in the setting of BE-associated adenocarcinoma exhibit endocrine cell hyperplasia in the associated adenocarcinoma. The tumors are reported to have a poor prognosis even in the absence of metastases (95), but this issue may be confused by the inclusion of atypical carcinoids or even small cell carcinomas in some reports of these lesions (92). Long-term survivors are reported (96) even with nodal metastases.

<table>
<thead>
<tr>
<th>TABLE 17.7 Types of Gastric Carcinoid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I ECL cell tumors associated with type A (autoimmune) chronic atrophic gastritis</td>
</tr>
<tr>
<td>Type II ECL cell tumors associated with combined MEN-1 and Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>Type III Sporadic ECL tumors</td>
</tr>
<tr>
<td>Type IV Non-ECL tumors (gastrin-, serotonin-, and ACTH-secreting tumors)</td>
</tr>
<tr>
<td>Type V ECL cell tumors associated with achlorhydria and parietal cell hyperplasias</td>
</tr>
</tbody>
</table>

Hypergastrinemic states.
ACTH, adrenocorticotropic hormone; ECL, enterochromaffinlike; MEN-1, multiple endocrine neoplasia type 1.
Chapter 17

Well-Differentiated Neuroendocrine Tumor (Carcinoid)

Benign: Nonfunctioning, confined to mucosa–submucosa, nonangioinvasive, <1 cm in size

- ECL tumor of corpus–fundus (usually multiple) associated with chronic atrophic gastritis or MEN-1
- Serotonin-producing or (very rare) gastrin-producing tumor

Benign or low-grade malignant (uncertain malignant potential): Nonfunctioning, confined to mucosa–submucosa with or without angioinvasion, 1–2 cm in size

- ECL tumor with chronic atrophic gastritis or MEN-1 or sporadic
- Serotonin-producing or (very rare) gastrin-producing tumor

Well-Differentiated Neuroendocrine Carcinoma (Malignant Carcinoid)

Low-grade malignant: Invasion of the muscularis propria and beyond of metastases, >2 cm in size

- Nonfunctioning, usually sporadic ECL cell carcinoma, rarely in chronic atrophic gastritis or MEN-1 or serotonin or gastrin producing
- Functioning with serotonin-producing carcinoma (atypical carcinoid syndrome) or gastrin-producing carcinoma (gastrinoma)

Poorly Differentiated Neuroendocrine Carcinoma

High-grade malignant

ECL, enterochromaffinlike; MEN-1, multiple endocrine neoplasia type 1.

Gastric Carcinoid Tumors

Gastric NETs arise from endocrine cells of the gastric mucosa, usually the ECL cells. They develop in five settings, four of which associate with ECL cell hyperplasia (Table 17.7). ECL-type tumors are frequently classified according to the Rindi classification that recognizes the first three types of tumors listed in Table 17.7 (97). Table 17.8 shows the latest WHO classification of gastric endocrine cell tumors (78). Tumors arising in the various settings differ significantly in their biologic behavior (98,99). In a large series of ECL carcinoids, 79% were associated with CAG, 10% of patients had ZES, and 11% of tumors were sporadic (97).

In the past, gastric NETs accounted for about 4% of the total number of gastrointestinal carcinoids (100) and 0.3% of gastric neoplasms (141). However, these lesions have become more common, related to improved diagnostic methods including endoscopy and immunohistochemistry and heightened awareness of their existence. They are now estimated to account for 11% to 30% of GI NETs (101). In Japan, a country with extensive use of gastric endoscopy, the stomach is the second most common site of NETs. The increased use of acid-suppressing therapies may also account for an increasing incidence of ECL cell proliferative lesions. Up to 100% of patients on high-dose acid suppressive therapies develop hypergastrinemia (58) and the possibility of developing NETs.

ECL cell proliferations (diffuse, linear, and/or micronodular hyperplasias) and their more advanced equivalents (ECL cell dysplasia and ECL carcinoid tumors) all associate with chronic hypergastrinemia (102). However, hypergastrinemia alone appears to be insufficient to induce carcinoid development as evidenced by the fact that ZES patients without the MEN-1 syndrome rarely develop gastric carcinoids despite prolonged serum gastrin levels more than 10-fold normal (99). In contrast, patients with familial MEN-1 who develop ZES, develop type II carcinoids 30 times more frequently than the normal population. These carcinoid tumors affect 13% to 30% of all MEN ZES cases (103). Therefore, both endocrine and genetic factors are implicated in the pathogenesis of type I and type II gastric carcinoids.

Genetic traits, as in patients with MEN-1; other genetic alterations, as discussed earlier; overexpression of the gastrin receptor gene or growth factors such as EGF or TGF-α; and alterations in the local microenvironment may all play a role in the subsequent development of the carcinoid tumors. Other substances may also play a role in tumor development. Recently it has been shown that the reg protein may also control ECL cell numbers by restraining the stimulatory effect of gastrin.

Neuroendocrine Tumors Arising in the Setting of Chronic Atrophic Gastritis (Type I Tumors)

Type I carcinoids account for approximately 74% to 79% of all gastric NETs. Five to ten percent of patients with CAG and hypergastrinemia develop ECL carcinoids (98,102). The demographics of the lesion mimic those of autoimmune gastritis. More than 70% of cases develop in older women with a mean age of 63 years (98,99). Type I carcinoids develop in part from the hypergastrinemia that results from loss of parietal cell mass and decreased acid output as a consequence of the autoimmune gastritis (98,99). Tumors developing in this setting arise on a background of ECL cell hyperplasia and dysplasia (Fig. 17.20). In more than half of the cases, the tumors are multifocal.
Recently two patients were reported with multiple gastric carcinoids arising in the setting of marked hypergastrinemia, associated with achlorhydria and hypertrophic parietal cells. The parietal cell hyperplasia caused Neuroendocrine Tumors Arising in the Setting of Achlorhydria and Parietal Cell Hyperplasia

Octreotide can control the hypergastrinemia, leading to regression of related ECL cell hyperplasia and NETs (111). Removal of all gastrinomas in patients with type II ECL carcinoids results in carcinoid tumor regression metastases (10%) than type I tumors (98). The histologic features of the tumors resemble type I gastric carcinoids described above.

ECL NETs arise on a background of parietal cell hypertrophy and hyperplasia and ECL cell hyperplasia and dysplasia. Since the patients present with a hypertrophic gastropathy characteristic of ZES, the gastric folds appear thickened. In addition, there are usually multiple, small tumor nodules. ECL tumors occurring in this setting are more likely to measure >1.5 cm and to produce local lymph node metastases (30%) and liver metastasize they may produce an atypical carcinoid syndrome (97).

Type I carcinoids are the most “benign” of the gastric carcinoid tumors (104). They present as small, tan submucosal nodules or polyps in the corpus usually measuring <1 cm. Most measure only 1 to 3 mm in diameter; 97% are <1.5 cm in diameter. The tumors tend to be limited to the mucosa and submucosa, with only 7% invading the muscularis propria. They infrequently cause liver metastases (2% to 5% of cases) (98).

Most tumors are characterized by small microlobular aggregates formed by regularly distributed cells that may create a mosaiclike pattern. They consist of solid nests, trabeculae, ribbons, tubular structures, or a combination of these patterns. The cytoplasm appears slightly eosinophilic, slightly basophilic, or amphophilic. Cytoplasmic granules may or may not be seen on routine preparations. The cells contain centrally located, round or oval, monomorphic nuclei, with generally inapparent nucleoli and little or no nuclear pleomorphism or mitotic activity. Angioinvasion is rare. The background mucosa shows the typical features of CAG, often with intestinal metaplasia.

The tumor cells are argyrophilic but not argentaffinic. They are consistently immunoreactive for NE markers including CgA, synaptophysin, and NSE. The tumor cells, as well as the surrounding hyperplastic endocrine cells, are positive for the newly discovered hormone ghrelin (19). VMAT-2 is a specific marker for ECL tumors. The cells variably produce mucin (105). A small population of tumor cells may be positive for serotonin, gastrin, somatostatin, pancreatic polypeptide, or α-human chorionic gonadotropin (α-hCG). A few ECL cell tumors produce histamine and 5-hydroxytryptophan (5-HT); when these lesions metastasize they may produce an atypical carcinoid syndrome (97).

Type I carcinoid tumors may regress after gastrin levels decrease, usually by antrectomy (106) or treatment with somatostatin analogs (107). These treatments result in resolution, regression, or stabilization of many ECL tumors (108). At some stage, however, ECL cell proliferations may become irreversible, making it difficult to estimate the degree of tumor regression following treatment. It is hard to predict which of multiple ECL tumors have progressed beyond the point of gastrin dependence and are autonomous in their growth. The octreotide suppression test may predict a beneficial outcome from antrectomy (109). The tumors may also be removed surgically or endoscopically depending on their size and number (110). Biopsy and observation are other possible therapeutic options. Gastrectomy is reserved for patients with extensive tumor involvement of the gastric wall, to control bleeding, or in patients in whom the tumors progress (110).

When the tumors metastasize, it is usually to the regional lymph nodes; distant metastases are rare. They almost never cause the death of the patient (98). The generally better prognosis of this type of gastric NET relates in part to earlier diagnosis because the patients are commonly seen for symptoms related to the underlying CAG. Alternatively, the better prognosis may relate to the intrinsically benign nature of tumors arising in this setting.

Neuroendocrine Tumors Arising in the Setting of Multiple Endocrine Neoplasia Type 1–Zollinger-Ellison Syndrome (Type II Carcinoid Tumors)

Type II carcinoids represent 6% to 10% of all gastric NETs. The tumors do not show any gender predilection and occur at an earlier age than type I tumors with a median age at development of 50 years (98). Gastric carcinoids arising in the setting of ZES usually associate with MEN-1 (98). The ECL cell NETs develop in the oxyntic mucosa and are frequently multiple (136). They are the consequence of hypergastrinemia resulting from a gastrin-secreting NE cell neoplasm (often a pancreatic islet cell tumor). Rare sporadic ZES-associated gastric carcinoids also occur, although generally these patients only have simple linear hyperplasia (57).

ECL NETs arise on a background of parietal cell hypertrophy and hyperplasia and ECL cell hyperplasia and dysplasia. Since the patients present with a hypertrophic gastropathy characteristic of ZES, the gastric folds appear thickened. In addition, there are usually multiple, small tumor nodules. ECL tumors occurring in this setting are more likely to measure >1.5 cm and to produce local lymph node metastases (30%) and liver metastases (10%) than type I tumors (98). The histologic features of the tumors resemble type I gastric carcinoids described above.

Octreotide can control the hypergastrinemia, leading to regression of related ECL cell hyperplasia and NETs (111). Removal of all gastrinomas in patients with type II ECL carcinoids results in carcinoid tumor regression (112).

Neuroendocrine Tumors Arising in the Setting of Achlorhydria and Parietal Cell Hyperplasia

Recently two patients were reported with multiple gastric carcinoids arising in the setting of marked hypergastrinemia, associated with achlorhydria and hypertrophic parietal cells. The parietal cell hyperplasia caused

---

**FIG. 17.20.** Carcinoid tumor. A: Low-power view demonstrates a proliferation of small, uniform cells within the deep mucosa and submucosa. B: The cells are arranged in nests and rosettelike structures. There is no nuclear pleomorphism and mitotic figures are not seen. Residual gastric glands lie among the tumor cells. C: The endocrine differentiation of this lesion is highlighted by the chromogranin stain. A focus of linear endocrine hyperplasia is present in a residual gastric gland (arrow).
mucosal thickening. Focal intestinal metaplasia was present. There were also areas of ciliated metaplasia. Multiple intramucosal and invasive carcinoid tumors involving the gastric body and fundus arose on a background of marked ECL cell hyperplasia. The largest tumor nodule measured 1.3 cm in diameter. A micrometastasis was present in a regional lymph node. The oxyntic mucosa showed marked parietal cell hyperplasia and hypertrophy. Some of the parietal cells appeared vacuolated and many displayed protrusions of their apical cytoplasm into dilated oxyntic glands filled with inspissated eosinophilic material. (113,114). This presentation appears to represent a rare form of gastric carcinoids associated with an intrinsic acid secretion abnormality as supported by the ultrastructural demonstration of the lack of the parietal cell canalicular system (114) and the failure of the parietal cells to stain with an antibody directed at the α and β subunits of the H^+/K^+-ATPase proton pump (113).

### Sporadic Gastric Neuroendocrine Tumors (Type III Carcinoids) (Well-differentiated Neuroendocrine Carcinomas)

Sporadic NETs are most common in men (74%), with a mean age of 55 years (98). They are unassociated with CAG and hypergastrinemia and represent a proliferation of various cell types including ECL, EC, and X cells. They are usually single lesions that do not arise on a background of NE cell hyperplasia. The incidence of multiple type III carcinoids is only 1% (98). The tumors occur anywhere in the stomach. Unlike type I and type II tumors, type III tumors are aggressive and larger than other gastric NETs. They generally present as a mass lesion mimicking the clinical presentation of adenocarcinomas with bleeding, obstruction, or metastasis as presenting findings. Patients may present with an atypical carcinoid syndrome with cutaneous flushing in the absence of diarrhea. Tumors producing these clinical symptoms usually produce histamine and 5-HT (115).

Grossly, type III tumors often appear as smooth, round, yellow, submucosal nodules measuring >2 cm in diameter (Fig. 17.21). They are usually covered by an intact mucosa, although larger lesions may develop an irregularly shaped, reddened depression or surface ulceration. Histologically, type III NETs exhibit various growth patterns, including trabecular, gyriform, medullary or solid, glandular, or rosette, or a mixture of all of these (Fig. 17.22). Often they show a prevalence of solid cellular aggregates (Fig 17.23) and large trabeculae with cellular crowding. The round, spindle-shaped, and polyhedral cells are irregularly distributed and have fairly large vesicular nuclei and prominent small, eosinophilic nucleoli. The cells may also contain smaller hyperchromatic nuclei with irregular chromatin clumping and increased mitoses. Sparse areas of necrosis may be present. Larger tumors may invade deeply and promote a prominent fibroblastic stromal response. These lesions extend intramurally and invade vascular or lymphatic channels to produce nodal and distant metastases (116). Factors that predict aggressive behavior include cellular atypia, two or more mitoses per hpf, angioinvasion, and transmural invasion (98,117). Although tumor size correlates with a tendency to metastasize, minute tumors are known to spread beyond the stomach (118). Thus, while the latest WHO criteria suggest that NETs tumors ≤1 cm are benign lesions, this criterion does not appear to be applicable to all of these tumors. Regional lymph node metastasis may be seen in tumors as small as 0.3 cm in diameter (119).

![FIG. 17.21. Gross appearance of sporadic gastric carcinoid tumor. A: Opened stomach showing the tumor. B: The tumor extends to the serosal surface (arrow). C: Cut surface of the tumor showing that it extends through the gastric wall. D: Metastatic tumor in a perigastric lymph node.](file:///F|/Gastro/Chapter%2017%20neuroendocrine%20CA.htm)
FIG. 17.22. Gastric carcinoid tumor. *A:* The tumor is composed of solid nests, ribbons, and glandlike structures. The cells are uniform and mucin has accumulated in many areas. *B:* Chromogranin stain highlights the cords of cells.
Chapter 17

FIG. 17.23. Gastric carcinoid. A: The tumor is completely submucosal in location. Alcian blue periodic acid–Schiff (PAS) stain. The neutral mucins of the gastric epithelium are strongly PAS positive. The carcinoid tumor is negative. B: The tumor nests are solid with peripheral palisading. C: Bone marrow metastases.

FIG. 17.24. Gastric carcinoid with oncocytic features. These tumors frequently express p53 and have a high Ki-67 labeling rate. Rare tumors show widespread ossification or have an oncocytic appearance (Fig. 17.24). These tumors are also positive for markers of bone formation and differentiation including bone morphogenetic protein, osteopontin, and osteonectin (120). Type III carcinoid tumors often display an aggressive local behavior and metastasize. Seventy-six percent of tumors invade the muscularis propria and/or subserosa and lymph node, and distant metastases are present in 2% to 71% and 22% to 75% of cases, respectively (98). The 5-year survival in patients with sporadic carcinoids is <50%, reflecting the high rate of metastasis. The 5-year survival rate is significantly higher for localized disease (64.3%) and for those with regional metastases (29.9%) than for lesions with distant metastases (10%) (91).

As noted above, patients with type I carcinoid tumors benefit from antrectomy, but this treatment has no value in sporadic carcinoid tumors (121). Therefore, it is important to distinguish between these two groups of patients. This is usually accomplished based on clinical and morphologic features, as well as on the presence or absence of adjacent ECL cell hyperplasia. The features of sporadic and hypergastrinemia-associated carcinoids are compared in Table 17.9.

Non–enterochromaffinlike Neuroendocrine Tumors

These tumors arise anywhere in the stomach and are usually single large lesions that are often highly malignant. Affected patients may present with ZES due to gastrin production by the tumor or with Cushing syndrome due to secretion of adrenocorticotropic hormone (ACTH). Serotonin-producing NETs are rare in the stomach (98). They resemble midgut carcinoids, consisting of rounded nests of tightly packed small tumor cells often showing peripheral palisading. Gastrin-producing tumors exhibit a characteristic thin trabecular pattern and the cells are strongly positive for NE markers and for gastrin. These tumors may metastasize and also cause ZES.
TABLE 17.9 Comparison of Sporadic and Hypergastrinemia-associated Carcinoid Tumors

<table>
<thead>
<tr>
<th></th>
<th>Sporadic Lesions</th>
<th>Hypergastrinemia-associated Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic atrophic gastritis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Endocrine cell hyperplasia</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Genetic associations</td>
<td>None</td>
<td>Multiple endocrine neoplasia syndrome</td>
</tr>
<tr>
<td>Size</td>
<td>Variable</td>
<td>Small</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Usually single</td>
<td>Multiple</td>
</tr>
<tr>
<td>Behavior and treatment</td>
<td>Aggressive, do not regress following antrectomy</td>
<td>Benign, regress following antrectomy</td>
</tr>
</tbody>
</table>

Small Intestinal Neuroendocrine Tumors

Duodenal Neuroendocrine Tumors

It used to be believed that duodenal NETs only accounted for 1.8% to 2.9% of gastrointestinal NETs (100), but with the advent of improved imaging and the increased use of upper endoscopy, they are currently estimated to account for up to 22% of all gut endocrine tumors (80). Gastrin cell tumors account for the largest group (62% to 65%) of tumors arising in the upper intestine, followed by somatostatin cell tumors (15% to 21%), gangliocytic paragangliomas (9%), undifferentiated tumors, and pancreatic polypeptide (PP) cell tumors (122). The WHO classification of these tumors is shown in Table 17.10. In one study, 72% of patients with duodenal NETs were male. Patient median age was 53 to 59 years with a range of 18 to 90 years (123). These tumors associate with MEN-1, ZES, and NF1. The majority of duodenal carcinoids exhibit a mixture of cribriform, insular, glandular, and solid and trabecular growth patterns. They produce various hormones as discussed below. In addition, xenin is said to be a marker of duodenal NETs because it is exclusively expressed in these tumors, regardless of their hormonal content and functional activity (124).

TABLE 17.10 Classification of Neuroendocrine Tumors of the Duodenum and Upper Jejunum

Well-Differentiated Neuroendocrine Tumor (Carcinoid)

Benign: Nonfunctioning, confined to mucosa–submucosa, nonangioinvasive, <1 cm in size

- Gastrin-producing tumor (upper part of duodenum)
- Serotonin-producing tumor
- Gangliocytic paraganglioma (any size and extension, periampullary)

Benign or low-grade malignant (uncertain malignant potential): Nonfunctioning, confined to mucosa–submucosa with or without angioinvasion, 1 cm in size

- Functioning gastrin-producing tumor (gastrinoma), sporadic or MEN-1 associated
- Nonfunctioning somatostatin-producing tumor (ampullary region) with or without NF1
- Nonfunctioning serotonin-producing tumor

Well-Differentiated Neuroendocrine Carcinoma (Malignant Carcinoid)

Low-grade malignant: Invasion of the muscularis propria and beyond or metastases

- Functioning with gastrin-producing carcinoma (gastrinoma), sporadic or MEN-1 associated
- Nonfunctioning somatostatin-producing carcinoma (ampullary region), with or without NF1
- Nonfunctioning or functioning carcinoma (with carcinoid syndrome)
- Malignant gangliocytic paraganglioma

Poorly Differentiated Neuroendocrine Carcinoma

High-grade malignant: Functioning or nonfunctioning, poorly differentiated intermediate or small cell carcinoma
MEN-1, multiple endocrine neoplasia type 1; NF1, neurofibromatosis type 1.

**G-cell Tumors (Gastrinomas)**

Seventy-five percent of patients have sporadic tumors; 25% associate with MEN-1 (125). These are the most common malignant functional NET. Tumors associated with overt ZES differ from their nonfunctioning counterparts by arising earlier in life in a nonbulbar location and having a higher incidence of metastases.

Ninety percent of gastrinomas arise within the so-called "gastrinoma triangle." Its superior margin crosses the cystic and common bile ducts, its inferior margin is formed by the junction of the second and third portion of the duodenum, and the medial margin is delineated by the junction of the neck and the body of the pancreas. Approximately 15% of gastrinomas arise in extrapancreatic sites; 13% originate in the second portion of the duodenum. The remainder arise in the stomach, upper jejunum, biliary tree, and lymph nodes within the gastrinoma triangle (126). It has been suggested that precursor cells of gastrin-producing tumors become dispersed during the dorsal rotation of the ventral pancreas during embryonic development and are incorporated into lymphatic tissues (127), thereby providing the anatomic basis for primary nodal gastrinomas. There are also reports of isolated gastrin- or synaptophysin-staining cells in 15% of normal lymph nodes from the gastrinoma triangle (128,129).

Duodenal gastrinomas arising in the setting of MEN-1 are multiple, in contrast to sporadic gastrinomas, which are typically single lesions (130). The multiple tumors seen in MEN-1 patients are thought to be multiple primary lesions based on clonality studies (32). Sixteen percent of duodenal gastrinomas are incidental findings in surgical resection specimens, usually removed for peptic ulcer disease. However, some tumors are large enough to cause clinical symptoms from mass effects, including bile duct obstruction. Approximately one third of patients with gastrinomas have diarrhea. Some patients present with the ZES.

The main features of duodenal gastrinomas include their small size and submucosal location. Most develop in the first and second portions of the duodenum. The tumors may appear slightly polypoid and are often endoscopically misinterpreted as heterotopic pancreas or gastric mucosa or as an inflammatory process. The tumors range in size from 0.2 to 20 cm in diameter (131). However, they measure ≤1 cm in diameter in 62% to 80% of patients. Very small tumors are easily missed during exploratory laparotomy or during gross examination of surgical specimens. Despite their small size, these tumors commonly metastasize and nearly half demonstrate nodal metastases (126,132). Such metastases are often larger than the primary tumors, probably leading to an overdiagnosis of primary nodal gastrinomas.

Gastrinomas display a trabecular/pseudoglandular and/or solid growth pattern. The tumors appear uniform with scanty cytoplasm arranged in solid clusters and ribbons (Figs. 17.25 and 17.26). Some contain a perinuclear collection of whorled microfilaments. Angioinvasion may be present. Gastrinomas cannot be differentiated from other functional and nonfunctional NETs based solely on their histologic appearance. Gastrin immunoreactivity in the majority of cells establishes the diagnosis. In addition, gastrinomas may produce other polypeptides including glucagon, somatostatin, serotonin, insulin, pancreatic polypeptide, ACTH, enkephalins (133), and hCG.

**FIG. 17.25.** Duodenal gastrinoma found incidentally at the time of resection for a duodenal ulcer. The tumor measured <0.4 mm in diameter.
D-cell Tumors (Somatostatinomas)

Somatostatinomas account for <1% of all NETs (142). Patients range in age from 29 to 83. Fifty percent of somatostatinomas associate with NF1 (123). Somatostatinomas sometimes develop in patients with neurofibromatosis and pheochromocytoma, suggesting that this triad may constitute a new multiple endocrine neoplasia syndrome (MEN-3) (143). Somatostatinomas may also arise on a background of D-cell hyperplasia in the setting of celiac disease, suggesting a relationship between D-cell growth and chronic inflammation (144).

The somatostatinoma syndrome (diabetes mellitus, diarrhea, steatorrhea, hypo- or achlorhydria, weight loss, anemia, and gallstones) usually affects patients with pancreatic somatostatin-producing NETs; the full-blown syndrome does not usually complicate duodenal somatostatin cell tumors. However, because duodenal somatostatinomas often develop in the ampulla of Vater, they cause jaundice and intestinal obstruction early in their development, resulting in resection before the full syndrome develops.

Somatostatinomas arise in the deep portion of the mucosa or possibly in Brunner glands and have a tendency to be invasive. These are usually single, but multiple (up to 30) tumors have been described in the absence of an underlying genetic syndrome (145). The histologic patterns of somatostatinomas resemble those seen in other NETs with the exception that they display a prominent glandular pattern and contain intraglandular psammoma bodies (Fig. 17.27) (146). These result from secretion of somatostatin by the tumor cells. The Grimelius stain is positive in only about one third of cases (144). Immunohistochemical techniques show a preponderance of somatostatin-positive cells (Fig. 17.27). Other substances produced by these tumors include gastrin (147), calcitonin (148), insulin, VIP, prostaglandin E2, substance P, serotonin, and carcinoembryonic antigen (CEA) (142,149). Somatostatinomas associated with NF1 are often pure so-matostatinomas, whereas similar tumors unassociated with NF1 are frequently multifunctional (149,150).

The combination of a striking glandular pattern with psammoma bodies and a negative Grimelius stain may lead to a misdiagnosis of adenocarcinoma. However, in contrast to most carcinomas, somatostatinomas consist of uniform cells with few mitoses, although rarely some metastatic carci-nomas can appear histologically bland. Somatostatinomas frequently metastasize (143). Prognosis is better in patients in whom the tumor is detected early. Features of malignancy include extension to the muscularis propria, the sphincter of Oddi, or the pancreas; a maximum diameter of >2 cm; and the presence of mitotic figures. The liver is most commonly involved...
followed by regional lymph nodes and bones.

**Other Hormone-producing Neuroendocrine Tumors**

EC cell, serotonin-producing tumors, the classic argentaffinic midgut tumors, may develop in the duodenum (Fig. 17.28), but are rare in this site. They have the characteristic features described below for distal jejunal/ileal tumors. One percent of insulinomas arise in the duodenal mucosa (151), the splenic hilum, or the gastrocolic ligament. The presence of multiple tumors suggests the diagnosis of MEN-1. Insulinomas secrete insulin autonomously; excessive insulin levels result in profound hypoglycemia with trembling, irritability, weakness, diaphoresis, tachycardia, hunger, headaches, blurred vision, personality changes, mental confusion, bizarre behavior, amnesia, obtundation, convulsions, and coma (152). Elevated plasma insulin levels and the low plasma glucose during prolonged fasting establish the diagnosis (153). The tumors histologically resemble other intestinal NETs. Insulinomas, unlike other endocrine tumors, are rarely malignant. They can be diagnosed by staining the tumors with antibodies to insulin.

Most glucagonomas arise in the pancreas, but primary duodenal lesions have been described (154,155). Glucagonomas secrete glucagon autonomously and patients with functional tumors present with a syndrome characterized by waxing and waning skin lesions known as neurolytic migratory erythema, abnormal glucose tolerance tests with or without clinical diabetes mellitus, hypoaaminoademia, weight loss, normochromic-normocytic anemia, and, occasionally, glossitis, stomatitis, cheilitis, diarrhea, abdominal pain, nausea and vomiting, a tendency to venous thrombosis, and mental status changes. Histologically, glucagonomas resemble other carcinoid tumors and show no distinctive features except for the presence of glucagon-positive cells in the tumors. Even though most glucagonomas are malignant, mitotic figures and nuclear atypia are rare. The tumors are immunohistochemically positive for glucagon.

GRFomas are NETs that produce growth hormone–releasing factor resulting in acromegaly. These are rare tumors and about 30% associate with MEN-1. Ten percent develop in the small intestines, where they are often multiple, large, and metastatic. Their presence should be suspected in patients with a NET and acromegaly (156).

**Nonfunctional Duodenal Neuroendocrine Tumors**

Nonfunctioning duodenal NETs usually consist of serotonin-producing EC cells or calcitonin-producing cells. They do not behave aggressively unless they extend beyond the submucosa (80). These tumors may occasionally have an amyloid stroma.

**Jejunal and Ileal Neuroendocrine Tumors**

NETs developing in this region of the gut are typically EC cell serotonin-producing carcinoid tumors, but L-cell, glucagonlike peptide, and PP/polypeptide YY (PYY)-producing tumors also arise in this location. These tumors have an incidence of 0.28 to 0.89 per 100,000 population per year (100,157,158). They account for 23% to 28% of all GI endocrine tumors (100). Jejunal and ileal carcinoids usually develop in individuals ranging in age from the 3rd to the 10th decades of life, with a peak incidence in the 6th and 7th decades. However, the tumors may develop in children, in which case they behave aggressively. Men and women are equally affected. Blacks are affected more than whites (100). Ileal carcinoid tumors may also complicate Crohn disease (159). The duration of the Crohn disease varies from months to years (160).
Asymptomatic small intestinal NETs may be discovered incidentally at the time of autopsy or surgery. Symptomatic lesions result from tumor mass effects, the effects of tumor-engendered fibrosis, or the presence of the carcinoid syndrome. Many symptomatic patients have a long history of intermittent crampy abdominal pain suggestive of episodic intestinal obstruction (161). The symptoms worsen with progressive intestinal obstruction; abdominal distension and vomiting develop. Other patients present with infarction, bleeding, weight loss, diarrhea, or lymphadenopathy.

Because patient survival has increased due to somatostatin receptor 2–targeted therapy and an increasing number of other therapeutic and diagnostic options, the clinical manifestations of the fibrosis are emerging as a major issue in the morbidity and mortality of the disease (80). Contraction of the desmoplastic (fibrotic) tissue associated with the tumor causes angulation, kinking, or distortion of the bowel wall and secondary intestinal obstruction. Serosal fibrosis-producing adhesions lead to volvulus, luminal constriction of the bowel lumen, or matting together of bowel loops. Fibrosis around mesenteric metastases causes fixation of the ileal mesentery to the retroperitoneum with fibrous bands obstructing the small intestine and transverse colon (162). Blood vessels caught in the mesenteric fibrosis may be secondarily compressed, leading to ischemic necrosis of the involved bowel segment. Bowel infarctions and gangrene (Fig. 17.29) (161) may also develop secondary to concentric vascular thickening (see below). Retroperitoneal fibrosis may also lead to hydronephrosis and renal failure (163). Symptomatic tumors have usually spread beyond the site or origin. Ninety-three percent of symptomatic patients with small intestinal NETs have metastases, compared to 9% of patients whose tumors are found incidentally (161).
The carcinoid syndrome affects 10% to 18% of patients with NETs, particularly those with ileal lesions (162). The syndrome usually, but not necessarily, requires the presence of hepatic metastases so that sufficient amounts of the substances produced by the tumor can reach the systemic circulation without undergoing metabolic degradation. The aggregate mass of metastatic tumor in the liver often exceeds that in the primary site, allowing the metastases to produce enormous amounts of secretory products. Furthermore, the blood supply of the metastases drains directly into the systemic circulation via efferent hepatic veins, thereby sequestering the hormones from hepatic metabolism (Fig. 17.30).
Serotonin forms from the essential dietary amino acid tryptophan by hydroxylation and decarboxylation. Serotonin is broken down in the liver and lung by monoamine oxidase and reduced to 5-hydroxyindoleacetic acid (5-HIAA), a biologically inactive metabolite excreted in the urine (Fig. 17.31) (164). Provocative tests using pentagastrin (PG) elicit the release of both 5-HT and tachykinins (165). Elevated levels of >30 mg of 5-HIAA in 24 hours diagnose the syndrome.

The classic carcinoid syndrome consists of vasomotor, cardiopulmonary, and GI symptoms. The syndrome is often precipitated by alcohol or food intake, emotional stress, exercise, or straining at stool. The major clinical manifestations include paroxysms of sweating, flushing, facial and anterior chest cyanosis, wheezing or asthmalike attacks, abdominal colic, and right-sided heart failure. Mild or explosive diarrhea is the second most common symptom. Minor features include abdominal pain, edema, malabsorption with pella-gralike or sclerodermalike skin lesions, peptic ulcers, myopathies, arthralgias, and retroperitoneal fibrosis (166).

Carcinoid heart disease affects 50% to 66% of patients with classic carcinoid syndrome (167). Endocardial or subendocardial lesions involve the right side of the heart, causing tricuspid and pulmonary valve dysfunction and repeated episodes of ventricular failure (167). Patients with extensive endocardial involvement may present with a restrictive cardiomyopathy (168). Plaquelike thickenings develop on the affected endocardium in the right atrium, papillary muscles of the tricuspid valve, valvular leaflets, and cardiac chambers. The majority of the lesion consists of an acid mucopolysaccharide-rich stromal tissue, reticulin fibers, and collagen. The cells in the plaques are smooth muscle cells, fibroblasts, and myofibroblasts (169). Pulmonary fibrosis may also occur, usually in the setting of advanced metastatic disease.
FIG. 17.31. Metabolism of serotonin (see text).

Many peptides are produced by carcinoid tumors (170,171,172,173) and these may mediate the carcinoid syndrome symptoms. Neuropeptide K (NPK), the most abundant tachykinin in the plasma of carcinoid patients and in tumor tissue extracts, may mediate the carcinoid flush. Substance P also causes flushing, hypertension, tachycardia, and increased intestinal motility (174). GI hypermotility and diarrhea probably result from 5-HT, VIP, glucagon, prostaglandins, substance P, secretin, motilin, and/or neurotensin production (175). Some of the secreted substances are also implicated in the fibrosing disorders. These include serotonin, TGF-β family members, connective tissue growth factor, bone morphogenic protein, nerve growth factor-2, and platelet-derived growth factor (176,177).
FIG. 17.32. Small intestinal carcinoid. The carcinoid tumor (yellow area) kinks the bowel wall because of the associated desmoplasia. Approximately 80% of small bowel carcinoid tumors develop in the ileum. Multiple tumors develop in 25% to 30% of patients (161). In some cases, dozens of tumors are present. The practical implication of this multifocality is that the entire small intestine should be carefully palpated when a small bowel carcinoid has been identified to find additional tumors. Clonality studies show that multiple tumors appear to be clonally identical, raising the possibility that these “multiple” tumors are actually metastases from a single lesion (178). Twenty-nine percent of patients also have other noncarcinoid neoplasms, possibly secondary to the production of growth factors that might induce secondary neoplasms.

FIG. 17.33. Ileal carcinoid. A: Gross appearance of polypoid carcinoid. The mucosal surface is smooth and not ulcerated. B: The margins are well defined and there is no extension into muscularis propria.
FIG. 17.34. Ileal carcinoid showing the focal kinking of the bowel wall secondary to tumor growth through the muscularis propria and secondary fibrosis with serosal adhesions.

NETs develop deep in the mucosa, growing slowly and extending into the underlying submucosa as well as into the overlying mucosa. They form small, firm tan, yellow, or gray-brown intramural nodules bulging slightly into the intestinal lumen (Figs. 17.32, 17.33, and 17.34). They range from barely palpable thickenings to nodules measuring up to 3.5 cm in diameter (179). It is rare for primary tumors to be larger than this. Carcinoid tumors developing in the setting of Crohn disease tend to be small lesions measuring <1 cm (160). Small NETs are not encapsulated and usually demonstrate minimal invasion at their borders. Tumors that reach the lumen may ulcerate. As the tumors increase in size, they infiltrate beyond the submucosa into the muscularis propria, eventually reaching the serosa and mesentery. As the tumor becomes more deeply invasive, the bowel appears constricted or fibrotic (Fig. 17.35).

Midgut NETs demonstrate a characteristic insular (type I) growth pattern, which consists of solid nests or cords of cells with clearly defined boundaries, although the other growth patterns (Table 17.6) can also be seen. The cells lie in closely packed, round, regular, and monomorphous cell masses, buds, and islands (Figs. 17.36 and 17.37). The cells often palisade at the edges of the nests. Some tumors contain a mixture of both insular cords and tubules and rosettes. Individual cells as well as the tubular lumens may contain mucin (Fig. 17.38). Prominent capillaries represent a common feature. Rare tumors contain a dense eosinophilic stroma. NET cells usually contain a moderate amount of slightly acidophilic, slightly basophilic, or amphophilic cytoplasm. Eosinophilic cytoplasmic granules may be identified, especially at the periphery of the cellular nests (Fig. 17.38). Typical NETs demonstrate little or no cellular pleomorphism, indistinct cell borders, small nucleoli, nuclear hyperchromasia, and little mitotic activity. The relatively small, round to oval central nuclei have well-defined, regular nuclear membranes. When NETs invade the muscularis propria, they appear to insinuate themselves between the muscle fibers, spreading the fibers apart rather than destroying them (Fig. 17.39). When the tumor cells infiltrate intramural nerves, the latter become hypertrophic (Fig. 17.40). NE cell hyperplasia and small proliferating endocrine cell aggregates within the crypts may associate with small intestinal carcinoids, suggesting that such lesions originate from intraepithelial endocrine cells and subsequently infiltrate into the lamina propria (180). Up to 110 grossly visible tumors have been observed along with numerous grossly invisible EC cell microproliferations in the lamina propria. These show no apparent connections to the intracryptal endocrine cells, which do not appear to be increased (181). There are also circumstances where multiple tumors associate with increased intracryptal endocrine cells (53). These intraepithelial endocrine cells form linear proliferations or intracryptal aggregates and lamina propria endocrine cell micronodules appear to bud off them. Thus, there appeared to be an EC cell hyperplasia–carcinoid sequence similar to the ECL cell hyperplastic continuum that occurs in the stomach.
FIG. 17.35. Small bowel kinking from carcinoid tumor that grows into the serosal fat (arrows). Concomitant fibrosis has caused adhesions of multiple bowel loops.

The classic carcinoid tumor contains granules that are both argentaffinic and argyrophilic. In most tumors, argentaffin cells (Fig. 17.41) constitute the major cell population (182). The outermost cells tend to be the most argentaffinic (Fig. 17.42). The tumors stain strongly with the usual neuroendocrine immunostains. Most midgut carcinoids are multihormonal, with the most frequently encountered hormones being serotonin (Fig. 17.43), somatostatin, and gastrin. They may also produce enteroglucagon, PP, or PYY (171,182,183,184,185,186,187). Some of the substances are released into the circulation and their serum levels may serve as useful tumor makers. The two most helpful are CgA and neurokinin A (88).

Two thirds of these tumors produce CEA, 20% express prostate-specific antigen, and 7% contain S100-positive cells (80). Cytokeratin immunoreactivity is present in 68% of midgut carcinoid tumors (187). These tumors also display strong immunostaining for vascular endothelial growth factor, perhaps accounting for the rich vascularity commonly seen in these tumors. Ki-67 expression is low in these tumors, even in those that metastasize. Concentric elastic vascular sclerosis often affects the large mesenteric vessels (Fig. 17.44), sometimes obliterating the vascular lumens, leading to ischemia (188). The elastosis and fibrosis are not confined to the vessels. It may also surround nests of tumor cells, resulting in extensive matting of involved tissues and lymph nodes, sometimes producing fibrous adhesions.

It is estimated that 1% to 35% of all small intestinal NETs metastasize (161,189). Metastases first involve the regional lymph nodes and then the liver (Figs. 17.45 and 17.46). Lymph nodes with metastases can measure up to 5 to 6 cm in diameter or they may be matted together, secondary to the tumor-associated desmoplasia. The cut surface of the nodes often has the yellow or tan color characteristic of NETs. The primary neoplasm may remain relatively small (<3.5 cm), even when extensive metastatic disease involves the lymph nodes or liver. The right lobe of the liver, which receives most of the blood supply from the ileum, is involved more often than the left. NETs may also metastasize to the ovaries (190), peritoneum (191), and spleen (192). Ovarian carcinoid tumors may present a diagnostic dilemma because the lesions may be primary in the ovary or represent a metastasis of an intestinal lesion. Features that distinguish primary from secondary ovarian carcinoid tumors are listed in Table 17.11 (190). Tumors rarely metastasize outside of the abdominal cavity (0.5% of cases). When they do, metastatic sites include the pleura, heart (193), breast (194), bone marrow (Fig. 17.46), skin (195), and eye (196). Metastases to the skin or subcutaneous tissues can be confused with Merkel cell tumors, particularly in the absence of a demonstrable primary elsewhere.

Identifying tumors that will behave aggressively can be difficult. The distinction between a benign and malignant tumor traditionally relies on the presence or absence of metastases because histologic features alone do not usually allow one to predict malignancy. Factors determining their relatively malignant nature include tumor size, extent of local spread, presence of metastases at the time of diagnosis, mitotic rate, multiplicity, female gender, depth of invasion and presence of the carcinoid syndrome, increasing patient age, histologic pattern, presence of another malignancy, proliferative rate, and ploidy status (87,161,197). Approximately 2% of tumors measuring <1 cm, 50% of tumors measuring from 1 to 2 cm, and 80% of tumors measuring >2 cm metastasize (161). An increased median survival (4 years) is seen in patients with tumors displaying a mixed insular/glandular pattern (198). Patients with a pure insular and trabecular pattern have a median survival of 2.9 and 2.5 years, respectively. NETs discovered incidentally have an excellent prognosis compared to tumors in symptomatic patients. In one series of 28 patients with operable tumors, including 11 without metastases and 17 with operable metastases, 68% survived 5 years; only 2 of the 28 patients died of metastatic carcinoid tumor within 5 years of surgical resection. In contrast, only 27% of inoperable cases survived 5 years (161). In another series, the overall 5-year survival for patients with small bowel carcinoids was 59%; the 10-year survival was 43%. The 5- and 10-year survival rates were 72% and 60% and 35% and 15%, respectively, for patients without and with hepatic metastases.
FIG. 17.36. Carcinoid tumor patterns. A: Varying-sized solid nests of tumor cells. B: Higher magnification of the lesion shown in A demonstrating solid nests and also marked tissue retraction artifact. C: Trabecular pattern. D: Higher magnification of the interanastomosing ribbons of tumor cells. E: Carcinoid composed of acinarlike structures. F: Tumor demonstrating solid nests as well as glandular structures. Some of these nests are less well differentiated than others.

**TABLE 17.11 Comparison of Primary Vs. Secondary Ovarian Carcinoid Tumors**
<table>
<thead>
<tr>
<th>Feature</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31–79 (mean 60)</td>
<td>21–82 (mean 51)</td>
</tr>
<tr>
<td>Laterally</td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Teratomatous elements</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Cut surface</td>
<td>Homogeneous</td>
<td>Nodular</td>
</tr>
<tr>
<td>Peritoneal abscesses</td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td>Postoperative 5-HIAA levels</td>
<td>Negative</td>
<td>Often positive</td>
</tr>
<tr>
<td>Dead of carcinoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>0%</td>
<td>38%</td>
</tr>
<tr>
<td>4 years</td>
<td>0%</td>
<td>77%</td>
</tr>
</tbody>
</table>

HIAA, hydroxyindoleacetic acid.

**FIG. 17.37.** Ileal carcinoid. *A:* The tumor islands are relatively closely packed together and a marked tissue retraction artifact is present. *B:* Higher magnification showing monomorphous cell masses. Some cells have large nuclei and small nucleoli as well as inconspicuous cytoplasm and fine chromatin. Other rare cells demonstrate gigantic nuclei. Mitoses are rare and there is less tissue retraction than seen in A.

Patients with resectable jejunal and ileal NETs should undergo wide excision of the involved intestinal segment, including a mesenteric node dissection, regardless of the size of the primary tumor (199). Tumors that are nonfunctioning, measure <1 cm, are confined to the mucosa/submucosa, and are not angioinvasive are generally cured by local excision. However, even if the tumor cannot be totally excised, the surgeon should attempt to resect as much grossly visible tumor as possible, for palliation (161) and to avoid later complications such as bleeding, intestinal obstruction, or perforation. Some patients suffer more from disabling hormonal syndromes than from the tumor itself. Such patients may warrant aggressive therapy to reduce the tumor burden to achieve a comfortable life. Hepatic arterial occlusion may result in significant relief of hormonal symptoms. The 5-year survival rate of patients with hepatic
metastases is 18% to 32% (100,200). Today there is a tendency to treat patients with metastatic disease aggressively with surgery, somatostatin analogs, interferon, and possibly radiation and/or chemotherapy (80).

FIG. 17.38. Carcinoid tumor stained with a combination periodic acid–Schiff and chromogranin stain demonstrating luminal secretions and basal cytoplasmic neuroendocrine granules.

FIG. 17.39. Small separate nests of carcinoid tumor infiltrate the smooth muscle fibers of the muscularis propria without causing destruction of the native tissues.

Neuroendocrine Tumors in Meckel Diverticulum

Carcinoid tumors developing in Meckel diverticulum have a propensity to develop in males. Patients range in age from 14 months to 82 years. Seventy-seven percent of symptomatic patients have metastases (201). It is likely that these neoplasms are more analogous to gastric ECL tumors than to small intestinal carcinoids since they likely arise in areas of heterotopic gastric mucosa.
FIG. 17.40. Neural cell adhesion molecule immunostain of the wall of the small bowel demonstrating the presence of marked neural hypertrophy. A: Higher magnification demonstrating the hypertrophic nerves. B: Nerve infiltrated by tumor cells.

FIG. 17.41. Argentaffin-positive carcinoid tumor (Fontana-Masson stain).

Appendiceal Neuroendocrine Tumors

NETs account for between 50% and 85% of all surgically diagnosed appendiceal tumors and approximately 20% of all GI carcinoid tumors (91). This number reflects a decreasing incidence from previous studies, perhaps reflecting a decline in the practice of incidental appendectomies. They affect approximately 0.02% to 1.5% of all surgically removed appendices, and 4.4% are multifocal with evidence of carcinoid tumors elsewhere (202). Appendiceal NETs affect patients ranging in age from 6 to 80 years (91,202,203), with a mean age of 49.3 years (80), some 20 years earlier than that seen for carcinoids involving other parts of the gut. Tubular carcinoids occur at a significantly younger age than goblet cell carcinoids (average 29 vs. 53 years) (123). Patients with IBD sometimes develop appendiceal NETs (160). Fourteen percent of patients also have a histologically confirmed second primary malignant tumor of some other type, with the colon, cervix, and endometrium being among the most common sites of origin (202,204). A preponderance of women exists in older age groups, whereas men predominate in younger ages. In nongynecologic patients, the most common reason for the appendectomy is acute appendicitis caused by tumor obstruction of the lumen. The carcinoid syndrome rarely occurs in association with appendiceal lesions. It generally develops in patients with widespread metastases, and appendiceal carcinoid tumors rarely give rise to distant metastases.
Unlike other gastrointestinal NETs, the cell of origin of appendiceal carcinoids is the subepithelial Kulitschzyk cell, which has both endocrine and neural features (205). These subepithelial cells are more numerous toward the appendiceal tip, consistent with the observation that 70% to 80% of appendiceal carcinoid tumors occur at the tip, 5% to 22% arise in the body, and only 7% to 8% arise in the base of the appendix (202,204).

The gross appearance of the tumors varies from a subtle deformity and kinking of the appendiceal wall to a mass protruding into the lumen obliterating it or diffusely infiltrating the appendiceal wall (Fig. 17.47). It may also appear as an area of firm, gray-yellow tissue simulating distal fibrous occlusion. In some cases, the tumor produces circumferential narrowing; in other cases the lumen appears eccentrically narrowed. Ninety-five percent of tumors measure <1 cm in diameter. Carcinoid tumors usually spread by extending into the serosa (Fig. 17.48) or by permeating serosal lymphatics and veins. However, metastases are rare. Only 1% to 9% of appendiceal NETs metastasize, usually to regional lymph nodes. Distant metastases are rare (202,204).

Appendiceal NETs display several distinct histologic patterns: The typical EC cell, serotonin-producing carcinoid; the L-cell, glucagon-like peptide- and PP/PYY-producing carcinoid; the tubular carcinoid; the goblet cell carcinoid; and mixed carcinoid–adenocarcinoma. The last two entities are discussed in the section on mixed endocrine–exocrine neoplasms.
EC Cell Tumors

EC cell tumors are indistinguishable from ileal carcinoids. They produce serotonin and substance P and exhibit a typical insular pattern of solid nests with little nuclear pleomorphism and peripheral palisading (Soga type A pattern) (Fig 17.48). A minority of tumors exhibit glandular formations (type C patterns) or a mixture of the two (types A and C). If an acinar component is present, the cells differentiate into solid rosettes containing small amounts of inspissated mucin. If this variant is present, some of the cells may appear clear. This pattern has been termed the clear cell or balloon cell carcinoid (206). The NE granules lie scattered evenly throughout the cytoplasm or concentrate at the periphery of the tumor cell clumps, imparting a prominent eosinophilic border to the cells. Occasional cells may appear vacuolated, perhaps related to degeneration (207). These tumors are argentaffinic, argyrophilic, and positive with the usual NE cell markers and serotonin. Occasional cells stain for somatostatin, glucagon, calcitonin, CCK, gastrin, ACTH, neurotensin, motilin, and PP (208), but CEA is usually negative or only weakly positive. The majority of the tumor involves deeper layers of the appendiceal wall, often accompanied by fibrosis and hypertrophy of the muscularis propria. The tumors may show perineural or lymphatic invasion. Approximately two thirds of the tumors extend to the peritoneal surface. In the infiltrative portions of the tumor, the typical insular pattern is replaced by narrow cords and ribbons. Retraction artifacts mimic angioinvasion, but since angioinvasion is not used in the classification of appendiceal neoplasms (Table 17.12), it is not a major concern in evaluating these tumors. More aggressive tumors display nuclear pleomorphism and a higher mitotic rate than their less aggressive counterparts (179). Metastases to the peritoneum, regional lymph nodes, and liver rarely develop (204). Conventional appendiceal carcinoids tend not to express cytokeratin (209), and this factor, along with the presence of S100-positive sustentacular cells (Fig. 17.49), may make these tumors more similar to paragangliomas than to ileal NETs.
FIG. 17.45. Metastatic carcinoid involving the regional lymph nodes. Multiple tumor masses are seen on the cross section of the specimen.

<table>
<thead>
<tr>
<th>TABLE 17.12 Classification of Neuroendocrine Tumors of the Appendix</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well-Differentiated Neuroendocrine Tumor (Carcinoid)</strong></td>
</tr>
<tr>
<td>Benign: Nonfunctioning, confined to appendiceal wall, nonangiinvasive, ≤2 cm in size</td>
</tr>
<tr>
<td>- Serotonin-producing tumor</td>
</tr>
<tr>
<td>- Enteroglucagon-producing tumor</td>
</tr>
<tr>
<td>Benign or low-grade malignant (uncertain malignant potential): Nonfunctioning, invading the mesoappendix, angioinvasive, &gt;2 cm in size</td>
</tr>
<tr>
<td><strong>Well-Differentiated Neuroendocrine Carcinoma (Malignant Carcinoid)</strong></td>
</tr>
<tr>
<td>Low-grade malignant: Infiltrating deep in the mesoappendix, &gt;2.5 cm in size or metastases</td>
</tr>
<tr>
<td>- Nonfunctioning or functioning serotonin-producing carcinoma (with carcinoid syndrome)</td>
</tr>
<tr>
<td>High-grade malignant: Poorly differentiated intermediate or small cell carcinoma</td>
</tr>
<tr>
<td><strong>Mixed Exocrine–Neuroendocrine Carcinoma</strong></td>
</tr>
<tr>
<td>Low-grade malignant</td>
</tr>
<tr>
<td>- Goblet cell carcinoid</td>
</tr>
</tbody>
</table>
L-cell Tumors

Nonargentaffinic L-cell carcinoids are much less common than EC cell carcinoids. They produce glucagonlike peptides and PP/PYY. These tumors are usually small, measuring only 2 to 3 mm in size, and they are easily overlooked lesions on gross examination of the appendix. They consist of tubular or trabecular patterns (Soga type B) resembling rectal carcinoid tumors. The round, solid cellular nests typical of argentaffinic carcinoids are absent. The regular, neoplastic endocrine cells show little mitotic activity. Although they are nonargentaffinic, the cytoplasmic granules are frequently argyrophilic with the Grimelius technique (210), contain various peptide hormones, and react with antibodies to CgA and/or synaptophysin. The tumors also produce mucin and are cytokeratin immunoreactive (209). L-cell tumors with a dominant glandular pattern correspond to tubular carcinoids (203,211,212). L-cell tumors behave in the same way as EC tumors.

Appendiceal carcinoids have the best prognosis of all the carcinoids, probably reflecting the fact that the lesions are often detected early as well as the inherent biology of the tumor. In Godwin’s (100) review of patients with appendiceal carcinoid tumors, the 5-year survival was 99%! Prognosis directly relates to tumor size, the presence of vascular or perineural invasion, and mesoappendiceal extension. Moertel found no recurrence among 108 patients with tumors measuring <1 cm, followed for 5 years. Tumors measuring 2 cm in greatest diameter may present with widespread metastases at the time of initial detection (202,204). Seventy-one percent of the patients who undergo resection survive 5 years, with a median time to subsequent recurrence of 8 years (204). These data are based on measurement of the tumor in the fresh state, and it should be kept in mind that formalin fixation causes carcinoid tumors to shrink by almost one third of their original volume (213). Tumors measuring <2 cm in diameter with mesoappendiceal invasion may metastasize or spreading transcelomically.
FIG. 17.47. Appendiceal carcinoid. A: Stricture of the appendix secondary to the presence of a carcinoid tumor. The surrounding mucosa appears inflamed due to the presence of coexisting appendicitis. The distal appendicitis results from the obstruction by the carcinoid tumor present in the middle of the appendix. B: Small carcinoid (arrow) in the distal end of the appendix. The yellow-gray area could easily be missed on gross examination. The lesion diffusely infiltrated the bowel wall and extended to the serosa.

TABLE 17.13 Indications for Hemicolecotomy in Patients with Carcinoid Tumors
Tumor arises at appendix base  
Tumor present in resection margin  
Tumor extension to mesoappendix  
Tumor in extra-appendiceal lymphatics  
Tumor measures $\geq 2$ cm  
Evidence of metastases  
High mitotic activity  
Lymphatic invasion  
Mucinous histology

Simple appendectomy represents adequate treatment for most tumors, but an ileocollectomy should be performed if the tumor meets one of the criteria listed in Table 17.13 (202,204). Simple appendectomy is recommended for tumors measuring <2 cm if no gross evidence of metastatic disease is found at laparotomy (204).

**D-cell Tumors**

These are extremely rare in the appendix. A case of a psammomatous somatostatinoma was reported in a patient with NF1. It was histologically identical to the same tumor arising in the duodenum (214).

**Colonic Neuroendocrine Tumors (Carcinoids)**

Large intestinal carcinoid tumors account for approximately 6% of all GI NETs (100). Patients range in age from 9 to 83 years and average 64 to 66 years of age (100). The age-adjusted incidence is 0.07 to 0.31 cases per 100,000 population per year. The tumors exhibit an equal gender distribution. Whites are more frequently affected than blacks (91). Colorectal carcinoid tumors may complicate longstanding chronic inflammatory diseases such as ulcerative colitis (215). Additionally, the incidence of NETs may be higher in Japan and Southern Asia than in Western countries (100). As with other GI carcinoid tumors, colorectal NETs associate with tumors in other sites, particularly in the GI tract. The overall incidence of secondary tumors ranges from 3% to 15% (216,217). These tumors include both adenocarcinomas as well as other carcinoid tumors.

Forty-eight percent of the NETs arise in the cecum, 16% in the ascending colon, 6% in the transverse colon, 11% in the descending colon, and 13% in the sigmoid colon; in the remainder it is difficult to tell the exact site of origin. The clinical presentation varies depending on the size and site of the tumor. The symptoms associated with these neoplasms include pain, rectal bleeding, and diarrhea. These usually result from mechanical trauma associated with the passage of solid feces over the tumor surface. Some colonic NETs cause profound and unexplained weight loss; most lack humoral manifestations. The carcinoid syndrome is uncommon, even in the presence of liver metastases. Early lesions are polypoid and tend to have an excellent prognosis following resection. More advanced tumors appear ulcerated and aggressive. Some NETs present as large bulky masses, sometimes measuring up to 16 cm in greatest diameter (216). These deeply invade the bowel wall and involve regional lymph nodes by the time they are detected.
FIG. 17.48. A: Brownish stain (antibody to chromogranin) represents presence of neurosecretory granules. The tumor is present within the central fibrous occluded portion of the appendix, as well as extending all the way out to the serosa (arrow). B: Cross section through a different lesion showing central fibrous occlusion of the appendix and peripheral carcinoid tumor (brown cells) reaching the serosa.
FIG. 17.49. Carcinoid tumor. S100-immunostained preparation showing the presence of prominent peripheral S100-positive sustentacular cells. Many are spider shaped.

The histology of large intestinal EC cell tumors resembles carcinoid tumors arising in the small intestine or appendix. The WHO classification of colonic NETs is shown in Table 17.14. Solid clumps or islands of uniform pale cells with peripheral cords and trabeculae are present. The cells at the periphery may appear hyperchromatic and contain bright eosinophilic granular cytoplasm. Other patterns include the formation of tubules containing luminal periodic acid–Schiff (PAS)-positive material. However, they generally exhibit a more undifferentiated pattern with clinically more aggressive features, whereas well-differentiated features such as insular, trabecular, and glandular patterns are less common (217). A significant number of hindgut NETs exhibit moderate atypia and a high mitotic rate, and these lesions tend to behave more aggressively than the average midgut carcinoid tumor. Silver stains are generally negative, although populations of argyrophilic cells and even argentaffinic cells do occur in some cases (218). CgA immunostains may be negative (219). However, synaptophysin is usually positive (219).

Colonic carcinoids exhibit the worse prognosis of all GI carcinoid tumors with an overall 5-year survival of 33% to 42% (100,200). Although tumor size and microinvasion are major prognostic features in other GI NETs, these features tend to be less useful in assessing the prognosis of colonic NETs because most of these lesions exceed 2 cm in size and involve the muscularis propria at the time of presentation (217). Mitotic rate, overall tumor grade, and the histologic pattern all influence survival (217,220).

| TABLE 17.14 Classification of Neuroendocrine Tumors of the Ileum, Colon, and Rectum |

---

P.1135
Well-Differentiated Neuroendocrine Tumor (Carcinoid)

Benign: Nonfunctioning, confined to mucosa–submucosa, nonangioinvasive, <1 cm in size (ileum) or ≤2 cm colon and rectum

- Serotonin-producing tumor
- Enteroglucagon-producing tumor

Benign or low-grade malignant (uncertain malignant potential): Nonfunctioning, confined to mucosa–submucosa, angioinvasive, or <1 cm in size (ileum) or ≤2 cm colon and rectum

- Serotonin-producing tumor
- Enteroglucagon-producing tumor

Well-Differentiated Neuroendocrine Carcinoma (Malignant Carcinoid)

Low-grade malignant: Invasion of the muscularis propria and beyond or metastases

- Nonfunctioning or functioning serotonin-producing carcinoma (with carcinoid syndrome)
- Nonfunctioning enteroglucagon-producing carcinoma

Poorly Differentiated Neuroendocrine Carcinoma

High-grade malignant

Colonic NETs can be treated by local excision if they are found at an early stage (<2 cm) (219). Larger tumors should be treated aggressively with a standard colonic resection and lymph node dissection. Only 16.6% of lesions <2 cm metastasize, whereas 74% of lesions >2 cm metastasize. These tumors metastasize to the lymph nodes, liver, mesentery, peritoneum, pancreas, ureters, ovaries, omentum, and, rarely, heart, diaphragm, kidney, uterus, adnexa, and colon (216).

Rectal Neuroendocrine Tumors

Rectal NETs constitute 0.7% to 1.3% of all rectal tumors (100,216,221) and 10% to 20% of all gastrointestinal NETs (100). The autopsy incidence is <0.04% (223), but this is probably an underestimate, since the rectum is rarely carefully examined at the time of autopsy. Rectal carcinoids equally affect males and females (222). The tumors develop most frequently in the 5th to 7th decades, with an age range of 1 to 93 years (222,223). Patients with IBD have an increased tumor incidence. Multiple carcinoids occur in 2% to 4.5% of rectal cases (100,223).

Overall, patients with rectal carcinoids fit into two groups: Small solitary lesions measuring <1 cm and larger lesions with the possibility of metastases. Many rectal carcinoids present as asymptomatic firm, yellowish submucosal nodules usually measuring <0.5 cm in diameter and are detected at the time of endoscopy or digital rectal examination. Others appear as nodular mucosal or submucosal plaquelike thickenings, while a few appear polypoid or sessile (Fig. 17.50). These rounded neoplasms usually lack surface ulceration. When symptoms referable to NETs are present, they usually manifest as anorectal discomfort or constipation. Patients rarely exhibit the carcinoid syndrome. Patients with the syndrome usually have extensive hepatic metastases. Less than 0.5% of patients with extensive nodal metastases but without hepatic involvement exhibit the syndrome. Rare patients with benign tumors may also exhibit the carcinoid syndrome (223).

Uncommonly, the tumors present as larger, ulcerated growths (>2 cm), which may metastasize (221). Larger tumors have a capacity to invade directly to the urinary bladder. Three histologic patterns are encountered in rectal carcinoids that are typically L-cell tumors: Ribbon, acinar, and mixed (Fig. 17.51). The ribbon pattern is the most common, followed by the mixed and acinar patterns, respectively (224). The ribbons consist of two or more cell layers arranged along a delicate vascularized connective tissue core. The ribbons may be straight, convoluted, or interlacing. In the tubular or acinar pattern, the neoplastic cells lie within a delicate fibrovascular stroma. These NETs are rarely argentaffinic, but many are argyrophilic (219). Chromogranin immunostains are often negative. However, antibodies to synaptophysin delineate the true nature of the lesion (219). Most rectal carcinoids produce multiple hormones including any of the following: serotonin, glucagon, insulin, glicentin, somatostatin, pancreatic polypeptide, substance P, enteroglucagon, enkephalins, α-hCG, and PYY (224,225,226,227,228,229). Prostate-specific acid phosphatase is found in 80% to 100% of rectal carcinoids (230). Unlike other gastrointestinal NETs, trabecular hindgut carcinoid tumors may express vimentin. Rectal carcinoid tumors are also CEA immunoreactive (231).
FIG. 17.50. Whole mount section of a polypoid rectal carcinoid tumor.
FIG. 17.51. Rectal carcinoid. A: Low-power photomicrograph demonstrating a carcinoid tumor, which is present in both the mucosa and submucosa of the rectum. The tumor shows solid, ribbonlike, and acinar growth patterns. B: The tumor infiltrates the muscularis mucosae and extends upward into the mucosa. C: Acinar pattern of growth. The cells have round, uniform nuclei. D: Ribbons of cells infiltrate the submucosa. E: Solid nests of uniform cells are identifiable in some areas.

NE cell hyperplasia surrounds some rectal NETs (220). Multiple rectal carcinoid tumors and numerous extraglandular exocrine cell proliferations and microcarcinoids may be present. There are also circumstances where multiple tumors associate with increased intracryptal endocrine cells (75). A rare example of a psammomatous rectal carcinoid was recently reported. However, no data were presented as to whether it produced somatostatin as is seen in duodenal psammomatous carcinoids (232).

Because most rectal carcinoids are small, the metastatic potential is low. The tumors generally have a favorable prognosis with an overall survival rate of 88.3% (220). Features of rectal endocrine tumors that suggest malignancy include presenting symptoms (221), a ribbon histologic pattern, histologic microinvasion, tumor size, spread into and beyond the muscularis propria, a diffusely infiltrating and invasive margin, ulceration, and features of atypical carcinoids (221,222,226). Tumor size is the most useful prognostic factor. Tumors <1 cm in diameter rarely (0% to 3%) metastasize (233). In contrast, tumors measuring ≥2 cm in greatest diameter exhibit regional lymph node metastases or liver metastases in 60% to 100% of cases (221,233). Tumors measuring from 1 to 1.9 cm have a 10% to 15% incidence of metastases (216,231). Metastatic sites include the lung, liver, lymph nodes (222), bone, cranium (234), and endocrine organs. Ki-67 or p53 staining does not appear to add additional information above standard histologic examination (235), and the value of ploidy assessments is controversial (236,237).

Rectal NETs are treated with surgery. Lesions measuring <1 cm in size that are purely submucosal are usually managed by a minor procedure (endoscopic removal or a transanal resection) (238). For tumors measuring 1 to 2 cm without evidence of nodal metastases, a wide excision with meticulous evaluation to exclude muscular invasion is recommended (239). Radical surgery is required for tumors >2 cm in diameter, with muscular invasion or with nodal metastases. If the tumors display atypical histologic patterns, then radical operation should be considered even if the tumor measures <2 cm. While the WHO criteria suggest that tumors ≤1 cm are benign lesions, this does not appear to be true of some rectal lesions (240). Metastases have been reported from lesions measuring 5 mm or less.

**Tubular Carcinoid Tumors**

Tubular carcinoids are rare tumors that most commonly develop in the appendix in younger patients, but they also develop elsewhere in the gastrointestinal tract. They tend to develop in the tip of the appendix and show little contact with the overlying mucosa. They cause an ill-defined thickening of the appendiceal wall.

The tumors have a distinctive appearance with small discrete tubules (Fig. 17.52) or linear structures in an abundant stroma. Comma-shaped structures may also be present, but solid nests are generally absent. The tumor cells have round or oval nuclei; nucleoli may be prominent in some cells. The cells contain variable amounts of eosinophilic cytoplasm. Occasionally, mucin is present in the lumens of the tubules. Argentaffin and argentophilic cells are present in a majority of tumor cells (241). The tumors are positive for CgA, synaptophysin, serotonin, and IgA. S100-positive cells are absent (242).
FIG. 17.52. Tubular carcinoid tumor of the appendix. The tubular structures intermingle with a proliferation of fibrous tissue. The lesion was associated with neural hyperplasia.

Features that are helpful in diagnosing these tumors include an origin from the base of the crypts, an orderly growth pattern, integrity of the overlying mucosa, and absence of mitoses or cytologic atypia. Tubular carcinoids, but not other types of carcinoids, produce proglucagon mRNA (243), and they are frequently immunoreactive for glucagon, an unusual feature in other types of carcinoids. It is important to distinguish this lesion from goblet cell carcinoids that have a worse prognosis and require more aggressive treatment (241). Tubular carcinoids have a better prognosis, behaving more like classic carcinoids.

Gangliocytic Paragangliomas

Rare neoplasms known as gangliocytic paragangliomas combine elements of three different cell lineages: Epithelioid cells resembling paraganglioma or carcinoid tumor cells; spindle cells reminiscent of Schwann cells; and ganglion cells. Most patients present in the 5th to 6th decades, with ages ranging from 17 to 80 years and a male-to-female incidence of 1.8:1 (244). NF1 patients have an increased propensity to develop gangliocytic paragangliomas.

Patients present with GI bleeding, nausea, vomiting (245), or hemorrhage (246). The extent of the bleeding may vary in both severity and chronicity, with some patients presenting with mild bleeding over several years' duration or others presenting in hypotensive shock requiring transfusion. Obstructive jaundice develops in periampullary lesions (247).

Most gangliocytic paragangliomas arise in the medial aspect of the second part of the duodenum, especially at the ampulla of Vater. Some also originate in the jejunum (244,245,246,247,248,249,250), stomach, or appendix. Gangliocytic paragangliomas present as small polypoid submucosal lesions, frequently with an ulcerated mucosal surface and an average diameter of 2 cm. The lesions are usually not encapsulated and have an infiltrative pattern.

Histologically, the tumors contain a mixture of several distinct histologic patterns including (a) typical neurofibroma, with proliferating neurites and Schwann cells; (b) ganglion cells mixed with Schwann cells; and (c) proliferations of clear epithelioid cells arranged in clusters or radial patterns resembling carcinoid tumors (Fig. 17.53). The feature that distinguishes these lesions from ganglioneuromas is the presence of the carcinoidlike epithelial islands. The tumors insinuate themselves into the overlying lamina propria, often involving the underlying tissues and extending into the submucosa or the serosa.

The epithelioid cells stain positively with a variety of antibodies including chromogranin, synaptophysin, pancreatic polypeptide, neuron-specific enolase, serotonin, somatostatin, Leu-enkephalin, insulin, glucagon, and vasoactive intestinal peptide. The spindle cells almost always are strongly positive for S100 protein, but may also stain with NSE, neurofilament protein, and vimentin. The ganglion cells frequently stain positively with NSE and neurofilament protein.
Gangliocytic paragangliomas usually follow a benign clinical course. With complete excision, surgical therapy is usually curative. Recurrences are possible in lesions that are incompletely excised. Rarely, gangliocytic paragangliomas metastasize (249, 250). The metastases are to the regional lymph nodes; distant metastases do not occur.

**Neuroendocrine Carcinoma**

Most neuroendocrine carcinomas are either atypical carcinoids (well-differentiated NE carcinomas) or poorly differentiated NE carcinomas (Tables 17.5, 17.8, 17.10, 17.12, and 17.14). The tumors may be either pure or mixed with adenocarcinomatous and/or squamous cell carcinomatous components. Foci of necrosis and high mitotic indices are commonly observed in these neoplasms. CgA immunoreactivity in these lesions is generally poor, and synaptophysin represents a better marker of NE differentiation. Neuroendocrine carcinomas result from multidirectional differentiation of malignant epithelial cells.

**Well-differentiated Neuroendocrine Carcinomas (Atypical [Malignant] Carcinoid Tumors)**

Well-differentiated NE carcinomas have histologic features and a biologic behavior between that of typical carcinoid tumors and poorly differentiated NE carcinomas (small cell carcinomas) described below. They develop sporadically and in the setting of IBD. These lesions develop in the stomach, often in its proximal third (251); in the rectum; and in the esophagus (252). These are aggressive lesions and represent poorly differentiated forms of carcinoid tumors with increased mitotic activity and absent or limited extent of necrosis.

The cells range in appearance from uniform, large, polygonal, or fusiform types with abundant eosinophilic granular cytoplasm and round to oval nuclei similar to the cells seen in typical carcinoid tumors to pleomorphic epithelioid cells with scanty cytoplasm and hyperchromatic variably sized and shaped nuclei. The pleomorphic epithelioid cells are two to three times the size of small cells with abundant eosinophilic to amphophilic cytoplasm. Mitoses range from 1 to 10/10 hpf. The tumors exhibit prominent fibroblastic host responses and obvious lymphatic invasion. There may be peripheral palisading. Neoplastic cells are arranged in sheets, trabeculae, ribbons, and nests, with necrotic foci and neuroepithelial-like rosettes (Fig. 17.54). However, sometimes definite cellular nests or trabeculae may be hard to find and often require an extensive examination of the tumor to identify them. Focal areas may resemble classic small cell carcinoma (SCC). The lesions show transmural involvement with limited mucosal involvement. The tumors are nonargentaffinic but strongly argyrophilic and they stain with the usual immunohistochemical markers of NE cell differentiation. The tumors may show vascular or lymphatic invasion; extensive local invasion, including invasion of the muscularis propria; an anaplastic appearance; cellular pleomorphism; mucin production; and necrosis. When these features are present, 50% of the tumors metastasize (250).

**High-grade Neuroendocrine Carcinomas**

High-grade NE cell carcinomas are typically divided into small cell carcinomas and large cell (also called intermediate cell) NE carcinomas.

**Poorly Differentiated Endocrine Cell Carcinoma/Small Cell Carcinoma**

SCCs are malignant epithelial tumors that are similar in morphology, immunophenotype, and behavior to pulmonary SCC (253, 254, 255, 256). They are clinically aggressive and have an extremely poor prognosis, even when discovered at an early stage. SCCs represent 0.1% to 1% of all GI malignancies, with the esophagus being the most common primary GI site of origin (256). Most patients present with overt distant metastases. Systemic symptoms are common. Ectopic hormone secretion may occur.
FIG. 17.53. Duodenal gangliocytic paraganglioma. A: Lesion located predominantly in the submucosa. Villous atrophy is present overlying the lesion. The mass lesion obliterates the underlying normal architecture. B: At high-power magnification one sees the presence of epithelial nests, neurofibromatous components, and ganglion cells. C: Low-power picture of a different tumor showing less neural components and cells resembling a paraganglioma. D: Higher-power view of the lesion in C demonstrating the cytologic features of the tumor. These small blue cell tumors consist of densely packed, small, and oval-, spindle-, or fusiform-shaped anaplastic cells with dark, round or oval, hyperchromatic nuclei containing coarse chromatin (Fig. 17.55). A small but discernible amount of eosinophilic to amphophilic cytoplasm without discrete cell borders surrounds the nuclei. The nuclei are approximately twice the diameter of mature lymphocytes. The small cells and intermediate cells
form solid sheets, nests, and rosettes as well as ribbonlike cellular strands. Nucleoli are usually not prominent and may be completely absent. Significant nuclear molding may be present. Intermediate-sized cells and rare giant cells may intermingle with the small cells. The tumors may contain mono- and multinucleated tumor cells with large, angulated or fusiform, intensely hyperchromatic nuclei (Fig. 17.56). Crush artifacts (Azzopardi effect) are often present. Mitoses range in number from 10 to 125/10 hpf. Necrosis occurs in the central areas of the tumors (Fig. 17.57). Focal necrosis and vascular invasion are present in all cases.

**FIG. 17.54.** Well-differentiated neuroendocrine carcinoma (malignant carcinoid). A: The tumor consists of large eosinophilic cells, vaguely arranged in closely packed cell nests. B: Isolated large cells may be present. C: Another tumor that has a histologic pattern that begins to approach large cell undifferentiated neuroendocrine carcinoma. The cells are large and the nuclei have marked chromatin clumping.

The stroma varies from scanty reticulin fibers surrounding closely apposed nests of tumor to zones of marked desmoplasia. Typically, little or no inflammation associates with the tumor. Mucin stains are negative in the tumor cells. Argyrophil reactions vary, but a few argyrophilic granules are usually present. Cytokeratin stains may show punctate perinuclear cytoplasmic reactivity. Immunostaining with antibodies to CgA are often disappointing, but antibodies to synaptophysin are strongly positive, making the latter the most reliable stain for detecting this tumor (Fig. 17.58). The tumors may also stain with NSE, Leu7, and neurofilament protein (Fig. 17.59). The tumors have a high proliferative rate and often display p53 immunoreactivity (Fig. 17.60). Recently it has been suggested that expression of human achaete-scute homolog gene-1 protein may be a more sensitive and specific marker of these highly aggressive tumors (257). The cytology of small cell carcinoma resembles that of the corresponding lung tumor (Fig. 17.61). Small blue cells that are argyrophilic display the typical small cell immunophenotype. SCCs can resemble lymphomas, but the use of immunohistochemical and special stains usually resolves this differential diagnosis (Table 17.15).
FIG. 17.55. Small cell carcinoma. A: Subepithelial small cell carcinoma. B: This highly cellular neoplasm consists of small cells with overlapping nuclei.
FIG. 17.56. Small cell carcinoma. A: A population of small, undifferentiated-appearing cells infiltrates the lamina propria. Several residual colonic crypts are present. B: The tumor is composed of sheets and nests of cells with hyperchromatic nuclei and scant cytoplasm. C: Sheets of neoplastic cells are present. A tumor giant cell is located in the center of the photograph. Note also the presence of numerous mitotic figures, some of which are very atypical. D: Higher-power view of a multinucleated tumor giant cell.

FIG. 17.57. Small cell carcinoma. A: This tumor demonstrates extensive necrosis. Viable tumor cells are present only surrounding vascular structures. B: Higher magnification demonstrating the perivascular clusters of viable tumor cells.
FIG. 17.58. Immunohistochemical markers in small cell carcinoma. 

A: Weak neuron-specific enolase immunoreactivity. 
B: Synaptophysin stains are almost always strongly positive in small cell carcinoma. 
C: Chromogranin immunoreactivity is often negative. 
D: Cytokeratin stain shows focal punctate cytoplasmic staining.
FIG. 17.59. Duodenal small cell carcinoma. A: Small cells with little cytoplasm and hyperchromatic nuclei. B: Trabecular pattern with prominent mitotic activity. C: Ki-67 immunoreactivity demonstrates that approximately 70% of the cells are proliferating. D: Focal cytokeratin immunoreactivity in small cells. The overlying ductal epithelium is strongly positive. E: Neurofilament positivity in the small cells. F: Cytokeratin positivity in the trabecular region showing strong membrane staining and strong dotlike cytoplasmic reactivity. G: Chromogranin immunostains decorate more than half of the tumor cells. H: Weak neuron-specific enolase positivity of the tumor cells. (Pictures courtesy of Dr. G. Zamboni, University of Verona, Italy.)
Esophageal Small Cell Carcinomas

The esophagus is the most common site of extrapulmonary SCCs. Its incidence ranges from 0.5% to 7.6% of all esophageal tumors, depending on the country of origin of the patient (258,259). The tumor is more common in Japan than elsewhere in the world (260). Median patient age is 67 years, with a range of 45 to 89 years (260,261). Patients with SCC are often males in their 5th to 8th decades of life (260,261), and they often have a history of heavy smoking (260,261). There is also an association with longstanding achalasia (262). Presenting symptoms include dysphagia, weight loss, and chest pain. Most develop in the lower and middle thirds of the esophagus (261), and they may be single or multiple. The tumors range in size from 1 to 14 cm. The gross features of esophageal SCC are nonspecific, except perhaps for a tan, fleshy appearance. The tumors appear polypoid, fungating, or ulcerating. Invasion into the tracheobronchial tree causes a transesophageal fistula. In this setting it may be difficult to determine whether the tumor arises primarily in the lungs or in the esophagus.

<table>
<thead>
<tr>
<th><strong>TABLE 17.15 Comparison of Small Cell Carcinoma Vs. Lymphoma</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stain</strong></td>
</tr>
<tr>
<td>H&amp;E</td>
</tr>
<tr>
<td>Cytokeratin</td>
</tr>
<tr>
<td>Vimentin</td>
</tr>
<tr>
<td>Epithelial membrane antigen</td>
</tr>
<tr>
<td>Leukocyte common antigen</td>
</tr>
<tr>
<td>CD45</td>
</tr>
<tr>
<td>Chromogranin</td>
</tr>
<tr>
<td>Neuron-specific enolase</td>
</tr>
<tr>
<td>Synaptophysin</td>
</tr>
<tr>
<td>Neurofilament protein</td>
</tr>
</tbody>
</table>

± indicates cases that may be positive or negative.

a May be positive in anaplastic large cell lymphoma and lymphocyte-depleted Hodgkin disease, myeloma, histiocytic lymphoma, and rare T- and B-cell lymphomas.

H&E, hematoxylin and eosin.

SCCs may invade the submucosa and deeper layers of the esophageal wall. Lymphatic and blood vessel involvement is common. The overlying squamous epithelium often remains intact. Most small cell tumors demonstrate a pure small cell morphology (261), but they may also contain foci of squamous carcinoma in situ (260), invasive squamous carcinoma (261), adenocarcinoma, carcinoid tumor, or mucoepidermoid carcinoma (259), suggesting that the tumors arise from pluripotential basal cells present in the squamous epithelium or in the ducts of the submucosal glands (260). The tumors may also arise in areas of Barrett esophagus (263).
FIG. 17.61. Characteristic cytologic features of small cell carcinoma are seen in this brushing from an esophageal tumor.

FIG. 17.62. Poorly differentiated gastric neuroendocrine carcinoma. The tumor is polypoid and demonstrates surface ulceration, necrosis, and hemorrhage. (Photograph courtesy of Dr. Onja Kim, ANSA Medical Center, Seoul, Korea.)

The tumors may produce ACTH (264), calcitonin (264), vasoactive intestinal polypeptide, gastrin, secretin parathormone, colony-stimulating factor (264), and antidiuretic hormone, causing various syndromes, including hypercalcemia, Cushing syndrome, watery diarrhea, and hypokalemia–achlorhydria (265). Microsatellite instability may be more frequent in esophageal SCC than in squamous cell carcinomas (259,266). The tumors express p53 in 50% to 100% of cases (266,267,268), lose Rb expression, and overexpress bcl-2 (267). Proliferating cell nuclear antigen (PCNA) labeling rates range from 64% to 91% (268).

Esophageal SCCs show more aggressive lymphatic spread than squamous cell carcinomas at an equivalent stage. As a result, the tumors tend to disseminate rapidly. Most patients have disseminated disease when first seen. Metastases of esophageal SCCs are to the abdominal and cervical lymph nodes. Median survival is 3.1 months. Survival is in the range of several weeks for untreated patients to 6 to 12 months for those receiving therapy. Some patients benefit from aggressive combination chemotherapy. In local regional disease, treatment may be initiated using chemoradiation and then if metastatic disease is excluded, surgical resection may be considered and may produce long-term remission and possibly long-term survival (269). In patients with limited stage disease, surgery with curative intent may also be considered as part of the multimodality therapy (259).

**Gastric Small Cell Carcinomas**

Gastric SCCs account for 6% of gastric NE tumors and are more common in men than women. The mean age of presentation is 63 years (98). SCCs are more common in the body and fundus (Fig. 17.62), although there are examples of antral tumors. The tumors exhibit the typical SCC morphology described above. They may also contain areas of adenocarcinoma and squamous cell carcinoma. Molecular analyses of these mixed tumors show identical p53 and ras mutations in all components, suggesting a monoclonal origin (270). When the tumors extend to the peritoneum, they may be diagnosed on cytologic examination of peritoneal washings. The malignant-appearing small cells are present on a necrotic background with naked hyperchromatic nuclei. Some tumor cells may contain paranuclear blue inclusions (271). Most patients with gastric small cell carcinoma die
Chapter 17

Intestinal Small Cell Carcinomas

Large and small intestinal SCCs are rare tumors. They are more prevalent in Japan than in the United States. Most SCCs develop in males. It is a tumor of older adults, with ages ranging from 20 to 74 years, and a mean of 64 to 66 years (273). The majority of duodenal SCCs arise at the ampulla of Vater. Extra-ampullary duodenal SCCs are very rare (255). These ampullary tumors are grossly small (2 to 3 cm) tumors that are focally ulcerated or protuberant lesions (Fig. 17.63). Small intestinal SCCs may appear as ulcerated neoplasms.

SCCs arise anywhere within the large bowel, but are most common in the right colon (274). Colonic tumors range from localized bulky, polypoid lesions to neoplasms projecting into the bowel lumen (Fig. 17.64) or perforating the bowel wall. Annular or linitis plastica–like tumors or partly obstructing tumors may also be present. SCCs may also present as tiny foci in adenomatous polyps (256). The tumors may also develop in the setting of ulcerative colitis (274), where they may be multifocal (275). They may also arise on a background of endocrine cell hyperplasia (275). Virtually all of these undifferentiated neoplasms remain clinically silent. However, when symptoms develop, they include crampy abdominal pain, malaise, weight loss, fever, diarrhea, and rectal bleeding. In most reported cases, symptom duration is only a few weeks.

FIG. 17.63. Small cell carcinoma. A: Gross appearance of a tumor that arises at the ampulla of Vater. B: Whole mount of the lesion illustrated in A. The exophytic ampullary tumor has strictured the pancreatic duct. (Pictures courtesy of Dr. G. Zamboni, University of Verona, Italy.)

The tumors arising in the small bowel may show focal squamous differentiation. They often show direct invasion into the duodenum, pancreas, and/or bile duct. These aggressive tumors have a propensity for invasion and early metastasis. At the time of surgery almost all patients have metastases in the regional lymph nodes and the liver. Metastases also affect the peritoneum and lungs.
FIG. 17.64. Small cell carcinoma. A polypoid tumor mass projects into the colonic lumen.

The histologic features are typical of SCC. Overlying villous or tubulovillous adenomas are present in 45% of cases. When associated with adenomas, the interface of the adenoma with the SCC is abrupt, without evidence of transitional forms. Because of their association with adenomas and the demonstration of glandular, endocrine, squamous, and Paneth cell differentiation, most believe that SCCs arise from uncommitted “stem cells” in colorectal adenomas (274,276). The lesions may infiltrate transmurally, with limited involvement of the lamina propria, or they may be predominantly intramucosal, with only focal submucosal invasion.

The prognosis for SCCs is worse than for adenocarcinomas of comparable stage. They are able to widely disseminate from only superficially invasive foci (274). Nodal metastases are frequently present at the time the tumors are detected. Seventy-one percent of tumors metastasize to the liver. Even after aggressive treatment, patients die between 3 and 12 months following diagnosis, with 64% of patients dying within 5 months of diagnosis. However, some patients may exhibit a dramatic remission in response to a combined radiation and multidrug regimen designed to treat pulmonary SCC. However, even these remissions are usually followed by widespread metastases and death. The residual tumor may be of pure small cell histology or may have evidence of squamous cell carcinoma and/or adenocarcinoma, either along or in combination with the small cell carcinoma.

Anal Small Cell Carcinomas

The most anaplastic and most lethal of the anal canal tumors are the rare SCCs. The tumors arise in the upper part of the anal canal (276), grow rapidly, and metastasize early. The patients have an invariably fatal outcome. The differential diagnosis of these lesions includes basaloid squamous carcinomas. The latter are positive for high molecular cytokeratins, whereas SCCs are positive for neuroendocrine markers. Most patients present with advanced disease.

Large Cell Neuroendocrine Carcinoma

Large cell NE carcinomas (LCNECs) are rare, poorly differentiated endocrine carcinomas. They comprise <1% of colorectal cancers. Average patient age is 57 years, with a range of 29 to 86 years. The tumors develop in the colon, rectum, and anal canal (277). They have a histology intermediate between a conventional carcinoid tumor and a SCC. These malignant neoplasms are composed of large cells arranged in organoid, nested, trabecular, rosettelike, and palisading patterns that suggest NE differentiation (Fig. 17.65). In contrast to SCC, the cytoplasm is more abundant, nuclei are more vesicular, and nucleoli are prominent. Large multinucleated tumor cells may be present. The cells may appear discohesive, and there is less nuclear overlapping than is seen in typical SCC. Mitoses are easy to find, as is lymphovascular invasion. Focal necrosis is often present. As with SCCs, the tumors may exist alone or associate with adjacent adenoma or conventional adenocarcinoma. These tumors express cytokeratins mimicking the poorly differentiated adenocarcinomas that they resemble. However, in contrast to poorly differentiated adenocarcinomas, LCNECs express NE markers and lose retroblastoma (RB) expression (278).

<table>
<thead>
<tr>
<th>TABLE 17.16 Possible Spectrum of Composite Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
</tr>
</tbody>
</table>

**Chapter 17**

### Nonendocrine Component | Endocrine Component
--- | ---
Adenoma | Carcoid tumor (well-differentiated neuroendocrine tumor)
Adenocarcinoma | Malignant carcinoid (well-differentiated neuroendocrine carcinoma)
Well–poorly differentiated | Poorly differentiated neuroendocrine carcinoma
Signet ring cell | Small cell carcinoma
Diffuse gastric cancer | Intermediate cell carcinoma
Adenocarcinoma with squamous components | Pleomorphic giant cell tumor
Squamous carcinoma | Increased numbers of normal-appearing neuroendocrine cells
Pancreatic acinar differentiation | 

*aOne or more elements from each of the columns can be combined with each other.

![FIG. 17.65. Large cell neuroendocrine cell carcinoma.](image)

The biologic behavior of these tumors resembles that of SCC. Most patients have metastases at the time of detection (277).

### Mixed Endocrine–Glandular Neoplasms

#### Definitions and General Comments

Mixed endocrine–exocrine tumors constitute a heterogeneous group of rare neoplasms that includes different histopathologies and prognostic classes. The presence of occasional NE cells is common in many gastrointestinal adenocarcinomas. The degree of NE cell differentiation varies between tumors; when it is extensive the tumors may contain areas that resemble conventional carcinoids. More typically, the endocrine cells are inconspicuous and the quantity present is not obvious until the tumors are stained with NE cell markers. Carcinoid tumors or SCCs may coexist with adenomas or adenocarcinomas as composite tumors. The possible spectrum is shown in Table 17.16. The Lewin classification for these mixed neoplasms is shown in Table 17.17. These elements may intermingle with each other, as in goblet cell carcinoid tumors, or be distinctly separated from each other, as in collision tumors. The relative proportion and degree of differentiation of the glandular and endocrine components in these tumors are highly variable. The prognosis of these lesions depends on the histologic features and degree of differentiation of each of the components.

<table>
<thead>
<tr>
<th>Nonendocrine Component</th>
<th>Endocrine Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>Carcoid tumor (well-differentiated neuroendocrine tumor)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Malignant carcinoid (well-differentiated neuroendocrine carcinoma)</td>
</tr>
<tr>
<td>Well–poorly differentiated</td>
<td>Poorly differentiated neuroendocrine carcinoma</td>
</tr>
<tr>
<td>Signet ring cell</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Diffuse gastric cancer</td>
<td>Intermediate cell carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma with squamous components</td>
<td>Pleomorphic giant cell tumor</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>Increased numbers of normal-appearing neuroendocrine cells</td>
</tr>
<tr>
<td>Pancreatic acinar differentiation</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 17.17 Lewin Classification of Composite Tumors

...
● Carcinomas with interspersed endocrine cells
● Mixed tumors with admixed glandular and endocrine elements, each element comprising at least one third of the tumor
● Amphicrine tumors with glandular and endocrine differentiation in the same cell
● Collision tumors with juxtaposition of two elements without admixing of the two cell types

Mixed endocrine–glandular tumors may represent either the simultaneous proliferation of different cell lineages or the proliferation of multipotential stem cells capable of differentiating along multiple cell lineages. In tumors, amphicrine cells are present that contain both endocrine granules and mucin droplets. The presence of such cells supports the idea of a common precursor stem cell giving rise to two lines of differentiation within an individual cell (21).

Mutational studies support a monoclonal origin for tumors with mixed histologies when identical genetic mutations are present in each of the components as occurs in some tumors. In contrast, in collision tumors, where separate tumors may arise in close proximity to one another, there is evidence of a polyclonal origin as shown by immunohistochemical staining and genetic studies. Allelotyping studies also suggest that many mixed tumors are monoclonal in origin, whereas collision tumors have a polyclonal origin.

**Goblet Cell Carcinoid**

Goblet cell carcinoids have been described by a number of terms including mucinous carcinoma, adenocarcinoid, crypt cell carcinoma, and microglandular carcinoma. They exhibit features of both adenocarcinoma and carcinoid tumor. Goblet cell carcinoids may develop in the esophagus, duodenum (123,279), colon, and rectum (280,281); they are most common in the appendix. Sometimes they develop in patients with IBD (282). Goblet cell carcinoids may present with acute appendicitis or as an abdominal or pelvic mass (283).

Goblet cell carcinoids arise in any part of the appendix. They display a primarily submucosal growth pattern and appear as areas of firm whitish, sometimes mucoid discoloration. They range in size from 0.5 to 2.5 cm (209), although their exact size may be difficult to determine because of their diffusely infiltrative nature. A well-defined tumor mass may not be appreciated in lesions that grow circumferentially.

The tumors consist of uniform nests of mature-looking goblet cells arranged in small smooth-bordered cell nests (Figs. 17.66, 17.67, and 17.68), small tight cellular clumps, cellular rosettes, and signet ring cells (241,283). Most cells contain abundant intracytoplasmic mucin; smaller numbers of endocrine cells with finely granular eosinophilic cytoplasm are also normally present, as are Paneth cells (283). In addition, there may be amphicrine cells present. Foci resembling Brunner glands that are lysozyme positive may also be seen (283). None of the cell types demonstrates conspicuous nuclear pleomorphism or mitotic activity.

The EC cell component varies markedly within the lesions. In a minority of lesions, the EC component represents the predominant feature; in such lesions, small parts of the tumor may be indistinguishable from a conventional carcinoid tumor. Other tumors resemble a signet ring cell carcinoma because an inconspicuous NE component is only detectable after the use of stains for NE differentiation. For this reason, we advocate that all appendiceal lesions that look like signet ring cell carcinomas be stained with NE markers to exclude the presence of the biologically less aggressive goblet cell carcinoid. Some tumors produce enough mucin to create pools of extravasated, extracellular mucus within the appendiceal wall.

The tumors arise deep in the mucosa and infiltrate the lamina propria without lymphatic or venous invasion. The mucosa is typically spared, except where the tumor touches the bases of the crypts. These tumors tend to infiltrate all layers of the bowel wall extending to the serosa in a manner resembling traditional carcinoid tumors. They often elicit a considerable desmoplastic response. Mucin stains are intensely positive in the signet ring cells and in the extracellular mucinous pools. Argentaffinric and argyrophilic cells are often present and the cells are immunoreactive with antibodies to CEA and NE markers (Fig. 17.67). Duodenal goblet cell carcinoids may produce somatostatin. Cytology preparations of peritoneal washings show small round carcinoid cells with stippled chromatin and occasional signet ring cells.

The differential diagnosis of these tumors includes tubular carcinoids, which have a better prognosis (241). In the latter tumor, all of the tumor cells are positive with NE markers, the glandular lumens contain mucin but there is no intracytoplasmic mucin, and Paneth cells are generally absent. Goblet cell carcinoids should also be differentiated from clear cell carcinoids that are considered to be variants of classic carcinoids (208). The finding of preinvasive neoplasia (adenoma or dysplasia) in the mucosa suggests that one is dealing with a carcinoma rather than an adenocarcinoid.

Goblet cell carcinoids are thought to represent a line of differentiation that is intermediate between a classic carcinoid tumor and an adenocarcinoma. Their clinical behavior supports this concept. These tumors are more aggressive than carcinoid tumors, typically behaving as a low-grade carcinoma and spreading less quickly than conventional adenocarcinomas (241). Unlike adenocarcinomas, goblet cell carcinoids have a propensity for transperitoneal spread and frequent ovarian involvement. In some patients, regional lymph nodes and the liver become involved as a result of direct lymphatic or vascular dissemination. Metastases may appear as a pure carcinoid tumor or goblet cell carcinoid.
FIG. 17.66. Appendiceal goblet cell carcinoid. A: Longitudinal cross section of the appendix. The tumor is subtle in this low-power photomicrograph. Small tumor nests diffusely infiltrate the muscular wall (arrows). B: The tumor cells form clusters of mucin-secreting cells without lumen formation. Here they subtly infiltrate the lamina propria. C: Tumor cells present in the muscularis propria. Well-defined tumor cell nests are surrounded by a looser myxoid stroma. A prominent desmoplastic response as might be seen in an infiltrating adenocarcinoma is absent. D: Both glands (arrows) as well as linear arrangements (arrow) of the tumor are present.

The 5-year actuarial survival of patients with goblet cell adenocarcinoids is 73% to 84% (241), and the 10- and 15-year actuarial survival estimate is 66% (241). Patients with abdominal or pelvic metastasis have a more ominous prognosis, with most patients experiencing tumor recurrence within 5 years, despite treatment. Some patients with extensive regional disease die of their cancer within a year of diagnosis (241). Thirty percent of patients with Krukenberg tumors from the appendiceal adenocarcinoids die within 5 years of their initial diagnosis.

Some authors conclude that simple appendectomy represents adequate treatment for appendiceal goblet cell carcinoids localized to the appendix with less than mitoses per 10 hpf and no foci of cytologic atypia (241,284). Others suggest routine hemicolectomy in patients with localized disease (285) and aggressive surgical resection for patients with ovarian or other intra-abdominal or pelvic tumor or diffuse appendiceal involvement (286).

These tumors may strongly express the p53 protein in the majority of the tumor cells (287).

**Mixed Goblet Cell Carcinoid–Adenocarcinoma**

Mixed goblet cell carcinoids–adenocarcinomas are lesions in which adenocarcinomas appear to arise from a pre-existing goblet cell carcinoid. They are most common in the appendix, the most common site of goblet cell carcinoids, but they also develop in the colon and duodenum (279,288). The tumors contain areas that show typical features of goblet cell carcinoid as well as areas that appear to be less differentiated and exhibit a more carcinomatous growth pattern with solid sheets of cells, cribriform glands, or infiltrating signet ring cells in a single-file pattern. The tumors may also contain attenuated glandular cords lined by mucin-depleted cuboidal cells or mucin-containing columnar cells resembling more typical intestinal adenocarcinomas. They occur in the apparent absence of neoplastic change in the overlying mucosal epithelium (123). The lesions differ from signet ring cell carcinomas, which show much more architectural and cytologic atypia and frequently produce pools of extracellular mucin. These tumors have a propensity for transcoelomic spread, especially to the ovaries and less frequently to peritoneal surfaces (123,241,281). The tumors may also spread to lymph nodes or the liver as the result of lymphatic or vascular invasion. Aggressive tumors may be recognized by the following: the presence of lymphovascular invasion, 20 or more mitoses/10 hpf, a carcinomatous growth pattern in >50% of the tumor (presence of fused or cribriform glands, single-file pattern, densely infiltrating signet ring cells, solid sheets of cells), and spread beyond the appendix (123,241,281). Tumors with these features should be treated aggressively with radical hemicolectomy.
FIG. 17.67. Goblet cell carcinoid. A: Synaptophysin stain showing positive cells. B: Mucicarmine stains the goblet cells. C: Carcinoembryonic antigen immunostain stains the glandular lumens.

FIG. 17.68. Adenocarcinoid. A: Low-power photomicrograph demonstrating nests of palestaining cells within the mucosa and submucosa. B: The tumor is composed of clusters of cells containing abundant cytoplasmic mucin. Some of the cells resemble signet ring cells, but they lack the cytologic and architectural atypia characteristic of signet ring cell carcinomas. C: Synaptophysin immunostains are strongly positive.

Pleomorphic (Giant Cell) Neuroendocrine Carcinoma

Both the large bowel and the small bowel give rise to rare NE neoplasms containing highly pleomorphic multinucleated cells. Histologically, the tumors consist of solid sheets of poorly cohesive cells broken into clusters by delicate stromal strands. They contain a mixture of eosinophilic giant cells, small polygonal cells, and spindle cells (Fig. 17.69). The giant cells are identical to those seen in giant cell carcinomas of the lung. Large
pleomorphic nuclei, with distinct nuclear membranes, a vesicular chromatin pattern with irregular clumping, and one or more prominent nucleoli, are present. The nuclei may be pushed to the edge of the cells, often resulting in a bent or reniform eccentric appearance. Cell size varies, with larger cells having two or more nuclei. Numerous typical and atypical mitoses are frequently present. Lymphocyte tumor cell emperipolesis is frequently seen. The spindle cells and smaller polygonal cells have a smaller amount of cytoplasm, and the nuclei do not appear as pleomorphic but otherwise show similar characteristics. Because these pleomorphic carcinomas contain evidence of NE differentiation, some regard them as poorly differentiated variants of neuroendocrine carcinomas. Ultrastructurally, the cells show glandular as well as endocrine differentiation. Intracytoplasmic perinuclear whorls of intermediate filaments and dense core secretory granules are present. The tumors are positive for cytokeratin, vimentin, epithelial membrane antigen (EMA), NSE, and chromogranin. They are also immunoreactive for various hormones. These tumors are mucin negative.

<table>
<thead>
<tr>
<th>Component</th>
<th>Pleomorphic Neuroendocrine Carcinoma</th>
<th>Sarcoma</th>
<th>Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulin pattern</td>
<td>Epithelial</td>
<td>Mesenchymal</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Mucin or PAS stains</td>
<td>Some focally positive cells</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Often negative but some can be positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>HMB45</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>S100</td>
<td>Negative</td>
<td>May be positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Positive</td>
<td>Negative, except in neural tumors</td>
<td>Usually negative</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>May be positive</td>
<td>Negative, except in neural tumors</td>
<td>Negative</td>
</tr>
<tr>
<td>Actin</td>
<td>Negative</td>
<td>Some positive</td>
<td>Negative</td>
</tr>
<tr>
<td>CD117</td>
<td>Usually negative</td>
<td>GISTs positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Myosin</td>
<td>Negative</td>
<td>Some positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

GISTs, gastrointestinal stromal tumors; PAS, periodic acid–Schiff.

The differential diagnosis of the lesion includes pleomorphic carcinoma, sarcoma, and amelanotic malignant melanoma. It may closely resemble the latter. The use of special stains serves to establish the diagnosis (Table 17.18). The few tumors that the authors have seen have behaved aggressively with prominent lymphatic involvement and metastases present at the time of diagnosis. Prognosis is poor due to early tumor spread with only a few months of postoperative survival.

**Composite Adenoma–Carcinoid Tumors**

Adenomas containing carcinoid tumors are rare. Adenomas often contain endocrine cells but, despite the frequency of endocrine cells, they seldom give rise to a carcinoid tumor in or near the adenoma. These lesions fall within the general category of composite tumors and arise either from a common stem cell exhibiting multidirectional differentiation or from multiple cellular events affecting several cell lineages. In the colon there are two distinct patterns of adenoma–carcinoid tumors (289). In one, the carcinoid cells intimately intermingle with the adenomatous glands (Fig. 17.70); in the other, the two tumors appear to arise as separate lesions juxtaposed to one another (Fig. 17.71). The first lesion probably arose from a common stem cell. The second probably arose as a separate event, with the adenoma and the carcinoid tumor arising from separate cell lineages.
FIG. 17.69. Pleomorphic carcinoma of the small intestine. A: Low-power magnification photograph showing the presence of a large small intestinal tumor that diffusely invades the bowel wall. B: High-power magnification of individual tumor cells showing the cytologic features. Signet ring–like cells, as well as other noncohesive carcinoma cells, are present. C: Many of the cells have the appearance of multinucleated neoplastic giant cells. D: Reticulin demonstrating the carcinomatous nature of the proliferation. E: Marked lymphangitic spread is evidenced by the presence of submucosal lymphatic involvement, as well as dilation of the central lacteals. F: Paucity of neurosecretory granules; electron micrograph of one of the rare cells that contained evidence of neurosecretory granules. G: Higher-power magnification of the neurosecretory granules showing the typical dense core morphology.
FIG 17.70. Carcinoid tumor intermingling with a tubular adenoma. A: Areas where the adenomatous epithelium is more evident. The solid areas are the carcinoid tumor. The neuroendocrine (NE) cell proliferations resemble either an area of high-grade dysplasia or a squamous morule. B: Another area of the same polyp with a more solid proliferation of NE cells. C: Synaptophysin immunostain highlights the NE cell proliferations.

One could postulate that substances produced by the carcinoid tumor stimulated the immediately adjacent mucosa to undergo increased proliferation and neoplastic transformation (290,291). The carcinoid component in both lesions was small, and we have not seen any examples of metastases from the carcinoid component. However, an ileal lesion was reported in which the carcinoid component had metastasized to the liver, peritoneum, and lymph nodes at the time of diagnosis (291). It arose in the terminal ileum producing a cecal protrusion. The lesion contained two components, an adenoma with low-grade dysplasia and a carcinoid tumor. The adenomatous component stained positively for EMA and CEA and negatively for NSE. The carcinoid component stained positively for NSE and negatively for EMA (292).

FIG 17.71. Carcinoid tumor developing beneath a tubulovillous adenoma. The neuroendocrine cell proliferation is highlighted in brown by the synaptophysin immunostain.

A rare example of a composite gastric adenocarcinoma and adenocarcinoid has also been reported (293).

**Adenoendocrine Carcinoma**

Adenoendocrine carcinomas are rare. They develop throughout the gastrointestinal tract from the esophagus to the anus (280,294). They develop sporadically as well as in sites of chronic inflammations such as in association with Barrett esophagus or in patients with IBD (186). Lewin (281) restricts the term to those tumors in which the endocrine cells comprise 30% to 50% of an adenocarcinoma. They contain a carcinomatous component that is glandular in origin; squamous cell carcinoma may also be present. In most, the glandular component resembles a high-grade adenocarcinoma (intestinal or signet ring cell type) and the endocrine...
component consists of either a carcinoid tumor or SCC. Some forms of highly malignant carcinomas consist of mixtures of undifferentiated cells focally intermingling with neuroendocrine, exocrine, and squamous cells, sometimes arranged in an organoid manner (Fig. 17.72). An interesting patient was recently reported who had a gastric carcinosarcoma with prominent SCC components (295). In some tumors, the cell populations are demarcated fairly well from one another, whereas in others they intermingle. The histochemical and immunohistochemical findings reflect the individual components. The glandular parts tend to be PAS, Alcian blue, and mucicarmine positive. CEA immunoreactivity occurs in the glandular and squamous components. Argyaffin reactions are often negative. Argyrophilic reactions may be positive in the NE areas. The NE components may stain with the usual NE immunohistochemical markers. Cytokeratin immuno-stains may stain all the components, but the pattern of staining differs in the different areas. Well-differentiated glandular or squamous areas tend to be the most strongly positive. The NE areas stain like SCCs. When the tumors are those in which there are merely increases in the number of NE cells, the biology of the tumors resembles that of the usual adenocarcinoma of a comparable stage and grade. However, these tumors tend to be aggressive when the endocrine component is a SCC. The latter places them in a poor prognostic group and liver metastases are frequent. When reporting these tumors, one can make the diagnosis of a composite tumor, but each of the tumor types should be specified in the diagnosis along with the relevant degree of differentiation of each of the components so that the clinicians may be able to estimate the patient prognosis and treat the component types.

**FIG. 17.72.** Composite neuroendocrine tumor with adenocarcinoma. A: Chromogranin staining confirms the neuroendocrine differentiation in a proportion of the cells. B: Another area of the same tumor demonstrating adenocarcinoma adjacent to a poorly differentiated, small cell carcinoma. C: Higher-power view demonstrating the close apposition of the adenocarcinoma and the poorly differentiated endocrine component of the lesion. The neuroendocrine cells in this area are hyperchromatic, and the nuclear:cytoplasmic ratio is high. D: Chromogranin stain in another area of the tumor demonstrating positivity in the well-differentiated neuroendocrine portion of the tumor but negative staining in the small cell component.

**Composite Tumors with Pancreatic Acinar Differentiation**

An unusual variant of composite tumors are tumors that show areas of glandular, endocrine, and pancreatic acinar differentiation. These may develop in the stomach (296) or the ampulla of Vater (297). The tumors are predominantly submucosal in location with focal involvement of the overlying mucosa. They infiltrate into the muscularis propria or beyond. The surrounding mucosa is normal. The cut surfaces of the tumors are smooth and gray-white to tan. The predominant histologic pattern consists of circumscribed cellular islands composed of solid nests of polygonal NE cells surrounded by numerous vessels. Small acinar lumina punctuate the nests. Another glandular component consists of well-differentiated adenocarcinoma. The cells lining the neoplastic glands may resemble foveolar cells. Interspersed goblet cells may be present. CK-7, CEA, and Muc are positive in the glandular areas. Markers of pancreatic acinar differentiation are positive in the solid areas and overlap with the endocrine cell markers. When the tumors metastasize, all of these components are present in the metastatic lesions (296,297). Tumors such as this could result from neoplasia developing in heterotopic pancreatic or from

file:///F|/Gastro/Chapter%2017%20neuroendocrine%20CA.htm (70 of 78)2/4/2009 2:04:22 PM
pluripotential stem cells.

Collision Tumors

Collision tumors of the gut are exceedingly rare. They consist of tumors with NE differentiation abutting an adenocarcinoma or adenoma or squamous cell carcinoma into another. The endocrine areas must be in intimate juxtaposition to a neoplastic glandular and/or squamous cell lesion, but they should not intermingle with one another (Fig. 17.73). Collision tumors occur when two tumors that have arisen at independent topographic sites meet and eventually intermingle with one another. One makes the diagnosis of a collision tumor most easily when clear-cut evidence suggests that the tumor originated in two separate epithelia with clear separation of the two components. Often, if both tumor types metastasize, the two types of growth also remain clearly separated in the metastasis. Collisions occur between SCCs and/or adenocarcinomas, and with sarcomas, lymphomas, melanomas, or metastases (155,156).

Probably the most common setting for collision tumors to occur is in the setting of CAG, where the hypergastrinemia causes the formation of ECL cell hyperplasia and multiple ECL cell carcinoids. The hypergastrinemia is also trophic for the growth of the glandular cells and varying degrees of glandular dysplasia, and neoplasia may coexist with the carcinoid tumors.

Increased Endocrine Cells in Treated Adenocarcinomas

The presence of focal endocrine cells in colorectal adenocarcinomas is a frequent finding. However, NE cells may account for up to 20% of the cell population in tumors that have been treated with chemoradiation. The NE cells may form nests and cords appear deeply eosinophilic. They usually have round and uniform, but sometimes pleomorphic, nuclei. The proportion of endocrine cells significantly associates with the extent of the treatment response. Tumors treated with chemoradiation are more likely to contain abundant endocrine cells than those treated with radiotherapy alone. These cells also frequently express the p53 protein (298).

References


**FIG. 17.73.** Collision tumor with adenocarcinoma (*left*) and carcinoid tumor (*right*).


Chapter 17


P.1159


Chapter 17


295. Yamazaki K: A gastric carcinosarcoma with neuroendocrine cell differentiation and undifferentiated spindle-shaped sarcoma component possibly progressing from the conventional tubular adenocarcinoma; an...


Chapter 18
Lymphoproliferative Disorders of the Gastrointestinal Tract

In this discussion of gastrointestinal lymphoproliferative disorders the emphasis will be on neoplastic diseases. The lymphoid hyperplasias will be considered only in the context of their differential diagnosis from lymphomas. Being the most common site of primary extranodal lymphoma, the gastrointestinal tract accounts for between 30% and 50% of all cases (1,2). These lymphomas are almost exclusively of non-Hodgkin type; primary gastrointestinal Hodgkin lymphoma, although well documented, is vanishingly rare. In the West, gastrointestinal lymphoma comprises between 4% and 18% of all non-Hodgkin lymphomas, but there is some evidence that the incidence is rising (3,4). There is considerable geographic variation in the incidence of primary gastrointestinal lymphoma best illustrated by the high incidence in the Middle East. Exact figures are difficult to obtain but in the Middle East, excluding skin tumors, lymphoma as a whole is the most common malignancy, and 25% of these lymphomas arise primarily in the gastrointestinal tract (5). Considerable differences in incidence also exist between Western countries; there is, for example, a 13-fold higher incidence of primary gastric lymphoma in northeastern Italy compared to Britain (6).

Definition
Nodal lymphoma frequently involves the gastrointestinal tract as a secondary phenomenon; this frequency has almost certainly been underestimated as shown by the study of Fischbach et al (7), who performed gastroscopies on newly diagnosed nodal lymphomas and found gastric involvement in over 25%, including cases of low and high histologic grade lymphoma. Strict criteria for a diagnosis of primary gastrointestinal lymphoma are, therefore, necessary if its incidence is not to be overestimated. The criteria laid down by Dawson et al in 1961 (8), which require that the lymphoma be limited to the gastrointestinal tract and its contiguous lymph nodes, are still applicable, although they do not take account of modern staging procedures, which can detect small foci of disease in the liver and bone marrow, the presence of which does not necessarily exclude a primary gastrointestinal tumor. An operational definition of primary gastrointestinal lymphoma is that lymphoma presents with the main bulk of disease in the gastrointestinal tract necessitating the direction of treatment primarily to that site. Inevitably, this definition is blurred at its edges, and some widely disseminated gastrointestinal lymphomas will not be included while occasional cases of selectively disseminated nodal lymphomas might be wrongly assigned.

Sites of Origin
The stomach is by far the most common site of primary gastrointestinal lymphoma in the West and Far East (9,10), followed by the small intestine. The opposite is true in the Middle East (5), where most arise in the small intestine and the stomach is next in frequency. In all regions, colonic, rectal, and esophageal lymphomas account for a very small minority of cases. The distribution of gastrointestinal tract lymphomas is paradoxical since the normal gastric mucosa is almost devoid of lymphoid tissue and many primary intestinal lymphomas arise proximal to the terminal ileum, where there is the greatest concentration of mucosa (gut)-associated lymphoid tissue (MALT) in the form of Peyer patches.

Staging
The Musshoff modification of the Ann Arbor staging system for extranodal lymphoma (11) is most commonly used for staging gastrointestinal lymphomas. In stage I_E (where _E signifies an extranodal site), the lymphoma is confined to the wall of the stomach or intestine. In stage II_E, there is involvement of regional lymph nodes that are contiguous with the primary site, while in stage II2_E, there is involvement of a regional but noncontiguous lymph node group. Stage III refers to involvement of lymph nodes on both sides of the diaphragm, the spleen (stage III_S), or both (stage III_E+S). In stage IV, there is dissemination to the bone marrow or other nonlymphoid organs.

Classification of Primary Gastrointestinal Lymphoma
With the few exceptions of other “organ-specific” lymphomas such as certain cutaneous T-cell lymphomas, splenic...
marginal zone lymphoma, and some other rare entities, most lymphomas listed in the World Health Organization (WHO) lymphoma classification (12) can arise in the gastrointestinal tract. In terms of frequency, however, the types of lymphomas occurring in lymph nodes and the gastrointestinal tract are quite different, and there are also certain gastrointestinal lymphomas that do not occur in peripheral lymph nodes. A classification of primary gastrointestinal lymphomas is given in Table 18.1.

<table>
<thead>
<tr>
<th>TABLE 18.1 Primary Gastrointestinal Non-Hodgkin Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B Cell</strong></td>
</tr>
<tr>
<td>Mucosa-associated lymphoid tissue (MALT) lymphoma</td>
</tr>
<tr>
<td>Immunoproliferative small intestinal disease</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>With a MALT lymphoma component</td>
</tr>
<tr>
<td>Without a MALT lymphoma component</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>Lymphomas and lymphoproliferations associated with immunodeficiency</td>
</tr>
<tr>
<td>Other types of lymphoma corresponding to lymph node equivalents</td>
</tr>
<tr>
<td><strong>T and NK Cell</strong></td>
</tr>
<tr>
<td>Enteropathy associated T-cell lymphoma</td>
</tr>
<tr>
<td>Other types unassociated with enteropathy</td>
</tr>
<tr>
<td>Nasal-type NK-cell lymphoma</td>
</tr>
<tr>
<td><strong>Rare Types</strong></td>
</tr>
<tr>
<td>Includes conditions that may simulate lymphoma</td>
</tr>
</tbody>
</table>

**B-cell Lymphomas**

Amongst B-cell lymphomas, MALT lymphoma, of which gastric MALT lymphoma is the prototype and most intensively studied, is the most interesting, if not the most common gastrointestinal lymphoma. Immunoproliferative small intestinal disease (IPSID) is a specific subtype of MALT lymphoma distinguished by its epidemiology and association with the synthesis of an abnormal α heavy chain (13,14). MALT lymphoma, including IPSID, may undergo transformation into diffuse large B-cell lymphoma (DLBCL) with loss of the characteristic histologic hallmarks of the original disease, but in at least a proportion of gastrointestinal DLBCL, careful examination will reveal residual foci of MALT lymphoma (15). However, most gastrointestinal DLBCLs, which comprise the majority of gastrointestinal lymphomas, appear to have arisen de novo without any evidence for transformation from a MALT lymphoma, and some of these express antigens such as CD10, which clearly indicates that they are not related to MALT lymphoma. Other B-cell tumors that arise in the gastrointestinal tract include mantle cell lymphoma, which often results in the condition called lymphomatous polyposis (16); a variant of follicular lymphoma; and Burkitt lymphoma, the latter being particularly common in the Middle East (17). Immunodeficiency-associated lymphoproliferative disorders and lymphomas also tend to arise primarily in the gastrointestinal tract. Finally, any type of B-cell lymphoma other than those listed above may present primarily in the gastrointestinal tract although not necessarily arising there.

**T-cell and NK-cell Lymphomas**

Primary gastrointestinal T-cell lymphomas are much less common than B-cell tumors. Enteropathy associated T-cell lymphoma (EATL) (18,19), which occurs as a complication of celiac disease, is the only distinctive T-cell tumor of the intestine and, in some ways, is the equivalent of B-cell MALT lymphoma in that it appears to arise from a gut-committed T-cell. Other T-
cell lymphomas less commonly arise in the gastrointestinal tract. NK-cell lymphomas of nasal type, although, as their name suggests, are more common in the upper respiratory tract, not infrequently present as primary intestinal tumors (20).

A number of other tumors of hematopoietic tissue, including histiocytic neoplasms (21) and granulocytic sarcoma (22), may also occur as primary gastrointestinal tumors. Although these are, strictly speaking, not lymphomas, they are easily mistaken for lymphoid tumors and are included in the WHO lymphoma classification.

**MALT Lymphoma**

In formulating classifications of non-Hodgkin lymphomas, considerable attention has been paid to architectural, cytologic, and functional similarities between the various lymphomas and normal lymphoid tissue as exemplified by the peripheral lymph node. However, studies of extranodal lymphomas, particularly gastrointestinal lymphomas, have suggested that their clinicopathologic features are not related to lymph nodes but instead to the structure and function of MALT (23,24).

The anatomic distribution and structure of lymph nodes are adapted to deal with antigens carried to the node in afferent lymphatics, which drain sites at various distances from the node. Permeable mucosal sites, such as the gastrointestinal tract, however, are particularly vulnerable to pathogens and antigens since they are in direct contact with the external environment, and specialized lymphoid tissue has evolved to protect them. This MALT includes gut-associated lymphoid tissue, nasopharyngeal lymphoid tissue (the tonsils), and other less well-characterized aggregates of lymphoid tissue related to other mucosae. Gut-associated lymphoid tissue serves as the paradigm for MALT.

**Histology and Immunology of MALT**

MALT in the gastrointestinal tract consists of four lymphoid compartments that include organized collections of lymphoid tissue, which, when concentrated in the terminal ileum, form Peyer patches; the lamina propria lymphocytes; plasma cells and accessory cells; intraepithelial lymphocytes; and the mesenteric lymph nodes. MALT lymphomas essentially recapitulate the features of Peyer patches.

**Peyer Patches**

Organized lymphoid nodules are distributed throughout the small intestine, the appendix, and the colorectum. These nodules concentrate in the terminal ileum, where they collectively form the Peyer patches, the generic term applied to this compartment of MALT. Peyer patches are unencapsulated aggregates of lymphoid cells that bear a certain resemblance to lymph nodes (Fig. 18.1). Each Peyer patch nodule consists of B- and T-cell areas and associated accessory cells. The B-cell area is composed of a germinal center surrounded by a mantle zone of small B lymphocytes, which is broadest at the mucosal aspect of the follicle. Surrounding the mantle zone is a broad marginal zone in which most of the cells are small to intermediate-sized B lymphocytes with moderately abundant, pale-staining cytoplasm and nuclei with a slightly irregular outline leading to a resemblance to centrocytes. The marginal zone extends toward the mucosal surface and some marginal zone B cells enter the overlying dome epithelium, where they form the lymphoepithelium, which is a defining feature of MALT (Fig. 18.2). Immunohistochemical studies of Peyer patches (25,26,27) have shown that the B-cell follicles are identical to those of lymph nodes. In contrast to the IgM- and IgD-positive mantle zone, the peripheral marginal zone cells are IgM positive but IgD negative. Lateral to the deep aspect of the B-cell follicle, there is a T-cell zone in which high endothelial venules are prominent, equivalent to the paracortical T zone of the lymph node.
**FIG. 18.1.** Normal Peyer patch. A B-cell follicle with a subepithelial marginal zone covered by the dome epithelium.
Chapter 18

**FIG. 18.2.** Detail of the dome epithelium showing intraepithelial B lymphocytes constituting the lymphoepithelium that defines mucosa-associated lymphoid tissue.

**Definition of MALT Lymphoma**

MALT lymphoma is listed in the WHO classification (12) under the designation “extranodal marginal zone lymphoma of mucosa associated lymphoid tissue” (MALT lymphoma) and defined as a lymphoma that recapitulates the histology of MALT (Peyer patches); the normal cell counterpart is the marginal zone B cell. MALT lymphomas arise in MALT acquired following chronic inflammation (acquired MALT) and consequently their clinical and pathologic features merge with those of the preceding chronic inflammatory disorder. MALT lymphomas consist of morphologically heterogeneous small B cells including marginal zone (centrocytike) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblast and centroblastlike cells. There is plasma cell differentiation in a proportion of the cases. The infiltrate appears to arise in the marginal zone of reactive B-cell follicles, which, although reactive, are an integral part of MALT lymphomas and extends into the interfollicular region. In epithelial tissues the neoplastic cells typically infiltrate the epithelium, forming lymphoepithelial lesions (12).

**Epidemiology**

MALT lymphoma comprises 7% to 8% of all B-cell lymphomas and at least 50% of primary gastric lymphomas (28,29). Most cases occur in adults with a median age of 61 years and a slight female predominance. There is a higher incidence of gastric MALT lymphoma in northeastern Italy, probably related to a high prevalence of *Helicobacter pylori*–associated gastritis in that region (6). Histologically, identical intestinal (30,31) and esophageal lymphomas also occur, but they are distinctly infrequent in comparison. A special subtype of small intestinal MALT lymphomas known as immunoproliferative small intestinal disease occurs in the Middle East, parts of the Indian subcontinent, and the Cape region of South Africa (14).

**FIG. 18.3.** Normal gastric antral mucosa. There is no organized lymphoid tissue.

**Etiology**

MALT lymphomas only rarely arise from native MALT; they more usually arise from MALT that has been acquired as a result of a chronic inflammatory disorder at sites normally devoid of MALT, including the stomach (Fig. 18.3). Here MALT is commonly acquired almost always as a result of the reaction to infection with *H. pylori*, which precedes development of most
cases of gastric MALT lymphoma (Fig. 18.4) (32). A similar relationship has been proposed between intestinal infection with *Campylobacter jejuni* and IPSID (33). The functional characteristics of acquired MALT and the degree to which it resembles normal MALT have not been investigated. Likewise, the factors that, in a small number of cases, result in transformation of this reactive MALT into a lymphoma that recapitulates many of its normal morphologic and functional properties remain speculative.

**Helicobacter pylori and Gastric MALT Lymphoma**

Several lines of evidence suggest that gastric MALT lymphoma arises from MALT acquired as a consequence of *H. pylori* infection. *H. pylori* can be demonstrated in the gastric mucosa of the majority of cases of gastric MALT lymphoma (Fig. 18.5) (34). The first study in which this association was examined showed that the organism was present in over 90% of cases. Subsequent studies have shown a lower incidence (35) but also that the density and detectability of *H. pylori* decreases as lymphoma evolves from chronic gastritis (36). A subsequent case control study showed an association between previous *H. pylori* infection and the development of primary gastric lymphoma (37). More compelling evidence confirming a role for *H. pylori* in the pathogenesis of gastric lymphoma has been obtained from studies that detected the lymphoma B-cell clone in the chronic gastritis that preceded the lymphoma (36) and from a series of in vitro studies showing that lymphoma growth could be stimulated in culture by *H. pylori* strain–specific T cells when crude lymphoma cultures were exposed to the organism (38). Finally, following the initial study by Wotherspoon et al (39), several groups have confirmed that eradication of *H. pylori* with antibiotics results in regression of gastric MALT lymphoma in 75% of cases (40) (see below).
Campylobacter jejuni and Immunoproliferative Small Intestinal Disease

Unlike gastric MALT lymphomas, relatively few cases of IPSID, which is in any case rare, have definitively been shown to respond to broad-spectrum antibiotics. Moreover, the presumptive organism linked to IPSID has remained unknown. In 2004, Lecuit et al (33), based on a single case report, suggested that C. jejuni may play the same role in IPSID as H. pylori does in gastric MALT lymphoma. Isaacson et al (unpublished) in a polymerase chain reaction (PCR) study confirmed an association between C. jejuni and IPSID but also detected the organism in other small intestinal lymphomas. To date, no laboratory study on the effects of C. jejuni on IPSID cells has been reported, and further studies on the effects of C. jejuni eradication are awaited.

Histology of Acquired Mucosa-associated Lymphoid Tissue

Tissues in which MALT lymphomas occur seem to mount a stereotyped response to certain known and unknown agents with accumulation of lymphoid tissue that forms Peyer patch–like structures (Fig. 18.4).

Because of its unique ability to withstand a low pH, H. pylori is the one organism, apart from some other, rare Helicobacter strains, that can survive in the human gastric mucosa. The prevalence of H. pylori gastritis in any given population varies from 20% to 100% depending on the locality and the age cohort (see Chapter 4). With some exceptions, the prevalence of gastric MALT lymphoma is related to that of H. pylori gastritis. Typically, infection results in active chronic inflammation with B-cell follicles and the formation of a lymphoepithelium by B-cell infiltration of glands immediately adjacent to the follicles (41) (Fig.
features of acquired MALT. Between the follicles, the gastric mucosal lamina propria is infiltrated by T lymphocytes, plasma cells, macrophages, and occasional collections of neutrophils. The lymphoid infiltrate may be extremely florid and at times difficult to distinguish from MALT lymphoma, especially when there are expanded sheets of mantle zone cells in biopsy fragments. Immunohistochemistry is useful in delineating the B-cell follicles and distinguishing the IgM- and IgD-positive mantle zone cells from IgM-positive, IgD-negative MALT lymphoma cells. Staining for immunoglobulin light chains can be useful in detecting monoclonal B cells and plasma cells in some cases of MALT lymphoma; however, the presence of polyclonal plasma cells does not exclude the diagnosis. PCR analysis normally reveals a polyclonal B-cell population in gastritis, but there are reports of spurious monoclonality detected in gastric biopsies from patients with \textit{H. pylori} gastritis (42). When the test is properly performed and interpreted this is extremely uncommon (43), but it is noteworthy that in patients with gastritis who have later developed MALT lymphoma, the identical monoclonal B-cell population has been detected in both lesions (36).

**Clinical Presentation**

Patients with gastric lymphoma usually present with nonspecific dyspepsia; severe abdominal pain and the presence of an abdominal mass are rare. The findings at endoscopy are usually those of nonspecific gastritis and/or a peptic ulcer, the presence of a mass again being unusual. Most gastric MALT lymphomas are at stage I\textsubscript{E} at the time of diagnosis. Gastric lymph node involvement (stage I\textsubscript{1E}) is present in 5% to 10% and bone marrow involvement (stage I\textsubscript{VE}) may be found in up to 10% of cases (44).

**FIG. 18.6.** Gastric mucosa-associated lymphoid tissue lymphoma resulting in a “cobblestone” appearance of the gastric mucosa.
FIG. 18.7. Gastric mucosa-associated lymphoid tissue lymphoma. The infiltrate accentuates the marginal zone around B-cell follicles.

Pathology of MALT Lymphoma

Gross Features
Macroscopically, MALT lymphomas, although sometimes forming obviously tumorous masses, frequently are indistinguishable from the inflammatory lesion that underlies the acquisition of MALT from which the lymphoma arises. Gastric MALT lymphoma, for example, may form a single dominant mass but often results in only slightly raised congested mucosa with superficial erosions easily confused at endoscopy with chronic gastritis (Fig. 18.6). MALT lymphomas are typically multifocal with small, even microscopic foci of lymphoma scattered throughout the organ involved. Each of these foci is clonally identical (45).

Histopathology
Although there are some differences determined by the site of origin, the histology of MALT lymphoma is essentially stereotyped in that, like acquired MALT, the lymphomas, especially in their early stages, recapitulate the histology of Peyer patches (46). The neoplastic B lymphocytes infiltrate around reactive B-cell follicles, external to a preserved follicular mantle, in a marginal zone distribution and spread out to form larger confluent areas, which eventually overrun some or most of the follicles (Fig. 18.7). Like marginal zone B cells, the neoplastic cells have pale cytoplasm with small to medium-sized, slightly irregularly shaped nuclei containing moderately dispersed chromatin and inconspicuous nucleoli. These cells have been called centrocyte-like because of their resemblance to germinal center centrocytes. The accumulation of more abundant pale-staining cytoplasm may lead to a monocytoid appearance of the lymphoma cells, while in some cases the cells more closely resemble small lymphocytes (Fig. 18.8). Scattered large cells resembling centroblasts or immunoblasts are usually present, but are in the minority and do not form confluent clusters or sheets (Fig. 18.9). Plasma cell differentiation is present in up to a third of cases (Fig. 18.10) and, in gastric lymphomas, tends to be maximal beneath the surface gastric epithelium. In a subset of cases there is extreme plasma cell differentiation characterized by a subepithelial band of confluent large eosinophilic plasma cells often accompanied by lakes of extruded immunoglobulin (Fig. 18.11). Small clusters of neoplastic marginal zone cells are present often invading individual gastric glands to form lymphoepithelial lesions (Fig. 18.12). In these lesions, glandular epithelium is invaded and destroyed by discrete aggregates of lymphoma cells (Fig. 18.13). Lymphoepithelial lesions are defined as aggregates of three or more neoplastic marginal zone lymphocytes within glandular epithelium preferably associated with distortion or necrosis of the epithelium. In gastric MALT lymphoma the lesions are often accompanied by eosinophilic degeneration of the epithelium (Fig. 18.13). Lymphoepithelial lesions, although highly characteristic of MALT
lymphoma, especially gastric lymphoma, are not pathognomonic. In some MALT lymphomas, such as those of the small and large intestine, they are difficult to find.

The MALT lymphoma cells sometimes specifically colonize germinal centers of the reactive follicles (47). Usually this imparts a vaguely nodular or follicular pattern to the lymphoma (Fig. 18.14). In some cases the lymphoma cells specifically target germinal centers, where they may undergo blast transformation (Fig. 18.15) or plasma cell differentiation (Fig. 18.16). The presence of transformed blasts confined to pre-existing germinal centers is not considered to be evidence of transformation to a large B-cell lymphoma.

Like other low-grade B-cell lymphomas, MALT lymphoma may undergo transformation to a diffuse large B-cell lymphoma (15). Transformed centroblast or immunoblastlike cells are present in variable numbers in MALT lymphoma (Fig. 18.9) and there is some evidence that grading of MALT lymphoma according to the number of transformed cells has subtle clinical relevance (48). However, only when solid or sheetlike proliferations of transformed cells are present should the lymphoma be considered to have transformed to diffuse large B-cell lymphoma (Fig. 18.17). This transformation may or may not result in complete overgrowth of the preceding MALT lymphoma. The current recommendation is that such cases are best designated as diffuse large B-cell lymphoma; the presence or absence of concurrent MALT lymphoma and the relative proportions of both should be documented (49).

**FIG. 18.8.** Cytology of gastric mucosa-associated lymphoid tissue lymphoma. The cells in the left-hand panel resemble small lymphocytes and include scattered transformed blasts. Typical “centrocytelike” cells are seen in the middle panel, while the cells in the right-hand panel resemble monocytes.
FIG. 18.9. Prominent transformed blasts in a gastric mucosa-associated lymphoid tissue lymphoma.

Biopsy Appearances

In small endoscopic biopsies the classic features of MALT lymphoma are not as easily observed as they are in resection specimens. Reactive follicles are not as easy to define and are particularly affected by crush artefact. Equally, the cytologic appearances of marginal zone cells may not be as clear. A diffuse, dense lymphoid infiltrate in a gastric biopsy (Fig. 18.18A) should always raise suspicion, particularly if it occupies the entire biopsy fragment. Careful evaluation of the cytology of the cells is indicated (Fig. 18.18B) and identification of lymphoepithelial lesions (Fig. 18.18B) is very helpful in establishing the diagnosis.

FIG. 18.10. Plasma cell differentiation in a gastric mucosa-associated lymphoid tissue lymphoma.
FIG. 18.11. Extreme plasma cell differentiation in gastric mucosa-associated lymphoid tissue lymphoma resulting in a subepithelial eosinophilic band.

Morphology of Gastric Mucosa-associated Lymphoid Tissue Lymphoma Following Eradication of Helicobacter pylori

Approximately 75% of gastric MALT lymphomas will respond to eradication of *H. pylori* with regression of the tumor over a period of up to 18 months (Fig. 18.19) (39). Repeated endoscopy with biopsy is necessary to determine whether or not the lymphoma is responding. The endoscopic appearances may revert within 6 months of the eradication of *H. pylori* but may take as long as 2 years. There is often a noticeable change in the histologic appearance of the biopsy within a few weeks with gradual clearance of the lymphoma in following months. Initially, there is disappearance of the inflammatory infiltrate accompanying the lymphoma with an empty-appearing eosinophilic lamina propria that may contain lymphoid aggregates (Fig. 18.20). These aggregates contain small B lymphocytes without transformed blasts and gradually become smaller with time. Immunohistochemistry shows that they contain few accompanying T cells and have a markedly reduced proliferation fraction compared to the original lymphoma. Such aggregates may not disappear altogether and may persist for long periods at the base of the mucosa or in the submucosa. In up to 60% of cases, B-cell monoclonality can still be demonstrated using PCR (50), suggesting that bacterial eradication represses but does not eliminate the lymphoma clone, which is still presented in the lymphoid aggregates. The fate of these small aggregates is not completely known but it is assumed that they eventually disappear. PCR analysis may reveal persistence of the neoplastic clone after disappearance of morphologic evidence of lymphoma; however, the clinical significance of this finding is not clear. It is important not to make a diagnosis of persisting lymphoma on the basis of molecular analysis alone in the absence of good histologic evidence.
**FIG. 18.12.** Higher magnification of extreme plasma cell differentiation. A single lymphoepithelial lesion is present in the center.

**FIG. 18.13.** Lymphoepithelial lesions in a case of gastric mucosa-associated lymphoid tissue lymphoma distorting glands and associated with eosinophilic change of gastric epithelium.
FIG. 18.14. Follicular colonization. Lymphoma cells in the marginal zone surround the follicles (above) and replace them (below), resulting in a follicular growth pattern.
FIG. 18.15. The germinal center of a B-cell follicle has been infiltrated by transformed mucosa-associated lymphoid tissue lymphoma cells.

FIG. 18.16. In this case of gastric mucosa-associated lymphoid tissue lymphoma the germinal center is infiltrated by plasma cells.
Multifocality of Gastric Mucosa-associated Lymphoid Tissue Lymphoma

Gastric MALT lymphoma typically disseminates within the stomach to form a multifocal lesion. Indirect evidence for this comes from the observation of recurrent MALT lymphomas in the gastric stump after partial gastrectomy in patients in whom clear resection margins were documented by histologic examination (51). Wotherspoon et al. (52) systematically examined gastrectomy specimens of five MALT lymphomas using a “Swiss roll” technique. They showed that numerous small tumor foci with identical immunoglobulin light chain restriction to the main tumor mass were distributed throughout the gastric mucosa, including macroscopically normal regions (Figs. 18.21 and 18.22). A subsequent investigation by sequence analysis of the rearranged immunoglobulin heavy chain genes confirmed the clonal identity of these multiple tumor foci (53). Further studies by microdissection and clone-specific PCR demonstrated that tumor cells were frequently present in reactive lymphoid tissue that showed no histologic evidence of lymphoma (54,55,56).
FIG. 18.18. A: Gastric biopsy showing diffuse lymphocytic infiltration of the lamina propria with residual B-cell follicles. B: Higher magnification shows that the infiltrating cells are “centrocyte-like” and invade individual glands to form lymphoepithelial lesions.

**Dissemination**

Most gastric MALT lymphomas are at stage I when they present; between 4% and 17% have disseminated to regional lymph nodes, and approximately 10% have already disseminated to the bone marrow at the time of diagnosis (44,57). Gastric MALT lymphomas have a tendency to disseminate to other sites where MALT lymphomas occur, including the small intestine, salivary gland, and lung.

When MALT lymphomas disseminate to lymphoid tissue, including lymph nodes and spleen, they specifically invade the marginal zone (Fig. 18.23). This can lead to a deceptively benign or reactive appearance, especially in mesenteric lymph nodes, in which a marginal zone is normally present. Immunohistochemistry for immunoglobulin light chains can be very helpful in discriminating a normal marginal zone from disseminated MALT lymphoma (Fig. 18.24). Subsequently, the lymphoma in the marginal zones expands to form more obvious sheets of interfollicular lymphoma. Occasionally, follicular colonization in involved lymph nodes can lead to an appearance that simulates follicular lymphoma (Fig. 18.25).
**Immunohistochemistry**

The immunophenotype of MALT lymphoma essentially recapitulates that of marginal zone cells (Table 18.2). The B cells are CD20, CD79a, CD21, and CD35 positive and CD5, CD23, and CD10 negative. CD43, indicative of a neoplastic phenotype, is expressed in approximately 50% of cases. The tumor cells typically express IgM and less often IgA or IgG, are IgD negative, and show immunoglobulin light chain restriction (Fig. 18.26). A significant intratumoral population of CD3-positive, predominantly CD4-positive T cells is characteristic. Expanded meshworks of follicular dendritic cells are typically detected with antibodies CD21 and CD23, corresponding to follicles that have been overrun or specifically colonized by lymphoma cells. Variable numbers of CD10- and Bcl6-positive germinal center cells may be seen in these areas, but the neoplastic MALT lymphoma cells are negative for these antigens.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Splenic MZ</th>
<th>Peyer Patch MZ</th>
<th>MALT Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IgMa</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IgD</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>CD5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD21b</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD35b</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

MALT, mucosa-associated lymphoid tissue; MZ, marginal zone.

*aOccasional case expresses IgA or IgG.

*bIn cryostat sections.

**Molecular Genetic Features of Mucosa-associated Lymphoid Tissue Lymphoma**

**Antigen Receptor Genes**

In the B cells of MALT lymphoma, immunoglobulin heavy and light chain genes are rearranged and show somatic mutation of their variable regions, consistent with a postgerminal center memory B-cell derivation (53,58). Ongoing mutations are thought to occur in most cases (58). Because of the difficulty in distinguishing between acquired MALT and MALT lymphoma, particularly in small biopsies (see below), there has been a tendency to rely on molecular evidence of monoclonality detected by PCR for the diagnosis of lymphoma. This technique may fail to detect monoclonality in up to 15% of cases of overt lymphoma and thus produce false-negative results (54). There are also reports of apparently spurious monoclonality in biopsies of acquired MALT, for example, gastric biopsies showing only chronic gastritis (42,55,56), where there is no histologic evidence of malignancy. The frequency of this spurious monoclonality varies between laboratories, which suggests that technique may be a factor. These findings serve to emphasize that MALT lymphoma should not be diagnosed in the absence of clear histologic evidence. This point is underlined by the frequent finding of persistent monoclonality in small residual, clinically insignificant lymphoid aggregates that persist following eradication of *H. pylori* for the treatment of MALT lymphoma (50).
FIG. 18.20. Gastric biopsy of a mucosa-associated lymphoid tissue lymphoma after eradication of *Helicobacter pylori*. The lamina propria has an “empty” appearance and an occasional lymphoid nodule persists.
Molecular Genetic Abnormalities

A number of molecular abnormalities have been described in gastric MALT lymphoma including trisomies 3, 12, and 18 and the specific chromosomal translocations t(11;18) (q21;q21), t(1;14)(p22;q32), and t(14;18)(q32;q21). T(11;18) involves the API2 and MALT1 genes and generates a functional API2–MALT1 fusion product (59,60,61). T(1;14) and t(14;18) juxtapose the BCL10 and MALT1 genes, respectively, to the immunoglobulin gene locus in 14q32 leading to deregulated expression of the oncogene (62,63,64,65). The oncogenic activities of the three chromosome translocations are linked by the physiologic role of BCL10 and MALT1 in antigen receptor-mediated nuclear factor (NF) κB activation (66). The three chromosome translocations occur at markedly variable incidences in MALT lymphoma of different sites but are always mutually exclusive (66). Among the three chromosome translocations, t(11;18) is the most frequent, occurring in 25% to 30% of gastric MALT lymphomas (67).

There is growing evidence suggesting that t(11;18)-positive cases are distinct from other MALT lymphomas, including those...
with t(1;14) or t(14;18). T(11;18)-positive MALT lymphomas rarely undergo high-grade transformation (68,69), despite the fact that the translocation is significantly associated with cases at advanced stages and that these cases typically do not respond to \textit{H. pylori} eradication (70,71). Cytogenetically, t(11;18)-positive tumors usually do not show other chromosomal aberrations, such as trisomies 3 and 18, frequently seen in t(11;18)-negative tumors, including those positive for t(1;14) and t(14;18) (72). Furthermore, t(11;18) MALT lymphomas show markedly fewer chromosomal gains and losses than translocation-negative tumors (71).

![FIG. 18.23. Lymph node involvement by gastric mucosa-associated lymphoid tissue lymphoma. The tumor is distributed in the marginal zones.](image)

T(11;18) can be detected in paraffin-embedded tissue by reverse transcription PCR (RT-PCR), while fluorescent in situ hybridization (FISH) is useful for demonstrating all three characteristic translocations. In cases positive for t(11;18) as well as 20% of translocation-negative cases, BCL10 protein is up-regulated in the nucleus where it stains weakly (Fig. 18.27). In the much rarer t(1;14) cases, nuclear BCL10 is expressed intensely both in the nucleus and cytoplasm (Fig. 18.28). The significance of these findings remains unknown at present.

**Postulated Normal Cell Counterpart of Mucosa-associated Lymphoid Tissue Lymphoma**

The architectural features of MALT lymphoma, particularly in early cases, show quite clearly that the neoplastic cells are infiltrating the marginal zone around B-cell follicles (Figs. 18.7 and 18.29). In non-neoplastic lymphoid tissue a prominent marginal zone is present only in the spleen, Peyer patches, and mesenteric lymph nodes. This allows a comparison of the cytology and immunophenotype of normal marginal zone cells with those of MALT lymphoma. Cytologically, MALT lymphoma cells bear a close resemblance to marginal zone cells. Both are slightly larger than small lymphocytes, have a slightly irregular nuclear outline, and moderate amounts of pale-staining cytoplasm. Interestingly, in Peyer patches collections of marginal zone cells are found within the dome epithelium. The immunophenotype of cells of the marginal zone and MALT lymphoma is virtually identical, both expressing CD20 and other pan B-cell antigens, CD21, CD35, and IgM, but not IgD.
FIG. 18.24. Gastric lymph node from a case of gastric mucosa-associated lymphoid tissue lymphoma appears normal (left), but immunohistochemistry (right) shows marginal zone involvement by lymphoma showing $\lambda$ immunoglobulin light chain restriction.
**Prognosis**

MALT lymphomas are among the most indolent of all lymphomas and have a good prognosis overall regardless of stage. Five- and 10-year overall survival rates of over 80% are the rule, although progression-free survival may be somewhat lower (73). Cases in which transformation to diffuse large B-cell lymphoma has occurred have a significantly lower survival of approximately 50% at 5 years (48).

The treatment of gastric MALT lymphoma has attracted considerable attention since the initial publication showing that the lymphoma may regress following eradication of *H. pylori* with antibiotics. The follow-up of MALT lymphoma patients following eradication of *H. pylori* is rather complex, requiring repeated gastroscopy with biopsy (see above), and it would be extremely useful to be able to identify the approximately 25% of cases of gastric MALT lymphoma that do not respond to eradication of *H. pylori*. Studies using endoscopic ultrasound have suggested that if the tumor has invaded beyond the submucosa, it is less likely to respond (74,75). Equally, cases that have transformed to large B-cell lymphoma are unlikely to respond, although there are reports of complete regression in such cases (76,77). Following the cloning of t(1;14) and t(11;18) breakpoints, these translocations have been shown to have a bearing on the response to *H. pylori* eradication. T(11;18)(q21;q21), present in up to 25% of cases, is strongly associated with failure to respond to eradication of *H. pylori* (78). Interestingly, both t(1;14) and t(11;18) are associated with nuclear expression of BCL10 protein that is particularly intense in t(1;14)-positive cases. Moreover, the frequency of both t(11;18)(q21;q21) and nuclear BCL10 expression is significantly higher in tumors that have invaded or disseminated beyond the stomach (78% and 93%, respectively) than those confined to the stomach (10% and 38%, respectively) (79). These findings in part explain the results based on the use of endoscopic ultrasound and suggest that both t(11;18)(q21;q21) and BCL10 nuclear expression are associated with failure to respond to *H. pylori* eradication and with more advanced stage MALT lymphoma. Therefore, before embarking on *H. pylori* eradication as definitive therapy, the pertinent genotypic and/or immunohistochemical investigations should be carried out.
FIG. 18.26. Gastric mucosa-associated lymphoid tissue lymphoma immunostained for κ (left) and λ (right) immunoglobulin light chains. There is κ light chain restriction.
FIG. 18.27. Gastric mucosa-associated lymphoid tissue lymphoma, t(11;18) positive, immunostained for BCL10. Tumor cells are weakly positive.
FIG. 18.28. Gastric mucosa-associated lymphoid tissue lymphoma, t(1;14) positive, immunostained for BCL10. Tumor cell nuclei are strongly positive.
FIG. 18.29. A focus of gastric mucosa-associated lymphoid tissue lymphoma occupying the marginal zone around a reactive B-cell follicle (left). The tumor cells show κ immunoglobulin light chain restriction (right).

Differential Diagnosis

Reactive Versus Neoplastic Mucosa-associated Lymphoid Tissue

The distinction between acquired MALT, the precursor of MALT lymphoma, and MALT lymphoma in the early stages of evolution is often diagnostically difficult. Gastric MALT acquired as a consequence of *H. pylori* infection comprises reactive B-cell follicles without an identifiable marginal zone (Fig. 18.30). The lamina propria around the follicles is infiltrated by a mixture of inflammatory cells, including plasma cells and T lymphocytes. A lymphoepithelium can be seen adjacent to the follicles and can mimic the lymphoepithelial lesion characteristic of MALT lymphoma (Fig. 18.30B). In the presence of these intraepithelial B cells immediately adjacent to follicles, the absence of a diffuse infiltrate of IgM-positive IgD negative B lymphocytes external to the IgD- and IgM-positive mantle zone cells is very helpful in distinguishing such cases from MALT lymphoma (Table 18.2). In the distinction between acquired MALT and MALT lymphoma, inference of monoclonality, either by the demonstration of immunoglobulin light chain restriction using immunohistochemistry or flow cytometry, is necessary. Coexpression of CD43 by B cells is a useful hint that the B-cell population is neoplastic. The use of PCR of immunoglobulin heavy chain genes to discriminate polyclonal-reactive lymphoid infiltrates from monoclonal MALT lymphoma is controversial but there is no doubt that, properly performed, a positive PCR result is strong evidence in favor of lymphoma. Wotherspoon et al (39) have proposed a scoring system to assist in the differential diagnosis of MALT lymphoma from chronic gastritis in biopsy specimens (Table 18.3).
**Mucosa-associated Lymphoid Tissue Versus Other Small B-cell Lymphomas**

Because of differences in clinical behavior and management, it is important to differentiate MALT lymphoma from the other small B-cell lymphomas that may present or involve extranodal sites (Table 18.1). These are discussed in greater detail in the section that follows on intestinal lymphomas. They include mantle cell lymphoma, lymphocytic lymphoma (chronic lymphocytic leukemia), and follicular lymphoma. The cytologic features of mantle cell lymphoma can closely simulate those of MALT lymphoma and occasional lymphoepithelial lesions may be present. However, absence of transformed blasts, together with expression of CD5 and IgD and, importantly, intranuclear expression of cyclin D1, a consequence of t(11;14), serves to distinguish mantle cell lymphoma. Small lymphocytic lymphoma (chronic lymphocytic leukemia) is characterized by small round lymphocytes, usually together with peripheral blood lymphocytosis and often with pseudofollicles, although these may be difficult to appreciate in extranodal sites. Expression of CD5, CD23, and IgD without nuclear cyclin D1 provides further distinction from MALT lymphoma. Finally, follicular lymphoma, which may arise extranodally, can be difficult to distinguish from MALT lymphoma with follicular colonization. The transformed MALT lymphoma cells within follicles may closely resemble centroblasts but typically are CD10 and BCL6 (nuclear) negative, in contrast to the cells of follicular lymphoma, which usually express both antigens both within and between follicles. Assessment of these antigens, together with stains for follicular dendritic cells (FDCs) such as CD21 or CD23, is useful. Cytogenetic and molecular genetic analyses to detect t(11;18) and t (14;18) are also helpful. MALT lymphoma with plasmacytic differentiation can be difficult to distinguish from lymphoplasmacytic lymphoma. Occurrence in an extranodal site like the stomach (as opposed to lymph node or spleen), the characteristic Peyer patch–like architecture, and the presence of cytologically characteristic marginal zone B cells and lymphoepithelial lesions all favor a diagnosis of MALT lymphoma.

**TABLE 18.3 Scoring System for Distinguishing MALT Lymphoma from Chronic Gastritis**
Chapter 18

Score | Interpretation                        | Histology                                                                 |
-------|---------------------------------------|---------------------------------------------------------------------------|
0      | Normal                                | Occasional plasma cells                                                  |
1      | Chronic active gastritis              | Lymphocyte clusters, no follicles                                        |
2      | Follicular gastritis                  | Prominent follicles, no lymphoepithelial lesions                         |
3      | Suspicious, probably reactive         | Follicles, occasional adjacent lymphoepithelial lesion, no diffuse infiltrate |
4      | Suspicious, probably lymphoma         | Follicles, diffuse marginal zone cell infiltrate, no lymphoepithelial lesions |
5      | MALT lymphoma                         | Follicles, diffuse marginal zone cell infiltrate, lymphoepithelial lesions present |

MALT, mucosa-associated lymphoid tissue.

Mucosa-associated Lymphoid Tissue Lymphoma and Adenocarcinoma

There are numerous reports of synchronous gastric MALT lymphoma and adenocarcinoma (80,81). In the series of 237 cases of gastric lymphoma reported by Nakamura et al (82), 10% of lymphomas were complicated by adenocarcinoma. Interestingly, the MALT lymphoma cells do not form lymphoepithelial lesions with neoplastic gastric epithelium (Fig. 18.31). The role of *H. pylori* in the pathogenesis of both conditions may be relevant (83).
FIG. 18.31. Gastric mucosa-associated lymphoid tissue lymphoma (left) with synchronous adenocarcinoma (right). The lymphoma cells do not form lymphoepithelial lesions with the neoplastic gastric glands.

**Diffuse Large B-Cell Lymphoma of the Stomach**

DLBCL of the stomach is at least as common if not more common than MALT lymphoma. Foci of DLBCL may be seen in MALT lymphoma, suggesting that there has been transformation from one to the other as occurs in other small B-cell lymphomas (Fig. 18.17). The extent of this secondary high-grade component varies; in some cases there is a minor large cell component composed of small cohesive sheets of transformed blasts within the MALT lymphoma, while others are characterized by a predominance of large cell lymphoma with only small residual foci of MALT lymphoma, which can be difficult to find. Some cases of DLBCL of the stomach in which a MALT lymphoma component cannot be detected are transformed MALT lymphomas that have been completely overgrown by DLBCL, but others are true primary DLBCL. Those cases that are CD10 positive are unlikely to be transformed MALT lymphomas. However, there is no difference in the clinical behavior between transformed MALT lymphoma and primary DLBCL (84).

**Histopathology**

The histologic features of gastric DLBCL of the stomach are no different from those found in nodal disease. The large cells may resemble centroblasts or immunoblasts but tend to have more cytoplasm than classic centroblasts, which imparts a plasmablastic appearance. Bizarre, often multinucleated cells are not uncommon and these sometimes resemble Reed-Sternberg cells (Fig. 18.32). The large cells infiltrate in sheets between glands, and invasion of individual glands with formation of lymphoepithelial lesions, although it occurs, is rare. There is often an accompanying population of small lymphocytes, which can be shown with immunohistochemistry to be T cells.

FIG. 18.32. Diffuse large B-cell gastric lymphoma.

**Immunohistochemistry**

Transformed MALT lymphomas are characteristically BCL2 and CD10 negative (85) but, in contrast to MALT lymphoma, usually express BCL6 (86). Primary gastric DLBCL, on the other hand, may be CD10 positive and a proportion are BCL2 positive. Immunostaining with CD21 may reveal numerous residual FDC meshworks that represent reactive follicles that have
been overrun or colonized by the lymphoma, a finding that may suggest that the DLBCL originated as a MALT lymphoma that has transformed. Immunophenotypic characteristics do not, however, reliably distinguish transformed MALT lymphoma from primary DLBCL, which may also be CD10 negative.

**Molecular Genetics**

Rearrangement and/or mutations of BCL6 have been reported in a proportion of cases (87,88) and mutation with loss of heterozygosity of p53 has been described in 29% of cases of transformed MALT lymphoma (89). Cases of MALT lymphoma with t(11;18) seldom transform to DLBCL (90). Some reports have suggested that transformed MALT lymphomas differ from primary DLBCL in showing \( c-myc \) rearrangement in a high proportion of cases (91), but in general there is no reliable genetic property that distinguishes transformed MALT lymphoma from de novo DLBCL.

**Prognosis**

It is generally agreed that gastric DLBCL shows less favorable behavior than MALT lymphoma. Cogliatti et al (84) found that the 5-year survival of gastric DLBCL was significantly worse than that of MALT lymphoma (75% vs. 91%) and that there was no difference between DLBCL and transformed MALT lymphoma. Chemotherapy is the treatment of choice for gastric DLBCL but, interestingly, there are several reports of cases of gastric DLBCL that have responded to eradication of \( H. \) pylori (92,93).

**Intestinal Mucosa-Associated Lymphoid Tissue Lymphoma**

Most intestinal MALT lymphomas arise in the small intestine, colorectal lymphomas being distinctly rare. There does not appear to be any difference in behavior between the two sites, and they will therefore be considered together. IPSID is a distinctive subtype of MALT lymphoma that is associated with the synthesis of \( \alpha \) immunoglobulin heavy chain and is restricted in its incidence to certain geographic areas, particularly the Middle East. Immunoproliferative small intestinal disease will be described as a separate entity following discussion of the more usual intestinal MALT lymphoma that has no special epidemiologic or immunologic features. To date, there are only a few studies of intestinal lymphoma in which the cases have been analyzed taking the MALT concept into account (22,94,95).

**Clinical Presentation**

Most cases of small intestinal lymphoma occur in elderly patients and present with intestinal obstruction, while rectal bleeding is a more common presenting sign in colonic lymphoma. A significant number of colonic lymphomas arise in the setting of inflammatory bowel disease, but this is not a recognized risk factor for small intestinal lymphoma (96). Any segment of the intestine may be involved and most tumors occur as single lesions, although cases presenting as multiple polyposis have been recorded (97,98). The mesenteric lymph nodes are usually involved (stage II\( _E \)), but spread outside the abdomen including bone marrow involvement is unusual at presentation. In some cases a cryptic simultaneous gastric MALT lymphoma is present and most of these cases are thought to be examples of secondary intestinal MALT lymphoma (99).

**Histopathology**

The histology of MALT lymphoma of the intestine is identical to that of gastric MALT lymphoma. Reactive B-cell follicles are prominent and these are surrounded by neoplastic marginal zone cells, which often show plasma cell differentiation (Fig. 18.33). Lymphoepithelial lesions (Fig. 18.34) are not as numerous in comparison to gastric lymphoma but can almost always be found. However, care must be taken not to overinterpret their presence, especially in the terminal ileum, since intraepithelial B cells occur normally in the dome epithelium of Peyer patches and may increase in lymphoid hyperplasia. Follicular colonization may also be seen.
Differential Diagnosis
Focal Lymphoid Hyperplasia

This condition occurs in the terminal ileum and can be subdivided into a more common form seen in children and young adults and a rarer form seen in older individuals (100). In the case of young patients, the condition is known by several names including enteritis follicularis, cobblestone ileum, nonsclerosing ileitis, pseudopolyposis lymphatica, and terminal lymphoid ileitis. It occurs more frequently in males and may present as ileocecal intussusception, as an appendicitis-like illness, or with bleeding. Since the diagnosis is usually made clinically, there are few histologic descriptions of this condition, but published reports describe marked hyperplasia of Peyer patches with sharply defined follicles and submucosal edema. There is no disorganization of lymphoid tissue or infiltration of the muscularis and little resemblance to lymphoma. In the adult form (101), the clinical presentation is one of weeks to years of abdominal pain, which may be associated with a mass in the right iliac

FIG. 18.33. Small intestinal mucosa-associated lymphoid tissue lymphoma.

FIG. 18.34. Lymphoepithelial lesion in a small intestinal mucosa-associated lymphoid tissue lymphoma.
fossa. The histologic features include follicular hyperplasia (Fig. 18.35) of the mucosa, which is frequently associated with ulceration, and a diffuse lymphoplasmacytic infiltrate extending deeply into the wall of the ileum, often involving the serosa. Eosinophils may be a prominent component of the infiltrate. The normal marginal zone cell component of Peyer patches participates in the hyperplastic process, leading to exaggeration of the normal association of these cells with dome epithelium. Structures resembling lymphoepithelial lesions may be seen in tangentially cut sections. The result is a picture that may closely simulate MALT lymphoma from which it can be distinguished once again by its polyclonal nature.

**Diffuse Nodular Lymphoid Hyperplasia of the Intestine**

Diffuse nodular lymphoid hyperplasia may occur in the small intestine, colon, or both. It is an extremely rare condition that involves long segments of bowel and occurs in two forms. The most well recognized of these is that associated with congenital or acquired hypogammaglobulinemia, which is only rarely associated with lymphoma (102). Histologically, there is enlargement of the mucosal B-cell follicles caused by hyperplasia of follicle centers (Fig. 18.36). These hyperplastic follicles are confined to the mucosa and surrounded by a normal-appearing mantle zone. The marginal zone is inconspicuous and there is no associated interfollicular infiltrate. In the second form of this condition (103), in which immunoglobulin deficiency is not present, there is a well-documented association with malignant lymphoma. The lymphoma is of MALT type and shows an interrelationship with the hyperplastic follicles as described above.

**FIG. 18.35.** Focal lymphoid hyperplasia of the terminal ileum, adult type.
Prognosis

The clinical behavior of intestinal B-cell lymphoma is not as favorable as that of gastric lymphoma. Histologic grade, stage of disease, and resectability have prognostic significance. A 5-year survival of 44% to 75% is reported for intestinal MALT lymphoma and 25% to 37% for DLBCL (94,95,104). Importantly, the behavior of intestinal DLBCL is not affected by the presence or absence of a MALT component (95).

Immunoproliferative Small Intestinal Disease

This condition, first described by Ramot in 1965 (105), is a variant of MALT lymphoma characterized by a diffuse lymphoplasmacytic (predominantly plasmacytic) infiltrate in the upper small intestine. The disease has been most frequently reported in the Middle East but appears markedly to have declined in incidence there. Significant numbers of cases have also been reported from the Cape region of South Africa (14) and sporadic cases from elsewhere. An important distinguishing feature of IPSID is the synthesis of α heavy chain, without light chain, by the plasma cells; this can be detected in the serum or duodenal juice in approximately two thirds of cases, hence the term α-chain disease. In the remaining one third of cases the α-chain protein is still synthesized but not secreted (106).

Clinical Presentation

Immunoproliferative small intestinal disease is a disease predominantly of young adults and usually presents with profound malabsorption. There are numerous reports describing remissions or even cure of IPSID in its early stages following the use of broad-spectrum antibiotics (107,108,109). There seems little doubt that the removal of either specific or nonspecific immune stimulants from the gut lumen can have a profound effect on some cases of IPSID in the early stages, but given the natural history of the disease, prolonged follow-up is needed before the term cure can be used with confidence. The fact that this type of MALT lymphoma is to a degree antigen responsive may be significant when considering the biology of the entire group of MALT lymphomas.

Gross Features

The macroscopic appearances of IPSID depend on the stage. In most cases there is diffuse, even thickening of the upper jejunum together with enlarged mesenteric lymph nodes. Circumscribed lymphomatous masses may be present and these may be multiple, sometimes producing multiple small intestinal polyps. The stomach is sometimes involved, but spread to other abdominal organs is rare.

Histologic Features
The histology of IPSID exemplifies all the features of MALT lymphoma with marked plasma cell differentiation. Three stages of IPSID are recognized (110). In stage A, the lymphoplasmacytic infiltrate is confined to the mucosa and mesenteric lymph nodes. In stage B, nodular mucosal lymphoid infiltrates are present and the infiltrate extends below the muscularis mucosa. Stage C is characterized by the presence of lymphomatous masses and transformation to DLBCL. The plasma cell infiltrate in the mucosa causes broadening, but not shortening, of the villi (Figs. 18.37 and 18.38). These cells are not invasive and show no evidence of mitotic division. Already present in stage A IPSID, and increasing in prominence in stage B, are aggregates of neoplastic marginal zone B cells, which cluster around epithelial crypts and form lymphoepithelial lesions (Fig. 18.39). Reactive follicles vary in number, and it is colonization of these by marginal zone cells that results in the lymphoid nodules of stage B IPSID (10) (Fig. 18.39) and the so-called follicular lymphoma variant (14,111). Transformation to DLBCL occurs in the same way as in gastric lymphoma, and the large cells frequently show bizarre cytologic features (Fig. 18.40).

**FIG. 18.37.** Immunoproliferative small intestinal disease. There is diffuse mucosal plasma cell infiltration with pericryptal pale areas corresponding to aggregates of marginal zone B cells.

### Lymph Node Involvement

The mesenteric lymph nodes are involved early in the course of IPSID. Initially, there is filling of the sinusoids by mature plasma cells, but later the characteristic marginal zone infiltrate of the neoplastic cells is seen (Fig. 18.41). Follicular colonization may occur in the lymph nodes usually characterized by the presence of $\alpha$ chain–positive plasma cells within germinal centers.

### Immunohistochemistry and Molecular Genetics

Immunohistochemical studies of IPSID (13,14) confirm the synthesis of $\alpha$ heavy chain, without light chain, by the plasma cells, marginal zone cells, and transformed blasts (Fig. 18.42). The IgA is always of subclass IgA1 but occasional cases have been described in which both IgA1 and IgA2 have been synthesized (13). In a minority of cases immunoglobulin light chain is synthesized and when this occurs, there is light chain restriction (112). The neoplastic marginal zone cells show the same immunophenotype as in other MALT lymphomas. In cases in which the infiltrate appears to consist only of plasma cells, staining with CD20 antibodies will often reveal clusters of B cells concentrated around small intestinal crypts and forming lymphoepithelial lesions.
**FIG. 18.38.** High magnification of lamina propria plasma cells in immunoproliferative small intestinal disease.
FIG. 18.39. A case of immunoproliferative small intestinal disease showing B-cell follicles and surrounding marginal zone cells that form lymphoepithelial lesions with intestinal crypts. The overlying lamina propria is heavily infiltrated by plasma cells.

Gene rearrangement studies in early (stage A and B) IPSID have shown monoclonal heavy and light chain gene rearrangement (113); t(11;18) is not found in IPSID (114).

FIG. 18.40. Transformation of immunoproliferative small intestinal disease to diffuse large B-cell lymphoma.

FIG. 18.41. Mesenteric lymph node from a case of immunoproliferative small intestinal disease showing infiltration of marginal zones by pale-staining tumor B cells (compare with Figure 18.23).

Prognosis

IPSID runs a prolonged course, often over many years, and rarely spreads out of the abdomen until the terminal stages when
high-grade transformation has occurred. Partial or even complete responses to broad-spectrum antibiotics have been reported (107,108,109).

**Pathophysiology**

Immunoproliferative small intestinal disease is in many ways the prototype of MALT lymphomas, exemplifying the prolonged natural history and the tendency of the lymphoma to remain localized in the abdomen with only few documented cases of spread to the periphery. Histologically, too, the marginal zonelike morphology of the lymphoid cells, the formation of lymphoepithelial lesions, plasma cell differentiation, and follicular colonization place IPSID firmly in the MALT category. The clinical indolence and response of some cases of stage A IPSID to broad-spectrum antibiotics has led to the common view that at this stage IPSID is a hyperplastic, nonneoplastic but prelymphomatous condition. However, observations on three cases of stage A IPSID in which light chain was being synthesized (112) (an uncommon event in IPSID) showed light chain restriction, and studies on a further three cases have shown clonal heavy and light chain immunoglobulin gene rearrangement (113). It is most likely, therefore, that IPSID is neoplastic de novo. How, then, can the response of some cases of stage A IPSID to antibiotics be explained? The extreme plasma cell differentiation that characterizes IPSID and that is maximal beneath the surface epithelium suggests that, although neoplastic, the lymphoid cells are not altogether autonomous and are exhibiting a degree of sensitivity to either a specific antigen or a nonspecific immune stimulant such as endotoxin. By removing the luminal source of immune stimulation, antibiotics could result in resolution of the plasma cell component of the mucosal infiltrate and even inhibit growth of the lymphoid element. In other words, the relationship between an immunologic, probably infectious agent and the lymphoma is identical to that between *H. pylori* and gastric MALT lymphoma.

**Mantle Cell Lymphoma (Lymphomatous Polyposis)**

Lymphomatous polyposis (also called multiple lymphomatous polyposis) is an uncommon but well-described disease (16,115). Most patients are over 50 years of age and there is no established sex preponderance. Presenting symptoms are those of abdominal pain, sometimes accompanied by melena, and barium studies or endoscopy reveals multiple polyps, which prove to be lymphomatous. Any part of the gastrointestinal tract may be involved, but in many of the cases the largest tumors are in the ileocecal region. The frequency of cases genuinely restricted to the gastrointestinal tract is very low, most patients having evidence of mantle cell lymphoma elsewhere.

Macroscopically, the intestinal mucosa is peppered with multiple white fleshy polyps ranging in size from 0.5 to 2 cm; much larger tumors may be present especially in the ileocecal region (Fig. 18.43). The mesenteric lymph nodes are usually obviously involved.

**Histopathology**

The smallest lesions consist of a single mucosal lymphoid nodule, which is diffusely replaced by lymphoma, sometimes with preservation of the reactive germinal center. The larger polyps may show either a diffuse or nodular lymphoid infiltrate that may, in some cases, be so nodular as to resemble follicular lymphoma (Fig. 18.44). Characteristically reactive “naked” germinal centers are trapped in the lymphomatous infiltrate, which appears selectively to replace their mantle zones. The nodular pattern appears to be a consequence of selective replacement of pre-existing nonneoplastic follicles by the tumor cells (16). Intestinal glands are displaced and obliterated and very occasional “lymphoepithelial lesions” (without the characteristic epithelial changes) can be seen. Typically, scattered, usually single epithelioid histiocytes and small sclerotic blood vessels are present. Cytologically, the infiltrate of mantle cell lymphoma consists of a uniform population of small to medium-sized lymphocytes with irregular nuclear contours, which resemble centrocytes (Fig. 18.45). Transformed blasts are conspicuously absent. The immunophenotype (see below) is in keeping with derivation from a subpopulation of mantle zone B cells (116). Several variants of mantle cell lymphoma are described but are beyond the scope of this book.
Immunohistochemistry and Molecular Genetics

Characteristically, the cells express pan B-cell antigens together with IgM, IgD, CD5, CD43, and, importantly, nuclear cyclin D1 (116). Other distinctive features of this type of lymphoma include negative immunostaining for CD10 and CD23 and the presence of rather loose nodular CD21-positive FDC meshworks (16).

Like its nodal counterpart, intestinal mantle cell lymphoma is characterized by t(11;14)(q13;q32) that results in bcl-1 gene rearrangement with overexpression of nuclear cyclin D1 in almost 100% of cases (116).

Differential Diagnosis

MALT lymphoma, follicular lymphoma, and lymphocytic lymphoma (chronic lymphocytic leukemia) can all give rise to multiple lymphomatous polyps in the intestine and, conversely, intestinal mantle cell lymphoma does not necessarily present with intestinal polyps. Moreover, all four lymphomas may be cytologically similar. Distinguishing between them is particularly difficult in small biopsies. The differential diagnosis of these small B-cell lymphomas of the intestine is summarized in Table 18.4. Monotony of the infiltrate and absence of transformed blasts favor a diagnosis of mantle cell lymphoma, but immunohistochemistry to show expression of CD5 and nuclear cyclin D1 is essential to distinguish it from the other small B-cell lymphomas.

Clinical Behavior

Like nodal mantle cell lymphoma, those presenting in the intestine have usually disseminated widely at the time of diagnosis.
Involvement of liver, spleen, bone marrow, and peripheral lymph nodes soon follows identification of the polyps. This aggressive clinical behavior is quite different from the indolent behavior of MALT lymphoma, and distinction between the two conditions is therefore important.

**FIG. 18.44.** Mantle cell lymphoma of the colon. The tumor has a follicular growth pattern.

**FIG. 18.45.** Typical cytologic appearance of mantle cell lymphoma.

**Follicular Lymphoma**

Follicular lymphoma may occur as a primary tumor in the small intestine, especially in the ileocecal region and duodenum (117). From examination of the gastrointestinal tract alone it is not possible to tell whether the tumor is primary or secondary, and careful staging is necessary to determine between the two.

**Histologic Features**

Follicular lymphoma consists of typical neoplastic follicles composed principally of centrocytes with fewer centroblasts and usually involves the full thickness of the intestinal wall with lateral extension into the mucosa. An interfollicular diffuse infiltrate is frequently present and is usually composed of smaller lymphocytes with somewhat irregularly shaped nuclei (Fig. 18.46).
This component may form rare lymphoepithelial lesions, which can cause confusion with MALT lymphoma, especially in endoscopic biopsies and if follicular colonization is a prominent feature.

A particular type of follicular lymphoma occurs in the duodenum, often in the region of the ampulla of Vater (118,119,120). It is often discovered incidentally at endoscopy, when the lesions appear as small mucosal nodules; these lymphomas comprise only one or two follicles restricted to the mucosa. On close inspection these follicles exhibit the characteristics of follicular lymphoma in that they lack polarity, consist principally of centrocytes, and are devoid of tingible body macrophages. Diagnosis of these tiny lesions as follicular lymphoma often depends on immunohistochemical and/or molecular evidence (see below).

### TABLE 18.4 Differential Diagnosis of MALT Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>MALT</th>
<th>Mantle Cell</th>
<th>Follicular</th>
<th>Lymphocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicles</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-(+)</td>
</tr>
<tr>
<td>Lymphoepithelial Lesions</td>
<td>+</td>
<td>-(+)</td>
<td>-(+)</td>
<td>-(+)</td>
</tr>
<tr>
<td>Cytology</td>
<td>CCL*</td>
<td>CCL</td>
<td>GCC**</td>
<td>L***</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>M+,D-</td>
<td>M+,D+</td>
<td>M-/+, D-/+</td>
<td>M+,D+</td>
</tr>
<tr>
<td>CD20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CYCLIN D1</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CCL, centrocytelike; GCC, germinal center cell; L, lymphocytic, occasionally centrocytelike; MALT, mucosa-associated lymphoid tissue.

**Immunohistochemistry and Molecular Genetics**

The follicles of follicular lymphoma usually express CD10 and BCL2 and show light chain restriction (Fig. 18.47). However, 20% of cases are CD10 negative and some fail to express BCL2. CD10 is often down-regulated in the interfollicular diffuse component. One study has reported that the cells of intestinal follicular lymphomas show a tendency to express surface IgA, the preferential immunoglobulin of the mucosa immune system and rarely expressed by nodal follicular lymphomas (121). Moreover, these cells also express the α4-β7 mucosal homing receptor.

Molecular evidence of monoclonal immunoglobulin gene rearrangement is often an important consideration in distinguishing follicular lymphoma from reactive hyperplasia. In the single study quoted above, the immunoglobulin heavy chain genes of intestinal follicular lymphoma were extensively mutated consistent with antigen-based selection. BCL2 rearrangement is also present in most cases (117).
**FIG. 18.46.** *A:* Follicular lymphoma of the ileum. *B:* Higher magnification of tumor cells showing characteristic nuclear irregularity.

**Differential Diagnosis**

The morphologic and phenotypic features that are useful in distinguishing follicular lymphoma are listed in Table 18.4. In those cases where the interfollicular cells form lymphoepithelial lesions, the differential diagnosis from MALT lymphoma becomes problematic. Expression of CD10 by cells outside germinal centers is diagnostic of follicular lymphoma, as is the finding of coexpression of bcl2 and CD10 in cells within germinal centers.

**Diffuse Large B-Cell Lymphoma of the Intestine**

Diffuse large B-cell lymphomas account for 45% of small intestinal lymphomas, and a residual focus of MALT lymphoma can be identified in half of these (95). Histologically,

the DLBCLs resemble their gastric counterparts and they exhibit the same immunohistochemical and molecular genetic features.
Chapter 18

FIG. 18.47. Follicular lymphoma of the ileum. A: CD20. B: CD10. C: BCL2 CD10-positive cells are seen outside the B-cell follicle and this, together with BCL2 expression by germinal center B cells, is diagnostic.

Burkitt Lymphoma

In the Middle East, primary gastrointestinal Burkitt lymphoma is a relatively common disease of children. It has been comprehensively studied in Algeria (17,122), where Burkitt lymphoma accounts for 46.5% of all childhood non-Hodgkin lymphomas and 60% of these cases arise primarily in the intestine. The disease is more common in boys and shows a peak incidence between 4 and 5 years of age. There is a predilection for the terminal ileum, but any part of the small intestine may be involved. Cases frequently present with intussusception. The cytogenetic alterations in this form of Burkitt lymphoma are similar, but possibly not identical, to those seen in the classic African form, as is the association with the Epstein-Barr virus. In Western countries, childhood gastrointestinal lymphoma is the most common manifestation of so-called sporadic Burkitt lymphoma. This tumor, which also occurs in young adults, closely resembles endemic Burkitt lymphoma (described above). Macroscopically, the lesions vary from localized obstructing tumors to huge masses involving long intestinal segments. Mesenteric and retroperitoneal lymph node involvement is common.

Histopathology

The histologic appearances are characteristic of classic African Burkitt lymphoma with mucosal effacement by sheets of medium-sized monomorphic blasts interspersed with phagocytic histiocytes. The blasts are characterized by a narrow rim of
cytoplasm around nuclei with multiple small basophilic nucleoli and clumped chromatin (Fig. 18.48).

In Western countries, cases of so-called sporadic Burkitt lymphoma most often involve the ileocecal region and the histologic appearances may be identical. More commonly, however, there is greater cytologic variability and, unlike classic Burkitt lymphoma, immunohistochemistry may show synthesis of cytoplasmic as well as surface immunoglobulin. The cytogenetic characteristics of these rare tumors have not been well characterized and they do not show the same consistent association with Epstein-Barr virus infection.

Other Types of Primary B-Cell Lymphoma Corresponding to Peripheral Lymph Node Equivalents

There is no reason why any type of lymphoma cannot arise from mucosa-associated lymphoid tissue, but in practice, entities common in peripheral lymph nodes only infrequently arise in the gastrointestinal tract. Likewise, the rarer nodal lymphomas such as lymphocytic lymphoma and lymphoplasmacytic lymphoma hardly ever occur as primary gastrointestinal tumors. The reasons for this are obscure.

Immunodeficiency-Associated B-Cell Lymphoproliferative Conditions and Lymphoma

The gastrointestinal tract is a favorite site for the occurrence of immunodeficiency-associated lymphoproliferative disorders (LPDs) and lymphomas (Table 18.5). The broad causes of the immunodeficiency include (a) primary immune disorders and immunodeficiency syndromes, (b) HIV infection, (c) iatrogenic immunosuppression for solid organ or bone marrow allografts, and (d) iatrogenic immunosuppression associated with methotrexate treatment for autoimmune disease. There are certain histologic features that are common to lymphomas associated with all these causes of immunodeficiency; these include a predominance of a B-cell phenotype, high-grade histology, and Epstein-Barr virus (EBV) positivity. The exception is MALT lymphoma, a low-grade lesion, unassociated with EBV that has occasionally been reported in association with immunodeficiency (123,124). The LPDs and lymphomas associated with specific causes of immunodeficiency will be discussed separately.

| TABLE 18.5 Lymphoproliferative Lesions and Lymphomas Associated with Iatrogenic Immunosuppression for Organ Transplantation |
Primary immune disorders and immunodeficiency syndromes include conditions that result in ineffective immune surveillance such as the X-linked lymphoproliferative disorder, ataxia telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, autoimmune lymphoproliferative syndrome, Nijmegen breakage syndrome, and hyper-IgM syndrome. The nature of the immune defect is highly variable between these different conditions and the LPDs and lymphomas associated with them are equally heterogeneous, although EBV is involved in most of them. The intestinal tract is a common site of involvement, where the defect in immunity may manifest as polymorphic lymphoproliferation similar to that associated with iatrogenic immunosuppression (see below) or, more commonly, as a diffuse large B-cell lymphoma. T-cell lymphomas may occur, especially in the setting of ataxia telangiectasia. Hodgkin lymphoma also occurs, but small lymphocytic lymphomas, with the exception of rare MALT lymphomas, are not seen.

HIV Infection

The gastrointestinal tract is a favored site for HIV-associated lymphomas that may include Burkitt lymphoma and its plasmacytic variant, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and unspecified and Hodgkin lymphoma. EBV is commonly found in the B-cell and Hodgkin lymphomas. MALT lymphoma has also been associated with HIV disease, where it is not associated with EBV.

Iatrogenic Immunosuppression for Solid Organ or Bone Marrow Allografts

Lymphomas that complicate iatrogenic immunosuppression, collectively known as posttransplant lymphoproliferative disorders (PTLDs), are, not surprisingly, very similar to those occurring in association with other forms of immunodeficiency. They are becoming increasingly common and, together with HIV-associated lymphomas, comprise the most important of the group of immunodeficiency-associated LPDs and lymphomas. Once more, the gastrointestinal tract is a common site. The spectrum of PTLDs is summarized in Table 18.5. Most PTLDs appear to be caused by EBV-induced poly- or monoclonal B-cell proliferations (125), and EBV can be demonstrated in the proliferating cells using in situ hybridization to demonstrate EBV-encoded RNA (EBER). However, approximately 20% are EBV negative and in these the underlying factor driving the proliferation of the lymphoid cells is unknown. PTLDs can occur at any time after transplantation depending on the type of allograft and the agent(s) used for immunosuppression.
Early Lesions

In reactive plasmacytic hyperplasia, the intestinal lamina propria is heavily infiltrated by mature plasma cells with occasional transformed blasts forming single or multiple localized lesions but without evidence of tissue destruction. The plasma cells can be shown to synthesise both κ and λ immunoglobulin light chains. In infectious mononucleosis-like PTLD, the lesion is composed of a polymorphic proliferation of transformed B and T cells with scattered, large, sometimes multinucleated cells that resemble Hodgkin and Reed-Sternberg cells. Immunoglobulin light chain expression is again polytypic.

Polymorphic Posttransplant Lymphoproliferative Disorder

Polymorphic PTLD lesions infiltrate and destroy intestinal tissues with consequent ulceration. The lesions are composed of a mixture of cell types from small lymphocytes and plasma cells to large transformed blasts (Fig. 18.49); there may be areas of necrosis and evidence of florid proliferation. The cells may or may not show evidence of EBV infection. Once more, the B cells in these lesions can be shown to synthesize polytypic light chains and PCR shows no evidence of monoclonal proliferation. Reduction in immunosuppression may lead to lesional regression in some cases (126,127,128), but others may resist treatment and progress to monomorphic PTLD or lymphoma.

Monomorphic Posttransplant Lymphoproliferative Disorder

Monomorphic PTLD may manifest as any type of diffuse large B-cell lymphoma, Burkitt lymphoma with or without plasmacytoid features (129) (Fig. 18.50), or plasmacytoma (130). Most are EBV positive and can be shown to be monotypic by immunohistochemistry and/or monoclonal by molecular techniques. They rarely regress following withdrawal of immunosuppressive drugs. T-cell monomorphic PTLDs occur but are distinctly rare (131).

Hodgkin Lymphoma

PTLD with the characteristics of Hodgkin lymphoma (HL) must be discriminated from polymorphic PTLD by applying the strictest criteria for the diagnosis of HL. This can be a difficult exercise compounded by the fact that HL PTLD is always EBV positive.

Methotrexate-associated Lymphoproliferative Disorders
These infrequent LPDs have been reported in patients treated with methotrexate for a variety of autoimmune diseases, especially rheumatoid arthritis (132). The intestine is the most common site of origin, and these LPDs cover the same histologic spectrum as PTLD. A few cases of follicular lymphoma have also been recorded.

**Enteropathy Associated T-Cell Lymphoma**

An association between malabsorption and intestinal lymphoma was first reported in 1937 (133), at which time it was thought that the lymphoma was in some way responsible for malabsorption. It subsequently became clear that the reverse is true (134) and that intestinal lymphoma was a complication of celiac disease or gluten-sensitive enteropathy. In 1978 Isaacson and Wright characterized celiac-associated lymphoma as a single entity, namely a variant of malignant histiocytosis (135). Later, Isaacson et al showed that both the phenotype and genotype of this disease were those of T cells rather than histiocytes (136). This type of lymphoma is now included in the WHO classification of lymphoma as “enteropathy associated T-cell lymphoma” (EATL).

**FIG. 18.50.** A: Monomorphic posttransplant lymphoproliferative disorder in a patient who had received a renal transplant 8 years previously. The tumor cells have a plasmacytoid appearance. B: Immunostaining with Ki-67 shows a proliferation fraction of 100%. C: Epstein-Barr virus–encoded RNA in situ hybridization is positive.
**Definition**

Enteropathy associated T-cell lymphoma is a tumor of intraepithelial lymphocytes showing varying degrees of transformation but usually presenting as a tumor of large lymphoid cells (5).

**Epidemiology**

Enteropathy associated T-cell lymphoma characteristically occurs in the 6th and 7th decades, although there are sporadic reports of cases in younger individuals. Males and females are affected equally. Most, if not all, patients with EATL have the celiac disease–associated human leukocyte antigen (HLA) DQA1 and DQB1 genotype (137). Enteropathy associated T-cell lymphoma is most common in those regions with the highest prevalence of celiac disease such as Northern Europe and very rare in regions such as the Far East, where celiac disease does not occur.

**Etiology**

There is strong evidence that EATL complicates celiac disease (gluten-sensitive enteropathy), discussed further in Chapter 6 (138,139). The lymphoma may complicate established celiac disease, sometimes only manifested by celiac-associated conditions such as dermatitis herpetiformis, of long standing but more usually follows a short history of adult-onset celiac disease and/or dermatitis herpetiformis. The assumption in these cases is that the patients have indeed had lifelong, albeit cryptic, gluten sensitivity. In keeping with this, in a proportion of cases there is no history of malabsorption but jejunal villous atrophy and crypt hyperplasia are found in the small intestinal mucosa when the tumor is resected. The only manifestation of celiac disease in some cases is an increase of intraepithelial T cells, while in a minority the jejunum appears normal or near normal. Studies showing that the jejunal mucosa can appear completely normal in celiac disease, so-called latency (140), provide an explanation for this finding, which was previously thought to argue against a strict association of EATL with celiac disease.

Further evidence for this association includes the identical HLA types of celiac patients and those with EATL (137), demonstration of gluten sensitivity in EATL patients, and the observation that in patients with celiac disease a gluten-free diet may protect against the development of lymphoma (141). There is controversy over the actual magnitude of the risk of lymphoma in celiac disease patients. In a recent study (142) the risk was increased sixfold, but this figure referred to lymphoma in general. Had specific risk of EATL been calculated, it would have been many times this figure.

**Clinical Presentation**

The most common presentation is the reappearance of malabsorption accompanied by abdominal pain in a patient with a history of adult or childhood celiac disease who has previously responded to a gluten-free diet. This may be accompanied by an ichthyotic skin rash and finger clubbing. Other presentations include the sudden onset of severe, usually gluten-insensitive malabsorption in a previously well individual or an acute abdominal emergency due to small intestinal perforation or hemorrhage. In most cases the lymphoma involves multiple segments of small intestine and has already disseminated at the time of diagnosis. Common sites of dissemination include mesenteric lymph nodes, liver, spleen, bone marrow, lung, and skin. Rarely, the lymphoma presents at one of these sites and intestinal involvement becomes apparent only later.

**Gross Features**

EATL may involve any part of the small intestine and occasionally other parts of the gastrointestinal tract including the colon and stomach, but in most cases arise in the jejunum. The tumor is usually, but not always, multifocal and forms ulcerating nodules, plaques, strictures, or, less commonly, large masses, which may be accompanied by benign-appearing ulcers and strictures (Fig. 18.51). The mesentery is often infiltrated and mesenteric lymph nodes are commonly involved. There is sometimes remarkably little macroscopic evidence of disease in the intestine as opposed to the mesenteric lymph nodes.
Histologic Features

The histologic features of EATL show great variation both between cases and within any single case (Fig. 18.52). The most characteristic appearance is that of a pleomorphic tumor of large lymphoid cells (Fig. 18.52A). Other cases may be composed of strikingly bizarre, often multinucleated giant cells (Fig. 18.52B) or more monomorphic cells with prominent central nucleoli leading to an immunoblastic appearance (Fig. 18.52C). In a substantial number of cases the number of inflammatory cells, particularly eosinophils, may be so great as to almost obscure the neoplastic T cells, especially in the presence of the extensive necrosis that often occurs in this variant (Fig. 18.52D). There is a subgroup of cases (143) (see below) in which the neoplastic T cells characteristically express CD56 and are only slightly larger than normal small lymphocytes. They often form monomorphic sheetlike infiltrates in the submucosa and muscularis propria (Fig. 18.53). In all variants intraepithelial tumor cells are usually prominent (Fig. 18.54). Granulomas may be present and cause confusion with Crohn disease.

The histology of the small intestinal mucosa remote from the site of the tumor is an important consideration in the diagnosis of EATL. In most cases the changes are identical to those of celiac disease. Thus, there are villous atrophy with crypt hyperplasia, plasmacytosis of the lamina propria, and increased numbers of intraepithelial lymphocytes (Fig. 18.55). Like uncomplicated celiac disease, the mucosal changes are maximal proximally and improve distally so that the lower jejunum and ileum may be normal. This must be borne in mind when the lymphoma arises in the more distal small intestine. In some cases of celiac disease the changes in the mucosa are much less severe. The villous architecture may be normal and the only hint of celiac disease is an increase in intraepithelial lymphocytes best seen in immunostained preparations. The degree of intraepithelial lymphocytosis may be spectacular and so extreme as to virtually obscure the epithelial cells. The lymphocytes are small, without neoplastic features, and in these extreme cases spill into the lamina propria, where they may merge with the lymphomatous infiltrate (Fig. 18.56).

Numerous shallow ulcers extending into the submucosa are frequently present in the mucosa remote from the lymphoma (Fig. 18.57). The bases of these ulcers contain an inflammatory infiltrate of small lymphocytes and plasma cells with an overlying acute inflammatory exudate. Episodes of ulceration followed by healing lead to scarring with stricture formation and distortion of mucosal architecture accentuated by destruction of the muscularis mucosae and the emergence of glands lined by cells of the ulceration-associated cell lineage (144), previously called pseudopyloric metaplasia.
**FIG. 18.53.** Subtype of enteropathy associated T-cell lymphoma composed of monomorphic small cells.

**FIG. 18.54.** Mucosa in enteropathy associated T-cell lymphoma showing intraepithelial invasion by tumor cells.

**FIG. 18.55.** The uninvolved mucosa in enteropathy associated T-cell lymphoma shows villous atrophy with crypt hyperplasia.

---

**Lymph Node Involvement**

The pattern of mesenteric lymph node involvement may be predominantly intrasinusoidal, paracortical, or both (Fig. 18.58).
Selective necrosis of lymph nodes, often involving entire nodes, remote from the main lesion is a feature of some cases (145) (Fig. 18.59). The cause of this necrosis is obscure.

**Immunohistochemistry and Molecular Genetics**

In most cases of EATL the tumor cells express CD3, CD7, CD103, and granzyme B. They are usually CD4 and CD8 negative and express either the α/β or the γ/δ T-cell receptor. This immunophenotype is not consistent, however, and in some cases the cells fail to express CD3 or, more often, express CD8. Those cases of EATL composed of large anaplastic cells are usually CD30 positive. In the subset of EATL cases composed of monomorphic sheets of small lymphoid cells, the immunophenotype is distinctive in that the tumor cells express CD3, CD8, CD56, and granzyme B. The immunophenotype of the intraepithelial T cells in the uninvolved small intestinal mucosa may be normal, but more often, in common with the accompanying lymphoma, they fail to express CD8 (Fig. 18.60).

Genotypic studies of EATL have shown clonal rearrangement of the T-cell receptor (TCR) β- and γ-chain genes (146). PCR amplification of the T-cell receptor γ-chain gene has shown that the tumor cell clone can be amplified from the uninvolved mucosa in a significant number of cases. Chromosomal gains at 9q have been reported in a series of ETL cases, while a further study has shown loss of heterozygosity at chromosome 9p (147,148). Baumgartner et al showed that there was a high frequency of chromosomal alterations in EATL (149), and later the same group showed that these involved amplification of NOTCH1 and ABL1 genes (150). In common with some other T-cell lymphomas, EBV DNA in monoclonal form and latent membrane protein 1 have been demonstrated in EATL, particularly in cases reported from central America (151).

**FIG. 18.56.** Florid intraepithelial lymphocytosis with spillage of small intraepithelial lymphocytes into the lamina propria (**right**).
Postulated Normal Cell Counterpart

The immunophenotypic features of EATL approximate those of intraepithelial T lymphocytes (IELs), which are thought to be the normal cell counterpart of this lymphoma (152). Intraepithelial lymphocytes are, however, phenotypically heterogeneous (153,154,155). Most are cytotoxic T cells that express CD3 and CD8 and have rearranged TCR γ-chain genes. There is a minority population of CD4- and CD8-negative IELs with rearranged γ/δ- but not α/β-chain genes. These γ/δ positive T cells comprise 10% to 15% of IELs in normal mucosa and may increase in concentration in patients with celiac disease up to a level of 30%. Finally, there is a third population of CD56-positive cells that accounts for a very small fraction of IELs that is virtually undetectable in immunostained paraffin sections (unpublished observations).

![FIG. 18.57. Uninvolved mucosa in enteropathy associated T-cell lymphoma showing inflammatory ulceration.](image)

Prognosis

The clinical course of ETL is very unfavorable except in a minority of cases in which resection of a localized tumor has been followed by long remission. In most cases the lymphoma involves multiple segments of intestine, rendering resection impossible, or has already disseminated beyond the mesenteric lymph nodes or out of the abdomen. Chemotherapy, sometimes with added bone marrow transplantation, may result in temporary remission of the disease.
Refractory Celiac Disease

Some cases of celiac disease become unresponsive to a gluten-free diet or may be unresponsive de novo. The term refractory celiac disease or, more commonly, refractory sprue has been used for these cases (156). While the onset of refractory celiac disease may more or less immediately precede EATL, other cases persist as refractory celiac disease for many years without the emergence of overt lymphoma. Nonspecific inflammatory ulcers of the small intestinal mucosa, identical to those that occur in EATL, are often present in refractory celiac disease, when it has been termed ulcerative jejunitis (Fig. 18.61) (157). Studies of TCR genes in both ETL and refractory
celiac disease have now elucidated the relationship between the two conditions.

**FIG. 18.60.** Uninvolved mucosa from a case of enteropathy associated T-cell lymphoma double-stained for CD8 (*brown*) and CD3 (*blue*) showing increased numbers of phenotypically aberrant CD8-negative intraepithelial T cells. The main tumor was also CD3 positive, CD8 negative.

**FIG. 18.61.** A case of refractory celiac disease showing nonspecific inflammatory ulceration (ulcerative jejunitis).

Using PCR followed by sequence analysis of TCR γ genes, Murray et al (146) showed that there was a T-cell population in the “uninvolved” enteropathic small intestinal mucosa adjacent to EATL that shared the same monoclonal TCR γ rearrangement as the lymphoma. Ashton-Key et al confirmed this finding and further showed TCR γ monoclonality in the nonspecific “inflammatory” ulcers that accompanied EATL as well as in the ulcers and intervening mucosa of refractory sprue (158). In cases where lymphoma subsequently developed, the same clone could be detected in the malignant cells by PCR and sequence analysis. Cellier et al (159) investigated cases of refractory sprue and showed that in this condition, monoclonal
populations of T cells are present in the small intestinal mucosa. They showed that this monoclonal population is constituted by phenotypically abnormal CD3-positive/-negative, CD4-negative, and CD8-negative intraepithelial lymphocytes (Fig. 18.62). Cellier et al later drew together the clinical and laboratory features of refractory sprue (160). Importantly, they definitively clarified the relationship between celiac disease and refractory sprue by showing the presence of celiac disease–specific antiendomysial or antigliadin antibodies, in most cases together with other characteristics of celiac disease including a previous response to gluten withdrawal or the characteristic HLA DQA1*0501 and DQB1*0201 phenotype (137). Additionally, they showed that in all truly refractory cases, the intraepithelial lymphocytes were either monoclonal, expressed an abnormal immunophenotype, or both.

**FIG 18.62.** Adjacent intact mucosa in same case illustrated in Figure 18.61. Increased CD3-positive intraepithelial T cells are CD4 negative but positive for cytotoxic granules (TIA-1) (*bottom right*).
Bagdi et al (161) showed that in double-stained (CD8/CD3) preparations of sections of small intestine from refractory celiac disease patients with a monoclonal T-cell population in their small intestinal mucosa, there was a marked decrease in the...
proportion of CD8-positive intraepithelial lymphocytes (Fig. 18.63). Moreover, in cases of EATL, the cytologically bland intraepithelial lymphocytes in the intervening mucosa shared the immunophenotype and genotype of the lymphoma. Specifically, in monomorphic CD56-positive cases, these lymphocytes also expressed CD56 (Fig. 18.64). Interestingly, these clonal and immunophenotypically aberrant intraepithelial lymphocytes were often present in the crypt epithelium, in contrast to uncomplicated celiac disease, where they are confined to the surface epithelium. Moreover, these cells were widely distributed throughout the gastrointestinal tract from stomach to anus.

It would seem safe to conclude, therefore, that the monoclonal intraepithelial lymphocytes in patients with refractory sprue are neoplastic, although they are not cytologically abnormal and they do not form tumor masses. The accumulation of phenotypically aberrant, monoclonal intraepithelial lymphocytes appears to be the first step in the genesis of EATL. Patients with refractory celiac disease and/or ulcerative jejunitis are therefore suffering from a neoplastic T-cell disorder, possibly involving most of the gastrointestinal tract. Treatment of this group of patients, most of whom have severe unremitting malabsorption, is difficult. It is uncertain whether chemotherapeutic regimens appropriate for lymphoma have anything to offer in this respect or whether new strategies will need to be devised. Further, cell and molecular biologic investigations are indicated, particularly to establish the precise relationship between the neoplastic intraepithelial lymphocytes and the cells of fully developed EATL.

**Other Types of T-Cell Lymphoma Unassociated with Enteropathy**

Carbonnel et al described a distinctive intestinal *T-cell lymphoma composed of small CD4-positive lymphocytes* widely distributed throughout the lamina propria of the intestinal mucosa (162). In common with ETL, this suggests a specific association with native gut lymphoid tissue, in this case the lamina propria rather than the intraepithelial T-cells. These cases are characterized by a slow relentless course and prolonged survival, an unusual feature for T-cell lymphomas. Cases of *CD56-positive T/NK-cell lymphoma of nasal type*, although typically occurring in the upper respiratory tract, not only frequently spreads to the gastrointestinal tract, but may arise there as a primary tumor (20). The lymphoma involves multiple sites, forming tumor masses. Typically, it also infiltrates long segments of intestinal mucosa, where it is associated with villous atrophy, but unlike EATL, this is seen only in mucosa infiltrated by lymphoma; the villous architecture of uninvolved mucosa is normal.
FIG 18.65. Histiocytic sarcoma of the small intestine. A: The tumor cells in the mucosa have abundant foamy cytoplasm and hyperchromatic, polymorphic nuclei. B: The tumor cells invading the serosa are spindle shaped. C: The tumor cells express histiocytic antigens such as CD163.

There are numerous isolated case reports of a wide variety of T-cell lymphomas arising in the gastrointestinal tract, but they do not comprise recognized clinicopathologic entities.

Histiocytic Sarcoma

True histiocytic neoplasms of the intestine are well documented (163,164,165,166). All the tumors arose in the small intestine, where they produced ulcerating masses. The tumor cells typically have abundant cytoplasm that is sometimes foamy (Fig. 18.65A). They may be bizarre, are often multi-nucleated, and in some case are focally arranged in a spindle cell sarcomalike pattern (Fig. 18.65B). Lymph nodes have been involved in all of the cases. The immunophenotype is that of histiocytes (macrophages), CD11c, CD163 (Fig. 18.65C), lysozyme, and CD68 positive. Cells with dendritic cell properties manifested by tortuous nuclei and focal S100 positivity are also often present. These tumors have a high mortality.

Langerhans Cell Histiocytosis

Langerhans histiocytosis occasionally involves the digestive tract, where it presents as isolated foci of histiocytes with abundant eosinophilic cytoplasm and grooved or “coffee bean–like” nuclei (Fig. 18.66). The cells are typically CD1a and S100
positive (Fig. 18.66B,C).

**Granulocytic Sarcoma**

Rarely, acute myeloid leukemia presents as an isolated gastrointestinal tumor that can easily be confused with a lymphoma (167). The characteristic, finely granular nucleus lacking nucleoli (Fig. 18.67) and the presence of eosinophil metamyelocytes should lead to the correct diagnosis. This can be confirmed by appropriate immunohistochemical staining for myeloperoxidase, CD56, CD34 (Fig. 18.67), and lysozyme. Acute leukemia usually manifests soon after the diagnosis, but intervals as long as 15 years have been reported.

**FIG. 18.66.** Langerhans cell histiocytosis of the colon. *A:* The tumor cells are characterized by abundant eosinophilic cytoplasm and “crumpled,” sometimes grooved coffee bean–like nuclei. *B:* The tumor cells express S100 protein. *C:* The tumor cells are CD1a positive.
**FIG. 18.67.** Granulocytic sarcoma of the small intestine. 

*A:* There is invasion of the mucosa and submucosa. 

*B:* Higher magnification shows large cells with granular nuclear chromatin, lacking nucleoli. 

*C:* The tumor cells are CD56 positive. 

*D:* The tumor cells express CD34.

---

**References**


P.1200


Chapter 18


123. Wotherspoon AC, Diss TC, Pan L, et al: Low grade gastric B-cell lymphoma of mucosa-associated lymphoid tissue in


133. Fairlie NH, Mackie FP: The clinical and biochemical syndrome of lymphadenoma and allied disease involving the mesenteric lymph nodes. *BMJ* 1937;i:3792.


Mesenchymal Tumors

General Comments
Gastrointestinal stromal tumors (GISTs) were long considered diagnostic confusion for decades. Previously, most were diagnosed as either smooth muscle or neural tumors. However, following decades of ultrastructural and immunohistochemical studies, and more recently genetic investigations, it is now evident that most gastrointestinal tumors arise from interstitial cells of Cajal (ICCs), the gastrointestinal pacemaker cells. For this reason, the term gastrointestinal pacemaker cell tumor (GAPCT) has been suggested (1); however, the more general term gastrointestinal stromal tumor (GIST) has long been in vogue and has taken hold. While GISTs are the most common gastrointestinal tumors, an array of other mesenchymal tumor types also develop in the GI tract.

Gastrointestinal Stromal Tumors

Demography
An estimated 3,000 to 6,000 new cases of GIST are diagnosed annually, with 10% to 30% of them being malignant (2). Most tumors are exoplant in nature, affecting individuals in their 5th or 6th decades of life. However, GISTs may arise in very young patients (3), and rare congenital tumors also exist (4). There is a right-to-left predominance. However, GISTs developing in the setting of the Carney triad (gastrointestinal GISTs, pulmonary chondromas, and extratesticular paraganglioma) generally affect women under the age of 20 (5). GISTs developing in this setting are often multicentric, are purely epithelial, and have a low risk of metastasis. GISTs arising in association with paragangliomas but without pulmonary chondromas may represent a variant of the Carney triad (6).

Familial GISTs develop in patients with germline activating KIT (6) or platelet-derived growth factor receptor-α (PDGFRA) mutations (see below). Hyperpigmentation, mast cell tumors, and dysphagia are common to some kindreds (6). GISTS also develop in young patients with neurofibromatosis type 1 (NF1). The tumors are often multiple, usually developing in the small intestine (7). GISTS also complicate tuberous sclerosis (8) or following radiation therapy.

Cell of Origin
Most GISTs arise from CD117+ ICCs present in and around the muscularis propria. ICCs show both myogenic and neuroendocrine features (9), explaining the immunohistochemical heterogeneity of the tumors that derive from them. Some GISTs arise from a CD14+ subset of ICC (9) or from primitive cells that can differentiate into ICC or smooth muscle cells (10).

Molecular Genetic Features
Consistent activation of the KIT proto-oncogene is approximately 66% of GISTs. The KIT gene encodes a tyrosine kinase receptor for stem cell factor (SCF), a ligand that plays a central role in the development of the hematopoietic system. Activating mutations, resulting in a truncated or constitutively active KIT (11), have been found in approximately 90% of GISTs (11,12). Approximately 85% of the activating mutations involve the juxtamembrane domain of KIT (11,13). Spindle cell GISTs are most likely to contain exon 11 mutations, and most 9 mutations most commonly affect familial GISTs (17). Most familial mutations result in a truncated tyrosine kinase domain (11,12,14). Activating mutations result from single base pair substitutions to cause deletions/insertions, internal deletions or substitutions may also be found (16). Generally, only one type of KIT mutation occurs in a given tumor. However, one tumors contain two different somatic mutations. Recurrent tumors show a different molecular phenotype than the primary tumor. For example, the primary tumor may show a mutation in exon 11 and the recurrence may contain both the exon 11 mutation as well as a new mutation in exon 12 (13).

Approximately 1% to 10% of GISTs harbor PDGFRA activating mutations (17). The PDGFRA gene is adjacent to the KIT locus and its structure and organization suggest that both genes derive from a common ancestral gene. In familial paragangliomas, the PDGFRA gene likely plays a role in the development of pheochromocytoma (17). Some familial GISTS develop in patients with germline activating PDGFR mutations, usually in association with paragangliomas but without pulmonary chondromas (17). Approximately 50% of GISTs lack both KIT or PDGFR mutations (16). GISTs developing in the setting of Carney triad (gastrointestinal GISTs, pulmonary chondromas, and extraadrenal paragangliomas) generally affect women under the age of 20 (5). GISTs developing in this setting are often multicentric, are purely epithelial, and have a low risk of metastasis. GISTs arising in association with paragangliomas but without pulmonary chondromas may represent a variant of the Carney triad (6).

Gastrinomas may also develop in association with familial multiple endocrine neoplasia type 1 (FMEN1), usually in association with paragangliomas but without pulmonary chondromas (17). Some familial GISTS develop in patients with germline activating PDGFR mutations, usually in association with paragangliomas but without pulmonary chondromas (17). Approximately 50% of GISTs lack both KIT or PDGFR mutations (16). GISTs developing in the setting of Carney triad (gastrointestinal GISTs, pulmonary chondromas, and extraadrenal paragangliomas) generally affect women under the age of 20 (5). GISTs developing in this setting are often multicentric, are purely epithelial, and have a low risk of metastasis. GISTs arising in association with paragangliomas but without pulmonary chondromas may represent a variant of the Carney triad (6).

Common Histologic Features
Gastrointestinal stromal tumors (GISTs) have a broad spectrum of morphologic appearances. The most common sites of mutation are illustrated. Familial GISTs associate with exon 9, 11, 12, and 17 KIT mutations (6,16) or mutations in the platelet-derived growth factor receptor-α (PDGFRA) gene (18). Hyperpigmentation, mast cell tumors, and dysphagia are common to some kindreds (6). GISTS also develop in young patients with neurofibromatosis type 1 (NF1). The tumors are often multiple, usually developing in the small intestine (7). GISTS also complicate tuberous sclerosis (8) or following radiation therapy. Generally, only one type of KIT mutation occurs in a given tumor. However, one tumors contain two different somatic mutations. Recurrent tumors show a different molecular phenotype than the primary tumor. For example, the primary tumor may show a mutation in exon 11 and the recurrence may contain both the exon 11 mutation as well as a new mutation in exon 12 (13).

Approximately 85% of the activating mutations involve the juxtamembrane domain of KIT (11,13). Spindle cell GISTs are most likely to contain exon 11 mutations, and most 9 mutations most commonly affect familial GISTs (17). Most familial mutations result in a truncated tyrosine kinase domain (11,12,14). Activating mutations result from single base pair substitutions to cause deletions/insertions, internal deletions or substitutions may also be found (16). Generally, only one type of KIT mutation occurs in a given tumor. However, one tumors contain two different somatic mutations. Recurrent tumors show a different molecular phenotype than the primary tumor. For example, the primary tumor may show a mutation in exon 11 and the recurrence may contain both the exon 11 mutation as well as a new mutation in exon 12 (13).

Approximately 1% to 10% of GISTs harbor PDGFRA activating mutations (17). The PDGFRA gene is adjacent to the KIT locus and its structure and organization suggest that both genes derive from a common ancestral gene. GISTs with KIT or PDGFRA mutations exhibit unique expression profiles and the genes identified by this technology may contribute to distinct clinicopathologic phenotypes. These gene products may also serve as highly selective therapeutic targets in GISTs containing KIT or PDGFRA mutations.

Demography
An estimated 3,000 to 6,000 new cases of GIST are diagnosed annually, with 10% to 30% of them being malignant (2). Most tumors are exoplant in nature, affecting individuals in their 5th or 6th decades of life. However, GISTs may arise in very young patients (3), and rare congenital tumors also exist (4). There is a right-to-left predominance. However, GISTs developing in the setting of the Carney triad (gastrointestinal GISTs, pulmonary chondromas, and extratesticular paraganglioma) generally affect women under the age of 20 (5). GISTs developing in this setting are often multicentric, are purely epithelial, and have a low risk of metastasis. GISTs arising in association with paragangliomas but without pulmonary chondromas may represent a variant of the Carney triad (6).

Familial GISTs develop in patients with germline activating KIT (6) or platelet-derived growth factor receptor-α (PDGFRA) mutations (see below). Hyperpigmentation, mast cell tumors, and dysphagia are common to some kindreds (6). GISTS also develop in young patients with neurofibromatosis type 1 (NF1). The tumors are often multiple, usually developing in the small intestine (7). GISTS also complicate tuberous sclerosis (8) or following radiation therapy.
GISTs can be divided into spindle cell, epithelioid, mixed, and pleomorphic lesions. Seventy percent of tumors are predominantly spindle cell in nature. The spindle cell component may exhibit a storiform, palisading, or herringbone pattern. The nuclei typically have blunt ends and are bullet or cigar shaped, but they can also be long and pointed. Some tumor cells have abundant cytoplasm; there may be areas of hyalinization and stellate fibers. Epithelioid tumors consist of polygonal cells with abundant cytoplasm and are most common in the small intestine. Spindle tumors contain sheets of spindle cells with an anastomosing pattern. A small proportion of intestinal tumors contain focal highly pleomorphic cells. These tumors usually have high mitotic rates measuring in excess of 10 mitoses/10 high-powered field (hpf).

FIG. 19.3. Cut surface of a small intestinal gastrointestinal stromal tumor with a multilobulated irregular architecture.

There is a wide clinical and pathologic spectrum ranging from indolent diminutive tumors to rapidly progressing sarcomas. The histologic features of the more common forms of GISTs are discussed below. There are also rare histologic variants that occur anywhere in the gut. Gastrointestinal autonomic nerve tumors (GANTs) are now known to represent a GIST variant. This variant is relatively more common in the small intestine and is associated with gastrointestinal autonomic nerve tumors of the small intestine (GANTs). GANTs have a characteristic microscopic appearance, with sheets of tumor cells surrounding autonomic nerve fibers. Mitoses range from 1 to 23 mitoses/hpf.

FIG. 19.4. Small intestinal gastrointestinal stromal tumor with dumbbell-shaped (exophytic and endophytic) growth pattern.

Another histologic GIST variant contains cells with signet ring cell features. These tumors frequently affect women and present as small (<2.5 cm), well-circumscribed, gastric, small intestinal, or appendiceal lesions. The tumor cells are large, with centrally located nuclei that are surrounded by a clear cytoplasmic halo. The tumor cells are arranged in short, comma-shaped cords or sheets. The tumor cells are usually positive for CD34, CD117, and KIT. Immunohistochemical staining shows a heterogeneous staining pattern, with strong positivity for vimentin and variable staining for CD34, CD117, and KIT. The tumor cells are usually positive for CD34, CD117, and KIT. Immunohistochemical staining shows a heterogeneous staining pattern, with strong positivity for vimentin and variable staining for CD34, CD117, and KIT. The tumor cells are usually positive for CD34, CD117, and KIT.

The mesenchymal GIST variant typically consists of epithelioid cells that are distributed in a myxoid stroma. CD34 is positive for CD34, CD117, and KIT. Immunohistochemical staining shows a heterogeneous staining pattern, with strong positivity for vimentin and variable staining for CD34, CD117, and KIT. The tumor cells are usually positive for CD34, CD117, and KIT. Immunohistochemical staining shows a heterogeneous staining pattern, with strong positivity for vimentin and variable staining for CD34, CD117, and KIT. The tumor cells are usually positive for CD34, CD117, and KIT.

Intestinal cells of Cajal hyperplasia. A: Histologically, this lesion appears as a neural hyperplasia in the enteric neural plexus. B: c-kit immunostain discloses the true nature of the lesion.

Mesenchymal GISTs are characterized by sheets of tumor cells that are arranged in a myxoid stroma. CD34 is positive for CD34, CD117, and KIT. Immunohistochemical staining shows a heterogeneous staining pattern, with strong positivity for vimentin and variable staining for CD34, CD117, and KIT. The tumor cells are usually positive for CD34, CD117, and KIT. Immunohistochemical staining shows a heterogeneous staining pattern, with strong positivity for vimentin and variable staining for CD34, CD117, and KIT. The tumor cells are usually positive for CD34, CD117, and KIT.

NF1-associated GISTs resemble non-NF1 spindle cell GISTs. Most contain skeinoid fibers and the tumors are typically surrounded by ICC hyperplasia. NF1-associated GISTs show dual differentiation with CD117+ ICCs and S100+ Schwann cell.
Chapter 19

FIG. 19.7. Gastric gastrointestinal stromal tumor. A. A patient with known chronic active gastritis developed a mass lesion. Biopsy fragments of the most recent biopsy. The fragments differ in their appearance. The lower and middle biopsy fragments show evidence of chronic active gastritis. In the upper fragment, the gastric architecture is destroyed by the presence of an infiltrating mass.

B. Higher magnification of an area of the upper biopsy fragment showing the replacement of the gastric mucosa by a cellular population with a high nuclear/cytoplasmic ratio that invades the lamina propria. This lesion can be diagnosed as malignant since there is mucosal invasion. C. Another area of the biopsy demonstrates a cellular neoplasm with a prominent myxoid stroma. D. This fragment is composed exclusively of spindle cells.

TABLE 19.1 Consensus Recommendations for Defining Risk of Aggressive Behavior in Gastrointestinal Stromal Tumors

<table>
<thead>
<tr>
<th>Size</th>
<th>Mitotic Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2 cm</td>
</tr>
<tr>
<td>Low risk</td>
<td>2–5 cm</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>&lt;5 cm</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td>Any size</td>
<td>Any mitotic rate</td>
</tr>
</tbody>
</table>

hpf, high-powered field.


FIG. 19.8. Fine needle aspirate of a gastric gastrointestinal stromal tumor. A highly cellular tissue fragment is present that consists predominantly of spindle cells. There are no mitoses.

FIG. 19.9. Gastrointestinal stromal tumor with signet ring features.
FIG. 19.10. Small intestinal gastrointestinal stromal tumor that presented in an inguinal hernia and had a pattern reminiscent of a mesothelioma. The photos are from the primary lesion in the ileum. A: Note the mixture of spindle cells and epithelioid areas. B: Ileal serosal surface showing epithelioid nests (left). Higher magnification (right). C: Other areas of the primary tumor. Epithelial cells are seen on the left and spindle cells on the right. D: Retractin stain demonstrating absence of retinulin.

There is no consensus on the appropriate classification of gastric GISTs. One can follow the consensus recommendations or divide gastric GISTs into benign and malignant GISTs, either of which may be spindle cell, epithelioid, or mixed. Alternatively, one can use the classification described below:

Trupiano et al divided gastric GISTs into benign and malignant spindle cell GISTs, benign and malignant epithelioid GISTs, and benign and malignant mixed lesions (38). The predominant cell type is determined by the presence of >75% of the tumor being represented by either spindle cells or epithelioid cells. Tumors that do not meet these criteria are classified as mixed tumors. Nuclear grade is considered to be high if the nuclei are large with irregular nuclear membranes and vesicular chromatin. Tumors without these features were classified as low grade (34).

FIG. 19.11. Gastric gastrointestinal stromal tumor with a rhabdoid phenotype. According to this classification, benign cellular spindle cell GISTs are highly cellular tumors, with uniform spindle cells with an abundant pale to eosinophilic cytoplasm. The compact cells exhibit a patternless, fascicular, whorled, or palisading architecture. The uniform pale nuclei contain evenly distributed chromatin, inconspicuous nucleoli, and regular nuclear borders (Fig. 19.13). Mitotic activity is typically less than or equal to two figures per 50 hpf. Perinuclear vacuoles may be present. The tumor cells are often separated by a hyalinized or calcified stroma. There may be areas of liquefactive necrosis with pools of acellular material separating perivascular tumor islands (34).

Benign epithelioid GISTs, the most common gastric GISTs, consist predominantly, or exclusively, of epithelioid cells, often with well-defined borders, arranged in nests or sheets (Fig. 19.14). The cells have abundant eosinophilic cytoplasm that may be vacuolated, angiomatoid, or clear. There is often a rimmed vacuolated cytoplasm adjacent to the nucleus with peripheral cytoplasmic clearing that is only appreciated on hematoxylin and eosin (H&E) examination, due to the fact that this is a fixation-induced artifact (Fig. 19.15). The nuclei are usually round with small nucleoli, but scattered multinucleated giant cells or cells with bizarre nuclei can be present. Mitotic figures are rare (usually two or less per 50 hpf). Stromal alterations include hyalinization and calcification (34). A rich vascular supply can cause a nevus-like or glomus appearance.

FIG. 19.12. Gastric gastrointestinal stromal tumor with scattered cytotoxic T cells. In contrast to benign cellular GISTs, malignant spindle cell GISTs are larger, more cellular tumors containing cells with a high nuclear/cytoplasmic ratio (Fig. 19.16). The cytoplasm may appear eosinophilic, basophilic, or amphophilic. The nuclei vary in size and often appear vesicular. Perinuclear vacuoles typical of benign lesions are often absent, areas of tumor necrosis are common, individual tumor cells may be arranged in storiform or fascicular patterns. Some tumors show prominent nuclear palisading. Mitoses are often numerous (high or low magnification). Mucosal invasion, as defined by infiltration of tumor cells across the muscularis mucosae between the glands at the base of the mucosa, may be seen (Fig. 19.7).

FIG. 19.15. Epithelioid gastrointestinal stromal tumor with so-called "fried egg" appearance.

Malignant epithelioid GISTs consist of densely packed cells with less cytoplasm than the spindle cell variant. They are more cell dense than the benign counterparts. The cells may be arranged in small anaplastic clusters or large sheets. A prominent myxoid stroma is often present. The nuclei are generally hyperchromatic and monomorphous in appearance. Some cells are pleomorphic; however, scattered bizarre cells are more common in benign epithelioid GISTs. Since the mitotic activity overlaps with that seen in benign epithelioid tumors unless the mitoses are numerous, mitoses cannot be used to separate benign from malignant lesions. Furthermore, because benign-appearing areas are often present in malignant epithelial GISTs, extensive sampling is required to identify the malignant component (34).

FIG. 19.16. Malignant spindle cell gastrointestinal stromal tumor.

A: Low-power view showing atypical cells and focal necrosis.

B: Medium-power view showing moderate cellular atypia and increased mitotic activity.

C: Immature spindled and stellate cells with increased mitotic activity are present in a myxoid stroma.

FIG. 19.17. Sclerosing spindle cell gastrointestinal stromal tumor.

FIG. 19.18. Sclerosing epithelioid gastrointestinal stromal tumor. The figure demonstrates the presence of a densely cellular lesion with crowded nuclei. No mitotic activity is present. This area was surrounded by more typical spindle-shaped cells.

A recent large study of gastric GISTs (195 cases with long-term follow-up) delineated eight histologic subtypes of gastric GISTs, an admixture of the subtypes, and a group of tumors that were unclassified (8). The eight types are as follows:

- Sclerosing spindle cell GISTs are paucicellular tumors that show extensive extracellular collagen (Fig. 19.17), no nuclear atypia, low mitotic activity, and common calcification. They are usually small, although 13% were >10 cm.
- Palisading and vacuolated spindle cell GISTs (Fig. 19.13) consist of cellular, plump, uniformly sized cells with nuclear palisading, perinuclear vacuolization, and limited atypia. The mitotic activity rarely exceeded 10 mitoses/50 hpf.
- Hypercellular spindle cell GISTs contain uniformly densely packed cells with diffuse sheets of spindle cells exhibiting limited atypia, nuclear palisading, and perinuclear vacuolization. The mitotic activity rarely exceeded 15 mitoses/50 hpf.
- Sarcomatous spindle cell GISTs (Fig. 19.16) contain spindle or oval cells with diffuse atypia, and the tumor cells were often in tufts separated by a myxoid stroma. The mitotic activity is <20 mitoses/50 hpf, except that tumors >10 cm in diameter.
- Sclerosing epithelioid GISTs (Fig. 19.17) exhibit a syncytial pattern and consist of cohesive uniform polygonal cells with indistinct cell borders and diffuse collagenous matrix. Multinucleation and low mitotic rate are characteristic.
- Epithelioid GISTs with discohesive patterns (Fig. 19.19) consist of large polygonal cells with well-defined borders, nuclear pleomorphism, and a higher nuclear:cytoplasmic ratio than the epithelioid GISTs with discohesive patterns. The mitotic activity was <5 mitoses/50 hpf.
- Sarcomatous epithelioid GISTs consist of epithelioid cells with well-defined borders, high nuclear:cytoplasmic ratio, uniform nuclei, prominent nucleoli, and conspicuous mitotic activity (>20 mitoses/50 hpf).

The tumors are also divided into eight groups, based on maximum tumor diameter and mitotic activity (Table 19.2).

TABLE 19.2 Suggested Guidelines for Assessing the Malignant Potential of Gastric Gastrointestinal Stromal Tumors of Different Sizes and Mitotic Activity

(8) The spectrum from the sclerosing, palisading–vacuolated, hypercellular, to sarcomatous among spindle cell GISTs reflected increasing frequency of adverse outcome. The sarcomatous type differed significantly from the others in terms of tumor-specific survival. The epithelioid sarcomatous tumors had a slightly better prognosis than neoplastic spindle cell tumors. Malignant changes may be seen in both spindle cell and epithelioid cell lesions (Fig. 19.21).
Benign (no tumor-related mortality detected)

- Group 1 (≤2 cm, ≤5 mitoses/50 hpf)
- Group 2 (>2 and ≤5 cm, ≤5 mitoses/50 hpf)
- Group 3a (>5 and ≤10 cm, ≤5 mitoses/50 hpf)
- Group 4 (≤2 cm, >5 mitoses/50 hpf)

Probably benign (very low malignant potential, <3% PD)

- Group 5 (>2 and ≤5 cm, ≤5 mitoses/50 hpf)

Low to moderate malignant potential (12%–15% tumor-related mortality)

- Group 6a (>5 and ≤10 cm, >5 mitoses/50 hpf)

High malignant potential (49%–86% tumor-related mortality)

- Group 6b (>10 cm, >5 mitoses/50 hpf)

hpf, high-powered field; PD, progressive disease.


Small Intestinal Gastrointestinal Stromal Tumors

As a group, a larger percentage of small bowel GISTs are malignant when compared to gastric GISTs. The classic benign small intestinal GIST is a small lesion (measuring ≤5 cm) that consists of a uniform population of cytologically bland spindle cells with abundant eosinophilic cytoplasm and an oval low tumor cellularity. The cells are usually distributed in nests separated by fine fibrovascular septae producing an organoid growth pattern reminiscent of paragangliomas. Eosinophilic collagen globules (skeinoid fibers) are characteristic and are often numerous, especially in jejunoileal lesions [Fig. 19.12]. The tumors are most common in small, subserosa, less active tumors; focal calcifications may be present. Nuclear palisading suggestive of neural tumors occurs in many tumors. The tumors may also contain distinctive tumor necrosis, serpiginous or hemorrhagic vascular proliferations lying between the sheets of tumor cells. Perivascular hyalinization is also common [33]. Mitoses are low (less than five per 50 hpf). Benign tumors lack tumor cell necrosis and mucosal invasion [35].
Small intestinal gastrointestinal stromal tumor with skeinoid fibers. A: Hematoxylin and eosin section demonstrating the presence of amorphous aggregates of eosinophilic material typical of skeinoid fibers within the tumor. The tumor cells themselves are round and epithelioidlike in appearance or more elongated. B: Periodic acid–Schiff (PAS) stain demonstrating the PAS positivity of the material.

Malignant small intestinal gastrointestinal stromal tumor. A: Low-power photograph showing the presence of a cellular spindle cell lesion with numerous mitoses (arrows). B: Gross features of the lesion shown in A. A mass surrounds the bowel.

Most malignant small intestinal GISTs consist of highly cellular spindle cell proliferations with more synaptophysin and watery, but not null, malignant small intestinal GISTs have tumor cell necrosis and/or mucosal invasion. Tumors with a camouflaged epithelioid component complicating more than 25% of the tumor are usually locally malignant (36,37). Since many malignant small intestinal GISTs contain benign areas, as well as malignant areas, these tumors should be well sampled to detect the malignant areas. In some cases, small intestinal GISTs are divided into the six categories shown in Table 19.3. Significant prognostic factors include tumor size (tumor sizes greater than 5 cm), tumor mitotic rate (five or more mitoses per 50 hpf), the presence of tumor necrosis, an epithelioid histology, the absence of hyalinized vessels and skeinoid fibers, and the presence of mucosal invasion (33,38).

Table 19.3: Miettinen Classification of Small Intestinal Gastrointestinal Stromal Tumors

<table>
<thead>
<tr>
<th>Group Size</th>
<th>Mitoses</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 cm</td>
<td>≤ 5 mitoses/50 hpf</td>
<td>Generally behave in benign fashion</td>
</tr>
<tr>
<td>&gt; 2–5 cm</td>
<td>≤ 5 mitoses/50 hpf</td>
<td>6% develop metastases and die of their disease</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>≤ 5 mitoses/50 hpf</td>
<td>31% develop metastases; median survival 18 months</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>&gt; 5 mitoses/50 hpf</td>
<td>3% have no tumors in this group</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>&gt; 5 mitoses/50 hpf</td>
<td>50% risk intra-abdominal spread, metastasis, or death</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>&gt; 5 mitoses/50 hpf</td>
<td>86% intra-abdominal spread or metastasis</td>
</tr>
</tbody>
</table>

hpf, high power field.


Appendiceal and Large Intestinal Gastrointestinal Stromal Tumors

Appendiceal GISTs are spindle cell tumors that may contain skeinoid fibers. They lack atypia and mitotic activity (39). Colorectal GISTs are almost always spindle cell tumors, of which 50% are malignant, often with a highly aggressive clinical course. An infiltrative tumor, greater than 5 mitoses per 50 hpf (h), and mucosal invasion (Fig. 19.26) correlate with metastases or death. The prognostic impact of tumor size is more controversial than in tumors arising in other locations (40). Colonic GISTs that contain skeinoid fibers have a better prognosis than those without them. Occasionally, malignant large intestinal GISTs contain osteoclast-like giant cells (40).

Anorectal GISTs are rare, most arise within the muscularis propria (41). They are generally a homogeneous group of cellular tumors composed predominantly of spindle cells, skeletal fibers are absent. Small submucosal lesions without mitoses and lack of abnormal features in a benign fashion (41,42).

Histologic Features of Gastrointestinal Stromal Tumors Following Treatment

Treated tumors may change their histology following treatment. Spindle cell tumors may develop an epithelioid or pseudosarcomatous epithelioid growth pattern characterized by rounded cells with an eosinophilic cytoplasm and uniform nuclei to avoid nuclei. There is a decrease in tumor cell density with the formation of a myxoid stroma, extension hemorrhage, necrosis, and cystic transformation. There is usually a marked decrease in its proliferative rate (h). The tumor may lose all CD117 positivity with only a few residual positive cells (h). Some tumors also become COX-2 negative. Some tumors become desmoplastic positive (h).

Table 19.4: c-kit–expressing Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>c-kit–Expressing Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISTs</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>GISTs</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Melanotic schwannomas</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>Synovial sarcomas</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Malignant gliomas</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>Seminomas</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Malignant fibrous histiocytoma</td>
</tr>
<tr>
<td>Angiomatoid fibrous hemanofibroma</td>
<td>Mesenchymal tumors</td>
</tr>
<tr>
<td>GISTs, gastrointestinal stromal tumors; PNET, primitive neuroectodermal tumor.</td>
<td></td>
</tr>
</tbody>
</table>

Immunohistochemical Features of Gastrointestinal Stromal Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Immunohistochemical Features of Gastrointestinal Stromal Tumors</th>
</tr>
</thead>
</table>
Chapter 19

The definitive marker for a GIST (benign and malignant) is c-kit protein (CD117) expression (26,46). However, c-kit immunoreactivity can be seen in other tumors (Table 19.6) and not all GISTs are positive. The interpretation of the staining patterns is complicated by the fact that there are several commercially available antibodies and variable staining methodologies may result in false-positive and false-negative results. Additionally, CD117 positivity may be lost in treated tumors. Efforts are currently under way to validate c-kit staining. Further, CD117 immunohistochemistry is available in most major pathology laboratories, and some dilution occurs in tumors (45). The predominant pattern of staining is a diffuse cytoplasmic positivity (Fig. 19.25). Membrane staining or dotlike positivity is also seen in a minority of cases. CD117 immunoreactivity can be helpful in discriminating between c-kit-negative GISTs and other mesenchymal lesions. Other mesenchymal tumors may have a positive reaction for a subset of monoclonal antibodies (46). Approximately 70% of GISTs express CD34 (Fig. 19.26) (47). CD34 immunoreactivity varies from 67% in small intestinal GISTs to 10% in rectal and extraperitoneal tumors. Absence of CD34 expression in benign GISTs may indicate that they arise from more mature ICCs, whereas malignant GISTs may contain dedifferentiated ICCs that also express CD34 (48).

GISTs are variably positive with both smooth muscle (Fig. 19.27) and neural markers. Smooth muscle actin expression is most common in small intestinal GISTs (47) and variable in rectal and extraperitoneal GISTs (10–15%), whereas neural markers are not expressed in most cases. Another important marker is cytokeratin (Fig. 19.28). Eighty percent of GISTs stain with BCL2 (49). GISTs also express the intermediate filament nestin, a protein that is not expressed in other mesenchymal tumors, unless there is neural differentiation (50). Almost 100% of GISTs strongly express the dog1 (discovered in GISTs) gene. The cell surface protein expression is highly specific for GISTs (51). PKC conversion is positive in up to 96% of GISTs (52). The GANT variant of GIST may show patchy immunostaining for neuron-specific enolase (NSE), S100, synaptophysin, vasoactive intestinal polypeptide, substance P, chromogranin, and neurofilament protein. Muscle cell markers are variably positive.

Differential Diagnosis

Because the morphologic spectrum of GISTs is wide, the differential diagnosis is also wide. It includes smooth muscle tumors, schwannomas, malignant peripheral nerve sheath tumors, solitary fibrous tumors, inflammatory fibroblastic tumors, synovial sarcomas, mesothelioma, rhabdomyosarcoma, leiomyosarcoma, and angiosarcoma. Immunohistochemical analysis is required to distinguish among the entities within this differential diagnosis (Table 19.6). CD117 expression confirms the diagnosis in most tumors. Malignant major GISTs express CD34 in the absence of CD117. Since some epithelial GISTs show intratumor immunoreactivity, coexpression of either CD34 or CD117 becomes critical in avoiding misdiagnosing these cases as carcinomas. Inflammatory GISTs raise the differential diagnosis of follicular dendritic cell sarcoma, inflammatory myofibroblastic tumor, inflammatory myoepithelial carcinoma, inflammatory malignant fibrous sarcoma, and inflammatory fibroepithelial process.

| Table 19.5 Differential Diagnosis of Gastrointestinal Stromal Tumors (GISTs) |
|---------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Epithelial GISTs                | CD117  | CD138  | CD34   | CR     | CK     | S100   | Melan A | BMB45  | SVN    | VIM    | Desmin | SM actin | HHC35  | CD99   |
| GIST                           | 98%+   | 70%+   | 70%+   | 70%+   | 30%+   | 30%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Mesothelioma                   | 70%+   | 50%+   | 30%+   | 30%    | 30%+   | 30%+   | 30%+    | 30%+    | 30%+   | 30%+   | 30%+   | 30%+    | 30%+    | 30%+   |
| Carcinoma                     | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Paraganglioma                  | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Carcinoid tumor                | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Lymphoma                      | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Leiomyosarcoma                 | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Spindle Cell GISTs             | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| GIST                           | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Schwannoma                     | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Leiomyosarcoma                 | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| leiomyosarcoma                 | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
| Neurofibroma                   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   | 50%+   | 50%+   | 50%+    | 50%+    | 50%+   |
TABLE 19.8 Molecular Classification of Gastrointestinal Stromal Tumors (GISTs)

<table>
<thead>
<tr>
<th>GIST Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic GIST</td>
<td>KIT mutation</td>
</tr>
<tr>
<td>Exon 11</td>
<td>Best response to imatinib</td>
</tr>
<tr>
<td>Exon 9</td>
<td>Intermediate response to imatinib</td>
</tr>
<tr>
<td>Exon 13</td>
<td>Sensitivity to imatinib in vitro, clinical responses observed</td>
</tr>
<tr>
<td>PDGFRA mutation</td>
<td>Exon 12</td>
</tr>
<tr>
<td>Exon 18</td>
<td>D842V has poor response to imatinib; other mutations are sensitive</td>
</tr>
<tr>
<td>Wild-type</td>
<td>Poor response to imatinib</td>
</tr>
<tr>
<td>Familial GIST</td>
<td>KIT exon 11 (V560A, dV559, W557R)</td>
</tr>
<tr>
<td>KIT exon 13 (K542D)</td>
<td>No skin pigmentation or myositis</td>
</tr>
<tr>
<td>KIT exon 17 (D820V)</td>
<td>No skin-pigmentation or myositis; aberrations in suspensepid gladular metastases</td>
</tr>
<tr>
<td>GIST with paraganglioma</td>
<td>Autoimmune dominant; endocrine symptom common</td>
</tr>
<tr>
<td>Pediatric GIST</td>
<td>Sporadic GIST</td>
</tr>
<tr>
<td>Carney complex</td>
<td>Gastro GIST with pulmonary chondroma and/or paraganglioma; femур/male ratio = 7:1; no KIT mutations identified</td>
</tr>
<tr>
<td>NF1-related GIST</td>
<td>No KIT Mutations Identified</td>
</tr>
<tr>
<td>NF1-neurofibromatosis type 1; PDGFRA, placental-derived growth factor receptor-α.</td>
<td></td>
</tr>
</tbody>
</table>

Occasionally, however, DPL may progress, recur, or undergo malignant transformation. Mitotic figures are rare (less than two mitoses per 100 hpf). Atypical mitoses are absent. The histogenesis of DPL cases behave in a clinically benign fashion and, in some cases, the lesions may partially or completely regress.

**Leiomyomatosis Peritonealis Disseminata**

Disseminated peritoneal leiomyomatosis (DPL) typically affects women in the reproductive age group; many are pregnant, perimenopausal, or taking oral contraceptives. Symptoms (pelvic pain and abnormal uterine bleeding) usually result from congestion of the muscularis propria and not from the lesions themselves. Occasionally, small (millimeter) nodules may be found in the smooth muscle of the uterus, fallopian tubes, and ovaries.

**Epstein-Barr Virus–Associated Smooth Muscle Tumors**

Epstein-Barr virus (EBV)-associated smooth muscle tumors are rare lesions that develop in immunocompromised individuals, particularly pediatric AIDS patients and organ transplant recipients. The lesions typically develop in children under the age of 10 (74). In transplant patients, the tumors usually develop 3–5 years after the transplant surgery. The tumors differ from conventional leiomyomas in that the tumors are frequently multiple and in housing microcalcifications that appear on imaging studies.

**Epstein-Barr Virus–Associated Smooth Muscle Tumors**

Epstein-Barr virus (EBV) usually results from multiple independent primary tumors (i.e., each tumor is an independent event) or metastases from a single primary tumor. Most data support multiple infection events (74).

**Leiomyomatosis Peritonealis Disseminata**

Leiomyomatosis peritonealis disseminata (LPD) is a rare, benign, nonneoplastic condition that affects the peritoneum. The disease is characterized by the presence of nodules composed of smooth muscle cells that have a benign histological appearance. The nodules may range in size from 0.1 to 5 cm and can be found throughout the peritoneal cavity, including the omentum, mesentery, and serosa of the bowel and uterus.

**Epstein-Barr Virus–Associated Smooth Muscle Tumors**

Epstein-Barr virus (EBV) is implicated in the development of smooth muscle tumors in immunocompromised individuals, particularly pediatric AIDS patients and organ transplant recipients. The tumors typically develop in children under the age of 10 (74). In transplant patients, the tumors usually develop 3–5 years after the transplant surgery. The tumors differ from conventional leiomyomas in that the tumors are frequently multiple and in some cases, the lesions may partially or completely regress.

**Disseminated Peritoneal Leiomyomatosis (Leiomyomatosis Peritonealis Disseminata)**

Disseminated peritoneal leiomyomatosis (DPL) typically affects women in the reproductive age group; many are pregnant, perimenopausal, or taking oral contraceptives. Symptoms (pelvic pain and abnormal uterine bleeding) usually result from congestion of the muscularis propria and not from the lesions themselves. Occasionally, small (millimeter) nodules may be found in the smooth muscle of the uterus, fallopian tubes, and ovaries.

**Smooth Muscle Hamartomas**

Smooth muscle hamartomas develop spontaneously or in the setting of tuberous sclerosis or Cowden syndrome. They present as a single or multiple, sessile, or, rarely, pedunculated, intramural polyps. The hamartomas consist of proliferating, mature, spindle-shaped smooth muscle cells arranged in interwoven bundles that replace the lamina propria and entrap the epithelium (Fig. 19.31). They may also be fibrous tissue proliferation.
Chapter 19

Smooth muscle hamartomas differ from Peutz-Jeghers–associated hamartomas in that the latter contain prominent arborizing smooth muscle proliferations that divide the epithelium and its surrounding normal-appearing lamina propria into segments. In contrast, smooth muscle hamartomas show proliferating smooth muscle cells obliterating
P.1224
the lamina propria lying between the crypts without the prominent smooth muscle arborizations. Hamartomas also differ from leiomyomas in that leiomyomas are generally solitary and well circumscribed.

FIG. 19.32. Small intestinal leiomyosarcoma. A: These spindle cell lesions typically show much more pleomorphism and atypical mitoses than malignant gastrointestinal stromal tumors. B: Actin immunostain of the same lesion. The tumor was kit negative.

Leiomyosarcomas
True leiomyosarcomas do develop in the luminal gut, the omentum, and the mesentery, but they are not nearly as common as GISTs. Leiomyosarcomas, particularly vascular ones, affect older individuals. Leiomyosarcomas generally present in the same way as malignant GISTs, often as luminal, sometimes ulcerated, polypoid tumors (40). Grossly, the lesions appear lobular, gray-beige with pinkish tan areas and greenish areas of necrosis (50). The tumors range in size from
10 to 23 cm and may be multiple.
Gastrointestinal, omental, and mesenteric leiomyosarcomas contain well-differentiated smooth muscle cells with elongated or oval, often blunt-ended (cigar-shaped) atypical nuclei and eosinophilic cytoplasm. The tumors resemble soft tissue leiomyosarcomas. All of the tumors exhibit nuclear pleomorphism, which, unlike GISTs, can be extensive (Fig. 19.32). Coagulative necrosis is usually present; skeinoid fibers are absent. Mitotic activity is often high (sometimes >50
mitoses/50 hpf) (88). The differential diagnosis includes the entities listed in Table 19.5. Leiomyosarcomas are globally positive for α-smooth muscle actin and variably positive for desmin. They may be focally positive for cytokeratin-18, but negative for cytokeratin-19. The tumors are negative for CD34, CD117, S110, glial fibrillary acidic protein (GFAP), and other neural markers. Leiomyosarcomas lack KIT mutations.
Leiomyosarcomas are treated with surgical resection. Lesions that are completely excised may be cured. However, tumors with positive tumor margins tend to recur locally as well as metastasize to the liver, causing patient death (88).

Neural Tumors
Primary gastrointestinal neurogenic tumors are rare. They fall into two major groups: Those of peripheral nerve sheath origin (schwannomas, neurofibromas, ganglioneuromas, neuromas, and perineuromas) and those arising from the sympathetic or chromaffin system (neuroblastomas, ganglioneuromas, and paragangliomas).

Schwann Cell Tumors
Isolated gastrointestinal schwannomas constitute only 2% to 6% of all GI mesenchymal tumors and 0.2% of all gastric tumors. Patients range in age from 10 to 81 years with an average age of 52.6 (89). Women are slightly more commonly affected than men. Gastrointestinal Schwann cell
P.1225
tumors are particularly common in NF1 patients (90). Some patients have associated lesions (conditions), including colonic adenomas or Gorlin syndrome (90). The clinical features vary depending on lesional size and location. They present in the same ways as GISTs. Schwannomas preferentially affect the stomach (91) followed by the colon and rectum (92). Less commonly, they arise in the small intestine and esophagus. A subset of schwannomas, the benign mucosal
epithelioid nerve sheath tumors, preferentially affects the colon (93), although this may reflect the large number of colonic biopsies that are examined annually.

FIG. 19.33. Gastric schwannoma. A: Cut section of a pigmented gastric schwannoma. The overlying mucosal surface is not ulcerated. B: Whole mount of the lesion shown in A. Note pushing margins and lack of necrosis or hemorrhage.
Schwannomas average 6.4 cm in diameter with a range of 0.5 to 14 cm. Grossly and endoscopically, they resemble other mesenchymal neoplasms (Fig. 19.33). They arise in the submucosa and muscularis propria and are usually covered by an intact mucosa. Larger tumors ulcerate. These spherical or ovoid tumors may protrude into the bowel lumen in a polypoid fashion, or they may lie primarily in an intramural location or present as a subserosal mass projecting from the
antimesenteric bowel surface (Fig. 19.34). Schwann cell tumors may grossly appear to be well encapsulated, but histologically they interdigitate with the surrounding stroma. Schwannomas are generally glistening, rubbery to firm, yellow, white-tan tumors, often with speckled cut surfaces resembling soft tissue schwannomas. Myxoid areas may be present. An exceptional schwannoma diffusely involved the entire large bowel (94).
Most schwannomas arise from the myenteric plexus (Fig. 19.35). Benign schwannomas consist almost entirely of Schwann cells without neurites (Fig. 19.36). They contain woven nests of compact bundles of slender, wavy S100-positive spindle cells admixed with a loose myxoid stroma. The tumor cells may also form compact fascicles, occasionally aligning in rows or vague palisades (Verocay bodies). Some exhibit classic Antoni A and B areas, although these are
commonly absent (95). Individual cells have a distinct eosinophilic cytoplasm. The dark fusiform nuclei vary in shape and size. Pleomorphism is generally mild, although some tumors focally may show significant nuclear atypia. However, even in these areas the nuclei have a uniform chromatin distribution. Mitotic activity is minimal to scanty and never exceeds five mitoses per 50 hpf. When the tumor bundles are cut transversely, the cells appear round and epithelioid. The
cells are often intimately admixed with collagenous fibers highlighted by trichrome stains. Schwannomas often contain a sprinkling of lymphocytes and mast cells. Features unique to GI schwannomas include peripheral lymphoid cuffs and an uncommon microtrabecular pattern (95). The peripheral lymphoid foci sometimes contain germinal centers. GI schwannomas also differ from their soft tissue counterparts in that they often lack hyalinized blood vessels, a fibrous capsule,
or degenerative changes (95).
Mucosal benign epithelioid nerve sheath tumors, a subset of GI schwannomas, show an infiltrative growth pattern and consist of spindled to predominantly epithelioid cells arranged in nests and whorls. The lesions center in the lamina propria and extend toward the mucosal surface and superficial submucosa. The proliferating cells contain uniform round to oval nuclei with frequent intranuclear pseudoinclusions and an eosinophilic fibrillary cytoplasm. The lesion may be
surrounded by eosinophils (93).
The vast majority of schwannomas are benign. Histologic criteria for the diagnosis of malignancy are based on the number of mitotic figures, cellularity, nuclear atypia, and tumor necrosis. A rare esophageal malignant schwannoma measuring 8.2 cm in diameter contained a proliferation of
P.1226
spindle-shaped cells with variably sized, chromatin-rich nuclei and a palisading structure. The nuclei showed marked atypia with high cellularity without necrosis and minimal mitotic activity. Nonetheless, metastases were present in the regional lymph nodes (96).



Schwannomas may show melanocytic differentiation (Fig. 19.37) and other mesenchymal elements. Tumors containing skeletal muscle cells are called leiomyosarcoma (Fig. 19.38). Schwannomas are diffusely S100 (nuclear and cytoplasmic) and vimentin positive. Schwannomas are also immunoreactive for Leu7, laminin, GFAP, and PGP 9.5. Most tumors are also positive for nestin, a marker also commonly expressed in GISTs (50). Epithelial membrane antigen staining is limited to the neoplastic peripheral cells. The tumors are also variably positive for CD34+ (95). They are CD117, smooth muscle actin, and desmin negative unless they contain heterologous elements (Fig. 19.36).

Tumors without (ominous) dysplasia or significant mitotic activity generally follow a benign clinical course. Malignant tumors require resection.

Perineuromas

Perineuromas are rare benign peripheral nerve sheath tumors. They generally arise in soft tissues and only a handful of cases have been reported in the stomach and intestine (77). There is a marked female predominance. The age of diagnosis ranges from 55 to 70, with a median age of 51. Most lesions present as small sessile polyps often found during routine screening for colorectal cancers. Rare tumors present with abdominal pain or GI bleeding. One unusual case presented with intermittent abdominal pain, nausea, and vomiting, culminating in small bowel obstruction and necessitating partial resection (97).

Incidentally detected colorectal tumors range in size from 0.2 to 0.6 cm. The tumors arise in the mucosa or submucosa and measure 3 to 5 mm in size. The cut surfaces of these well-circumscribed tumors appear smooth without necrosis. Histologically, perineuromas consist of proliferation of cytologically bland spindle cells with avid to tapered nuclei. The eosinophilic cells have pale, indistinct, elongated, lipoidal cytoplasmic processes. The lesions may show a focal whorled growth pattern. Immunohistochemistry may reveal the fibroblastic nature of the neoplastic cells. The cells lack cytologic atypia, mitotic activity, or pleomorphism. A fine collagenous stroma lies among the tumor cells.

The tumors are epithelial membrane antigen (EMA), vimentin, and neural cell adhesion molecule (NCAM) positive. EMA positivity ranges from very strong in some areas to very weak in others. This is due to the in situ nature of the cell cytoplasmic processes. Fifty percent of cases are positive for the tight junction–associated protein claudin-1 (97).

All tumors are negative for S100 protein, GFAP, neurofilament protein, smooth muscle actin, desmin, caldesmon, CD117, and keratin. The differential diagnosis includes ganglioneuroma, neurofibromatosis, and leiomyomas (Table 19.8).

Neurofibromatosis

Gastrointestinal neurofibromas develop either as sporadic isolated lesions or as a more diffuse GI involvement in NF1 patients. NF1, an autosomal dominant disorder, affects at least 1 in every 3,000 people, making it one of the most common inherited human diseases. Approximately 25% of all NF1 patients develop gastrointestinal neurofibromas, including neurofibromas as well as enteric tumors (Table 19.9).

The NF1 gene resides on chromosome 17q11.2. NF1 alterations include translocations, deletions, insertions, and point mutations, all of which interrupt the coding sequence. The NF1 gene product neurofibromin reduces signal transduction by accelerating inactivation of the ras protooncogene (98). NF1 is a tumor suppressor gene that regulates a number of cellular processes including the extracellular signal–related kinase (ERK) mitogen-activated protein (MAP) cascade, adenyl cyclase, and cytoskeletal assembly. NF1 mutations generally lead to an increased risk of both benign and malignant tumors, especially malignant peripheral nerve sheath tumors (MPNSTs). The development of MPNSTs is a multistage process involving many altered cell cycle regulators in addition to the biallelic inactivation of the NF1 gene. Other altered genes include p16 and p53 (98,100). Neurofibromas also aberrantly express the epidermal growth factor receptor (EGFR) and suggest a possible relationship between NF1 and hereditary nonpolyposis colorectal cancer syndrome. Children who have homozgous somatic NF1 mutations exhibit clinical features of NF1 and early onset of extracutaneous tumors including hemangioendothelioma and central nervous system megacell carcinomas (101). Most of these patients do not develop gastrointestinal neurofibromas, but one report of two patients with homozgous NF1 mutations did show coatic and small intestinal neoplasms in addition to NF1-like features (102).

TABLE 19.8 Intramural Perineuroma: Differential Diagnosis

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Types</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>GISTs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Schwannomas</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Perineuromas</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Leiomyomas</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; GISTs, gastrointestinal stromal tumors; IHC, immunohistochemistry; NF, neurofibromatosis; PDGFRα, platelet-derived growth factor receptor-α.

FIG. 19.37. Histology of the lesion shown in Figure 19.33. A: Gastric schwannoma demonstrating Antoni A and Antoni B zones. B: Pigmented Schwann cells are present. C: Malignant schwannoma with numerous mitotic figures and melanin-containing Schwann cells.

Seven important components characterize NF1 patients; two must be present to establish the diagnosis (103) (Table 19.10). In addition to the dysplastic tumors and benign and malignant tumors, NF1 patients also tend to have a shorter than normal stature, and up to 60% of patients suffer from a learning disability.

Neurofibromas, present in small numbers during childhood, becoming more numerous with growth, puberty, pregnancy, and advancing age. Of neurofibromas, cause keloidal nodules, atrophy, subcutaneous, and other problems. Megalocytes and pseudo-destruction affect 10% of patients due to neurofibroma disseminatum (Fig. 19.36) (103). Neurofibromas most commonly develop in the jejunum, followed by the stomach, small intestine, colon (103), and oesophagus. Rare lesions arise in the mesocorpus and appendix (103). The tumors are usually subcutaneous unless the patient has NF1, in which case multiple nodular and mucosal polypoid nodules develop (Fig. 19.40) (104). Most neurofibromas arise from the myenteric plexus and project from the serous-serosal surface of the bowel. Rarely, they present as polyps.

Neurofibromas appear as encapsulated or nonencapsulated spherical or cylindrical tumors.

Neurofibromas consist of a mixture of ganglion cells with plump dark nuclei, small clear cytoplasm, and varying amounts of myxoid stroma. The cells include Schwann cells, perineurial cells, fibroblasts, endothelial cells, mast cells, and occasional axons, along with scattered neurons and, rarely, melanocytes (Figs. 18.41). Definitive characteristics exist for each of the five major cell types present in these lesions (Table 19.11). A storiform pattern may be seen, but this is uncommon.

Neurofibromas contain large numbers of mast cells. In NF1 patients, proliferation of nerve fibers involve the lamina propria, submucosa, and/or serosa (Fig. 18.61). Submucosal lesions that extend through the muscularis mucosae may separate the elevating cycle, causing the lesion to resemble a submucosal polyp or a perineurioma. Nerve fibers often appear abnormally with a prominent decrease in the number of argyrophilic neurons and a marked increase in nerve fibers, particularly in the descending and sigmoid colon. Because of the increased density, the circular and longitudinal muscle layers become both atrophic and hypertrophic. The neurofibromas are frequently pleomorphic in the setting of NF1.

Neurofibromas are not usually removed in the setting of NF1 due to their large number and the lack of symptoms in small lesions. Symptomatic larger lesions or those that cause secondary problems such as ulcers or intraepithelial are resected. Currently, clinical trials in NF1 patients are evaluating the efficacy of epidermal growth factor receptor (EGFR) inhibitors in the treatment of these tumors.

### TABLE 19.9 Gastrointestinal Lesions Seen with Increased Frequency in Neurofibromatosis Type 1 Patients

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromas</td>
<td>Spherical or cylindrical tumors.</td>
</tr>
<tr>
<td></td>
<td>Contain large numbers of mast cells.</td>
</tr>
<tr>
<td></td>
<td>May appear as encapsulated or nonencapsulated tumors.</td>
</tr>
<tr>
<td></td>
<td>Consist of a mixture of ganglion cells with plump dark nuclei.</td>
</tr>
<tr>
<td></td>
<td>Small clear cytoplasm, myxoid stroma, and varying amounts of myxoid stroma.</td>
</tr>
<tr>
<td></td>
<td>Include Schwann cells, perineurial cells, fibroblasts, endothelial cells,</td>
</tr>
<tr>
<td></td>
<td>mast cells, and occasional axons.</td>
</tr>
<tr>
<td></td>
<td>May expand through the muscularis mucosae.</td>
</tr>
<tr>
<td></td>
<td>May resemble submucosal polyps or perineuriomas.</td>
</tr>
<tr>
<td></td>
<td>Nerve fibers may appear abnormally.</td>
</tr>
<tr>
<td></td>
<td>May cause secondary problems such as ulcers or intraepithelial resections.</td>
</tr>
</tbody>
</table>
Chapter 19

Neurofibromas
Schwannomas
Dopaminecontaining tumors
Neuroendocrine tumors
Ganglionocytoma
Gangliogliomas
Duodenal carcinoid tumors
Somatostatinomas
Gastrointestinal stromal tumors
Paragangliomas
Gangliocytic paragangliomas
Ganglieneuromas
Esophageal hyperplastic polyps
Hyperplasia of the enteric nervous system
Gastrointestinal adenocarcinomas
Intestinal adenomas
Intestinal malignant mixed tumors

Neuromas
Spontaneous neuromas develop almost exclusively in the appendix unless there is pre-existing trauma, in which case traumatic neuromas develop. Appendiceal neuromas are discussed in Chapter 8. Traumatic neuromas consist of proliferating endoneural and perineural connective tissue. Schwann cells, and regenerating neurons. When a nerve is damaged, the zone of the central stump of the distal end of the normal segment proximal to the site of injury begins to sprout by budding and then grows in a zigzag fashion. Traumatic neuromas develop near anastomotic sites or following other bowel injuries.

Malignant Peripheral Nerve Sheath Tumors
MPNSTs often affect NF1 patients and usually exhibit Schwann cell differentiation. However, since not all tumors in this group are clearly schwannian in origin, most prefer the diagnosis of MPNST for this group of neoplasms. These tumors are characterized by overgrowth of nerve sheath cells, including Schwann cells, and by the presence of mitotic activity. Other features include the presence of necrosis, atypia, and embryonal elements.

TABLE 19.10 Features of Neurofibromatosis

- Six or more café-au-lait spots (macules), the greatest diameter of which measures >3 mm in prepubertal patients and >15 mm in postpubertal patients
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal region
- Optic gliomas
- Two or more Lisch nodules
- A distinctive osseous lesion known as sphenoid dysplasia or pseudoarthrosis
- A first-degree relative with the diagnosis of neurofibromatosis type 1 defined by the preceding criteria

Other tumors resemble neurofibromas and mitotic activity is important in identifying these lesions as malignant. Other features suggestive of malignancy include the presence of focal, dense cellularity or necrosis. Occasional cases display extreme nuclear pleomorphism with a malignant fibrous histiocytoma (MFH) like appearance. Any tumor containing more than one mitotic figure per 20 hpf should be construed as evidence of potential malignant behavior.

TABLE 19.11 Immunoreactivity of Cells in Neurofibromas


FIG. 19.40. Neurofibromatosis coli. A: Partial small intestinal reaction demonstrating numerous small, pedunculated serosal and subserosal polypoid lesions. B: Higher-power view of small intestinal neurofibromatosis. (Courtesy of Dr. G. Atkinson, Department of Pathology, Presbyterian Hospital, Albuquerque, NM.)

FIG. 19.41. Neurofibromatosi coli a. Focal neurofibromatous proliferation elevating overlying mucosa and producing a "polyp." B: Intercalating bundles of nerves, Schwann cells, and fibroblasts. C: Area of proliferating neurons, Schwann cells, and fibroblasts arising from nerve. (Courtesy of Dr. G. Atkinson, Department of Pathology, Presbyterian Hospital, Albuquerque, NM.)

Lessons that can be especially difficult to diagnose are those that are superficially epithelioid in nature. These tumors typically grow in a nodular pattern, usually associated with necrosis, and may be confused with either a melanoma or carcinoma since the epithelial cells are often packed and grow in sheets. The cytoplasm of the epithelial cells is pale and the nuclei are usually rounded with evenly dispersed chromatin or prominent nucleoli. Strong positivity is seen in 50% to 75% of all MPNSTs. This staining is never diffuse and its positivity is as strong as in cellular schwannomas. Some MPNSTs show perineural differentiation that is recognized by significant SMA reactivity.
Gangliomatous polyposis

The lesions develop in the stomach and duodenum of elderly men and women. The stalks are pedunculated and are usually less than 1 cm in diameter. The lesions usually present as multiple polyps, but they may also be solitary. The lesions are usually asymptomatic, but they may cause abdominal pain, nausea, vomiting, or bleeding. The lesions are often found during endoscopic or surgical procedures performed for other reasons. The lesions are benign and do not require treatment, except for lesions that cause symptoms or are unsightly. The lesions are usually found in patients with familial adenomatous polyposis, multiple cutaneous lipomas and extraintestinal neurofibromas, or other syndromes associated with gangliomatous polyposis.

Isolated Ganglioneuroma

Isolated ganglioneuromas are rare and are usually found in children or young adults. The lesions are usually solitary and are usually located in the appendix, duodenum, or ileum. The lesions are usually asymptomatic, but they may cause abdominal pain, nausea, vomiting, or bleeding. The lesions are usually found during endoscopic or surgical procedures performed for other reasons. The lesions are benign and do not require treatment, except for lesions that cause symptoms or are unsightly. The lesions are usually found in patients with familial adenomatous polyposis, multiple cutaneous lipomas and extraintestinal neurofibromas, or other syndromes associated with gangliomatous polyposis.

Diffuse Ganglioneuromatosis

Diffuse ganglioneuromatosis is a rare condition that is characterized by the presence of multiple ganglioneuromas throughout the gastrointestinal tract. The lesions are usually asymptomatic, but they may cause abdominal pain, nausea, vomiting, or bleeding. The lesions are usually found during endoscopic or surgical procedures performed for other reasons. The lesions are benign and do not require treatment, except for lesions that cause symptoms or are unsightly. The lesions are usually found in patients with familial adenomatous polyposis, multiple cutaneous lipomas and extraintestinal neurofibromas, or other syndromes associated with gangliomatous polyposis.

Gangliomatous Polyposis

The lesions are usually solitary and are usually located in the appendix, duodenum, or ileum. The lesions are usually asymptomatic, but they may cause abdominal pain, nausea, vomiting, or bleeding. The lesions are usually found during endoscopic or surgical procedures performed for other reasons. The lesions are benign and do not require treatment, except for lesions that cause symptoms or are unsightly. The lesions are usually found in patients with familial adenomatous polyposis, multiple cutaneous lipomas and extraintestinal neurofibromas, or other syndromes associated with gangliomatous polyposis.
Chapter 19

**FIG. 19.44.** Patient with juvenile polyposis coli and ganglioneuromatosis. Low-power magnification of the mucosa demonstrating the replacement of the muscularis mucosae with proliferation of neurofibromatous-like elements as well as isolated ganglion cells.

Diffuse ganglioneuromatosis consists of nodular, usually transmural proliferations of nerve fibers, ganglion cells, and supporting cells of the extrinsic nervous system. The growth pattern varies from multifocal to hyperplastic expansions of the myenteric plexus to confluent irregular lamellar ganglioneuromatous proliferations that destroy the myenteric plexus and infiltrate the adjacent bowel wall. The histopathologic changes are highlighted by antibodies directed at S100, GFAP, chromogranin A, and synaptophysin. These lesions represent a complex hyperplasia of peptidergic, cholinergic, and probably adrenergic nerve fibers instead of a selective overgrowth of one type of nerve fiber (117). Transmural ganglioneuromatosis exhibit increased immunoreactivity for vascular smooth muscle actin, nerve growth factor, kallikrein, and somatostatin (118). In patients with the transmural form of the disease, there may be associated intestinal hamartomatous polyps (119) and neurofibromatous-like hyperplasia.

**Paragangliomas**

Rare gastrointestinal paragangliomas affect the esophagus, stomach, and small bowel, especially the duodenum (Fig. 19.45) (120,121,122). Abdominal paragangliomas are usually sporadic lesions, although familial forms have been reported (123). These familial forms associate with pheochromocytomas in the SDH4, SDH5, and SDH6 genes (124,125,126). Some patients have NF1 (127), MEN-2 (128), von Hippel-Lindau disease (129), the Carney triad (5), or a variant GIST-spectrum syndrome (129). In the latter setting the paragangliomas are frequently multifocal and extra-adrenal (129). Paragangliomas may be large, measuring up to 10 cm or diameter. Unlike ganglioneuromatous paragangliomas, they do not primarily affect the submucosa but rather the bowel from its external surface. The tumors appear grayish white with multiple cystic and hemorrhagic foci histologically resembling paragangliomas arising elsewhere. They consist of spindled cells (Schwann cells) and round or polygonal epithelioid cells arranged in a lobular or alveolar pattern. The epithelioid cells are argyrophilic and surrounded by a capillary network. The tumors lack the neurofibromatous and carcinoid-like components found in ganglioneuromatous paragangliomas. Malignant tumors contain significant pleomorphism and numerous mitoses. Immunoperoxidase staining is an unreliable criterion of malignancy, contrasting with mitotic activity and vascular invasion. There is diffuse cytokeratin positivity for GFAP and NSE in most cells. Chromogranin A and synaptophysin positivity may be more heterogeneous. The tumor cells can be focally positive for neurofilament protein. Cytookeratin staining demonstrates strong reactivity in scattered tumor cells. The tumor may also produce eosinophilic substances such as adrenomedullin (ADT) and vasoactive intestinal peptide. 5-hydroxyindolacetic acid levels highlight the exocrine tumor. An unusual patient with the Carney triad exhibited dual CD117 expression in both a stromal tumor and a paraganglioma (129).

**Granular Cell Tumors**

Gastrointestinal granular cell tumors, once thought to be rare, are now more commonly encountered due to the increased use of upper endoscopy. The tumors develop in individuals from ages 25 to 75, equally affecting men and women and often affecting blacks. Some tumors develop following radiation therapy (130). Granular cell tumors may coexist with other tumors, including GISTs, leiomyosarcomas (131), other granular cell tumors, esophageal squamous cell carcinomas (132), and esophageal adenocarcinomas (133).

Granular cell tumors are often discovered incidentally at the time of esophagoscopy, surgery, or autopsy. Larger lesions are likely to be symptomatic. Symptoms depend on tumor location. Esophageal tumors present with dysphagia. Intestinal tumors present with intractable diarrhea, bleeding, or a mass. Anal lesions cause perianal discomfort and bleeding. Granular cell tumors arise throughout the gastrointestinal tract, but are most common in the esophagus (Figs. 19.46 and 19.47) and large intestines (134). Up to 50% of lesions are malignant within a given organ. Sometimes granular cell tumors develop at several GI sites (135). Most esophageal granular cell tumors arise distally. Gastric granular cell tumors tend to affect the antrum. The tumors usually appear as smooth, waxy, localized, yellowish-white lesions measuring 1 to 4 cm in diameter. They arise in the submucosa or muscularis propria and are covered by an intact mucosa. Larger lesions are often infiltrative (134).

**FIG. 19.45.** Duodenal paraganglioma. A: Whole mount of specimen demonstrating foci of cystic change. B: Histologic features of a typical paraganglioma are present. C: Periodic acid–Schiff stain delineating the presence of prominent basement membranes surrounding the “Zellballen.” D: Reticulin stain demonstrating a pattern similar to that seen in C.

**Granular cell tumors are also classified as either solitary or multiple lesions.** Gastrointestinal granular cell tumors may arise throughout the gastrointestinal tract, but are most common in the esophagus, stomach, small intestine, and colon (134). The tumors may be solitary or multiple. Some patients may have multiple tumors in the same organ (135). Larger tumors are more likely to be malignant (136). Gastric granular cell tumors are randomly distributed between the submucosa and muscularis propria. Smaller lesions may infiltrate or obliterate the muscularis mucosae and extend into the base of the mucosa, between individual glands. The tumor cells are round in shape and are strongly S100 positive.


**FIG. 19.47.** Biopsy of esophageal granular cell tumor. A: The biopsy contained fragments of large eosinophilic cell clusters in a loose stroma. These cells are neuroendocrine in nature. The nuclei are round and small. The cytoplasm is eosinophilic. B: The cells are positive for S100 protein. C: Immunoperoxidase staining with synaptophysin shows that the tumor cells are positive for this neuroendocrine marker.
Lipomatosis and Related Lesions

Gastrointestinal adipose tissue proliferations include lipomas, angiolipomas, liposarcomas, lipomatosis polyposis, and lipomatosis hyperplasia of the ileocecal valve. All of these lesions are neoplastic except the last entity, which is discussed in Chapter 14.

Lipomas

Lipomas predominantly arise in the large bowel (51% to 70%), decreasing in incidence in the small bowel, stomach, and esophagus. In the stomach, the antrum is preferentially affected; in the colon, the right side is preferentially affected.

Lipomas range in incidence from 0.035% to 4% of all intestinal neoplasms. They affect men and women equally and are often found in the stomach or intestines in older adults. They occur in adults as well as children. Most patients with symptomatic lipomas are 60 to 60 years old. Gastrintestinal lipomas are usually solitary, although some patients develop multiple lesions. Small lipomas are usually asymptomatic. Larger lesions may cause abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric lipomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal lipomas may present with rectal polyps.

Large intestinal lipomas range in incidence from 0.035% to 4.4% of all intestinal neoplasms. They affect men and women equally and are more common in the rectosigmoid region of the colon. An exceptional patient was reported in whom there were between 700 and 1,000 polyps. The vast majority were lipomas, but multiple adenomas and hyperplastic polyps were also present.

Diffuse lipomatous polyposis of the colon is rare, affecting both children and adults with a male predominance (145). Patients present with polyposis, weight loss, iron deficiency anemia, and intestinal obstruction.

Grossly, one sees dozens to hundreds of submucosal, sessile, and occasionally pedunculated lesions. The lesions are usually <1 cm in size. Larger lesions may cause symptoms, and larger lesions may be associated with the clinical impression of a mass. The lesions are usually yellow to gray and well demarcated. The lesions are usually submucosal and are not encapsulated.

Histologically, the lesions are composed of mature adipose tissue with an overlying intact or eroded mucosa. In some cases, the lesions may extend into the submucosal tissue, replacing the lamina propria and sometimes displacing the glands.

Areas remain. Such lesions are sometimes termed atypical lipomas. Lipomas consist of sharply circumscribed submucosal masses of mature adipose tissue with an overlying intact or eroded mucosa. They are usually yellow to gray, round, greasy, and encapsulated. Rare lesions develop in the stomach, duodenum, and ileocecal valve. All of these lesions are neoplastic except the last entity, which is discussed in Chapter 14.

Liposarcomas

Liposarcomas are neoplastic lesions of the gastrointestinal tract, occurring at all sites but most commonly in the antrum of the stomach and the transverse colon. They are rare but may occur in the esophagus, jejunum, ileum, cecum, appendix, and rectosigmoid. The lesions are usually solitary but may be multiple. They may be large and cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Mucosal pseudolipomatosis (air within the mucosa) may superficially resemble lipomas. Unlike true lipomas, mucosal pseudolipomatosis consists of irregularly shaped air spaces and the lesions are not encapsulated.

Invasive liposarcomas are neoplastic lesions of the gastrointestinal tract, occurring at all sites but most commonly in the antrum of the stomach and the transverse colon. They are rare but may occur in the esophagus, jejunum, ileum, cecum, appendix, and rectosigmoid. The lesions are usually solitary but may be multiple. They may be large and cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Agranular liposarcoma is a variant of liposarcoma that lacks the characteristic atypical features of other types of liposarcoma. It has a lower incidence of metastases and a better prognosis than other types of liposarcoma. It is characterized by the presence of bland, oval to spindle-shaped cells with a low mitotic rate. The lesions are usually solitary and may be large. They may cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Mucosal pseudolipomatosis (air within the mucosa) may superficially resemble lipomas. Unlike true lipomas, mucosal pseudolipomatosis consists of irregularly shaped air spaces and the lesions are not encapsulated.

Invasive liposarcomas are neoplastic lesions of the gastrointestinal tract, occurring at all sites but most commonly in the antrum of the stomach and the transverse colon. They are rare but may occur in the esophagus, jejunum, ileum, cecum, appendix, and rectosigmoid. The lesions are usually solitary but may be multiple. They may be large and cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Agranular liposarcoma is a variant of liposarcoma that lacks the characteristic atypical features of other types of liposarcoma. It has a lower incidence of metastases and a better prognosis than other types of liposarcoma. It is characterized by the presence of bland, oval to spindle-shaped cells with a low mitotic rate. The lesions are usually solitary and may be large. They may cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Mucosal pseudolipomatosis (air within the mucosa) may superficially resemble lipomas. Unlike true lipomas, mucosal pseudolipomatosis consists of irregularly shaped air spaces and the lesions are not encapsulated.

Invasive liposarcomas are neoplastic lesions of the gastrointestinal tract, occurring at all sites but most commonly in the antrum of the stomach and the transverse colon. They are rare but may occur in the esophagus, jejunum, ileum, cecum, appendix, and rectosigmoid. The lesions are usually solitary but may be multiple. They may be large and cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Agranular liposarcoma is a variant of liposarcoma that lacks the characteristic atypical features of other types of liposarcoma. It has a lower incidence of metastases and a better prognosis than other types of liposarcoma. It is characterized by the presence of bland, oval to spindle-shaped cells with a low mitotic rate. The lesions are usually solitary and may be large. They may cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Mucosal pseudolipomatosis (air within the mucosa) may superficially resemble lipomas. Unlike true lipomas, mucosal pseudolipomatosis consists of irregularly shaped air spaces and the lesions are not encapsulated.

Invasive liposarcomas are neoplastic lesions of the gastrointestinal tract, occurring at all sites but most commonly in the antrum of the stomach and the transverse colon. They are rare but may occur in the esophagus, jejunum, ileum, cecum, appendix, and rectosigmoid. The lesions are usually solitary but may be multiple. They may be large and cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Agranular liposarcoma is a variant of liposarcoma that lacks the characteristic atypical features of other types of liposarcoma. It has a lower incidence of metastases and a better prognosis than other types of liposarcoma. It is characterized by the presence of bland, oval to spindle-shaped cells with a low mitotic rate. The lesions are usually solitary and may be large. They may cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Mucosal pseudolipomatosis (air within the mucosa) may superficially resemble lipomas. Unlike true lipomas, mucosal pseudolipomatosis consists of irregularly shaped air spaces and the lesions are not encapsulated.

Invasive liposarcomas are neoplastic lesions of the gastrointestinal tract, occurring at all sites but most commonly in the antrum of the stomach and the transverse colon. They are rare but may occur in the esophagus, jejunum, ileum, cecum, appendix, and rectosigmoid. The lesions are usually solitary but may be multiple. They may be large and cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Agranular liposarcoma is a variant of liposarcoma that lacks the characteristic atypical features of other types of liposarcoma. It has a lower incidence of metastases and a better prognosis than other types of liposarcoma. It is characterized by the presence of bland, oval to spindle-shaped cells with a low mitotic rate. The lesions are usually solitary and may be large. They may cause symptoms, including abdominal pain, intestinal obstruction, intussusception, and bleeding with iron deficiency anemia. Gastric liposarcomas >3 cm tend to ulcerate, causing peptic ulcer–like symptoms. Anorectal liposarcomas may present with rectal polyps.

Mucosal pseudolipomatosis (air within the mucosa) may superficially resemble lipomas. Unlike true lipomas, mucosal pseudolipomatosis consists of irregularly shaped air spaces and the lesions are not encapsulated.
Angiolipoma. A: Note the lack of distinguishing gross features. B: This histologically pedunculated lesion consists of a proliferation of fat and blood vessels within the submucosa, elevating an intact mucosal surface. C: Higher magnification of one of the less cellular areas, demonstrating the presence of mature fat and small vessels. D: Sometimes the vascular proliferations are more extensive than shown in this figure.

Patients present with abdominal discomfort, vomiting, or intestinal obstruction. The tumors vary in appearance from flat, yellow, greasy masses that partially obstruct the intestinal lumen (Fig. 19.52) to soft, indurated, painless lesions in rare cases. Site of origin is frequently demarcated from surrounding normal-appearing adipose tissue. Hemorrhage and necrosis are common. The tumors are generally large (2.5 to 40 cm) at the time of presentation (148).

The mucosa overlying the tumor often becomes ulcerated. Primary liposarcomas grow out from the intestinal wall and spread into the mesentery. In large tumors with extensive involvement of the abdominal cavity, one may be unable to determine whether the tumor arises in the bowel or extended into it from an extragastrointestinal site.

The histologic features of gastrointestinal liposarcomas resemble liposarcomas arising in soft tissues. Liposarcomas contain pleomorphic areas of mono- and multivacuolated lipoblasts with irregularly shaped, hyperchromatic nuclei that are often situated on, or within septae that divide the tumor into lobules. Atypical stromal cells are also present. The tumors may contain focal necrotic areas. The diagnosis rests on finding atypical lipoblasts with cytologic features of malignancy (Fig. 19.53).

Liposarcomas arise in the retroperitoneum and secondarily involve the bowel. Liposarcomas contain pleomorphic areas consisting of multinucleated giant cells divided into smooth muscle areas. The smooth muscle areas exhibit lowularity, oval to polygonal nuclei, and low mitotic activity. The areas seem to arise from or blend with the vascular smooth muscle cells within the tumors (149).

Lipoleiomyosarcomas arise in the retroperitoneum and secondarily involve the bowel. Lipoleiomyosarcomas show typical well-differentiated liposarcoma with multifocal glandular transitions into smooth muscle areas. The smooth muscle areas exhibit lowularity, oval to polygonal nuclei, and low mitotic activity. The areas seem to arise from or blend with the vascular smooth muscle cells within the tumors (149).

Aggressive Mesenteric Fibromatosis (Desmoid Tumors)

Aggressive mesenteric fibromatoses (AMF) is a neoplastic, monoclonal myofibroblastic proliferation that is prone to aggressive local recurrence, but does not metastasize (150). Despite its rarity, AMF is the most common mesenteric tumor (151). The lesions arise de novo, secondary to trauma, or in association with familial adenomatous polyposis (FAP), Gardner syndrome (152), or Crohn disease (153). Patients range in age from 8 to 72 years (154), with a mean of 34 to 46.2 years. In FAP patients, desmoid tumors arise in the surgical bed of the previously resected bowel. They also arise in the mesoappendix. Patients may have a history of previous abdominal surgery (155). Deep fibromatoses have somatic APC gene mutations leading to nuclear accumulations of β-catenin (156). In contrast, superficial fibromatoses lack these mutations (157). The APC mutations tend to occur at or beyond codon 125 (see Chapter 13).

AMF affects the intestines and stomach and may extend into the liver, retroperitoneum and pancreas. It presents as a slow-growing tumor that causes obstruction, ischemia, intestinal fistulas, or intestinal obstruction. Tumor behavior varies from that of a benign neoplasm to a deeply invasive tumor characterized by the presence of numerous mitoses. Many regard these locally aggressive tumors as low-grade fibrosarcomas. Patients usually die from obstruction, as large bulky tumor masses compress the bowel loops or infiltrate the bowel wall. The lesions appear as localized, firm, irregularly demarcated masses (Fig. 13.10). These lesions may be quite large, measuring up to 15 cm in diameter. Their cut surfaces have a gray whitish homogeneous fibrous appearance without hemorrhage, necrosis, or cyst formation, differentiating the lesions from GISTs. Occasional foci of myxoid degeneration are present.
The hemangiomas consist of a proliferation of densely packed small capillaries without interanastomosing vascular channels (Fig. 19.56). The vascular channels are lined by a single layer of endothelial cells and semi-obliterated vascular spaces that alternate with large blood-filled sinuses lined by a single layer of endothelial cells. Venous hemangiomas contain thick-walled vessels and smooth muscle bundles. The lack of an inflammatory component, as well as the absence of cellular atypia and mitotic activity, helps distinguish it. The diagnosis of gastrointestinal hemangiomas is based on histopathologic examination, typically performed by endoscopic biopsies or during surgical resection. In cases where the diagnosis is uncertain, immunohistochemical staining with specific markers, such as CD31 and factor VIII-related antigen, can be helpful in confirming the diagnosis.

Inflammatory Myofibroblastic Tumors (Inflammatory Pseudotumors)

Inflammatory myofibroblastic tumors (IMTs) are a diverse group of inflammatory proliferations that involve various organs, including the gastrointestinal tract. These tumors are characterized by a proliferation of spindle cells with variable degrees of inflammation. The natural history of IMTs is generally favorable, with most patients experiencing complete spontaneous resolution or regression without treatment. However, some cases may require surgical resection or other forms of therapy. The differential diagnosis of IMTs includes various other conditions, such as GISTs, inflammatory fibrous tumors of soft parts, and other mesenchymal tumors. The diagnosis of IMTs is typically made based on histopathologic examination, often complemented by immunohistochemical and molecular analyses.

TABLE 19.12 Gastrointestinal Stromal Tumor (GIST) Versus Aggressive Mesenteric Fibromatosis (AMF)

<table>
<thead>
<tr>
<th>Feature</th>
<th>GIST</th>
<th>AMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Primarily bowel wall</td>
<td>Primarily mesentery or retroperitoneum</td>
</tr>
<tr>
<td>Histology</td>
<td>Spindle epithelial cells</td>
<td>Variable cellularity</td>
</tr>
<tr>
<td>Spindle cell proliferation</td>
<td>Monotonous spindle cells</td>
<td>Variable cellularity</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Variable (30%), CD34+ (63%), SMA+ (75%), desmin+ (8%), CD117+ (6%)</td>
<td>Variable (30%), CD34+ (63%), SMA+ (75%), desmin+ (8%), CD117+ (6%)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Generally good outcome</td>
<td>May have recurrences</td>
</tr>
<tr>
<td>Gross</td>
<td>Expansile multilobular lesion</td>
<td>Infiltrating margins</td>
</tr>
<tr>
<td>Histology</td>
<td>Liquefactive necrosis</td>
<td></td>
</tr>
<tr>
<td>Stromal</td>
<td>Myxoid, hyalinized</td>
<td>Collagenous with fine collagen fibrils</td>
</tr>
<tr>
<td>Immunohistochemical</td>
<td>No-stained fibrillar collagens</td>
<td>No-stained fibrillar collagens</td>
</tr>
</tbody>
</table>

The tumors develop in patients of average age and race. Histologically, affected patients are children with a mean age of approximately 10 years. The tumors have been described in patients with NF1 (98%), Ewing sarcoma (98%), and chronic myelogenous leukemia (98%). The radiologic findings of NF1 are similar to those seen in NF2. Histologically, the tumors are characterized by a proliferation of spindle cells with variable degrees of inflammation. The natural history of IMTs is generally favorable, with most patients experiencing complete spontaneous resolution or regression without treatment. However, some cases may require surgical resection or other forms of therapy. The differential diagnosis of IMTs includes various other conditions, such as GISTs, inflammatory fibrous tumors of soft parts, and other mesenchymal tumors. The diagnosis of IMTs is typically made based on histopathologic examination, often complemented by immunohistochemical and molecular analyses.

The signs of NF1 are similar to those seen in NF2. Histologically, the tumors are characterized by a proliferation of spindle cells with variable degrees of inflammation. The natural history of IMTs is generally favorable, with most patients experiencing complete spontaneous resolution or regression without treatment. However, some cases may require surgical resection or other forms of therapy. The differential diagnosis of IMTs includes various other conditions, such as GISTs, inflammatory fibrous tumors of soft parts, and other mesenchymal tumors. The diagnosis of IMTs is typically made based on histopathologic examination, often complemented by immunohistochemical and molecular analyses.
Cavernous Hemangiomas

Cavernous hemangiomas generally arise in the large or small intestine (Figs. 19.57 and 19.58). The esophagus is the least common site of origin (176). Cavernous hemangiomas are bluish purple, soft, and compressible lesions arising from larger submucosal arteries and veins. They diffusely infiltrate large segments of the bowel wall, adjacent soft tissues, or other organs (177). The lesions often demonstrate an irregular varicosed vascular network (177).

Four types of cavernous hemangioma exist: (a) multiple phlebectasia type, (b) simple polypoid type, (c) diffuse expansile type, and (d) multiple diffuse expansile type. Cavernous hemangiomas often measure 5–10 mm, but lesions can extend to involve the submucosa, where they may exceed 1 cm in diameter. Cavernous hemangiomas of the multiple phlebectasia type consist of multiple small discrete lesions found in any gastrointestinal segment. As many as 50 separate tumor masses may exist in a 20-cm length of the small intestine. The lesions are easily overlooked during pathologic examination since the vessels collapse when the vessels collapse when they are no longer filled with blood. Cavernous hemangiomas of the simple polypoid type consist of single isolated cavernous lesions associated with the submucosal vascular plexus (Fig. 19.59). When they enlarge, they prolapse into the GI lumen causing obstruction, hemorrhage, and intussusception. These lesions are less common than the phlebectasia type. Cavernous hemangiomas of the diffuse expansile type exhibit great variability in size and shape. Many tumors involve up to 30 to 50 cm of the GI tract in one contiguous segment. Grossly, they produce soft, compressible, violaceous, submucosal structures. The periphery of these tumors often shows numerous dilated tortuous vessels as well as an abundance of smooth muscle and fibrous connective tissue stroma, suggesting that normal vessels may become incorporated into the tumor. Cavernous hemangiomas of the multiple diffuse expansile type may occur simultaneously in separate organs throughout the body, including the skin.

Capillary Hemangiomas

Capillary hemangiomas with features of granuloma pyogenicum. A: Whole mount section demonstrating the presence of a large polypoid mass. B: Higher magnification shows that the small intestinal tumor consists of a proliferation of capillaries. C: Higher magnification demonstrating the presence of capillaries and inflammatory cells. D: Higher magnification showing the presence of a proliferation of large numbers of capillary-sized vessels.
Cavernous hemangiomas consist of large blood-filled spaces or sinuses lined by single or multiple endothelial layers. The expanding etiome occurs scat contact tissue, may involve variable numbers of smooth muscle fibers. Growth occurs in the tumor periphery by angioadipo proliferation, dilation of the capillary spaces, and fusion of intervascular connective tissue walls to form septa. Degenerative and sclerosing changes include the presence of thrombi in the cavernous spaces, pannus of fibrous tissue, hyalinization, edema, and focal calcification (177).

Angiomatoses

The Klippel-Trenaunay syndrome consists of a triad of congenital anomalies: (a) port wine stain hemangiomas (naevus flammeus), (b) varicose veins, and (c) hypertrophy of the soft tissue and bone with overgrowth of the ipsilateral limb. Vascular complications are common and may cause life-threatening complications. Patients may present with recurrent intestinal bleeding. Congenital hemangiomas and venous fibromuscular dysplasias are the most prominent and consistent vascular lesions other than the cavernous hemangioma, which are present, but they are not specific for the syndrome. The dysplastic veins may also have dilated and insufficient or absent valves (185).

Osler-Weber-Rendu disease is widespread among various ethnic groups and ranges in frequency from about 1 in 2,000 to 40,000 depending on the geographic location. Involvement in the extracranial sella turcica phlebolith leads to the disease (191). The three requisites for establishing the diagnosis include: (a) a history of repeated hemorrhages; (b) telangiectasia of the mucous membranes, viscera (liver, genitourinary tract), G1 tract, and skin; and (c) familial occurrence (192). Epistaxis in early childhood or youth is often the first manifestation of the disease. The vascular tumors increase in number and severity with age, leading to the later appearance of angiomatous lesions on the skin, bone, and mucous membranes. These lesions become symptomatic at an early age, and can cause severe anemia. A significant difference exists in the age of onset of epistaxis (median 11 years) and of GI bleeding (mean 55.5 years) (183).

Hemangiomas develop anywhere in the GI tract, but are most common in the stomach and duodenum (194). There are two major types of mucosal lesions: telangiectasias or angiomatos lesions. Telangiectasias consist of a flat or raised punctiform central area, from which radiate easily visible vessels that appear bluish red and fade on pressure. Telangiectatic angiomata are sometimes surrounded by a pale halo, appear as solid tumors that are bluish red and fade on pressure. These are usually multiple, flat, dilated venules and capillaries lined by a single layer of benign endothelial cells.

Angiosarcomas

GI angiosarcomas are very rare (177). The gut may be affected by either primary or secondary lesions (187). Angiosarcomas typically involve longstanding lymphadenopathy, radiation (186), or foreign bodies (190). The latency period following radiation ranges from 37 months to 50 years (190). Clinically, symptoms include intermittent bleeding, anemia, abdominal pain, perforation, acute abdomen, and intestinal obstruction (187). Primary tumors arise in the stomach, small intestine, colon, rectum, lesser omentum, and appendix, with the small intestine being the most common site (191). The tumors tend to be multicentric in origin and extensively invade the bowel wall. They present as palpable, vascular, or purplish lesions with poorly defined margins and prominent submucosal or serosal hemorrhagic nodules. They may appear edematous and ulcerated.
Kaposi Sarcoma

Incidence/Epidemiology


Pathogenesis

KS arises from the proliferation of vascular endothelial cells infected with HHV-8. HHV-8 is a lymphotropic virus that infects lymphocytes and is involved in the pathogenesis of KS. The virus produces latency-associated nuclear antigen (LANA) that acts as a transcriptional activator for KS-associated herpesvirus (KSHV) genes. HHV-8 can alter the expression of angiogenic growth factors, promote cell survival and proliferation, and evade immune surveillance.

Clinical Course

The clinical course of KS is varied and depends on the type of KS present. AIDS-associated KS is more aggressive and can disseminate quickly, leading to rapid death. Classic indolent KS progresses slowly over many years. Endemic African KS is typically indolent and presents as skin lesions.

Table 19.13 Variants of Kaposi Sarcoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Risk Group</th>
<th>Gastrointestinal Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Elderly men of Eastern European or Mediterranean origin</td>
<td>80% of patients</td>
</tr>
<tr>
<td>Endemic</td>
<td>African adults and children</td>
<td>Rare</td>
</tr>
<tr>
<td>Immunosuppression-related</td>
<td>Organ transplant patients</td>
<td>50% of patients</td>
</tr>
<tr>
<td>AIDS associated</td>
<td>HIV-infected persons</td>
<td>Common</td>
</tr>
</tbody>
</table>

Angiosarcomas consist of a network of irregular interanastomosing dilated vascular channels lined with endothelial cells containing lipid. They are typically associated with advanced age, with a peak incidence in the 7th to 8th decade of life. Angiosarcomas can be primary or secondary, with secondary cases more common. They are often found in the skin, subcutaneous tissues, or internal organs, including the liver and spleen.

Angiosarcomas are characterized by the proliferation of endothelial cells that form dilated, often anastomosing vessels. These vessels can be capillary, venous, or lymphatic in nature. The tumors are typically solitary, although multiple lesions can occur. They can involve any part of the body, including the skin, subcutaneous tissues, and internal organs such as the liver, spleen, and bone.

Florid vascular proliferations developing secondary to inflammation and muscular proliferation may show features that overlap with angiosarcoma and are in the differential diagnosis of this lesion. The latter is a vascular proliferation due to repeated mucosal injuries and ischemia (195). The benign histologic features help distinguish the lesion from angiosarcoma.

Clinical Course

The development of antibodies to the HHV-8 latency-associated nuclear antigen (LANA) is considered the hallmark of latent infection. The presence of LANA antibodies in HIV-infected patients strongly associates with the risk of developing KS (206).

Growth factor. These result in a hyperplastic polyclonal spindle cell lesion derived from lymphoid endothelia. HHV-8 infection stimulates the production of angiogenic growth factors such as vascular endothelial growth factor and matrix metalloproteinases, allowing the tumors to progress and grow (204).

Since HHV-8 infection can occur in a latently infected host, HHV-8 latency in endothelial cells and HHV-8 infection in endothelial cells can coexist. HHV-8 latency in endothelial cells can be associated with the development of KS.

Angiosarcomas consist of a network of irregular interanastomosing dilated vascular channels lined with endothelial cells containing lipid. They are typically associated with advanced age, with a peak incidence in the 7th to 8th decade of life. Angiosarcomas can be primary or secondary, with secondary cases more common. They are often found in the skin, subcutaneous tissues, or internal organs, including the liver and spleen.
In the lesion progresses from early to later stages, one sees loss of vascular spaces and an increase in the number of spindle cells. Mucosal spindle cell areas blend with more angiomatous areas. Intercussion bundles of spindle cells extend in various directions throughout the tissues. Although nuclear changes and mitotic figures may be present, they are rarely prominent. Malignant lesions consist of proliferations of interweaving spindle-shaped cells that tend to form vascular spaces within a network of reticulin and collagen fibers. Distorted, thick-walled, ectomesenchymal vessels usually surround and invaginate spindle cells. Foci of plump endothelial cells line the vascular spaces. The endothelial cells may protrude into the vascular lumens, but they are not always and therefore differ from the endometrium seen in angiosarcoma. Extravasated erythrocytes (Fig. 19.62) permeate through the lesion and hematoxylin deposits are present in the surrounding tissue. Often to the diagnosis, especially in early lesions, includes an appropriate clinical history, knowledge of the endoscopic findings, recognition of haemorrhagic and hyperplastic in the spindle cells, recognition that these sites and spaces contain red blood cells and are thus vascular spaces, and the tendency for KS lesions to occur in or dilate the extravascular mucosa. The lesions may be surprisingly subtle and easily missed, even by experienced pathologists. Early lesions can be distinguished from granulomatous tissue by the presence of angioelastic disrupted vascular channels. The lining cells of well-developed vascular structures are usually positive with vascular markers. The spindle cells are consistently positive for CD34 and commonly positive for CD31 but are factor VIII negative. All cases, regardless of the epidemiologic subgroup, are positive for HHV-8.

Distinguishing KS from other malignant or benign spindle cell tumors as well as other angiomatous spindle cell neoplasms can be challenging. The differential diagnosis includes angiosarcoma, spindle cell hemangioma, leiomyoma, pyogenic granuloma, and spindle cell melanoma. IHH-8 expression is a highly sensitive and specific marker of KS and helps to correctly identify the lesion in difficult cases (208).

Lymphangioma

Lymphangiomas are less common than hemangiomas. They develop in patients ranging in age from 3.5 to 78 years (210). In Europeans and Americans, 21% of females are affected. This too-reveals the Japanese (211). Symptoms vary depending on location and size. Large polypoid lesions cause stricture of the esophagus. Esophageal lymphangiomas may cause dysphagia. In contrast, most cranial lymphangiomas remain asymptomatic and are discovered incidentally. Some patients develop portal hypertension (212), lymphangioesophageal fistulae, and T-cell lymphoma (213), a lymphoproliferative lesion that is used by lesions to react with CD34 and 214. Lymphangiomas cause pain or bleeding. These lesions may enlarge due to continuous engorgement with chyle and increased secondary inflammation rather than proliferation of the neoplastic cells (215). Generally, lymphangiomas are solitary, but multiple lesions do occur. The term lymphangioma describes the presence of multiple lymphangiomas. Gastrointestinal lymphangiomas occur most frequently in the colon, followed by the duodenum and stomach. Esophageal lesions are rare. When extensive, the lesions may involve the entire intestine, large intestine, appendix, meckel diverticulum, gallbladder, and biliary tree (215). Lymphangiomas can be recognized by their pale translucent cystic appearance and their deformation with pressure. They appear as spherical, tan, or yellow, soft submucosal lesion with a smooth mucosal surface, often with a broad base (Fig. 19.63). Small lymphangiomas may be grey or pale or appear as circumscribed, infiltrative, intramusosal, submucosal, or pedunculated lesions, ranging in size from 1.5 to 23 cm (average size 2 cm). Larger lesions may significantly impair esophageal function and cause obstruction to the esophagus. A major transition occurs between the lesions and adjacent normal tissue. When cut, lymphangiomas have a multilocular cut surface that exudes clear yellowish or milky fluid.

Treatment

GI involvement in AIDS patients associates with a poor prognosis. Patients with classic KS with a single lesion are typically cured by local excision. In immunocompetent patients with multiple lesions, observation may be appropriate and some lesions may regress or show little progression over time. In patients with disease limited to a single region, radiation therapy may be appropriate. In patients with extensive or recurrent disease, surgical resection of surgery, chemotherapy, and/or radiation therapy may be appropriate. Patients with HIV-associated KS may benefit from HAART. Patients may also require a combination of radiation therapy, chemotherapy, and biologic agents (216).
Lymphangiomas are characterized by a localized proliferation of abnormal lymphatics that drain into normal lymph nodes. In their simplest form, they are slow-growing, discrete masses of disorganized lymphatic vessels surrounded by fibrous tissue. In their more complex forms, they are multiloculated, multicystic masses that may contain a central collection of fluid. The lesions are composed of mature, non-neoplastic lymphatic channels. Infiltrative or infiltrating lymphangiomas may destroy adjacent tissues, such as bone or muscle, and can cause significant morbidity.

Multilocular Lymphangioendothelioma

Multilocular lymphangioendothelioma is a newly recognized congenital developmental disorder characterized by the presence of multiple cystic lesions. These lesions are typically found in the subcutaneous tissue and may involve the liver, spleen, and lungs. The lesions are composed of mature, non-neoplastic lymphatic channels that are often densely packed with endothelial cells. The lesions are asymptomatic and are usually discovered incidentally on imaging studies. Treatment is typically observation, and a surgical approach is reserved for patients with symptoms or complications.

Hemangiolympangioendothelioma

Some tumors have features of both a lymphangioma and a hemangioma with an interanastomosing meshwork of lymphatics and blood vessels. The lymphatics contain a fine eosinophilic precipitate consistent with lymph and valvelike structures surrounded by regular nodular smooth muscle. Such lesions are designated as hemangiolympangioendotheliomas with focal smooth muscle proliferation.
or slightly hyperchromatic. Mitotic activity is generally high. Necrosis is scanty and generally limited to areas where there is crowding of tumor cells. In other areas, a pattern of solid sheets of tumor cells may be present without zones of necrosis. Mitotic figures are rare. Immature giant cells may be present in some tumors. The tumors are composed of large, pleomorphic cells with dark nuclei and abundant eosinophilic cytoplasm and rare mitotic figures. These tumors are benign, and rare mitotic figures are present in a few cases. The term “benign” is used to indicate that these tumors are not likely to recur or metastasize.

Giant cell tumors

Giant cell tumors arise in the GI tract (262). Colonic lesions may present as a long, irregular, stiff homogeneous grayish white stricture (250). Other features include a sessile polypoid mass or a pedunculated polyp. The tumors are composed of large, multinucleated giant cells similar to those described for giant cell tumors arising in other sites (262). They contain multinucleated giant cells similar to those described for giant cell tumors arising in other sites (262).

Clear cell sarcomas

Clear cell sarcomas are rare, and arise in the GI tract (262). They are characterized by the presence of clear, cytoplasmic inclusions and eosinophilic cytoplasm. The tumors are composed of large, multinucleated giant cells similar to those described for giant cell tumors arising in other sites (262). They contain multinucleated giant cells similar to those described for giant cell tumors arising in other sites (262).

Angiomyolipomas

Angiomyolipomas are rare, and arise in the GI tract (262). They are characterized by the presence of clear, cytoplasmic inclusions and eosinophilic cytoplasm. The tumors are composed of large, multinucleated giant cells similar to those described for giant cell tumors arising in other sites (262). They contain multinucleated giant cells similar to those described for giant cell tumors arising in other sites (262).

Alveolar soft part sarcomas

Primary alveolar soft part sarcoma of the stomach. A: Gross photograph demonstrating the presence of a polypoid nodule in the wall of the stomach. B: Tumor arising from the muscular layer of the bowel wall. (Case courtesy of Dr. Y. Yamashita, Department of Pathology, Hiroshima University School of Medicine, Hiroshima, Japan.)
Chapter 2
The Nonneoplastic Esophagus
Esophageal Development

The esophagus develops from the cranial part of the primitive foregut, becoming recognizable at the 2.5-mm stage of development (approximately the third gestational week) as an annular constriction located between the stomach and pharynx (Fig. 2.1) (1). It elongates and grows in a cephalad direction becoming increasingly tubular. Early, the cephalad parts of both the esophagus and trachea lie within a single common tube. Lateral ridges of proliferating epithelium develop in the uppermost segment, dividing the lumen into anterior and posterior compartments. Primitive mesenchyme grows into the forming septum, eventually separating the esophagus and trachea. As soon as the esophagus and trachea divide, the esophagus lies dorsally, and the trachea and lung buds lie ventrally (Figs. 2.1 and 2.2).

The earliest identifiable esophagus consists of two to three layers of pseudostratified columnar cells (Fig. 2.3). The cell layers thicken and then vacuolate (Fig 2.4). Eventually the vacuoles disappear. Abnormalities in the vacuolation process account for the formation of some esophageal cysts. Mucin-secreting cells replace the ciliated cells (2). Glycogenated, nonkeratinized, stratified squamous cells then replace the mucinous epithelium. Squamous cells first appear in the midesophagus and extend both proximally and distally to line the remainder of the esophagus by the fifth gestational month. Submucosal glands appear following the development of the squamous epithelium; they fully mature after birth (2). The implication of these developmental changes is that residual nests of embryonic types of esophageal epithelium may persist in the adult esophagus giving rise to some congenital abnormalities.

Gross Anatomic Features

The esophagus begins in the pharynx at the cricopharyngeus muscle and ends at the gastroesophageal junction (GEJ) to the left of midline opposite the 10th or 11th thoracic vertebrae. The esophagus usually measures 25 to 35 cm in adults. For the endoscopist, the esophagus starts 15 cm from the incisor teeth; it ends with the appearance of gastric folds at the GEJ or Z line (Fig. 2.5). The esophagus follows the course of the vertebral column maintaining close proximity with the trachea, left mainstem bronchus, aortic arch, descending aorta, and left atrium (Fig. 2.6). It is customarily divided into thirds. The normal esophagus has constrictions (Fig. 2.7) at its cricoid origin, along its left side at the aortic arch, at the crossing of the left mainstem bronchus, at the fifth thoracic vertebra and left atrium, and where it passes through the diaphragm. These constrictions become clinically significant when food or pills lodge in them making them susceptible to ulceration. The esophagus enters the abdomen, passing through the esophageal hiatus formed by the diaphragmatic muscles. Its intra-abdominal portion measures 1.5 cm in length. The right side of the GEJ appears smooth, whereas the left side forms a sharp angle known as the incisura or angle of His.

Sphincters that maintain esophageal closure under resting conditions lie at the proximal and distal ends. The esophagus is mobile between the upper sphincter and its passage through the diaphragm, allowing it to be displaced by mediastinal or pulmonary diseases. Lower esophageal sphincter (LES) pressure involves a balance between neurogenic and tonic contraction of the musculature and various neural and possibly endocrine and paracrine influences that inhibit contraction resulting in relaxation. The LES keeps the esophageal lumen closed, preventing reflux during rest and regulating food passage into the stomach. The most distal portion of the LES defines the GEJ. The esophageal mucosa has a smooth, featureless, glistening, pink-tan appearance. The squamocolumnar junction appears as a serrated line known as the Z line (Fig. 2.5). Grossly, the Z line consists of small projections of red glandular epithelium measuring up to 5 mm in length and 3 mm in width extending through the pink-white squamous epithelium. Four arterial groups regionally supply the esophagus: (a) the thyroidal arterial trunk and branches of the subclavian artery that supply the upper esophagus, (b) bronchial arteries and esophageal arch arteries from the lower descending aorta that supply the upper and midesophagus, (c) intercostal arteries and periesophageal arteries from the lower thoracic aorta that supply the distal esophagus, and (d) branches from the inferior phrenic, left gastric, and short gastric artery that supply the diaphragmatic part of the esophagus. The arteries run within the muscularis propria,

P.12

giving rise to branches that course through the submucosal plexus (3). Extensive anastomoses among these arterial supplies account for the rarity of esophageal infarction.
between the systemic and portal venous circulations. The lower esophagus drains into the systemic circulation through branches of the azygos and left inferior phrenic veins. The lower segment also drains into the portal system through the left gastric vein and into the splenic vein through the short gastric veins. The azygos veins ascend on either side of the thoracic segment and drain the midesophagus. The anterior and posterior hypopharyngeal plexus, the superior laryngeal and internal jugular veins, and the inferior thyroidal vein and intercostal veins drain the proximal esophagus. These eventually drain into the superior vena cava.

![Diagram of esophagus and trachea](image)

**FIG. 2.2.** Septation events. *A:* The embryonic foregut begins as a single tube from which the tracheobronchial diverticulum develops. *B:* The more proximal portion of the foregut divides into the posterior esophagus and the anterior tracheal tree. *C:* Septation results from ingrowth of epithelium and mesenchyme in the area of constriction. *D:* This ingrowth eventually forms a complete septum between the trachea and the esophagus.

Seven lymph node groups drain the esophagus (Fig. 2.8). The nodes adjacent to the esophagus include paratracheal, parabronchial, paraesophageal, pericardial, and posterior mediastinal lymph nodes. The superior and inferior deep cervical lymph nodes lie further away from the esophagus. In general, the cervical esophagus drains into the internal jugular and upper tracheal lymph nodes. The thoracic esophagus drains into the superior, middle, and lower mediastinal lymph nodes. It also drains into the bronchial and posterior mediastinal paraesophageal lymph nodes and then to the thoracic duct. The distal esophagus drains into the pericardial lymph nodes at the GEJ. The infradiaphragmatic portion drains to the left gastric and perigastric nodes (4). The two sets of intramural lymphatics lie in the submucosa and in the muscularis propria. The rich mucosal lymphatic plexus connects with a less extensive submucosal one and communicates with longitudinally oriented channels in the muscularis propria. Because of this arrangement, esophageal cancers tend to display early and extensive intramucosal and submucosal intralymphatic spread (see Chapter 3).
FIG. 2.3. Section through developing fetus at approximately 12 weeks of age by dates. A: Hematoxylin and eosin–stained section demonstrating fetus in the amniotic sac with the forming heart (H) and gastrointestinal tract. The section indicated in the box represents the separated trachea and esophagus. B: Higher magnification of the area outlined in the box in A. It is stained with an antibody to cytokeratin. Two distinct lumens representing the esophagus and the trachea are present (arrows). Immature mesenchyme surrounds the two lumina.

FIG. 2.4. Cross section of fetal esophagus at 60-mm stage. A: The mucosal lining consists of pseudostratified cells. L represents the central lumen; N represents developing neural tissue. Epithelial vacuoles (V) are beginning to form. B: Higher magnification of the pseudostratified epithelium. The epithelium appears clear due to intracytoplasmic glycogen accumulations. The underlying tissues consist of immature mesenchyme. Two intraepithelial vacuoles (V) are present.
FIG. 2.5. Esophagogastric Z line. A: A double-contrast esophagogram demonstrates white zigzag line (arrows) representing the Z line. B: The Z line lies where the pinkish-gray squamous mucosa of the esophagus meets the velvety brown glandular gastric mucosa.

Parasympathetic and sympathetic nerves innervate the esophageal mucosa, glands, blood vessels, and musculature. Adrenergic, cholinergic, and peptidergic nerves richly supply the esophageal smooth muscle and serve several neurotransmitter functions, particularly in the LES (5,6,7). LES function is regulated in part by neural nitric oxide synthetase (8). Nitric oxide is a major mediator of LES relaxation. It also initiates the release of and enhances the effect of other transmitters. Intramuscular interstitial cells of Cajal also play an important role in nitric oxide–dependent neurotransmission in the LES (9).

Mucosal Defenses

Pre-epithelial, epithelial, and submucosal defenses protect the esophagus from injury. **Pre-epithelial defenses** include the coordinated actions of the LES and the esophageal muscles to minimize reflux of gastric contents and promote clearance of refluxed material. Microridges on squamous cells hold mucus on their surfaces, providing a protective coat (10). The esophageal epithelium is also protected by a luminal mucus–bicarbonate barrier and hydrophobic surfactants that derive from submucosal and salivary gland secretions. Other salivary components, including mucin, nonmucin proteins, epidermal growth factor (EGF), prostaglandin E₂, and carbonic anhydrase also significantly enhance the **pre-epithelial barrier**.

**Epithelial defenses** include the glycocalyx, permeability properties of the cell plasma membrane, cells junctions, and ion transport processes that regulate intracellular pH (11). The multiple layers of squamous cells functionally resist damage from the passage of substances over the epithelial surface (Fig. 2.9). **Submucosal defenses** mainly involve regulation of blood supply via responses of nerves, mast cells, and the blood vessels themselves.

Histologic Features

**The Squamous Mucosa**

Most of the esophagus is lined by squamous epithelium, except at its distal end. The normal squamocolumnar junction (SCJ) lies at the level of the diaphragm. The squamous mucosa contains three components: Squamous epithelium, lamina propria, and a thick muscularis mucosae (Figs. 2.10 and 2.11). The squamous epithelium consists of nonkeratinizing stratified squamous epithelium (Figs. 2.10, 2.11, and 2.12). The basal zone consists of several layers of cuboidal basophilic cells with dark nuclei arranged in an orderly fashion along the basement membrane. Its upper limit is defined as the level where the nuclei are separated by a distance equal to their diameter. It rarely contains mitoses unless some form of injury (esophagitis) is present. The basal layer gives rise to daughter cells that progressively differentiate as they move toward the surface and desquamate. Epithelial cell renewal takes an average of 7 days (12). The basal layer normally occupies the lower 10% to 15% of the epithelium, being one to four cells thick. However, most individuals without evidence of gastroesophageal reflux show basal cell
hyperplasia >15% in the distal 3 cm of the esophagus (13). Above the basal cell layer the glycogenated cells progressively flatten as they approach the surface (Fig. 2.13). Periodic acid–Schiff (PAS) stains, which detect intracellular glycogen, facilitate their identification (Fig. 2.14). As one approaches the luminal surface, cell polarity changes from a vertical to a horizontal orientation. This change is accompanied by conversion of a round to an elliptical cell shape. The esophageal mucosa may contain rare keratohyaline granules even though granular and keratinizing layers are usually absent; this finding suggests previous injury.

**FIG. 2.6.** The esophagus commences as an inferior extension of the pharynx. Superiorly it is related to the larynx and thyroid gland. Its middle region courses with the trachea, bronchi, and aortic arch, whereas the lower third descends with the aorta and passes through the esophageal diaphragmatic hiatus.
Endocrine cells lie scattered among the basal cells; they are not present in the mucous glands or ducts. Melanocytes are also present (Fig 2.15) (14). Occasional CD3+ intraepithelial lymphocytes populate the lower and middle squamous cell layers (15). As these lymphocytes interdigitate between the epithelial cells, their nuclei become convoluted, hence the term “squiggle cells.” Antigen-presenting S100+ Langerhans cells lie in a suprabasal location (Fig. 2.16) (15).

*Papillae*, projections of lamina propria, extend into the squamous epithelium at regular intervals creating an irregular lower border of the squamous epithelium. These *papillae normally do not extend more than 50% to 60% through the epithelial height*. One measures the height of the papillae from the basal lamina of the surrounding squamous epithelium to the basal lamina at the top of the papilla. The papillae and lamina propria contain blood vessels, lymphatics, fibrovascular tissue, elastic tissue, and occasional inflammatory cells. The lamina propria rests on a two-layer, relatively thick muscularis mucosae. The mucosa is maintained in part by EGF, a mitogenic polypeptide that helps maintain tissue integrity and cell maturation. The epidermal growth factor receptor (EGFR) possesses tyrosine kinase activity (16) and binds EGF. This may make the esophageal mucosa vulnerable to the anti-EGFR therapies used to treat multiple types of cancer.
FIG. 2.8. Lymph nodes draining the esophagus. See text for further description.
**Normal Histology at the Gastroesophageal Junction**

The normal histology of the GEJ is a contentious topic. Traditional teaching suggests that the normal Z line is a junction between squamous epithelium and cardiac epithelium with the cardiac mucosa being the most proximal part of the stomach (17). The crux of the current controversy centers on whether the distal esophageal mucosa normally contains cardiac mucosa and whether cardiac mucosa can contain parietal cells. Some suggest that the presence of any parietal cells precludes a histologic diagnosis of cardiac epithelium (18). Others contend that cardiac glands can contain occasional parietal cells provided that other architectural features typical of cardiac mucosa are present (19). Some recommend terms such as *oxyntocardiac* or *cardio-oxyntic* or *transitional* mucosa to describe a cardiac mucosa with occasional parietal cells (18). The histologic controversies are complicated by the fact that there are no uniformly accepted criteria by which the GEJ can be recognized grossly. Thus, it is difficult to establish whether the Z line normally lies precisely at or slightly proximal to the GEJ (20). Furthermore, the upper gastrointestinal (GI) tract easily undergoes metaplastic changes as a result of injury.

Most current authors agree that the extent of the cardiac epithelium is shorter than had been previously suggested. If cardiac epithelium is present at all, it rarely extends more than a few millimeters below the Z line or a few millimeters into the esophagus. Some view the cardia as a normal structure that is present at birth (21,22), whereas others suggest that cardiac mucosa develops as a metaplastic response to gastroesophageal reflux disease (GERD) (23,24,25). Thus, it remains unclear whether there is a tiny band of cardiac mucosa that is a normal structure and whether it lines the esophagus, the proximal stomach, or both. When cardiac mucosa or cardio-oxyntic mucosa overlies submucosal esophageal glands or squamous epithelial-lined ducts, one can be certain that one is in the esophagus and not in the proximal stomach. In the absence of this landmark, the location is less clear and it is perhaps best referred to as the area of the GEJ. Variability in the extent of the cardiac mucosa likely reflects the presence of underlying disorders such as GERD or *Helicobacter pylori* gastritis (25) and suggests that the area of the GEJ is a dynamic structure that may change over time.
FIG. 2.11. Histology of the normal esophagus. The following layers of the esophageal stratified squamous epithelium can be identified: basal layer of oval cells, intermediate layers of cuboidal cells, and outer layers of squamous cells with flattened nuclei. The papillary lamina propria (P) invaginates halfway into the epithelium carrying small blood vessels and inflammatory cells. Smooth muscle fibers of the muscularis mucosae (MM) are seen at the bottom of the photograph.

FIG. 2.12. Measurement of the height of esophageal papillae. The distance between the basal lamina of the adjacent flat squamous epithelium (A) and the basal lamina at the top of the papillae (B) is one-half the full measurement of the epithelium.

In our view, cardiac mucosa consists of a surface mucus-secreting columnar epithelium similar to gastric foveolar epithelium. This epithelium dips down to form foveolae into which branched or compound tubular glands open. In the proximal end of the cardiac mucosa the glands branch freely and show a distinctly lobular architecture (Fig. 2.17). Distally the glands are less branched and the lobular arrangement becomes less evident. The glands contain mucin-producing cells and may contain parietal cells or even rare chief cells. Abundant endocrine cells are also

P.18
The cells may also blend with pancreatic exocrine cells, a change described in a later section.

**FIG. 2.13.** Photograph of squamous mucosa stained with hematoxylin and eosin demonstrating the esophageal squamous lining. The star indicates the center of a papilla. It is surrounded by small basal cells with high nuclear-to-cytoplasmic ratios. The cells progressively enlarge, acquiring intracytoplasmic glycogen, and then eventually flatten out toward the surface. Normally, a small number of intraepithelial lymphocytes are present (arrows).

**FIG. 2.14.** *A:* The glycogenated superficial keratinocytes are demarcated from the basal epithelial layers by a periodic acid–Schiff (PAS) stain. The submucosal glands are also PAS positive. A lymphoid follicle (LF) is present. *B:* PAS-stained example of the gastroesophageal junction. Note the presence of the strongly PAS-positive glands both in the superficial portions as well as in the submucosa of the esophagus. The basal layer of the distal esophagus is thicker than elsewhere and is present in this photograph as a pale band underneath the pink-staining glycogenated epithelium superficial to it.
Lamina Propria

The lamina propria constitutes the nonepithelial portion of the mucosa above the muscularis mucosae. It consists of loose areolar connective tissue containing blood vessels, nerves, inflammatory cells, and mucus-secreting glands. Lymphocytes (mostly immunoglobulin-producing B cells), plasma cells, and, occasionally, lymphoid follicles are present.

Muscularis Mucosae

The muscularis mucosae begins at the cricoid cartilage and becomes thicker distally. Proximally it consists of isolated or irregularly arranged muscle bundles rather than being arranged in a continuous sheet. In the middle and lower esophagus, the muscularis mucosae forms a continuum of longitudinal and transverse fibers that may appear thicker than elsewhere in the GI tract (Fig. 2.11), especially at the GEJ. The muscularis mucosae may appear so thick as to be mistaken for the muscularis propria in biopsy specimens.
FIG. 2.16. An antibody to anti-S100 protein identifies the dendritic Langerhans cells scattered in the normal esophageal mucosa. Submucosal nerves and ganglia are also positive (diaminobenzidine—methylene blue).

FIG. 2.17. Submucosal glands. A: Mucous glands empty their secretions into the esophageal lumen via ducts that penetrate the muscularis mucosae (MM). The submucosa is designated by the letters SM; the muscularis propria is designated by the letters MP. B: Periodic acid–Schiff (PAS)–stained esophagus. Note the PAS-positive acini in the submucosal glands.

Submucosa

The submucosa is a wide zone that lies below the muscularis mucosae. It consists of loose connective tissue containing blood vessels, nerves, poorly formed submucosal ganglia, lymphatics, and submucosal glands (Fig. 2.17). The submucosa contains an extensive ramifying lymphatic plexus lying in a loose connective tissue network accounting for early and extensive submucosal spread of esophageal carcinomas. It also contains a rich vascular supply.

There are of two types of submucosal glands: Simple tubular mucous glands called superficial or mucosal mucous glands, and deep or submucosal glands. The former lie in the lamina propria, confined to narrow zones at the distal and proximal ends of the esophagus. They produce neutral mucins and because of their similarity to the glands of the gastric cardia, have also been termed cardiac glands. In contrast, deep or submucosal glands lie in the submucosa, along the length of the esophagus. These glands produce acidic mucins and drain their secretions via ducts lined by columnar epithelium surrounded by myoepithelial cells (26). Submucosal glands contain acini and tubules. From two to four lobules drain into a common duct lined by stratified columnar epithelium that passes obliquely through the muscularis mucosae into the lumen. Loose connective tissue...
often surrounds these ducts. They vary in position and number from patient to patient and may be purely mucinous, purely serous, or mixed seromucinous in nature. Four types of cells line the submucosal glands: mucous cells, serous cells, myoepithelial cells, and oncocytes. Mucous cells contain neutral sialated and sulfated mucins. The glands may be surrounded by lymphocytes.

**Muscularis Propria**

The muscularis propria consists of well-developed circular and longitudinal layers. In its upper part, the muscle fibers assume an oblique orientation and are striated in nature. The striated muscle gradually changes to smooth muscle in the middle third of the esophagus. The LES is not a clearly defined anatomic structure but consists of thickened smooth muscle fibers that extend approximately 2 cm above and 3 cm below the diaphragmatic esophageal hiatus.

**Adventitia**

The esophagus does not have a serosa as exists elsewhere in the GI tract. Rather, the external part is called the adventitia. It consists of loose connective tissue with longitudinally directed blood and lymph vessels and nerves; it gradually merges into the loose connective tissue in the mediastinum. Numerous elastic fibers at the GEJ attach the esophagus to the diaphragm.

**FIG. 2.18.** Normal esophagus. A: Normal superficial squamous epithelial cells without keratinization. (Unless otherwise specified, all figures are taken from brushing material and stained with Papanicolaou.) B: Normal intermediate squamous epithelial cells.

**Cytology of the Normal Esophagus**

Esophageal cells normally exfoliate from the esophageal mucosa. These include nonkeratinized superficial squamous cells, intermediate cells, and, rarely, parabasal cells (Fig. 2.18). Some squamous cells seen in esophageal cytology specimens derive from the oropharynx. Benign epithelial pearls may occasionally be found. The presence of large numbers of the latter suggests an inflammatory or erosive lesion. Metaplastic squamous cells may exfoliate from the subepithelial mucous glands and their ducts. Benign columnar gastric-type cells (Fig. 2.19) derive from the distal esophagus or from islands of gastric mucosa associated with inlet patches or Barrett esophagus (BE). Foreign material, particularly plant cells, may be present, especially if the esophageal lumen is obstructed. One may also find cells of respiratory origin, such as dust-containing macrophages and ciliated bronchial cells. These usually represent cells that are swallowed, although esophagobronchial or esophagotracheal fistulae or the presence of congenital abnormalities containing bronchial mucosa may account for these cells as well.
Heterotopias

Cervical Inlet Patch

Inlet patches affect 1% to 21% of the population (27,28,29), with the highest incidence occurring during the first year of life. A subsequent decline in incidence suggests that some lesions regress with age. Two pathogenetic mechanisms have been advanced to explain inlet patches. As noted earlier, columnar epithelium lines the fetal esophagus and remnants of columnar or ciliated epithelium may persist leading to the formation of inlet patches. Others suggest that inlet patches represent metaplastic replacement of the squamous mucosa in adults with GERD (30). Those favoring an association with GERD cite similar mucin and cytokeratin patterns in both inlet patches and BE (30). Inlet patches lie in the subcricoid and upper sphincteric region, usually within 3 cm of the upper esophageal sphincter. Most lesions remain asymptomatic. Acid or pepsin secretion by the ectopic gastric mucosa may produce peptic symptoms, ulcers, granulation tissue, webs, strictures, esophagotracheal fistulae, or perforations (31). Adenocarcinomas may also develop, although this is rare (32).

Inlet patches are easily visible velvety, ovoid, pink-red mucosal areas with distinct borders that vary in diameter from a few millimeters to complete esophageal encirclement. Histologically, the lesions consist of cardiac, antral, and/or oxyntic glands covered by foveolar epithelium (Fig. 2.20). In patients with gastric H. pylori (HP) infections, the heterotopic epithelium may become colonized by HP. Intestinal or pancreatic metaplasia may develop (28,29). Large amounts of lymphoid tissue accompany smaller lesions, as compared to larger ones, suggesting that the lymphocytes play a role in lesional regression. An intense inflammatory reaction may surround the lesion, especially following peptic ulceration.
Heterotopic Gastric Mucosa away from Inlet Patches

Ectopic gastric mucosa also occurs in the mid- or distal esophagus, usually in congenital malformations, including duplications or diverticula. It may also develop following atresia repair (33). Since it often contains oxyntic mucosa, it may present with peptic ulceration.

Heterotopic Pancreas

Heterotopic pancreas usually affects the distal esophagus. It may associate with trisomy 18, trisomy 13, esophageal atresia, and esophageal duplication. Complications include fat necrosis, bleeding, ulcers, diverticulum formation, cystic degeneration, inflammation, and, rarely, malignancy. Heterotopic pancreas usually presents as a submucosal mass and contains normal-appearing pancreatic acini and ducts (Figs. 2.21 and 2.22) without islets, although any pancreatic tissue component may be present. Injury due to heterotopic pancreas involves failure of the pancreatic ducts to empty into the esophageal lumen. Eventually the obstructed ducts dilate and rupture, releasing proteolytic enzymes into surrounding tissues. Inflammation and necrosis follow. Heterotopic pancreas differs from pancreatic metaplasia, which is discussed in a later section. The latter is usually a focal change consisting only of pancreatic acini that blend into cardiac or oxyntic mucosa. Pancreatic ducts are never present in pancreatic metaplasia.
Other Heterotopic Tissues

Ectopic esophageal sebaceous glands present grossly as multiple small, yellowish, mucosal plaques, typically lying in the mid- or distal esophagus. Mature sebaceous glands underlie the squamous mucosa (Fig. 2.23). The lesion represents a developmental abnormality without any clinical significance (34). Patches of *ciliated columnar cells* may lie within the esophagus. These represent residual fetal remnants and are particularly common in premature infants. They are rarely seen in adults unless they are found in inlet patches, duplications, and/or bronchogenic cysts. *Heterotopic thyroid tissue* may be present in the esophagus either alone or in tracheobronchial hamartomas.
Developmental Congenital Anomalies

**Congenital Esophageal Atresia, Fistula, and Stenosis (Tracheoesophageal Fistula)**

**Demography and Pathophysiology**

Complete esophageal atresia affects 1 in 3,000 live births. Atresia with a common tracheoesophageal fistula occurs in 1 of every 800 to 1,500 live births. Esophageal stenosis affects only 1 in every 25,000 live births (35). Atresia is more common in males than in females. Premature babies and monozygotic twins have a higher risk of atresia than other infants. Occasionally esophageal atresia affects siblings (36). Risk factors include prenatal exposure to lead (37), drugs, and physical agents; maternal diabetes; and a maternal age <20 years (38). Genetic factors include Down syndrome, trisomy 18, and various other chromosomal alterations (39). Severe etiologic insults occur in the first trimester when major organogenesis occurs, often resulting in many associated abnormalities (40).

In esophageal agenesis the proximal primitive foregut develops primarily into a trachea rather than an esophagus (41). Esophageal atresia results from failure of the primitive foregut to recanalize; tracheoesophageal fistula results from failure of the lung bud to separate completely from the foregut. The fistulas that develop vary depending on the amount of epithelium left behind to maintain foregut epithelial continuity. The distal esophageal segment may contain respiratory elements representing a transition zone between the upper foregut, which differentiates into the trachea, and the lower part, which differentiates into the lower esophageal segment (41).

Studies in animal models and in patients with syndromic forms of esophageal atresia indicate the importance of altered genes in the sonic hedgehog signaling pathway. These genes include N-myc and SOX2, which encode transcription factors, and CHD7, which encodes a homeodomain helicase DNA-binding gene, important for chromatin structure and gene expression (42). There are also a number of other genes that are important for normal tracheoesophageal development (Table 2.1); abnormalities in these may also account for some cases of tracheoesophageal malformations.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Human Chromosomal Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foxf1</td>
<td>16q24</td>
</tr>
<tr>
<td>Gli2</td>
<td>2q14</td>
</tr>
<tr>
<td>Gli3</td>
<td>7p13</td>
</tr>
<tr>
<td>Hoxc4</td>
<td>12q13.3</td>
</tr>
<tr>
<td>RARα</td>
<td>17q21</td>
</tr>
<tr>
<td>RARβ</td>
<td>3p24</td>
</tr>
<tr>
<td>Shh</td>
<td>7q36</td>
</tr>
<tr>
<td>Tbx4</td>
<td>17q21-q22</td>
</tr>
</tbody>
</table>

**Clinical Features**
Chapter 2

Esophageal atresia may be detected prenatally by finding a small or absent gastric bubble and maternal polyhydramnios or by the presence of a fluid-filled, blind-ending esophagus (Fig. 2.24). At birth, the presence of a single umbilical artery may alert clinicians to the possibility of esophageal atresia. Infants typically present in the first few hours or days of life with regurgitation, excessive drooling, choking, aspiration, cyanosis, and respiratory distress. Inability to pass a nasogastric tube into the stomach confirms the diagnosis. Air in the stomach and small bowel indicates the presence of a distal tracheoesophageal fistula. Most patients with esophageal stenosis present with dysphagia and regurgitation upon the introduction of solid food.

Approximately one third of infants with esophageal atresia have associated congenital anomalies involving the cardiovascular, gastrointestinal, neurologic, genitourinary, or orthopedic systems (43). Some of the more complex associations are described briefly. The *VATER syndrome* links vertebral defects, anal atresia, tracheoesophageal fistula, and renal dysplasia (44). The *VATER association* is defined by finding at least three of the VATER anomalies. A subset of infants with the VATER syndrome have other defects including diaphragmatic, genital, cardiovascular, and neural tube defects; oral clefts; bladder extrophy; small intestinal atresias; and omphalocele. A variant syndrome, the *VACTERL anomaly*, combines the VATER syndrome with radial or other limb defects (43). It affects approximately 1.6 of 10,000 live births (45). Defective development of the neural tube and preaxial mesoderm may result in the full spectrum of changes (45). Patients with VACTERL are most likely to be male, have a higher perinatal mortality rate, and have lower mean birth weights than control populations (46). Mothers of infants with VACTERL often exhibit a higher frequency of fetal loss in previous pregnancies than a control population. Patients with a familial form of X-linked VACTERL, X-linked VACTERL-H, develop hydrocephalus due to aqueductal stenosis.

![FIG. 2.24. Radiograph of esophageal atresia. The feeding tube (arrow) terminates in the air-distended proximal esophageal pouch.](image)

Esophageal atresia also associates with the *CHARGE syndrome* (coloboma, heart disease, atresia choanae, growth and developmental retardation, genital hyperplasia, and ear anomalies) (47). The *oculodigitoesophageoduodenal syndrome*, also known as *Feingold syndrome*, is a dominantly inherited combination of hand and foot anomalies, microcephaly, esophageal/duodenal atresia, short palpebral fissures, and learning disabilities. The abnormality maps to chromosome 2p23-p24 (48). The *Bartsocas-Papas syndrome* consists of bilateral renal agenesis, esophageal atresia, hypoplastic diaphragm, unilateral renal agenesis, agenesis of the penile shaft, or anal atresia (49).

### Pathologic Features

Six types of esophageal atresia and stenosis are recognized (Figs. 2.25 and 2.26). In esophageal atresia, hypertrophic esophageal and tracheal muscles intimately blend with one another and the muscle layer contains an extravascular plexus. This is a manifestation of incomplete tracheal–esophageal separation. Striated muscle is present in the upper esophagus but not in the lower. Accompanying congenital esophageal neural abnormalities contribute to esophageal dysmotility (50).

Several types of stenosis exist. The stenotic segment varies from 2 to 20 cm in length and is usually located in the mid- or distal esophagus. In the first type of stenosis, segmental narrowing and loss of esophageal mural...
elasticity produces a localized area of muscular hypertrophy. In rare cases, the muscular hypertrophy involves the entire esophagus. The muscular hypertrophy may result from inflammatory damage to the myenteric plexus, with loss of the muscle-relaxing nitric oxide–producing nerves (51), and may coexist with hypertrophic pyloric stenosis. In a second form of stenosis, cartilaginous tracheobronchial remnants and respiratory epithelium lie within the esophageal wall, as a result of sequestration of a tracheobronchial anlage during the period of cranial elongation before embryologic separation of the esophagus and trachea. In a third form, a membranous diaphragm or web arising from the esophageal wall, containing fibromuscular tissue with a small central perforation, obstructs the lumen. These anomalies are treated surgically but when the lesions are repaired, patients often suffer residual esophageal dysmotility due to underlying neural abnormalities in the remaining esophagus. The abnormal motility often leads to GERD with all of its complications (52). Restenosis commonly occurs, leading to aspiration and respiratory infections.

FIG. 2.25. Esophageal atresias and stenoses. A: In type I atresia, a segment of the esophagus is represented by only a thin, noncanalized cord with resultant formation of an upper blind pouch connecting with the pharynx and a lower pouch leading to the stomach. Most commonly, the atresia is located at or near the tracheal bifurcation. B: Rare type II atresia. The proximal and distal portions of the esophagus are completely separate. The upper part connects with the trachea. C: Type III is the most common anomaly. The lower pouch communicates with the trachea or mainstem bronchus. D: In type IV, both the upper and lower pouches connect to the trachea. E: Esophageal stenosis near tracheal bifurcation. Tracheoesophageal fistula is also illustrated. F: Simple esophageal stenosis.

Congenital Bronchoesophageal Fistulas
Bronchopulmonary malformations occur less commonly than tracheoesophageal abnormalities and result from imperfect separation of pulmonary and esophageal anlagen or from an accessory esophageal lung bud. If the communication between the pulmonary tissue and the esophagus is lost, the pulmonary tissue appears as a sequestration. Extralobar sequestrations remain anatomically separate from the lung and have their own pleura. They usually lie adjacent to the esophagus, with which they may communicate. Rarely, intralobar sequestrations communicate with the esophagus presenting as bronchoesophageal fistulas (53). Patients usually present in infancy with a mediastinal mass. Tracheobronchial chondroepithelial hamartomas represent an uncommon related lesion (54), which also results from the abnormal separation of the esophagus and trachea. They contain tracheobronchial lining epithelium, cartilage, and sometimes ectopic thyroid tissue or heterotopic pancreas. These lesions are extremely rare and usually lie in the distal esophagus (54).

Duplications
Esophageal duplications account for only 10% to 20% of all GI duplications. They affect approximately 1 of 8,000 persons (55). Duplications develop while columnar, ciliated columnar, or squamous epithelium lines the fetal esophagus and occur in three major forms: Cysts, diverticula (discussed in a later section), and tubular malformations. Cysts account for 80% of duplications. Duplications often present in infancy and childhood with dysphagia, nausea, vomiting, weight loss, pain, bleeding, anorexia, dyspnea, wheezing or recurrent coughing, and pneumonitis. Duplication cysts are single, fluid-filled cysts (55) that lie posteriorly in a periesophageal location, develop within the esophageal wall (Fig. 2.27), or present as pedunculated intraluminal lesions (56). They average up to 5 cm in diameter. Duplication cysts typically demonstrate continuity of the esophageal muscularis propria with the muscle layer of the cyst wall. It may be difficult to distinguish between esophageal duplication cysts and other intrathoracic cysts.
lined by respiratory columnar (Fig. 2.28), cuboidal enteric, stratified squamous, or gastric epithelium. Tubular duplications usually lie within the esophageal wall paralleling the true esophageal lumen. Unlike duplication cysts, tubular duplications communicate with the true lumen at either or both ends of the tube. Duplications usually have a duplicated muscularis propria.

**FIG. 2.26.** Tracheoesophageal fistula. Thoracic and upper abdominal organs viewed from the posterior surface in a neonate born with esophageal atresia. The upper esophagus terminates blindly in a blunted esophageal pouch (arrow) and distal esophageal communication with the trachea at the carina (arrowhead).

<table>
<thead>
<tr>
<th>Type</th>
<th>Prevalence</th>
<th>Pathology</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postcricoid web</td>
<td>Association with iron deficiency anemia</td>
<td>Thin mucous membrane</td>
<td>• Autoimmune</td>
</tr>
<tr>
<td>Low esophageal mucosal ring</td>
<td>10% autopsies</td>
<td>Consists of center of loose areolar tissue covered on each side by thinned squamous epithelium</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Low esophageal muscular ring</td>
<td>4% autopsies</td>
<td>Hypertrophy; muscle layer; mucosa thinned</td>
<td>Associated with hiatus hernia</td>
</tr>
<tr>
<td>Ringlike peptic stricture</td>
<td>Rare, complicates Barrett esophagus</td>
<td>Fibrous, inflamed tissue</td>
<td>Exaggeration of normal anatomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Secondary to esophagitis</td>
</tr>
</tbody>
</table>

**Bronchogenic Cysts**

Bronchogenic cysts lie anteriorly, representing defective tracheoesophageal separation and aberrant bronchial budding from the foregut. They occur in the mediastinum, within the lung, or in the abdomen. Histologically,
they contain cartilage, smooth muscle cells, and seromucinous minor salivary glands and are usually lined by ciliated, mucus-secreting, respiratory epithelium. Other bronchogenic cysts are lined by respiratory squamous epithelium but lack cartilage.

**Esophageal Rings and Webs**

The distal esophagus contains two rings that demarcate the proximal and distal borders of the esophageal vestibule (57). They occur alone or together. The **muscular ring** lies at its proximal border and corresponds to the upper end of the LES. It is a broad, 4- to 5-mm symmetric band of hypertrophic muscle covered by squamous epithelium that constricts the tubular esophageal lumen at its junction with the vestibule. The **mucosal ring** or **Schatzki ring** affects 6% to 14% of individuals and always associates with a hiatal hernia. Mucosal rings are thin, 2-mm transverse mucosal folds that protrude into the esophageal lumen. They usually lie at the SCJ with squamous epithelium covering the upper surface and columnar epithelium lining the lower. The core of the ring contains connective tissue, fibers of the muscularis mucosae, and blood vessels. The muscularis propria contributes little to its formation. Mucosal rings may progress to strictures due to coexisting inflammation (57). Mucosal webs and rings are compared in Table 2.2.

The incidence of **esophageal webs** ranges from 0.7% to 16%. Congenital esophageal webs are characterized by one or more thin horizontal membranes covered by stratified squamous epithelium arising in the upper and midesophagus. Unlike rings, webs rarely encircle the lumen, but instead protrude from the anterior wall, extending laterally. Webs rarely exceed 2 mm in thickness. Postinflammatory esophageal webs complicate many forms of esophagitis. As a result, they tend to be multiple and distributed throughout the esophagus. Histologically, webs consist of a thin layer of variably inflamed connective tissue covered on both sides by stratified squamous epithelium. Gastric mucosa may line the undersurface of distal webs. The epithelium covering esophageal webs may undergo neoplastic transformation.

![FIG. 2.27. Duplication cyst. A: Radiograph of a large intramural defect in proximal esophagus. B: Gross picture showing the presence of a bulging submucosal sausage-shaped mass from a different patient cyst (arrows).](file:///F|/Gastro/Chapter%202%20oesoph.htm#Gastro%202%20oesoph.htm)
explaining symptom reversal following iron replacement therapy in patients without webs (59). The patients often have other abnormalities, some of which have autoimmune etiologies including autoimmune gastritis, ulcerative colitis, thyroid disease, Sjögren syndrome, and celiac disease (60). Shelllike mucosal webs arise from the anterior wall of the proximal esophagus, occasionally extending laterally or becoming circumferential. They are sometimes multiple. Most lie within 2 to 3 cm of the postcricoid area.

**Diffuse Esophageal Intramural Pseudodiverticulosis**

Diffuse esophageal intramural pseudodiverticulosis (DEIP) affects 15% to 17% of patients seen at autopsy. Patients range in age from 8 to 83 years (61); males are more commonly affected than females. The disease has several known associations but since many are common, the relationships may be fortuitous rather than etiologic. Possible predisposing factors include alcohol abuse, esophageal reflux, candidiasis, herpes esophagitis, motility disorders, and squamous cell carcinoma. The diverticula result from ductal obstruction caused by inflammation, mucin, or squamous debris. Strictures are present in approximately 75% of patients. Patients present with dysphagia and acute bolus obstruction. These symptoms probably result from coexisting esophagitis or strictures rather than the pseudodiverticula themselves (62).

Multiple cystically dilated submucosal glandular ducts produce innumerable 1- to 3-mm flask-shaped diverticula with pinpoint mouths lying evenly distributed in a linear fashion along the esophageal wall (Fig. 2.29). These are most numerous proximally. The intramural cysts extend 3 mm or less beyond the esophageal lumen. The dilated ducts are lined by stratified squamous epithelium, which may appear hyperplastic (Fig. 2.30). The lumen may contain desquamated squamous cells or inflammatory cells. Organisms, including bacteria, fungi, and parasites, can secondarily colonize the cysts. Nonspecific acute or chronic inflammation often surrounds the acini and the ducts. The inflammation may lead to subsequent submucosal fibrosis or stricture formation.

**Diverticula**

Esophageal diverticula are saccular outpouchings that contain all, or part, of the esophageal wall. One can classify them by their location (pharyngoesophageal, thoracic, or epiphrenic), their pathogenesis (congenital, traction, or pulsion), or their status as true or false, or congenital or acquired (Fig. 2.31). The most important feature distinguishing congenital versus acquired diverticula is the absence of an intact muscularis propria in acquired diverticula. Zenker (hypopharyngeal) diverticulum represents the most common (up to 70%) esophageal diverticulum. Twenty-one percent of diverticula originate in the midesophagus; 8.5% originate in the supradiaphragmatic region. Histologically, squamous epithelium lines all acquired esophageal diverticula unless they develop in an area of Barrett esophagus. Congenital diverticula contain all of the components of the esophageal wall, including the muscularis propria, and may be lined by columnar, ciliated, or squamous epithelium.

**Zenker Diverticulum (Pharyngoesophageal Diverticulum)**

Patients with Zenker diverticula are generally in their 7th or 8th decades of life. There is a 2:1 male preponderance. The diverticulum originates in the proximal esophagus (Fig. 2.32) from mucosal outpouchings at points...
of weakness in the esophageal wall at its junction with the pharynx. Most develop posteriorly or posterolaterally between the inferior constrictor muscle and fibers of the cricopharyngeus muscle through a triangular zone of sparse musculature termed the Killian triangle. These pulsion diverticula result from uncoordinated muscular contractions during swallowing. As the diverticulum enlarges, it protrudes between the posterior wall of the esophagus and the vertebrae leading to anterior displacement of the proximal esophagus, sometimes causing esophageal compression. Patients typically present with dysphagia, halitosis, and regurgitation of food consumed several days previously. Aspiration and secondary pneumonitis occur. Secondary bacterial colonization results in diverticulitis. Zenker diverticulum and cervical esophageal webs or hiatal hernias sometimes coexist. Perforation leads to mediastinitis. Squamous epithelium lines Zenker diverticula (Fig. 2.33).

The muscle may appear attenuated and the wall is variably inflamed, sometimes with prominent lymphoid follicles. Ulcers may occur. There is a 0.31% to 0.7% incidence of squamous cell carcinoma secondary to longstanding inflammation (63).

**FIG. 2.29.** Esophageal intramural pseudodiverticulosis. Double-contrast esophagram demonstrates numerous irregular thin outpouchings from the esophageal lumen, some of which have flask-shaped bases. These represent ectatic submucosal glands.
FIG. 2.30. Diffuse esophageal intramural pseudodiverticulosis. A: Low-power magnification demonstrating the presence of a cystically dilated duct, which passes between lobules of the submucosal glands. Some of the ducts have also undergone squamous metaplasia. B: Higher magnification of one of the ducts showing the presence of inspissated secretions and flattened cuboidal lining epithelium. A mild inflammatory infiltrate surrounds the duct.

FIG. 2.31. Comparison of congenital versus acquired diverticula. A: False or acquired diverticula tend to demonstrate epithelial or mucosal outpouchings through the muscularis propria. In some instances, the submucosa follows the mucosa. B: In contrast, congenital or true diverticula represent herniations of the entire wall of the gastrointestinal tract, including the muscularis propria.
FIG. 2.32. Zenker diverticulum. Lateral view demonstrates the diverticulum as a large saclike structure containing barium.
**FIG. 2.33.** Histologic appearance of Zenker diverticulum. Herniation of the mucosa, submucosa, and part of the muscularis propria into the paraesophageal tissues. The resulting diverticulum consists of muscular wall, submucosa, and a hyperplastic squamous epithelium.

**Midesophageal Diverticula**

Diverticula arising at the level of the tracheal bifurcation are less common than those in the cervical esophagus. Midesophageal diverticula almost always represent incidentally discovered lesions, unless there is coexisting diverticulitis. They are single or multiple (Fig. 2.34), and usually develop in association with mediastinal inflammation that causes traction on the esophageal wall, pulling it outward. Other diverticula result from motility disturbances, including achalasia or diffuse esophageal spasm. These wide-mouthed diverticula (Fig. 2.35) consist of a variably inflamed squamous mucosa and submucosa with an attenuated muscularis propria.

**Epiphrenic Diverticula**

Epiphrenic diverticula are rare, developing in middle age, supporting an acquired etiology. They are almost always of the pulson type, resulting from increased intraesophageal pressure that pushes the mucosa outward in areas of muscular weakness. They frequently coexist with other disorders including hiatal hernia, diaphragmatic eventration, and carcinoma and/or motility disturbances (64). The presence of hypertrophic muscle distal to the diverticula supports the concept that functional or anatomic obstructions are important in their pathogenesis. Patients present with substernal pain, dysphagia, and weight loss. Complications include aspiration pneumonia and lung abscesses, diverticulitis, esophageal obstruction, perforation, mediastinitis, or hemorrhage. Epiphrenic diverticula develop in the distal 10 cm of the esophagus. They appear globular and wide mouthed and, in contrast to midesophageal lesions, may become quite large. The diverticula contain a squamous mucosa and submucosa but no muscularis propria (Fig. 2.36). Chronic inflammation is often present. Carcinomas may develop within epiphrenic diverticula for the same reason they do in other diverticula (i.e., stasis of luminal contents), leading to chronic inflammation.

**FIG. 2.34.** Esophageal diverticulum. Mucosal view of two esophageal traction diverticula (arrows).

**Pancreatic Metaplasia**

Pancreatic metaplasia develops in patients with BE (65), carditis, and inlet patches. Mean patient age is 52 years with a range of 18 to 89 years. It occurs in 24% to 60% of patients with biopsy specimens from the SCJ (65.66.67). These glands often lie in the deeper aspects of the mucosa and vary in size from 0.1 to 0.5 mm in greatest diameter (65). They form small clusters of compactly packed cells that either blend imperceptibly into the adjacent metaplastic gastric glands or form distinct nodules that can stand out prominently within the mucosa. The pyramidal pancreatic acinar cells have abundant apical and midcellular eosinophilic coarse granular cytoplasm and appear basophilic in the basal areas. The basally located nuclei are small, round, and uniform with occasional conspicuous but small nucleoli. The acinar cells are positive for pancreatic lipase and amylase. Mucous cells may intermingle with the pancreatic acinar cells within individual lobules. Endocrine cells may also be present. The foci of pancreatic metaplasia lack pancreatic ducts, periductal smooth muscle fibers, and islet cells.
**FIG. 2.35.** Esophageal diverticulum. *A:* Unopened esophagus and stomach with the dissected-out heart (*H*). A large saccular dilation (*D*) extends from the midesophageal region and lies next to the heart on the photography table. *B:* Opened specimen demonstrating the presence of a large diverticulum containing necrotic debris. This diverticulum was attached to the pericardium.

**FIG. 2.36.** Esophageal diverticulum. *A:* Midsagittal section of the diverticulum showing lining of tan squamous mucosa; the outer coat is thinned. *B:* Histologic section of *A.*
FIG. 2.37. Esophageal lacerations and perforations. A: Mallory-Weiss tear. This tear straddles the gastroesophageal junction. Deeper ulceration is present as well. This laceration occurred through an area of pre-existing esophagitis. B: Boerhaave syndrome with spontaneous transmural rupture.

Mucosal Lacerations, Ulcerations, and Perforations

Esophageal perforation complicates many settings (Fig. 2.37) (Table 2.3). A retrospective study of esophageal perforations in a large hospital found 26 instances in a 10-year time frame. Only six of these were spontaneous, while 19 were due to instrumentation with the largest number due to pneumatic dilation in cases of achalasia (68). Perforations due to foreign bodies occur in areas of physiologic narrowing. Spontaneous transmural perforations qualify for a diagnosis of Boerhaave syndrome. Spontaneous intramural tears qualify for a diagnosis of a Mallory-Weiss tear. When the esophagus perforates, free air enters the mediastinum and spreads to adjacent structures causing palpable cervical emphysema, mediastinal crackling sounds, and pneumothorax. Over time, secondary infections cause mediastinal abscesses, pyopneumothorax, and pleural-pulmonary suppurations.

TABLE 2.3 Causes of Esophageal Perforation

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis regardless of cause</td>
</tr>
<tr>
<td>Penetrating wounds</td>
</tr>
<tr>
<td>Iatrogenic trauma</td>
</tr>
<tr>
<td>Pneumatic dilation</td>
</tr>
<tr>
<td>Intubation</td>
</tr>
<tr>
<td>Intraoperative</td>
</tr>
<tr>
<td>Endoscopic</td>
</tr>
<tr>
<td>Foreign bodies</td>
</tr>
<tr>
<td>Blast injury</td>
</tr>
<tr>
<td>Postemetic (Mallory-Weiss syndrome)</td>
</tr>
<tr>
<td>Blunt trauma (auto accidents, etc.)</td>
</tr>
<tr>
<td>Esophageal diverticula</td>
</tr>
<tr>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>Corrosive injury</td>
</tr>
</tbody>
</table>
**Mallory-Weiss Syndrome**

The term Mallory-Weiss syndrome refers to cases of painless GI bleeding resulting from esophageal or gastroesophageal mucosal lacerations (Fig. 2.37), usually following severe vomiting. Sometimes, vomiting precipitates tears of pre-existing ulcers. Less traumatic events, even snoring, can produce partial esophageal tears, usually above the cardia (69). Most patients are males with a history of alcohol and/or salicylate abuse or hiatal hernias. Rarely lacerations develop in children (70), even neonates. Risk factors for bleeding include portal hypertension or a coagulopathy. These tears account for 5% to 10% of cases of upper GI hemorrhage (71). Single or multiple lacerations lie along the long axis of the distal esophagus crossing the GEJ or lying in the gastric fundus. Over 75% of lacerations are limited to the stomach; they average 1.5 cm in length. The lacerations vary in depth, often only affecting the mucosa; they rarely extend into the muscularis propria. Submucosal hematomas may form and dissect for a distance beyond the tear. Histologic changes reflect the temporal relationship to the tear. If acute, there may be little in the way of acute inflammation. Over time, acute and then chronic inflammatory cells infiltrate the area around the tear. Previous lacerations may associate with scarring. Bleeding from Mallory-Weiss tears usually stops spontaneously; <5% of patients rebleed.

**Boerhaave Syndrome**

The typical patient with Boerhaave syndrome is a middle-aged male, and frequently an alcoholic individual. The disease may also affect children, even neonates (72). Severe vomiting followed by constant excruciating chest pain are the classic clinical signs. Hematemesis occurs at times. The clinical and radiologic findings point to an intrathoracic catastrophe. The nonspecific symptomatology often delays the correct diagnosis. The mortality rate is approximately 31%. The sudden development of a pressure gradient between an internal portion of a viscus and its external supporting tissues represents the common pathogenetic denominator in cases of gastrointestinal rupture (73). The antecedent background varies; the viscus may become overdistended by food, drink, gas, or any combination thereof. Other antecedent events include abdominal blows, straining at stool, parturition, seizures, asthma, prolonged hiccups, and neurologic diseases. Characteristically, the rent is linear and longitudinal and occurs most commonly in a left lateral posterior location, 1 to 3 cm above the GEJ (Fig. 2.37). The tears measure 1 to 20 cm in length with an average length of 2 cm; the mucosal part of the tear is usually longer than the muscular part. Immediate surgical repair must occur if the patient is to survive. Persistent reflux often follows repair of the rupture (73).

**Esophagitis**

**General Comments**

Esophagitis has many causes (Table 2.4), the most common being gastroesophageal reflux, infections, and drugs. Esophageal biopsies are taken to determine the etiology of the esophagitis, to assess the consequences of the inflammation, to follow the course of the underlying disease, and to gauge therapeutic responses. Irrespective of its cause, most cases of esophagitis share common histologic features. Therefore, determining a specific etiology may be difficult unless one detects specific diagnostic features such as the presence of viral inclusions. Additionally, multiple etiologies may be present in any given patient. Esophageal inflammation can be acute, chronic, or mixed. Mild esophageal injury results in reversible mucosal changes and transient inflammation. Changes associated with acute damage include the presence of balloon cells and inflammatory cells (particularly mononuclear cells) and eosinophils. Basal cell hyperplasia and papillary elongation develop and vascular lakes form. In severe esophagitis, ulcers, erosions, or neutrophils may be seen. Chronic damage leads to submucosal fibrosis or strictures. Patients with longstanding reflux esophagitis may develop Barrett esophagus.

### TABLE 2.4 Causes of Esophagitis

<table>
<thead>
<tr>
<th>Gastroesophageal reflux</th>
<th>Uremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingested material</td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td>Corrosive agents</td>
</tr>
<tr>
<td></td>
<td>Food</td>
</tr>
<tr>
<td>Graft vs. host disease</td>
<td>Infections</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Systemic disorders</td>
</tr>
<tr>
<td></td>
<td>Behçet syndrome</td>
</tr>
<tr>
<td></td>
<td>Crohn disease</td>
</tr>
<tr>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td>Pemphigus</td>
</tr>
<tr>
<td></td>
<td>Sarcoïd</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
</tr>
</tbody>
</table>
Trauma
Intubation
Vascular disease
Motility disorders
Repaired tracheoesophageal fistula
Sclerotherapy

Multinucleated epithelial giant cell changes develop in esophagitis of varying etiologies, representing a nonspecific reparative response. The mucosa contains multinucleated (mean three nuclei per cell, range two to nine) squamous epithelial cells. They are often confined to the basal zone, but sometimes they involve both the basal and superficial epithelium. The nuclei contain single or multiple eosinophilic nucleoli with a perinuclear halo but no inclusions, hyperchromicity, or atypical mitoses (74). Multinucleated cells can also be seen in viral infections, but the use of immunostains or genetic tests allows one to separate nonspecific giant cell changes from virally induced changes.

Cytologic material obtained from patients with esophagitis may show a nonspecific acute and chronic inflammatory infiltrate with mixtures of neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes, and erythrocytes. Epithelial cells, if present, usually appear degenerative.

Reflux Esophagitis

The term gastroesophageal reflux (GER) refers to the retrograde flow of gastric and sometimes duodenal contents into the esophagus. The term gastroesophageal reflux disease is a symptomatic condition or histopathologic alteration resulting from episodes of GER. Reflux esophagitis describes a subset of GERD patients with histopathologic changes in the esophageal mucosa.

Demography/Epidemiology

GERD affects patients of all ages, even children and small infants. The prevalence of GERD ranges from 3% to 36%. GERD is equally present among men and women, but there is a male predominance of esophagitis and Barrett esophagus. GERD affects whites more frequently than members of other races. There is also geographic variability in the prevalence of GERD with very low rates in Africa and Asia and higher rates in North America and Europe (75). However, GERD is increasing in frequency in Asians. Nonerosive reflux disease appears to be the commonest form of GERD among Asians. Ethnic and geographic demographic differences suggest that both genetic factors and environmental factors play a role in predisposition to GERD (76).

Conditions predisposing to GERD include smoking; increased intra-abdominal or intragastric pressure, including pregnancy, ascites, and obesity; and delayed gastric emptying. Motility disorders including diabetes, alcoholic neatrophils, achalasia, and scleroderma also predispose to GERD. Patients with hiatal hernias and strictures are especially prone to develop GERD. It also follows surgical procedures. Erosive esophagitis is particularly common in acid hypersecretors such as those with the Zollinger-Ellison syndrome (77). GER in infants and children complicates congenital esophageal or gastric abnormalities. GER also associates with cystic fibrosis (78).

Pathophysiology

GERD is a multifactorial disorder (Table 2.5). Most patients have a lower mean LES resting pressure than is seen in patients without GERD. This allows acid to reflux into the esophagus, leading to the development of esophagitis. The inflammation further impairs LES pressure, increasing acid exposure in the esophagus (79). Patients also have inadequate or slowed clearance of refluxed material and delayed gastric emptying and/or increased gastric volume. The nature and amount of refluxed material and the length of time it remains in contact with the esophageal mucosa as well as the number of reflux episodes determine whether GERD develops (80). GERD results from reflux of both acid and alkaline secretions (Fig. 2.38). Acid alone causes relatively few changes, but when combined with pepsin or bile acids, more severe damage results (81). Pepsin requires an acid pH to exert its full damaging effects (82). Patient age, nutritional status, and other less well-understood factors also influence the mucosal capacity to withstand injury and to repair itself following injury. Reflux esophagitis may also be enhanced by the genesis of free radicals during reflux. These free radicals damage cell membranes, thereby altering the mucosal barrier. Lipid peroxidation increases with the increasing grade of esophagitis; it is highest in patients with BE (83).

**TABLE 2.5 Causes of, or Predisposition to, Gastric Reflux**

| Loss of lower esophageal sphincter (LES) pressure gradient |
| Loss of esophageal closure pressure |
| Abnormal LES sphincter position |
| Hiatus hernia |
| Certain foods, drinks |
| Smoking |
| Pyloric stenosis |
| Smooth muscle medications |
| Atropine |
| β-Adrenergics |
| Aminophylline |
Nitrates
Calcium channel antagonists
Smooth muscle relaxants
Iatrogenic destruction of the LES
Surgical resection
Myotomy
Balloon dilation
Gastroplasty
Gastrostomy feeding
Nasogastric intubation
Pregnancy
Esophageal dysmotility syndromes (inefficient mucosal clearing)
  Collagen vascular diseases
  Intestinal pseudo-obstruction syndromes
  Autoimmune neuropathies
  Diabetes
Zollinger-Ellison syndrome
Decreased esophageal mucosal resistance
Infections
Prior chemotherapy
Intubation (nasogastric)
Increased gastric pressure
Abnormally distended stomach
Refluxed duodenal contents
Esophageal and gastric structural abnormalities

Relationship of Reflux Esophagitis to Helicobacter pylori Infections

Studies addressing the relationship of HP infection to GERD often reach conflicting conclusions. This results from the fact that the interplay of HP infections and GERD is complex and complicated by the common use of proton pump inhibitor (PPI) therapy in these patients. At the heart of the debate is the link between gastric acid secretion, HP infection, and GERD. In patients with gastric ulcer and corpus gastritis, the impact of HP infection varies substantially producing wide variation in patterns of acid secretion. In many patients gastric acid is suppressed and is no longer produced in the amount necessary to induce GERD. Bacterial eradication in some of these individuals results in a substantial recovery of acid secretion with sufficient acid to increase the aggressiveness of refluxed gastric juice to the esophageal mucosa (84). In contrast, duodenal ulcer patients typically have antrum-predominant HP gastritis and a well-preserved acid-secreting mucosa. In these patients, HP infections may make the acid-secretory mechanism hyperresponsive to stimulation, increasing acid production. In this patient group, HP infections can increase the aggressiveness of the gastric juice to the esophageal mucosa.
Current epidemiologic trends indicate an inverse relationship in the Western world between the rising incidence of GERD and the decreasing incidence of *H. pylori* infections (85). The lower prevalence of *H. pylori* in GERD patients, the increase of GERD following *H. pylori* eradication, and the association with certain gastritis patterns (atrophic corpus gastritis) have led to the widespread opinion that *H. pylori* exerts a protective effect on the esophagus and may prevent the development of GERD and its complications (85). However, as noted, the data and their interpretations are conflicting, keeping this subject one of continuing interest.

**Clinical Features**

Transient mild reflux affects most individuals including children and adults. It is especially common in preterm infants (86). The degree of reflux must be severe for individuals to become symptomatic. Fifty percent of symptomatic patients have complications including esophagitis, strictures, or BE. Adults present with diverse symptoms including heartburn, regurgitation, bitter-tasting fluid in the mouth, dysphagia, odynophagia, nausea, vomiting, hiccup, anginalike chest, and hoarseness. The regurgitation can cause a spectrum of conditions, including asthma, chronic laryngitis or pharyngitis, subglottic stenosis, and dental disease. Some patients present with bleeding from esophageal ulcers. Complications peak between ages 50 and 70 years (87). The severest complication is carcinoma developing in the setting of BE. The clinical course and prognosis of infants and children with GER differ depending on the age at onset. Some children present with symptoms of asthma. GERD may also cause obstructive apnea in infants. Severe dental caries are common. The most frequent complication of recurrent GER in children is failure to thrive as the result of caloric deprivation, vomiting, recurrent bronchitis, or pneumonia caused by repeated episodes of pulmonary aspiration. Some children require gastroesophageal fundoplication and/or pyloroplasty to alleviate the symptoms.

**Gross and Endoscopic Features**

The gross appearance of the esophagus varies with disease severity. Approximately one third of patients with chronic GERD symptoms are endoscopically normal (88). Low-grade esophagitis is only evident histopathologically. Areas of patchy erythema and red streaks are the first endoscopic abnormalities. Later erosions and ulcers develop; these predominate distally and taper off proximally. The esophagus appears friable, diffusely reddened, and hemorrhagic (Fig. 2.39); it bleeds easily. As the disease progresses, the ulcers become confluent, even circumferential. Strictures or BE characterize severe chronic disease. Prolonged reflux may result in esophageal shortening. Inflammatory polyps may be present. The distinction between the squamous and the columnar epithelium becomes less clear. Several endoscopic classifications have been developed to evaluate the esophageal mucosa. The two most common are the Savary-Miller MUSE system and “Los Angeles” classifications (89,90).

**Histologic Features**

Biopsies are performed to confirm the diagnosis of GERD; to document complications, including esophagitis, BE, or tumor development; and to rule out the presence of coexisting infections. Since esophagitis tends to be a patchy process, it is easy to miss diagnostic changes on a single biopsy. The current wisdom is that biopsies should be taken in the area just distal to the Z line to detect carditis (see below), just proximal to the Z line to detect esophagitis, and 3 cm proximal to the Z line to detect hyperplastic changes that are more predictive of the presence of GERD than more distally derived biopsies. Repetitive episodes of tissue injury and healing produce histologic features that reflect disease activity at the time of...
examination, superimposed on changes from previous injurious episodes. Esophagitis can heal completely or it may progress on to a number of the complications discussed later. Biopsies from patients with heartburn commonly show only basal cell hyperplasia without inflammation. The basal hyperplasia can progress to frank esophagitis. There are four stages of reflux esophagitis: (a) acute (necrosis, inflammation, and granulation tissue formation); (b) repair (basal cell hyperplasia and elongation of the papillae); (c) chronic (fibrosis and formation of Barrett esophagus); and (d) complications (dysplasia and adenocarcinoma).

FIG. 2.39. Reflux esophagitis. Area of the Z line is destroyed. Acute hemorrhagic ulcerative reflux esophagitis demonstrating multiple areas of ulceration and erythema.

Various histologic features should be assessed when examining the biopsy for GERD (Table 2.6). No single feature described below represents an absolute criterion for the presence of GERD, but each is helpful in suspecting the diagnosis. In the absence of a known drug history or the presence of specific microorganisms, biopsies, particularly distal biopsies showing esophagitis, are most likely to be due to GERD.

**Epithelial Hyperplasia**

The normal basal cell layer is only one to four cells high; it should not constitute more than 15% of the epithelial thickness. In the setting of GERD, the basal zone increases from 10% to more than 50%; papillary height can increase to more than 50% to 75% of the total epithelial thickness (91). This change affects patients with an endoscopically normal mucosa as well as those with endoscopic evidence of esophagitis. Regenerative changes are characterized by nuclear enlargement, hyperchromasia, and mitoses that remain limited to the basal layer (Fig. 2.40). Prominent nucleoli may be present. EGFR expression is enhanced in the hyperplastic cells (92).

**TABLE 2.6 Histologic Features of Acute Esophagitis**
Chapter 2

| Basal zone hyperplasia (.15% to 20%) |
| Basal layer spongiosis (edema) |
| Nuclear enlargement |
| Mitoses in basal cell layer |
| Elongated papillae (.75%) |
| Venular dilation (vascular lakes) |
| Intraepithelial eosinophils |
| Polymorphonuclear leukocytes |
| Lymphocytes |
| Eosinophils |
| Acanthosis |
| Balloon cells |
| Erosions or ulcers |

Accurate assessment of the basal and papillary height requires evaluating well-oriented specimens. It is helpful to divide the epithelial thickness into thirds. Papillae should not extend into the upper third. When the lower third is divided in half, the basal cells should be confined to its lower half. PAS stains may help distinguish the basal layer from the superficial layers enabling more accurate measurements of basal cell hyperplasia (Fig. 2.41). In less optimally oriented specimens, basal zone thickness can be evaluated if one sees at least three to four papillae arranged in parallel to one another and not cut tangentially. In tangentially cut sections, a helpful feature is an increase in the number of papillae, which can be evaluated in an en face section. In this setting one may see overlapping capillaries. Since the biopsies may be small or have minimal or no lamina propria or they may be inappropriately oriented and therefore difficult to evaluate for basal hyperplasia and papillary elongation, we recommend that the biopsies be examined at three levels to increase their diagnostic accuracy.

If marked squamous epithelial hyperplasia develops, the elongated epithelial pegs extend into the underlying lamina propria, in a process known as acanthosis (Fig. 2.42). Extensive acanthosis, also termed pseudoepitheliomatous hyperplasia, can suggest the presence of an invasive carcinoma. The epithelium may appear markedly regenerative with cytoplasmic basophilia, an increased nuclear-to-cytoplasmic ratio, glycogen depletion, and increased mitotic activity. However, the reactive cells more or less maintain their polarity and abnormal mitoses are absent. The individual cell keratinization seen in high-grade dysplasia is absent. The cell nuclei may have prominent nucleoli but the nuclei appear relatively uniform in size and one may see some evidence of squamous cell maturation in the more superficial cell layers. The boundary between the epithelium and the underlying stroma appears smooth, unless extensive inflammation occurs.
FIG. 2.40. Esophagitis. A: Esophagitis with basal cell hyperplasia and a bandlike inflammatory infiltrate in the lamina propria. B: The mucosal vessels are dilated and congested. This histology corresponds to the hyperemia seen endoscopically in esophagitis. Numerous intraepithelial inflammatory cells are present. The epithelium appears poorly glycogenated.

FIG. 2.41. Periodic acid–Schiff stain demonstrating the regularity of the underlying basement membrane and lack of glycogenation of the epithelium.

The stroma underlying the epithelium may appear inflamed, but one should not see desmoplasia. Very small or poorly oriented biopsies, especially those with significant inflammation and associated inflammatory atypia, may be impossible to interpret. If one is completely unable to distinguish between reactive atypia and dysplasia, a diagnosis of indefinite for dysplasia can be made. In this situation, one may want to recommend repeat biopsies once the reflux has been treated, to rule out the presence of an ulcerated and inflamed carcinoma. The sensitivity of hyperplasia as a diagnostic feature is only 60% to 70% (93). Basal cell hyperplasia is a reversible change that disappears with treatment. Hyperplasia also complicates other forms of esophagitis so that it is not specific for GERD.

Balloon Cells

Balloon cells often develop in the midzone of the epithelium clustering around vascular papillae (94). These occur in approximately two thirds of cases of GERD (Fig. 2.43). The cytoplasm of the enlarged, globoid cells appears swollen; cells contain irregular pyknotic nuclei or demonstrate karyorrhexis.

Balloon cells can be accentuated by PAS stains since they lose the normal intensity of PAS staining characteristic of superficial epithelium. PAS stains also help distinguish balloon cells from the enlarged squamous cells seen in patients with glycogen acanthosis. The presence of balloon cells does not establish a diagnosis of GERD, since they develop in any damaged mucosa, irrespective of its cause. Nonetheless, in the absence of other more characteristic features, the presence of balloon cells may be the only clue to suggest that some form of injury has occurred.
**FIG. 2.42.** Esophagitis. *A:* Acanthosis and immaturity of the squamous epithelium is present. Note the long prolongations of the epithelium into the underlying lamina propria. The lymphatics appear dilated and lymphocytes infiltrate the epithelium. *B:* Higher magnification of *A* demonstrating the elongated acanthotic, glycogen-depleted squamous epithelial prolongations. The flattened cells between the epithelial ridges represent compressed endothelium in the papillae. Chronic inflammation underlies the hyperplastic process.

**Vascular Changes**

Papillary capillary ectasia (sometimes called vascular lakes) (Fig. 2.44) and hemorrhage represent an early but nonspecific histologic sign of GERD. These lakes correspond to the red streaks seen endoscopically. Capillary ectasia develops in up to 83% of patients with reflux, contrasting with its presence in only 10% of control patients (80). This change is often present in the absence of any inflammation. Dilated and congested venules are seen high up at the top of the lengthened papillae. This may be accompanied by mucosal red cell extravasation. This change develops in many other forms of esophagitis.

**FIG. 2.43.** Ballooning degeneration. *A:* Beginning hydropic degeneration of squamous epithelial cells is evidenced by vacuolization of the cytoplasm. *B:* The epithelium has become paler than usual. The underlying lamina propria appears hemorrhagic and the epithelium separates from the underlying lamina propria.

**Inflammation**

**Lymphocytes.**

Small numbers of lymphocytes populate both the normal mucosa and the lamina propria so that their presence does *not* aid in making a diagnosis of esophagitis. However, they are very conspicuous in patients with GERD (95). Biopsies with esophagitis average greater than six lymphocytes per high-powered field (hpf) (96). Since the lymphocytes have irregular elongated nuclear contours, they are sometimes referred to as “squiggle cells” or as “cells with irregular nuclear contours.” Squiggle cells contain scant to invisible cytoplasm. The nuclear shape often curves to fit between the squamous cells (Fig. 2.45). Squiggle cells exhibit a T-lymphocyte phenotype (96). They are part of the inflammatory response in GERD but are not an independent marker of reflux esophagitis (95). A small percentage of the lymphocytes are intraepithelial S100+ antigen-presenting cells. Occasionally, the mononuclear cell infiltration becomes severe enough to cause a focal lymphoid hyperplasia mimicking a lymphoma.
FIG. 2.44. Patients with esophagitis often develop vascular lakes and extravasated red cells. These begin at the area of the papillae and extend outward.
Chapter 2

**FIG. 2.45.** Intraepithelial lymphocytes in reflux esophagitis. *A:* Increased numbers of lymphocytes insinuate themselves between the epithelium. *B:* Lymphocyte common antigen–immunostained sample demonstrating the presence of numerous intraepithelial lymphocytes (*brown*).

**Neutrophils.**

The presence of isolated neutrophils, either in the squamous epithelium or in the lamina propria, serves as evidence for acute esophagitis of many etiologies. Neutrophils are present in the epithelium of 20% or less of patients with reflux esophagitis, making them a relatively insensitive marker. They tend not to appear until the inflammation becomes severe and the epithelium ulcerated. Large collections of neutrophils suggest that a biopsy comes from the area of an ulcer or erosion. Neutrophils decrease in number the further one goes away from the erosion or ulcer. Neutrophils are most commonly detected near the Z line.

**Eosinophils.**

A modest number of eosinophils (at least six) in the epithelium or in the lamina propria strongly suggest the diagnosis of GERD (Fig. 2.46) (97). Infiltration by eosinophils in GERD is more common in children than in adults. It occurs early and may occur in the absence of basal cell hyperplasia. Other causes for mucosal eosinophilia include the entities listed in Table 2.7. One can easily appreciate eosinophils in small endoscopic biopsies, even when the biopsies are not well oriented. They affect up to 60% of adults with severe disease but the intraepithelial eosinophils may be focal in nature, necessitating a search for them on serial sections; their presence does not correlate with disease severity (95,97). Eosinophils are not a sensitive marker for GERD, since they are only found in 40% to 50% of individuals with GERD. Significant esophageal eosinophilia (>20 intraepithelial eosinophils per hpf) and eosinophilic microabscesses are not characteristic of GERD but are part of the entity known as eosinophilic esophagitis discussed in a later section.

**Erosions, Ulcers, and Fistulas in Gastroesophageal Reflux Disease**

The mucosal changes of reflux esophagitis range from the changes already described to acute esophagitis, erosions, superficial ulcers (Figs 2.47, 2.48, and 2.49), and extension of the inflammatory process, leading to fistula formation. The depth of the process distinguishes an esophageal *erosion* from an ulcer. Erosions are superficial lesions that remain confined to the lamina propria and muscularis mucosae sparing all but the most superficial layers of the submucosa. The necrosis, hemorrhage, and inflammation associated with *ulcers* extend deeper into the underlying submucosa or muscularis propria. The epithelium close to erosions or ulcers often contains neutrophils, eosinophils, and many lymphocytes. The erosions or ulcers (Fig. 2.49) often contain granulation tissue, an inflammatory exudate, and fibrinoid necrosis in the ulcer base. Lymphoplasmacytic infiltrates, often forming lymphoid aggregates, tend to cluster around erosions and ulcers. Epithelium at the ulcer margin is usually attenuated. Marked basal cell hyperplasia may occupy the entire mucosal thickness and there may be marked acanthosis. These changes may be accompanied by occasional bizarre epithelial or stromal cells.

**TABLE 2.7 Eosinophil-associated Esophageal Disorders**
Primary eosinophilic disorders
Eosinophilic esophagitis

Secondary eosinophilic disorders
Eosinophilic gastroenteritis
Hypereosinophilic syndrome

Secondary noneosinophilic disorders
Infection
Gastroesophageal reflux disorder
Tumors
Vasculitis
Connective tissue disorders

Erosions or ulcers may be isolated or confluent; they commonly coexist with one another. The damaged mucosa present in reflux esophagitis becomes prone to secondary infections. For this reason, both ulcers and adjacent tissues need to be carefully examined for the presence of coexisting fungal or viral infections. If appreciable ulceration has occurred, longitudinal ridges with crests develop (Fig. 2.48). The ridges consist of hyperplastic, hyperkeratotic, acanthotic, squamous epithelium and extensions of lamina propria; the troughs represent linear ulceration. The alternating ridges and ulcers end abruptly at the cardia; they usually taper away gradually into the surrounding squamous mucosa as one proceeds proximally. Pyogenic granulomas may develop.

Esophageal peptic ulcers also develop in the setting of reflux esophagitis; they resemble peptic ulcers occurring elsewhere. These may erode through the muscular layers, resulting in perforation. Peptic ulcers appear large, oval, and well circumscribed with elevated borders and deep necrotic centers. As these heal strictures develop. This occurs in about 10% of patients with severe reflux esophagitis. Fibrosis is usually present and may extend into the submucosa or beyond, sometimes extending into the periesophageal tissues. Although peptic strictures nearly always involve the distal esophagus, they occasionally develop more proximally. Proximal strictures average 2 to 4 cm in length. Extensive strictures complicate fulminant reflux esophagitis as well as nasogastric intubation in patients with reflux esophagitis or Zollinger-Ellison syndrome.

Differential Diagnosis

The differential diagnosis consists of the esophagitis itself as well as the distinction from neoplasia in very reactive-appearing lesions. The histologic features discussed in the preceding sections suggest the diagnosis of reflux esophagitis, but, as indicated, none is specific for this entity, since they

represent a common pattern of response to diverse forms of injury. Entities to be considered in the differential diagnosis include those listed in Table 2.4.
Complications of reflux esophagitis. LES, lower esophageal sphincter.

Reactive changes in biopsies from patients with GERD may appear so atypical (Fig. 2.50) that the differential diagnosis includes both invasive and noninvasive neoplasia. When the basal cell hyperplasia occupies the full thickness of the mucosa and it is very reactive in appearance, it may mimic squamous cell dysplasia. The mucosa in reactive lesions remains architecturally uniform and orderly with relatively regular and uniform papillae. In contrast, dysplastic lesions tend to appear more disorderly (irregularly irregular) and lengthened papillae are generally not present, but if they are present, they are irregular in their configurations. Hyperplastic squamous epithelial cells may appear atypical, but they are uniformly atypical, resembling one another. The enlarged nuclei of hyperplastic cells have generally smooth nuclear membranes, prominent nucleoli, and open chromatin with little or no nuclear overlapping. The cells maintain their normal polarity and abnormal mitoses are absent.

Fragments or irregular nests of very regenerative-appearing squamous cells, areas of pseudoepitheliomatous hyperplasia, bizarre mesenchymal cells in ulcer bases, or enlarged reactive endothelial cells in the granulation tissue or ulcer bases can simulate an invasive carcinoma. Routine histologic examination and immunohistochemical stains using antibodies directed against endothelial cells and cytokeratin can distinguish between some reparative reactions and malignancy. The bizarre stromal cells are usually distributed singly or in groups of two to three cells, usually in obvious granulation tissue. The nuclei are normal or almost normal in size and are nonoverlapping. If the atypia remains confined to cells that mark with endothelial cell antibodies, one can be certain that the tissue is inflammatory in nature. The presence of isolated cytokeratin positive cells strongly suggests the presence of an invasive cancer, especially if the cytokeratin positive cells demonstrate significant nuclear atypia and lie within a desmoplastic stroma. However, care must be taken in interpreting the immunostains since some of the mesenchymal cells occasionally stain with antibodies to cytokeratin. Additionally, isolated benign epithelial cells can drop into a severely inflamed stroma. In some cases with significant atypia and severe inflammation a definitive diagnosis may need to be deferred until the inflammation subsides.

Pyogenic granulomas may mimic an esophageal carcinoma, especially if they are large and polypoid. These larger lesions may be removed by polypectomy. The use of cytokeratin stains and vascular markers allows one to make the correct diagnosis. Finally, marked lymphoid hyperplasia may simulate a lymphoma, but immunohistochemical stains serve to demonstrate the polyclonal nature of the inflammatory infiltrate.

**Carditis**

As noted earlier, there is debate about the cardia, where it is located, and whether it represents a normal structure or a metaplastic process. There is also debate as to whether cardiac mucosa contains parietal cells. We view the cardiac mucosa as one that contains lobular mucin-secreting glands, with or without parietal cells. Regardless of how one views the cardia, the diagnosis of carditis is usually straightforward. Carditis, as the name implies, is an inflammation of cardiac-type epithelium, whether it be in the distal esophagus or proximal stomach. This inflammation is usually chronic in nature consisting of lymphocytes and plasma cells. In acute carditis, acute inflammatory cells are present.
FIG. 2.48. Gross appearance of reflux esophagitis. A: This photograph demonstrates the presence of both stress gastritis and reflux esophagitis. The gastric folds extend over the brown discolored, more distal portions of the stomach and end in a hemorrhagic zone. The Z line has been destroyed. The overlying mucosa appears ulcerated, hemorrhagic, and eroded. B: Multiple linear continuous and noncontinuous erosions and ulcers are present. Histologically, the most distal lesion just above the Z line in the center of the esophageal mucosa demonstrated Barrett mucosa. The remaining erosive lesions appear more tan in the surrounding mucosa. The epithelium in the distal portion of the esophagus is also whiter than normal due to the presence of hyperkeratosis. C: Severe Barrett esophagus arising in the setting of reflux esophagitis. One can see the termination of the gastric folds and then the presence of more proximal red epithelium extending up into the esophagus. Just above the gastroesophageal junction are two linear ulcers lying in the longitudinal axis of the esophagus. Several more proximal erosions are seen. The more proximal portion of the mucosa demonstrates ridges and valleys. The tops of the ridges are associated with white epithelium consistent with areas of hyperkeratosis. D: Areas of hyperkeratosis and ulcerations. In this particular patient, the area of the Z line is maintained and there is no evidence of Barrett esophagus.

FIG. 2.49. Esophageal ulcer. The ulcer bed is filled with granulation tissue. Reactive hyperplasia is seen in the adjacent squamous mucosa.

The main question is whether the carditis is part of GERD, HP gastritis, or both. The answer is both since GERD and HP cause similar histologic features in cardiac epithelium and distinguishing the etiology requires evaluation of the carditis in the context of coexisting changes that may be present in either the esophagus or the stomach. Determining the etiology of the carditis is difficult if only a single biopsy is examined. In patients with multiple biopsies, one is often able to determine the etiology of the carditis by examining the histologic changes in the squamous epithelium and/or the gastric epithelium. If there are classic features of GERD in the esophageal squamous biopsies, then the carditis is most likely part of GERD. In this setting, the carditis occurs in the absence of similar changes in the stomach. Early studies suggest that chronic carditis may be a more sensitive marker for GERD than inflammation involving the squamous mucosa when compared with the results of pH monitoring studies (98). Carditis in this setting is characterized by the presence of lymphocytic, eosinophilic, or plasma cell infiltrates in the lamina propria (Fig. 2.51). Frequently there is foveolar hyperplasia. A villiform surface may be present. The inflammation tends to decrease with increasing distance from the SCJ. Pancreatic metaplasia is also common; this is not common in HP infections. The pancreatic acini imperceptibly merge with the cardiac glands. Some suggest that if the SCJ appears normal endoscopically, then the carditis associates with HP infections, whereas an irregular SCJ with short columnar segments and tongues more commonly associates with carditis due to GERD (99). Unfortunately, the appearance of the SCJ is frequently unknown to the pathologist interpreting the biopsy specimen. HP infections start in the distal stomach and move proximally. The presence of a chronic gastritis in gastric biopsies makes chronic carditis much more likely to reflect HP infections.
FIG. 2.50. In this example of severe reflux esophagitis, the epithelium is acanthotic and shows significant inflammatory atypia that mimics an invasive squamous cell carcinoma. However, the individual cells contain abundant cytoplasm, the nuclei are not overlapping, and there are no abnormal mitotic figures. There is also intercellular edema.

**Infectious Esophagitis**

**General Comments**

Infectious esophagitis is a major cause of morbidity, due to increased numbers of individuals with altered immune defenses as a result of organ transplantation, aggressive cancer treatments, an aging population, increased use of steroids and other immunosuppressive agents, and the AIDS epidemic. Various clinical settings predispose patients to infectious esophagitis. These include GERD, general debilitation, advanced age, immunodeficiency states, chronic alcoholism, diabetes, and motility disorders. Certain malignancies, especially hematologic malignancies, increase the risk of infections. GERD or an anatomic abnormality also predisposes patients to infectious esophagitis.
FIG. 2.51. Carditis. In both figures (A, B) cardiac mucosa is present that is heavily inflamed. The example in A has a villiform surface and the lobular appearance of the glands is less evident than in B. In B the surface is flatter and the glands are more obviously lobular.

The presence of bacteria within esophageal specimens does not always imply the presence of an infection. The bacterial biota of the normal esophagus resembles that of the oropharynx (100). Organisms are swallowed or carried into the esophagus by the endoscope. One commonly encounters round or small oval-shaped bacteria lying in pairs or tetrads in the esophageal lumen. Bacteria may be present in both the normal esophagus or in an esophagus affected by esophagitis due to other causes (Fig. 2.52). Bacteria lying free on mucosal surfaces or in the esophageal lumen are unlikely to be pathogenic. In contrast, bacteria invading the underlying tissues are usually pathogenic. Esophageal endoscopy with brushings and biopsies is the procedure of choice in the diagnostic workup of patients with suspected infections. Because different infections localize to different areas, ulcer bases as well as ulcer edges and intervening areas should be biopsied (Fig. 2.53). Candida, cytomegalovirus (CMV), and herpes infections are the commonest causes of infectious esophagitis in the Western world.

**Bacterial Esophagitis**

*Bacterial esophagitis is defined as the presence of histopathologically demonstrable bacterial invasion of the esophageal mucosa or deeper layers without concomitant fungal, viral, or neoplastic disease.* Esophageal bacterial infections are unusual and generally occur in profoundly granulocytopenic patients or they represent an extension of an infection from adjacent structures. Bacterial esophagitis often involves previous mucosal damage due to GERD, radiation, chemotherapy, or nasogastric intubation, processes that allow bacteria to invade the lamina propria, submucosa, or even the vasculature. The commonest causes of bacterial esophagitis include *Staphylococcus aureus, Staphylococcus epidermidis,* and streptococcus strains. Rare bacterial esophagitis results from *Klebsiella* or *Lactobacillus acidophilus* infections. Bacterial esophagitis may also complicate *diphtheria* (in which case, pseudomembranes form over the upper esophageal mucosa) anthrax (101), syphilis, brucellosis, or bacillary angiomatosi (102). Often, several bacterial species are present, supporting a polymicrobial nature of the infections.

Bacterial esophagitis presents with odynophagia, dysphagia, chest pain, or upper gastrointestinal bleeding. The most significant complications include perforation, fistulas, and sepsis; the risk of bacteremia correlates with the severity of the esophagitis. Bacteria are best seen by examining tissue sections stained with a Gram stain and examined under an oil immersion lens. Histologically, bacterial infections produce an intense neutrophilic exudate, cellular necrosis, and degeneration. However, ulcers and pseudomembranes without significant acute inflammation can be seen in severely granulocytopenic patients. Features of specific bacterial infections follow.

P.44
FIG. 2.52. Organisms in the esophagus. A: High magnification of desquamated epithelial cells, fungal hyphae, and spores, and numerous coccobacilli. B: Luminal contents demonstrating the presence of extravasated red cells and small clusters of Gram-negative diplococci belonging to the \textit{Vionella} group. C: Necrotic debris overlying an area of an ulcer in the esophagus. The right-hand part of the picture demonstrates large amounts of necrotic debris with degenerating epithelial cells and pyknotic nuclei. D: Higher magnification of C at the edge of the lesion demonstrates a fringe of bacteria. None of the organisms illustrated in A–D are pathogenic and represent either the transmission of oral flora into the esophagus via swallowing or being carried on the endoscope, or in C and D represent nonspecific colonization of necrotic tissue.

FIG. 2.53. Comparative features of viral infections of the esophagus. A: Herpes and varicella infections. Herpetic inclusions typically affect the epithelium in the area adjacent to the ulcer. The mesenchymal tissues at the ulcer base are negative. B: Cytomegalovirus (CMV). CMV inclusions typically occur in mesenchymal cells, especially macrophages, endothelial cells, and fibroblasts at the base of the ulcers. They are not found in the epithelium. C: In human papillomavirus infections, true viral inclusions are not seen in the same way they are seen in herpes or CMV infections. Instead, one sees koilocytic atypia affecting the superficial portions of the epithelium. These differential localizations of the viral cytopathic effects dictate where biopsies should be taken, depending on the nature of the infection suspected.

Individuals at risk for developing \textit{esophageal tuberculosis} include immigrants from underdeveloped countries and immunocompromised individuals. Patients present with dysphagia, weight loss, fever, chest pain, and cough. Rupture of mediastinal disease into the esophagus causes fistulae between the tracheobronchial tree and the esophagus (103). Mediastinal tuberculous lymphadenitis may present as an esophageal submucosal tumor. Typically, tuberculous esophagitis involves the midesophagus. Grossly, tuberculous lesions appear ulcerative, hyperplastic (pseudotumoral), or both (104). Since the esophagus is usually involved by direct extension of mediastinal or thoracic disease, the biopsy is often not deep enough to provide diagnostic material. When one is able to make the diagnosis in biopsy material, the histologic features resemble those seen elsewhere with caseating granulomas containing epithelioid histiocytes, giant cells, and acid-fast bacilli (Fig. 2.54). Cytologic smears of the esophagus may facilitate the detection of the infection. Polymerase chain reaction (PCR) evaluation may also yield a definitive diagnosis in cases without typical histologic features but in which the diagnosis is clinically suspected (105).

\textit{Actinomyces}, anaerobic Gram-positive bacteria frequently present in the oral flora, may colonize a damaged mucosa. If tissue invasion occurs, sinuses, fistulous tracts, and abscesses may develop. The diagnosis depends on recognition of the characteristic sulfur granules. The filaments at the periphery of the colonies are club shaped with enlarged ends. Usually, an acute inflammatory exudate surrounds the colonies.

\textbf{Viral Esophagitis}

Viruses commonly infect the esophageal mucosa, especially in immunocompromised persons. These infections include herpes simplex virus (HSV), CMV, Epstein-Barr virus (EBV), varicella, and human papillomavirus (HPV). Multinucleated epithelial giant cells suggest the diagnosis of a viral infection. However, as noted earlier, giant cells can be seen in nonviral forms of esophagitis. Occasionally, some viral infections, particularly CMV and HSV, produce a vaguely granulomatous-like lesion, which can be confused with other forms of granulomatous esophagitis.
Herpes Esophagitis

HSV-induced esophagitis affects 0.5% to 6% of patients, primarily those who are immunosuppressed due to AIDS, transplantation, or chemotherapy. However, immunocompetent individuals and neonates also acquire these infections. Primary infections are common in neonates with disseminated HSV (106); in adults the disease often represents reactivation of latent infection. The esophagus is the most commonly affected GI site. In immunocompetent individuals, HSV infections are self-limited; in immunocompromised individuals, the infections may be severe and prolonged. Patients present with acute-onset nausea and vomiting, odynophagia, fever, retrosternal pain, GI bleeding, or spontaneous esophageal perforation (107). Oral herpetic blisters may suggest the diagnosis. Up to 70% of patients have concurrent coinfections (108). Immunocompromised individuals develop serious complications, including mucosal necrosis, superinfections, hemorrhage, strictures, HSV pneumonia, tracheoesophageal fistulas, and disseminated infections (107).
FIG. 2.55. Herpetic esophagitis with numerous punched-out ulcers.
FIG. 2.56. Herpetic esophagitis. A: Superficial squamous epithelium demonstrating area of ulceration and discohesive squamous epithelial cells containing prominent ground-glass nuclei with margination of the nuclear chromatin. B: Epithelium demonstrating the typical multinucleated syncytial squamous cells with surrounding pyknotic nuclei, inflammation, and ground-glass nuclei. Cowdry type A inclusions are seen.

The lesions begin as discrete vesicles with erythematous bases that break down to form erosions that progress to isolated or confluent targetoid or aphthous ulcers with discrete punched-out erythematous or yellow raised margins (Fig. 2.55). Typically, the ulcers are shallow and surrounded by normal-appearing mucosa. Large areas of denuded mucosa develop in severe disease. Pseudomembranes may be present. Herpetic ulcers usually stop at the GEJ. The changes of herpetic esophagitis occur alone or are superimposed on pre-existing damage resulting from nasogastric tubes, caustic injury, other infections, or GERD. Since HSV preferentially infects squamous epithelium, the margins of esophageal ulcers and islands of residual squamous epithelium must be sampled to confirm the diagnosis. Herpetic changes may also be seen in submucosal gland ducts and acini. Biopsies from the base of herpetic ulcers reveal only nonspecific inflammation, necrotic debris, granulation tissue, and desquamated epithelial cells. Characteristic lesions include the presence of nuclear molding, multinucleated giant cells, ballooning degeneration, and eosinophilic Cowdry type A intranuclear inclusions (Figs. 2.56 and 2.57). The latter have a clear zone with an outer dark margin of condensed chromatin. Cowdry A inclusions are less common than Cowdry type B inclusions, which show ballooning degeneration, enlarged nuclei, and a faintly basophilic, ground-glass appearance. Only a small number of viral inclusions are present in immunocompetent patients, contrasting with large numbers present in immunosuppressed patients (109). Acute and chronic inflammation may be present. Prominent collections of mononuclear cells consisting of aggregates of large mononuclear cells with convoluted nuclei near an ulcer may suggest the diagnosis (Fig. 2.58) (110). The histologic features are not specific for HSV, but also develop in patients with herpes zoster infections. Immunostains or genetic probes distinguish between the two. Herpetic ulcers may become secondarily infected by bacteria, fungi, or CMV infections, and in severely immunocompromised individuals, multiple infectious organisms may contribute to the esophagitis. It is important to distinguish herpetic esophagitis from other forms of infectious esophagitis because specific drugs exist to treat each infection.

**Varicella Zoster Virus (Chickenpox)**

Varicella zoster virus (VZV), a DNA virus morphologically identical to HSV, causes chickenpox and herpes zoster and severe esophagitis in profoundly immunocompromised adults. VZV infections in immunocompromised children are particularly severe and visceral dissemination has a mortality rate of 7% to 30% (111). Esophageal involvement may precede the development of skin lesions (112). The epithelium, endothelium, and stromal cells may contain numerous intranuclear eosinophilic inclusion bodies indistinguishable from those seen in HSV (Fig. 2.59). The cells swell with rarefaction and vacuolization of the cytoplasm, and the basal layer separates from the lamina propria. Other characteristic morphologic features include edema and ballooning degeneration. Immunohistochemical staining using monoclonal antibodies to VZV antigens or molecular probes serves to differentiate HSV from VZV.
Cytomegalovirus

CMV infections commonly cause esophagitis, especially in debilitated, elderly, or immunocompromised individuals. However, they also affect immunocompetent individuals. Patients with disseminated CMV infections have circulating cytomegalic inclusion–containing endothelial cells in the peripheral blood. Nausea, vomiting, fever, epigastric pain, diarrhea, and weight loss constitute prominent symptoms, whereas odynophagia and retrosternal pain are less common than in HSV infections (113). CMV affects the entire GI tract; esophageal involvement may be the first manifestation of GI disease. Rarely, CMV infections cause massive esophageal bleeding.

CMV presents as multiple, discrete, well-circumscribed, superficial flat serpiginous or oval ulcers in the mid- or distal esophagus (Fig. 2.60). The ulcers may be quite extensive, extending for distances up to 10 to 15 cm. Giant ulcers may penetrate the esophagus causing fistulas. AIDS patients may develop pseudotumoral CMV esophagitis. Characteristic cytopathic effects include prominent eosinophilic, intranuclear inclusions, cellular enlargement, and occasional granular basophilic cytoplasmic inclusions. The histologic features differ from those seen in HSV infections (Table 2.8) in that CMV cytopathic effects typically develop in the glandular epithelium (Fig. 2.61), endothelial cells, macrophages, and fibroblasts in the granulation tissue of the ulcer bases rather than in the squamous cells. The cells in the stroma often appear enlarged (cytomegalic) with conspicuous intranuclear inclusions. For this reason, biopsies should be taken of the ulcer base rather than of the epithelium. The virus can also be diagnosed on esophageal brushings (Fig. 2.62) by finding the characteristic viral inclusions. Perivascular macrophage aggregates may be present (110). As in HSV infections, the use of specific antibodies or genetic probes for the virus may establish the diagnosis (Fig. 2.63). In situ hybridization reactions usually disclose the presence of many probe-positive cells that would not have been predicted by examination of only the hematoxylin and eosin (H&E)-stained slides, especially in immunocompromised individuals.
Fig. 2.59. Varicella zoster viral esophagitis from a young girl who died of disseminated chickenpox. Her varicella hepatitis was the immediate cause of death. However, this patient also demonstrated fulminant varicella esophagitis. A: One area of superficial ulceration demonstrating separation of the epithelium from the underlying tissues. B: Squamous epithelium in an area remote from active ulceration demonstrating multinucleated epithelial cells.

Other Viral Infections

Papillomaviruses belong to a family of epitheliotropic DNA viruses primarily involving skin and mucous membranes. They produce hyperplastic lesions as well as the well-defined papillomas and condylomas. For this reason, they are discussed further in Chapter 3. Epstein-Barr virus is a double-stranded DNA virus of the herpesvirus family that causes infectious mononucleosis. Odynophagia and hematemesis may affect otherwise healthy patients with infectious mononucleosis. EBV infections are also found in AIDS patients (114). Patients develop 3- to 5-mm esophageal ulcers with erythematous rims and gelatinous bases. In contrast to HSV, EBV ulcers are deep, linear, and located in the midesophagus. They resemble the lesions of oral hairy leukoplakia in AIDS patients (115). The virus is detectable by immunohistochemistry, ultrastructural examination, or in situ hybridization reactions.

Fungal Esophagitis

Like viral esophagitis, fungal esophagitis tends to affect debilitated or immunocompromised individuals. In cancer patients, radiation, chemotherapy, and neutropenia predispose to the infections. Motility disorders also predispose patients to fungal infections. Some patients acquire nosocomial fungal infections during hospitalization for serious illness. Fungal infections may be (and often are) superimposed on other infections, and one should diagnose all organisms that are present if the patient is to be optimally treated. Fungal esophagitis most commonly results from Candida species, although other organisms such as Histoplasma, Paracoccidioides, Trichosporon, Aspergillus, Cryptococcus, Coccidioides, Fusarium, Blastomyces, and Mucor can rarely cause esophagitis. The fungi may form large esophageal fungus balls.
**FIG. 2.60.** Gross appearance of cytomegalovirus esophagitis. Linear ulcerations and discrete oval ulcers are present.

**Candida Infections**

*Candida* species are both commensal organisms (frequently found in the oral cavity) as well as pathogens. The yeasts grow as round to oval eukaryotic cells, reproducing asexually by budding. Other morphologic features include pseudohyphae (linear arrangements of buds or blastoconidia) and occasionally true septated hyphae. *Candida albicans* is the predominant cause of fungal esophagitis, but other *Candida* species including *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida stellatoidea*, and *Candida krusei* can be pathogenic. *C. tropicalis* tends to be more invasive than *C. albicans*.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Gross Features</th>
<th>Location</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV VZV</td>
<td>Multiple discrete shallow ulcers</td>
<td>Esophagus (HSV) common site</td>
<td>Biopsy (BX) of base: Only granulation tissue; inflammation; necrosis; epithelial ballooning; inclusions in epithelium at ulcer edge</td>
</tr>
<tr>
<td>CMV</td>
<td>Resembles HSV</td>
<td>Tends to involve the stomach and intestines more frequently than esophagus</td>
<td>Cytopathic effects involve submucosal glands, endothelium, stromal fibroblasts; infection of squamous cells—rare</td>
</tr>
<tr>
<td>HIV</td>
<td>May resemble HSV and CMV</td>
<td>Esophageal involvement hard to document</td>
<td>No specific changes</td>
</tr>
<tr>
<td>HPV</td>
<td>Normal or papillomas</td>
<td>Esophageal occasionally involved</td>
<td>Koilocytosis, condyloma or normal appearing, and virus found by antigenic or molecular biologic tests</td>
</tr>
<tr>
<td>EBV</td>
<td>Deep, linear ulcers</td>
<td>Midesophagus</td>
<td>Resembles oral leukoplakia</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; EBV, Ebstein-Barr virus; HSV, herpes simplex virus; HPV, human papilloma virus; VZV, varicella zoster virus; BX, biopsy.
Candida causes acute, subacute, and chronic disease. The most common form is acute candidal esophagitis with a sudden onset affecting immunocompromised individuals. Patients present with dysphagia, odynophagia, and chest pain. Rare complications include stricture or fistula formation, perforation, extensive necrosis that denudes the entire esophageal mucosa, and Candida sepsis. Subacute candidal esophagitis is uncommon and occurs as an indolent, often asymptomatic infection in immunocompetent patients. Patients present with symptoms relating to esophageal strictures or pseudodiverticulosis. Chronic candidal esophagitis is rare and generally affects patients with chronic mucocutaneous candidiasis. These patients have other gastrointestinal abnormalities including malabsorption and loss of parietal cell function (116). Candidal infections result in significant morbidity and death, especially in high-risk patients. Chronic mucocutaneous candidiasis associates with neoplasms, especially thymomas.

Fungal attachment, adhesion, morphogenesis (conversion of the spore to a filamentous growth phase), and aggregation constitute important events in fungal colonization and virulence. *C. albicans* encounters the host tissue, where it replicates (colonization) or moves deeper into the host tissues (invasion), a process facilitated by proteolysis (117). Patients with intact immune systems may show an inflammatory reaction around the infected site, which usually limits the *Candida* epithelial penetration. A number of complications follow *Candida* infections.

Typically, whitish, raised, longitudinally oriented, discrete or confluent plaques or membranes measuring <1 cm cover a friable, erythematous, ulcerated mucosa, particularly in the mid- and distal esophagus (Fig. 2.64). Erosions, ulcers, and strictures may also develop. The fungi are densely adherent to the esophageal mucosa and are not easily removed. In advanced disease, the esophagus becomes narrow, with a shaggy or cobblestoned appearance easily confused grossly with pseudodiverticulosis, strictures, varices, or carcinoma. In chronic cases umbilicated wartlike lesions may be present. Rarely, fungal esophagitis assumes a polypoid multinodular shape resembling clusters of grapes. Mucosal bridges may also form. Severe esophageal candidiasis can cause necrosis of the entire esophageal mucosa (118).

FIG. 2.62. Cytologic preparation of esophageal brushing demonstrating the presence of typical viral inclusions in the stromal cells from a patient with a cytomegalovirus infection.
FIG. 2.63. Detection of cytomegalovirus. A: Hematoxylin and eosin (H&E) section demonstrating the presence of an esophageal ulcer. The epithelium, which remains intact, shows no evidence of viral inclusions. The stroma underlying the ulceration contains atypical cells. B: In situ hybridization detects many more cells that are positive for the virus than would be detected by H&E examination alone.

In tissue, Candida species show a mixture of spores (4 µm in diameter) and pseudohyphae without true branching. They stain poorly with H&E, but PAS or methenamine silver stains may highlight their presence (Fig. 2.65). The nonbranching pseudohyphae may become quite large (up to 2 µm in diameter) and interdigitate, forming large clumps. Fungal plaques consist of pseudohyphae and budding spores embedded in a fibrinous exudate and necrotic debris. Pseudohyphal or true hyphal forms should be present to make the diagnosis of a true infection. Inflammatory exudates at the ulcer bases often contain budding yeast without pseudohyphae or evidence of tissue invasion. Surface colonization, particularly of devitalized tissue, does not imply clinically significant disease. Patients treated with antifungal agents may only have spores. Examination of cytologic brushings made directly from the plaques (Fig. 2.66) significantly increases fungal detection rate, but biopsies are required to determine whether the fungus is invasive. It is helpful to indicate in the pathology report the types of fungal forms that are present (i.e., whether it is a yeast or pseudohyphae and whether it is in the exudate or invades the tissue).

Candidal infections may resemble other fungal infections. The major distinguishing characteristics between Candida and Aspergillus are differences in hyphal width, the presence of true dichotomous branching in Aspergillus, and the presence of blastoconidia in Candida species. The major differential point between Histoplasma and Candida is the absence of pseudohyphae in the former. If there are only yeast forms and no pseudohyphae, Candida may be impossible to differentiate from Histoplasma capsulatum solely on a morphologic basis, since the morphologic features overlap.
FIG. 2.64. Gross features of esophageal candidiasis. 

A: Characteristically, the esophageal mucosa is covered by densely adherent white plaques that are difficult to remove. One may also see erosions and ulcers. These may be confluent and produce linear streaks as seen in A. 

B: In some patients, the candidal lesions appear more discrete and complicate other disorders, in this case esophageal varices.
**FIG. 2.65.** *Candida.* *A:* Esophageal mucosa containing numerous *Candida* spores and rare hyphae. *B:* Silver stain demonstrating the presence of septated hyphae. The smaller rodlike structures represent bacilli derived from the mouth (arrow).

**FIG. 2.66.** Typical fungal hyphae are present in this esophageal brushing preparation from a patient with *Candida* esophagitis.

**Aspergillosis**

*Aspergillus* species occur worldwide, being ubiquitous in the environment. They reproduce by spores termed conidia. Infections generally affect severely immunocompromised patients. Nosocomial *Aspergillus* infections affect hospitalized patients. Spore inhalation is the commonest route of infection. Several species of *Aspergillus* infect the esophagus, including *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus flavus*. Prerequisites for tissue invasion include expression of specific receptors that recognize host tissues and excretion of proteases that facilitate fungal invasion (119). Patients present with painful or difficult swallowing and weight loss. Concurrent mucosal candidiasis may be present. The lesions typically extend from the mucosa into the muscularis propria (Fig. 2.67). When vascular invasion occurs, thrombosis and infarction create secondary damage, including perforation. The fungi are characterized by the presence of 45-degree right-angle, dichotomously branching, slender, septate hyphae with smooth, parallel walls, ranging in size from 2 to 4 µm in diameter. Characteristic conidiophores, if present, aid in their identification. These contrast with phycomycetes, which are broad and nonseptate and branch at right or obtuse angles.

**FIG. 2.67.** Esophageal aspergillosis. *A:* Low-power magnification demonstrating the presence of an erosive esophagitis. *B:* Higher magnification demonstrating the presence of branching hyphae infiltrating the muscularis propria.

**Other Fungal Infections**

North American blastomycosis is caused by the fungus *Blastomyces dermatitidis*. In the United States it is endemic to the Mississippi and Ohio River valleys. *Blastomyces* predominantly infects the lungs, skin, bones, and genitourinary tract. GI involvement develops in patients with disseminated disease. Grossly, esophageal infections cause an edematous friable mucosa with linear ulcers or strictures (120). *Blastomyces* appear larger than *Histoplasma*. In well-fixed tissues, multiple nuclei can be seen. The lesion may occasionally stain weakly for mucin. Biopsies show exudates of polymorphonuclear leukocytes containing yeast forms and granuloma formation.

*Histoplasmosis* affects endemic areas in the central United States and in other areas of the world. The fungus grows in soil with a high nitrogen content enriched by bird and bat guano. Individuals living in endemic areas are probably repeatedly infected but generally remain asymptomatic. The fungi usually gain access to the body through inhalation. Extrapulmonary dissemination occurs frequently in immunosuppressed or debilitated
patients. The disease also extends directly into the esophagus from the lungs or mediastinal lymph nodes. In patients with disseminated disease, the incidence of esophageal involvement may be as high as 13%. Patients present with dysphagia secondary to esophageal compression by mediastinal lymphadenopathy or from sclerosing mediastinitis. Mediastinal granulomas may cause traction diverticula. Grossly, ulcers or nodular lesions may be present. The fungus infects humans in the mycelial phase but converts to the yeast phase at body temperature. The yeast is ovoid, measuring 1.5 to 2.0 µm × 3.0 to 3.5 µm, and yeasts reproduce by budding within macrophages in the infected tissues. *Histoplasma* has a rigid cell wall. During fixation, the protoplasm retracts from the rigid wall leaving a clear space.

Infectious *Phycomycetes* include fungi from the genera *Absidia*, *Rhizopus*, and *Mucor*. *Mucor* usually causes more extensive necrosis and ulceration than other infections (Fig. 2.68). These infections are essentially limited to severely immunocompromised hosts. Esophageal infections result either from direct mucosal involvement from the lumen after swallowing inhaled organisms, from extension from contiguous structures, or following blood-borne dissemination. *Phycomycetes* are often difficult to see on H&E-stained sections but are easily delineated by mucin stains. They have irregular broad, nonseptated, haphazardly branched hyphae with obtuse to right-angle branches. Occasional hyphae may measure 3 to 4 µm in diameter but broad hyphae measuring 10 to 15 µm in diameter predominate. The irregular branching contrasts with the uniform acute angle branching of *Aspergillus*. Cross sections of large empty hyphae can be mistaken for empty spherules of *Coccidioides immitis*. The organism has a predilection for vascular invasion, leading to secondary ischemia.

**Parasitic Infections**

Esophageal parasitic infections are less common than other types of infections. They include Chagas disease (see Chapter 10), trichomoniasis, *Pneumocystis* (121), cryptosporidiosis (122), and leishmaniasis (123). Esophageal involvement also complicates amoebic liver abscesses and hepatic echinococcal cysts.

**Esophageal Diseases in AIDS Patients**

AIDS patients often first present with esophageal manifestations due either to the HIV infection itself or to the presence of another infection. Frequent clinical presentations include dysphagia and severe odynophagia. *Candida* esophagitis causes most esophageal disease followed by CMV and herpesvirus infections, idiopathic esophageal ulcers, and Kaposi sarcoma and lymphoma. Esophageal candidiasis is so common that esophageal *Candida* infection is a diagnostic criterion for AIDS (124). EBV and parasitic and bacterial infections (including *Mycobacterium avium*) must also be considered in the differential diagnosis of esophageal disease. The use of protease inhibitors in the treatment of HIV has had a major impact on improving the outcome of HIV-associated esophageal diseases (125).

Acute HIV infection produces multiple discrete esophageal aphthous ulcers (126). These develop in the first month or so following the HIV infection complicating a mononucleosislike febrile illness. Progressive weight loss results from the presence of multiple hypopharyngeal and esophageal ulcers. Dysphagia and odynophagia further compromise the patient's already compromised nutritional status. The esophagus exhibits variable inflammatory reactions, erosions, and esophageal ulcers (Figs. 2.69, 2.70, and 2.71). The ulcers often become quite large and are sometimes termed *giant esophageal ulcers* (127). These ulcers affect both children and adults with HIV infections and may progress to a life-threatening size, eroding vessels and limiting oral nutrition. Alternatively, one may only see focal edema coexisting with rare apoptotic cells (Fig. 2.69). The submucosa becomes densely infiltrated with neutrophils and a few mononuclear cells extend to the level of the muscularis propria (128). Ultrastructurally, one finds retrovirallike virions measuring 120 to 160 nm in diameter that contain 60- to 100-nm bar-shaped nucleoids (128) within mononuclear cells. In situ hybridization also shows HIV sequences within the mononuclear cells and sometimes in the epithelium. Ulcers
measuring up to 1.5 cm in diameter develop in patients taking zidovudine (AZT) and dideoxycytidine, antiviral agents capable of inhibiting HIV replication. GERD is uncommon in HIV-infected patients, perhaps because many have hypochlorhydria in late-stage disease.

**FIG. 2.69.** Nonspecific esophageal changes. The basal stromal junction (arrows) shows prominent subepithelial edema. This area is also infiltrated with polymorphonuclear leukocytes.

**FIG. 2.70.** Nonspecific ulceration with granulation tissue in an HIV-positive patient. Significant cytologic atypia is present in the stromal and endothelial cells.
**FIG. 2.71.** Idiopathic esophageal ulcer in AIDS. AIDS patients often demonstrate well-demarcated, punched-out ulcers and erosions that do not contain obvious microorganisms.

**Eosinophilic Esophagitis**

Eosinophilic esophagitis is well recognized in children, but it may also affect adults, in whom it is underdiagnosed (129). More than 75% of cases affect males. In adults, the peak incidence is in the 3rd and 4th decades of life. Most patients have personal family histories of allergic disorders, including asthma, food allergies, or atopic dermatitis. Its pathogenesis is poorly understood, although food and aeroallergens are suspected etiologic agents (130,131). Eosinophilic esophagitis often responds to dietary elimination, elemental diets, and corticosteroids. Some speculate that antigen sensitization occurs through the respiratory tract and that when sensitized individuals subsequently swallow or ingest aeroallergens, they develop a hypersensitivity response that leads to esophageal eosinophilic infiltrates. Alternatively, the esophageal eosinophilia may reflect a response to the lung inflammation by shared communicating T cells and eosinophils in both tissues. Eosinophilic infiltrates also occur in the lungs, but not in the stomach or intestine, suggesting that there is an intimate immunologic connection between pulmonary and esophageal abnormalities. There are also substantial increases in numbers of mast cells and CD3+ T cells. Eosinophilic esophagitis may be an interleukin (IL)-5–T_{H2} cell– and mast cell–associated disease similar to asthma (132).

Adults present clinically with progressive dysphagia, refusal of food, vomiting, and abdominal pain. Children present with refusal to eat and failure to thrive (131). Some patients develop obstructive symptoms that may lead to food impaction. Peripheral eosinophilia is often present. Many patients with eosinophilic esophagitis are referred to gastroenterologists for refractory GERD symptoms that are unresponsive to acid blockade and/or prokinetic treatment.

Endoscopically, the esophagus is abnormal in 91% of patients (133). Strictures are common and involve both focal as well as long-segment (small-caliber) esophagus. Corrugation, multiple esophageal rings, webs, vertical furrows, mucosal granularity, mucosal fragility white specks or exudates, and polypoid lesions (132) are other common findings. These represent inflammatory pseudomembranes containing numerous eosinophils breaking through the squamous mucosa (134). Some patients have white mucosal patches resembling Candida infections. The rings may also result from contraction of the fibers of the muscularis mucosae, perhaps in response to activation of acetylcholine by secretions from mast cells and eosinophils (135).

**TABLE 2.9** Features Distinguishing Eosinophilic Esophagitis and Gastroesophageal Reflux Disease (GERD)

---

**FIG. 2.72.** Eosinophilic esophagitis. A: The mucosa is heavily infiltrated with eosinophils. They lie at all levels of the squamous epithelium and form small clusters and microabscesses. Prominent suprabasal edema is also present. B: Numerous eosinophils infiltrate the mucosa.
### Typical Features

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Eosinophilic Esophagitis</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of atopy</td>
<td>Very common</td>
<td>Normal (possibly increased)</td>
</tr>
<tr>
<td>Sex preference</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Abdominal pain, vomiting</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Food impaction</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

### Endoscopic Findings

<table>
<thead>
<tr>
<th>Endoscopic furrowing</th>
<th>Eosinophilic Esophagitis</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH probe</td>
<td>Usually normal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

### Histologic Features

<table>
<thead>
<tr>
<th>Proximal involvement</th>
<th>Eosinophilic Esophagitis</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal involvement</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Epithelial hyperplasia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Number of eosinophils</td>
<td>20–24/hpf</td>
<td>0–7/hpf</td>
</tr>
</tbody>
</table>

The key histologic feature is an intense eosinophilic infiltrate involving the proximal and distal esophageal squamous mucosa. Generally the eosinophil density is >20 eosinophils per hpf (Fig. 2.72) (129). However, eosinophils can number up to 120/hpf (133). The eosinophils may show preferential clustering in both the superficial luminal portion of the mucosa as well as in the peripapillary area. Eosinophilic microabscesses frequently form and these correspond to the white specks seen at endoscopy. The eosinophilia is often accompanied by basal cell hyperplasia, edema, and papillary elongation (129).

The differential diagnosis of esophageal eosinophilic infiltrates centers around reflux esophagitis (Table 2.9), allergic esophagitis, parasitic infections, hypereosinophilic syndrome, idiopathic eosinophilic esophagitis, and eosinophilic gastroenteritis; there may be overlap among some of these entities. The histologic features help distinguish between GERD and eosinophilic esophagitis. The eosinophilia is greater in eosinophilic esophagitis than in GERD, with the eosinophil density usually exceeding 20 eosinophils per hpf. In contrast, the eosinophil density in GERD is usually less than five eosinophils per hpf. Further, superficial layering of the eosinophils and/or superficial eosinophilic microabscesses (greater than four eosinophils in a cluster) is a hallmark of eosinophilic esophagitis and are unusual in GERD. Cases with deeper eosinophilic infiltrates may represent esophageal manifestations of a more generalized eosinophilic gastroenteritis, whereas those with only mucosal disease may represent pure eosinophilic esophagitis. Thus, in some patients, eosinophilic esophagitis may represent one end of the eosinophilic gastroenteritis spectrum with eosinophilia elsewhere in the gastrointestinal tract and peripheral eosinophilia.

### Thermal Injury

Thermal injury follows consumption of boiling hot liquids or microwaved food due to the uneven heat distribution in the latter. Endoscopically, patients show bands of thin, white, densely adherent pseudomembranes alternating with bands of pink mucosa creating a candy-cane appearance that extends from the upper esophagus to the SCJ. Histologically, the mucosa is characterized by superficial mummified layers of gangrenous necrosis with anucleated, nonviable, squamous epithelium firmly adherent to the viable underlying squamous epithelial cells. The absence of inflammation suggests the diagnosis and differs from the inflammatory reactions seen in infectious or reflux esophagitis. The most important complications of thermal injury are seen in those who drink maté, a risk factor for the development of esophageal squamous cell carcinoma (see Chapter 3).
Chapter 2

**FIG. 2.73.** Strictures following radiation therapy. *A:* Esophageal stricture that narrowed the mucosa. The radiotherapy was given for esophageal carcinoma. Note that the mucosa retracts into an hourglass shape over the underlying submucosal tissues. *B:* More advanced stricture following radiation for esophageal carcinoma. It almost completely blocks the lumen. The proximal esophagus has become dilated.

**Radiation Esophagitis**

Patients receiving radiation therapy for cancers of the lung, head and neck, esophagus, mediastinum, or vertebral column may develop radiation esophagitis. The extent of the injury is influenced by the type of radiotherapy; its dose; time course of administration; tissue sensitivity; use of other therapies, particularly radiosensitizing chemotherapy; and various patient-related factors (136,137). Injuries seldom occur at doses below 4,200 to 4,500 cGy. One hundred percent of patients with 6,000 rads to the esophagus develop esophagitis. Four periods of radiation-induced tissue damage include the *acute period* (first 6 months following treatment), the *subacute period* (second 6 months), the *chronic period* (2 to 5 years following radiation), and the *late period* (after 5 years).

The spectrum of injury ranges from acute self-limited esophagitis to life-threatening esophageal perforation. Patients with radiation esophagitis present with dysphagia, odynophagia, or dysmotility. Symptoms are common during initial radiation damage. The symptoms mimic those of peptic esophagitis, opportunistic infections, or drug-induced mucositis. Esophageal strictures and webs develop following large radiation doses (Fig. 2.73), typically between 13 and 21 months after the initiation of therapy. The length of the strictures depends on the size of the radiation field. It is important to distinguish radiation ulcers or strictures from cancer.

Acute radiation esophagitis involves any part of the esophagus. Patients present with multiple small discrete ulcers or they have a distinctive granular mucosa. Esophageal narrowing and thickening of esophageal folds also occurs. Severe

P.58

P.59

esophagitis, stricture formation, and rare fistulas develop in patients treated with both chemotherapy and radiation therapy. Motility abnormalities result from secondary neuronal damage. Late complications include primary esophageal cancer, which may develop many years after irradiation.
Chapter 2

**FIG. 2.74.** Radiation esophagitis. *A:* Early esophageal damage demonstrating ballooning degeneration, edema, and acute and chronic inflammation. *B:* Higher magnification demonstrating the edge of an ulcer with prominent radiation fibroblasts. *C:* The lamina propria appears fibrotic and the vessels are hyalinized. *D:* Irregular stellate fibroblasts are present in the hyalinized tissue.

The different layers of the esophageal wall vary in their radiosensitivity. The squamous epithelium and the vasculature are the most radiosensitive. The muscularis propria and fibrous connective tissue are relatively radioresistant. Acute radiation esophagitis is characterized by basal cell necrosis, submucosal edema, capillary dilation, and endothelial swelling (Fig. 2.74). About 2 weeks after the initial dose, superficial erosions form. These may coalesce to form larger superficial ulcers. Prominent epithelial and endothelial cells lie in the edematous granulation tissue. Pseudomembranes may form. Occasional patients develop multinucleated epithelial giant cells that suggest a viral infection. Bizarre (radiation) fibroblasts suggest the diagnosis (Fig. 2.74). The regenerating epithelium may mimic dysplasia (138). Epithelial hyperplasia develops in an effort to re-epithelialize the mucosal surface. These changes resolve within 3 to 4 weeks following the last radiation dose (136). Deeper ulcers and esophageal fistulas develop during the subacute phase. The ulcers may become quite large, measuring up to 5 cm in diameter. They may also perforate into adjacent structures, possibly causing hemorrhage (139). Clues to the diagnosis at this stage include the presence of vascular changes and radiation fibroblasts. Mucosal bridges may develop. Histologically, they contain normal epithelium overlying the chronically inflamed lamina propria. These represent late sequelae of radiation esophagitis.

Most typically one sees radiation injury in its late stages. The epithelium shows nonspecific changes, including acanthosis, hyperkeratosis, and parakeratosis. The muscularis mucosae may appear normal or fibrotic. The submucosa commonly becomes fibrotic; frank areas of scarring or strictures may develop. The submucosal glands become atrophic and the acini disappear. Occasionally, the ducts contain inspissated secretions producing a lesion similar to intramural pseudodiverticulosis. Hyalinized blood vessels, submucosal fibrosis, and muscular degeneration are also present. Telangiectatic capillaries and thick-walled hyalinized arterioles sometimes showing foam cells are present in the submucosa (Fig. 2.75). The endothelial cells appear enlarged and bizarre. Chronic ulcers develop and may have granulation tissue at their base. Hemosiderin deposits follow previous hemorrhage from ischemia due to the arterial occlusion. Chronic arteriolitis may result in transmural ischemia, perforation, or fistula formation. Esophageal strictures demonstrate marked thickening of the esophageal wall and submucosal expansion.

**Caustic Esophagitis**

Caustic esophagitis results from ingestion of strong alkalis or acids usually following suicide attempts in adults or accidental ingestions in children. Commonly ingested agents include lye, sodium carbonate, ammonium hydroxide, and bleaches. Drain cleaners (NaOH), decalcifiers (formic acid), and detergents for automatic dishwashing machines (metasilicates) are also very caustic and responsible for the serious accidents in children.

The extent of the injury depends on the type and amount of the ingested agent, its concentration, physical state, and exposure duration (140,141). The most severe injury occurs in areas of esophageal luminal narrowing. Severe, corrosive esophagitis leads to esophageal hemorrhage, perforation, and death. Liquids tend to produce extensive geographically continuous erosive esophagitis, whereas granular agents produce more localized lesions. Alkalis damage the esophagus more severely than acids because alkalis penetrate the tissue (142). A pH of 12.5 is the critical boundary for the ability to generate injury. Deep ulcers and strictures complicate injury caused by substances with a pH over 13. Alkalis produce liquefaction necrosis with intense inflammation and saponification of the mucosa, submucosa, and muscularis propria (142). Vascular thrombosis leads to ischemic necrosis followed by bacterial or fungal colonization. The superficial necrotic layers slough 2 to 4 days following the injury, sometimes creating deep ulcers with underlying granulation tissue (Fig. 2.76). Complete separation of the squamous mucosa results in the formation of a mucosal cast, which the patient vomits up in a situation referred to as “esophagitis desiccans superficialis” (143). Other changes include swelling and hemorrhage, inflammatory exudates, and ulcers. The overlying surface appears normal, inflamed, ulcerated, hypertrophic, or atrophic, depending on when one examines the tissues in relation to the acute event and whether recurrent damage has occurred. The cytologic features of the cells usually appear normal without much reactive atypia. Corrosive burns can be graded as shown in Table 2.10. If the patient survives, the mucosal re-epithelialization and fibrosis occur. Caustics cause coagulative necrosis (Fig. 2.77) that produces a firm protective eschar, which delays injury and limits acid penetration (144).

**FIG. 2.75.** The vessels develop foamy degeneration of the intima and media. *L,* vascular lumen.
Chapter 2

**FIG. 2.76.** Corrosive esophagitis. *A:* Caustic ingestion in a suicide. The entire esophageal mucosa is diffusely hemorrhagic and edematous. The proximal stomach also shows an erosive gastritis. *B:* Higher magnification demonstrating the hyperemia, congestion, and mucosal ulceration. The esophageal wall also appears thickened and edematous. *C:* Esophagus in young girl who had ingested arsenic-containing rat poison in a suicide. Multiple acute ulcers and erosions are present. *D:* Esophageal perforation following lye ingestion (arrows).

Strictures, especially focal ones, must be distinguished from carcinomas, since carcinomas may develop at these sites. Strictures demonstrate dense, uniform mucosal and submucosal fibrosis throughout the involved esophagus. One of the most effective ways of evaluating strictures is to perform endoscopic brushings of the surface of the stricture, since the densely fibrotic scar tissue may be exceedingly difficult to biopsy. Longstanding focal strictures cause dilation and hypertrophy of the proximal esophagus. Esophagobronchial fistula represents a late complication. Other long-term sequelae include motility disorders, GERD, BE, and carcinomas; the latter have a latent period of 12 to 40 years (145).

**Drug-Related Esophagitis**

The incidence of drug-induced esophagitis is unknown because many cases go unrecognized. It is estimated to affect 3.9 people per 100,000 population per year. Elderly patients are particularly at risk for developing drug injury for at least four reasons: They take more medications, they are more likely to have altered esophageal motility, saliva production decreases with age, and they spend more time in a recumbent position. Drugs commonly associated with esophageal injury are listed in Table 2.11. The remaining 10% result from a long list of other drugs, often described in single case
The effects of the various drugs may be additive if combined. For example, bisphosphonates taken together with nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of gastrointestinal injury.

**TABLE 2.10 Grading of Corrosive Esophageal and Gastric Burns**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pathologic Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>Superficial involvement of the mucosa</td>
</tr>
<tr>
<td>Second degree</td>
<td>Transmucosal involvement with or without involvement of the submucosa</td>
</tr>
<tr>
<td></td>
<td>No extension into periesophageal or perigastric tissue</td>
</tr>
<tr>
<td>Third degree</td>
<td>Full-thickness injuries with extension into periesophageal or perigastric tissue</td>
</tr>
<tr>
<td></td>
<td>Mediastinal or intraperitoneal organs may be involved</td>
</tr>
</tbody>
</table>

Drug-induced injury results from three mechanisms: (a) a normal side effect of the pharmacologic action of the drug, (b) a complication of the therapeutic action of the drug, or (c) pill esophagitis (see below). Complications of therapeutic actions of drugs include viral or fungal esophagitis in patients treated with immunosuppressives, chemotherapeutic agents, or antibiotics, and immunologic reactions to certain drugs causing disorders such as Stevens-Johnson syndrome. Properties of drugs that cause esophageal injury include their chemical nature (acidity or alkalinity), their solubility, and their mucosal contact time. Many drugs cause damage because they are acidic in solution (iron salts, tetracycline, doxycycline, aspirin); others produce alkaline solutions (phenytoin). The effects of acidic drugs are made worse by acid reflux. Some drugs lower LES pressure, thereby predisposing to reflux esophagitis. Any condition that delays esophageal passage increases the risk of drug-induced damage. These include motility disorders, hiatal hernias, strictures, webs, and rings; taking pills while in a recumbent position; taking medication with small amounts of liquids; or extraneous structural abnormalities (cardiac enlargement, nodal disease, or enlarged thyroids). If drugs get stuck in the esophagus, there is prolonged mucosal contact with a high concentration of a toxic substance leading to local topical damage. These act as foreign bodies impacting in the esophageal lumen, especially if taken with minimal liquid. As the medication dissolves, localized esophageal damage, ranging from inflammation to severe hemorrhage and even perforation, develops (146).

**FIG. 2.77.** The esophageal wall shows extensive coagulative necrosis without inflammation.

**TABLE 2.11 Drugs Most Commonly Associated with Esophageal Injury**
Chapter 2

Like GERD, BE demonstrates geographic, temporal, and ethnic incidence differences. BE affects approximately 1.6% of the patient population (154). Its prevalence is approximately 9% in the elderly. However, BE was

Prevalence/Incidence

The clinical features of drug injury reflect patient age, comorbidities, and the nature of the drug. The most common clinical symptoms are retrosternal pain and/or odynophagia. Severe complications include massive bleeding, perforation, and death. Strictures complicate ingestion of iron, NSAIDs, potassium salts, quinidine, and alpenolod (147). Chemotherapy-induced vomiting leads to Mallory-Weiss tears, intramural hematomas, and esophageal perforation.

The most common gross abnormalities are ulcers ranging in size from pinpoint aphthous ulcers to large (up to 10 cm) circumferential ulcers. These tend to involve the mid- to distal esophagus. Most ulcers remain superficial and heal readily, except for those associated with potassium chloride, which may be deep or even perforate. NSAIDs also induce large, shallow, discrete midesophageal ulcers with a normal surrounding mucosa. Patients taking bisphosphonates develop confluent erosions or multiple deep, large ulcers in the distal esophagus. Endoscopically, the ulcers sometimes contain pills within them. Charcoal deposits complicate administration of activated charcoal as a therapy for overdoses in patients who have attempted suicides. They appear as black linear lesions in the distal esophagus and stomach.

There are no characteristic pathologic findings for drug-induced esophagitis since different drugs damage the esophagus via different mechanisms. The histologic features of the ulcers are nonspecific and vary depending on the age of the lesion. If one is lucky, one may see pill residue in the form of crystals (bisphosphonates or iron) on the surface or admixed with an inflammatory exude or a discolored mucosa (iron pills and Lugol). Apoptotic changes may be present as may mucosal eosinophilia. Enteric-coated potassium chloride tablets cause edema, ballooning degeneration, hemorrhagic erosions, and strictures. Tetracycline may cause marked spongiotic esophagitis (148). Allergic drug-induced esophagitis may associate with numerous degranulating eosinophils. Chemotherapeutic agents directly damage replicating cells, leading to mucositis (acute inflammation of the mucosa), ulcers, erosions, strictures, and fistulas. Early changes include increased numbers of apoptotic bodies in the basal mucosa. This is followed by a nonspecific esophagitis with or without ulcers. Basal cell hyperplasia, nuclear atypia, and numerous mitoses, some of which may appear atypical, characterize recovery from chemotherapeutic agents. The atypia affects both the epithelium and the mesenchymal cells, and the nuclear:cytoplasmic ratio is usually low, providing a clue to the fact that the lesion does not represent dysplasia or carcinoma. Taxol can be associated with striking mitotic arrest associated with necrosis and ulceration. The mitotic arrest associates with bundling of intermediate filaments secondary to the accumulation of polymerized microtubules causing ring-shaped mitoses. Vincristine causes myenteric plexus damage and pseudo-obstruction syndromes. Bisphosphonates cause an ulcerative and erosive esophagitis along with multinucleated giant epithelial cells simulating viral cytopathic effects. Excessive intake of vitamin E may lead to esophageal congestion and produce a histologic pattern similar to that seen in vitamin A–deficient individuals (149). Charcoal deposits appear as aggregates of coarse, black, foreign material in the underlying submucosal tissues where they can persist for decades. The esophagus may exhibit striking findings in colchicine toxicity where the basal layers show numerous mitotic figures and mitotic arrest (150).

Esophagitis in Otherwise Healthy Newborns

A very severe form of esophagitis characterized by the presence of circular esophageal ulcers without evidence of accompanying gastroenteritis affects newborns. The lesions generally disappear within 48 to 72 hours after diagnosis with a very rapid clinical and histologic recovery. The etiology remains obscure, but the distribution of the lesions (more severe in the upper esophagus), their early onset (almost at birth), the very rapid healing, and the absence of gastric or intestinal lesions suggest a possible traumatic origin, perhaps from perinatal pharyngeal, esophageal, and/or gastric suction (151).

Barrett Esophagus

Definitions

The old definition of BE included any columnar epithelium (gastric, cardiac, oxyntic, or intestinal) lining the distal esophagus. The current definition requires that both endoscopic and histologic criteria be met. The endoscopic component requires the presence of columnar mucosa identified endoscopically by its salmon pink color, extending proximally from the GEJ into the tubular esophagus. The histologic component requires that biopsies taken from the endoscopically identified columnar pink mucosa contain metaplastic or intestinalized columnar epithelium with goblet cells (152). The reason for this approach is a practical one: Dysplasia and carcinoma virtually never develop in any columnar epithelium other than in an intestinal metaplastic one. BE is generally divided into long-segment BE (LSBE), in which the columnar mucosa extends 3 cm or more above the GEJ, and short-segment BE (SSBE), in which the specialized columnar epithelium is restricted to <2 to 3 cm above the GEJ (153).

Prevalence/Incidence

Like GERD, BE demonstrates geographic, temporal, and ethnic incidence differences. BE affects approximately 1.6% of the patient population (154). Its prevalence is approximately 9% in the elderly. However, BE was

found in 25% of the asymptomatic male veterans over the age of 50 who underwent an upper endoscopy at the same time that they had a screening sigmoidoscopy (155). Most patients who seek medical help usually have underlying severe symptomatic GERD associated with esophageal ulcers, strictures, and hemorrhage. BE develops in up to 44% of patients with reflux esophagitis (153,156). It demonstrates a bimodal age distribution with one peak at 0 to 15 years and another at 40 to 80 years (153,157,158). BE preferentially affects white males; it is uncommon in blacks. The male:female ratio is 4:1 (153). Patients with complications of BE are usually older. Although BE is rare in Orientals, its incidence is increasing, perhaps due to westernization of the diet and rapid growth of an elderly and obese population (76). Familial cases also exist. These may result from either a familial genetic predisposition to BE or to common conditions associated with reflux. BE may also complicate chemotherapy (159) or lye ingestion (160). There is also an increased prevalence of BE in patients with celiac disease (161). The prevalence of BE in the asymptomatic population is probably much higher than might be expected from data based on endoscopic examinations of symptomatic patients. An autopsy study in Olmstead County, Minnesota, found BE in 7 of 733 (1%) cases. When adjusted for age and sex to correspond to the U.S. population, the true prevalence was 376 per 100,000 population, or 17 times that of the 27 cases per 100,000 diagnosed endoscopically during the study period (162).

Pathogenesis
BE is an acquired metaplastic change that results from longstanding GERD. It results from a combination of substances in the refluxate including acid, bile salts, lysophospholipids, and activated pancreatic enzymes. The interaction of these substances ultimately determines the degree of damage, repair, transformation, and eventual maturation of the clinical phenotype including esophagitis, BE, stricture, dysplasia, or carcinoma. In this abnormal milieu, multipotential immature stem cells differentiate into various epithelial types, including columnar epithelium, which is more resistant to acidic digestion and which is able to regenerate more rapidly than the native squamous epithelium (163,164). Once established, BE is a highly proliferative mucosa (165).

The development of BE is a multistep process with at least three distinct phases. During the initiation phase, genetically predisposed individuals (mostly white men) suffering from GERD develop reflux esophagitis. This leads to the formation of a metaplastic epithelium with features of intestinal columnar epithelium. The metaplastic columnar cells of BE could derive from three sources (166): (a) metaplasia of squamous epithelium, similar to that seen with vaginal mucinosis; (b) from the mixed squamous/columnar cell population at the transitional zone, as seen in cervical metaplasia; or (c) from the columnar cells of the esophageal glands, such as may be associated with ulcer repair. Circulating bone marrow–derived stem cells (BDSCs) have been proposed to be the source of metaplastic cells in the stomach in response to HP gastritis (167). Recruitment of BDSCs in response to reflux-induced inflammation might serve as another potential source of BE.

During the formation stage, the metaplastic epithelium, which continues to be exposed to the refluxate, establishes its presence and occupies a variable surface area of the distal esophagus. This results in the oral migration of the SCJ over time (168). A long and multifaceted progression phase follows, during which the metaplastic epithelium either remains dormant and clinically insignificant or progresses to dysplasia and eventually invasive adenocarcinoma. (The progression to dysplasia and invasive carcinoma is discussed in depth in Chapter 3.)

This multistep progression involves transient and permanent molecular alterations in the esophageal squamous cells or in the BE epithelium. These are under the influence of numerous factors and signal transduction cascades (169) that can be influenced by both host and environmental factors. It is not known why only a fraction of GERD patients develop BE or which host factors or combination factors in the refluxate lead to metaplasia. Prolonged acid exposure increases villin expression and correlates with the appearance of microvilli. Another factor important in intestinal differentiation is CDX2, a transcription factor that belongs to the caudal-related homeobox gene family (170). Its expression in the GI tract is intestine specific with a tightly regulated boundary in the duodenum (171).

Bile acids act as tumor promoters increasing cell proliferation. Activation of the CCK2 receptor may stimulate cell proliferation. It induces numerous humoral mediators, including EGF ligands (transforming growth factor-α [TGF-α], heparin-binding epidermal factorlike growth factor, and the trefoil peptide TFF1) (172,173,174) and growth of the BE, especially in patients treated with acid-suppressive therapies in whom gastric levels may be increased (175). Gastrin also induces cyclooxygenase, which plays a role in the inhibition of apoptosis, promotion of cell proliferation, invasion of malignant cells, and promotion of angiogenesis (176). Another factor that plays a role in the proliferation of BE is activation of mitogen-activated protein kinase (MAPK) activities due to acid exposure (169). Activation of the MAPK pathways increases cell survival and decreases apoptosis (169).

The molecular markers are discussed further in Chapter 3.

Gross and Endoscopic Features
BE appears beefy red and velvety, contrasting with the lighter pink-tan colored, smooth squamous mucosa. The SCJ often lies within 30 cm of the incisor teeth, and often coexists with a hiatal hernia, strictures, diffuse esophagitis, or esophageal ulcers. Grossly, there are several distinct patterns of BE: Circumferential, islands, and fingerlike projections or tongues (Fig. 2.78). The island type accompanies less severe epithelial injury than the circumferential type and probably represents an earlier stage, which then progresses to the circumferential lesion (177). Sometimes it is difficult to distinguish the distal border of the metaplastic epithelium from the adjacent gastric mucosa with which it may appear to merge. Locating the gastric folds helps delineate the beginning of the stomach. Patients with SSBE have short tongues or patches of red mucosa lying <2 cm above the GEJ.

Since it may be difficult to endoscopically distinguish areas of intestinal metaplasia from other columnar epithelium, various additional endoscopic approaches may be used to evaluate the mucosa. These include magnification endoscopy, endoscopic optical coherence tomography, chromoendoscopy, endoscopic confocal imaging, light-scattering spectroscopy, and in vivo fluorescence endomicroscopy. These advanced imaging methods may enable the endoscopist to detect intestinal metaplasia in a background of gastric epithelium; to detect foci of dysplasia and early neoplasia in a background of intestinal metaplasia; and to distinguish early invasive carcinoma from mucosal dysplasia (178,179).

Typically the endoscopist biopsies the following areas: The stomach just distal to the upper end of the gastric folds, particularly along the lesser curvature; 1 to 2 cm above the GEJ; tongues of mucosa or irregular areas above the SCJ; and the SCJ and squamous epithelium of the native esophagus. Biopsies at the upper end of the gastric folds may allow one to determine whether there is gastritis, particularly HP-induced gastritis and possibly intestinal metaplasia. This biopsy may be within a hiatal hernia. These biopsies can detect localized carditis, localized intestinal metaplasia, reactive changes, acute inflammation, and possibly eosinophils in the squamous mucosa.
Chapter 2

FIG. 2.78. Barrett esophagus. A: Islands of red-brown Barrett epithelium surrounded by white-gray squamous mucosa (arrows). B: Circumferential Barrett esophagus. In contrast to the island-type Barrett esophagus, the circumferential type completely surrounds the esophageal mucosa, although there may be tongues of squamous epithelium extending into it.

Histology of Barrett Esophagus

There are two major problems in the pathologic evaluation of patients with BE: Overdiagnosis of BE and overdiagnosis of dysplasia in the setting of BE. The diagnosis of BE is covered here. The diagnosis of dysplasia and its mimics is discussed in Chapter 3. The histology of the columnar-lined esophagus displays heterogeneous histologic features with respect to the types of glandular mucosa that are present and the surface architecture. As noted earlier, the definition of BE requires histologic confirmation of intestinal metaplasia in biopsies taken from the columnar regions of the esophagus (152). The metaplastic BE epithelium resembles either small intestinal absorptive cells (complete intestinal metaplasia) or incomplete intestinal metaplasia (resembling colonic epithelium). In the latter, the cells lack a distinct brush border and the associated enzymes that normally characterize small intestinal absorptive cells. There is debate over whether incomplete metaplasia poses a higher risk than the complete type, but since both types confer a neoplastic risk, subtyping is not indicated. If any goblet cells are seen, one can make the diagnosis of BE when the biopsy derives from the esophagus (Figs. 2.79 and 2.80).

Examination of multiple biopsies and multiple levels helps identify this patchy process. The epithelium covering the mucosal surface and pits commonly contains a mixture of gastric foveolar cells and intestinal cells (Fig. 2.79). The latter include goblet cells, intestinal columnar cells, endocrine cells (containing serotonin, somatostatin, calcitonin, pancreatic polypeptide, and secretin) (180,181), and sometimes Paneth cells. The majority of the intestinal columnar cells are so-called intermediate, principal, or pseudoabsorptive cells that have characteristics of both absorptive and secretory cells. A villiform architecture may be present on the surface. *H. pylori* may be found in the esophagus of some patients with BE but only when it is also present in the stomach. It may contribute to the severity of the inflammation seen in BE.

Goblet cells are usually readily identifiable in H&E-stained sections by their round supranuclear mucin accumulation (Figs. 2.79 and 2.80). While goblet cells contain acidic mucin that stains intensely blue with Alcian blue staining at pH 2.5, routine Alcian blue staining is usually not necessary (181a). Alcian blue–positive cells are also found in normal esophageal submucosal glands and their ducts. These submucosal glands are readily distinguished from BE because of their rounded, grouped lobular configuration and their resemblance to minor salivary glands as well as by their diffuse positivity for Alcian blue at pH 2.5. The entire esophageal glandular lobules stain intensely contrasting with the individually scattered intensely positive goblet cells typical of BE.

Careful histologic attention should be paid to potential BE mimics, particularly pseudogoblet cells. These columnar cells are hyperdistended gastric foveolar cells. They contain a mucinous droplet that is larger than the typical foveolar cell but smaller than the usual goblet cell. They occur in the surface epithelium at the GEJ and distal esophagus. They may occur in the presence or absence of true goblet cells. The cells stain positively with Alcian blue at a pH 2.5; for this reason they are sometimes referred to as the "columnar blues" (Fig. 2.81). However, the pseudogoblet cells stain less intensely than true goblet cells. If only Alcian blue–positive columnar cells are present in the absence of true goblet cells, the diagnosis of BE should not be made. Because of the lack of specificity of Alcian blue staining for true goblet cells, there has been interest in finding a more specific marker of intestinal goblet cells. Markers of interest have included stains for sulphomucins and sialomucins. Sulphomucin expression is
less sensitive (sensitivity 62%) but more specific (specificity 90%) for the presence of true goblet cells. However, sialomucins or sulphomucins can also be present in the surface epithelium of a small percentage of patients without goblet cells (182), contradicting the commonly held belief that gastric-type surface epithelial cells only contain neutral-type mucins. Another promising marker is MUC2, which may be specific for intestinal metaplasia in BE (183).

**FIG. 2.79.** Barrett esophagus. *A:* Specialized intestinal epithelium. Squamous epithelium at the surface merges with specialized epithelium as evidenced by the presence of goblet cells. A couple of intestinalized-type specialized epithelial glands are also present underlying the squamous epithelium. Prominent lymphoid aggregates containing both mature lymphocytes and histiocytes are present. *B:* Villous transformation in an area of specialized Barrett epithelium. Goblet cells intermingle with gastric foveolar cells.

**FIG. 2.80.** Barrett esophagus. Only intestinal-type epithelium is present in this figure. There are several mitoses present.
Chapter 2

Immunohistochemical/Molecular Features of Barrett Esophagus

Immunohistochemical/Molecular Features of Barrett Esophagus

Pathologic Features of Short-Segment Barrett Esophagus and Intestinal Metaplasia of the Cardia

Intestinal metaplasia at the GEJ is either SSBE, which has a cancer risk at most of 0.5% per year, or intestinal metaplasia of the proximal stomach, which appears to have a substantially smaller risk for malignancy (20). These two conditions cannot be distinguished reliably because the morphologic and histochemical features of gastric and esophageal intestinal metaplasia resemble one another and because the gross landmarks used to identify the GEJ do not have the precision necessary to localize a mucosa, whose extent may be measured only in millimeters. The significance of intestinal metaplasia in the cardia is currently unknown but it can be found in up to 25% of individuals without evidence of BE (153). Therefore, it is uncertain whether it reflects GERD or not. Recent immunohistochemical data show similar phenotypes in LSBE and SSBE and intestinal metaplasia at the GEJ, and a different phenotype from gastric antral intestinal metaplasia (185), suggesting that both LSBE and SSBE are related disorders and that they differ from the intestinal metaplasia resulting from HP infections. Intestinal metaplasia is relatively uncommon in North America as compared to other parts of the world so that the presence of intestinal metaplasia in the area of the cardia most likely represents GERD. This may be particularly true in white men, since this is the dominant demographic group that develops BE-associated carcinomas.

SSBE and endoscopically unsuspected intestinal metaplasia are far more common than LSBE; therefore, SSBE may represent the lesion in which most cancers develop (186). The risk of developing adenocarcinoma in these short intestinalized segments is unclear. Presumably, if intestinal metaplasia is found, the patient is at risk for neoplasia. The incidence of adenocarcinoma of both the esophagus and gastric cardia has increased at a rate far exceeding that of any other cancer, and short segments of intestinal metaplasia at the GEJ may underlie this phenomenon. Forty-two percent of all esophageal adenocarcinomas associate with SSBE because SSBE is more common than LSBE (187).

Rather than dealing with whether or not intestinal metaplasia at the GEJ represents BE or not, perhaps the more important questions are: Is the biopsy abnormal? Is it associated with GERD? Does it predispose to adenocarcinoma (153)? Intestinal metaplasia on either side of the GE junction is abnormal. Several approaches can be used practically. One approach utilizes three categories: (a) columnar-lined esophagus with specialized intestinal metaplasia, (b) columnar-lined esophagus without specialized intestinal metaplasia, and (c) specialized intestinal metaplasia at the GEJ (185). Using this classification, an association with adenocarcinoma is seen in columnar-lined esophagus with specialized epithelium and probably associated with specialized metaplasia at the GEJ. When using these three categories, it is unclear whether or not the specialized intestinal metaplasia at the GE junction represents an association with GERD (185). An alternative approach would be to consider any form of metaplasia detected in a biopsy regardless of where it comes from as a marker of a cell population at risk for transformation into a dysplastic cell population and therefore at least potentially able to become malignant. For patients found to have intestinal metaplasia at the GEJ, a conservative approach is to assume a worst-case scenario in which the condition is SSBE and to manage the patients according to guidelines established for Barrett esophagus (153). One could use the term intestinal metaplasia of the GEJ to describe the intestinal metaplasia found at the Z line (153). Once histologically confirmed, the presence of BE may serve as a marker for future cancer surveillance.

Immunohistochemical/Molecular Features of Barrett Esophagus

Cytokeratin staining (CK7/CK 20) has been proposed as a way to distinguish intestinal metaplasia of the cardia from SSBE (189,190). Specialized intestinal metaplasia of BE frequently exhibits strong immunoreactivity for CK7 in its superficial and deep glands and immunoreactivity for CK20 in the superficial glands and superficial epithelial cells (189,190). In contrast, intestinal metaplasia in the gastric body infrequently shows the so-called “Barrett CK7/20” pattern. However, BE and SSBE show marked variability in the cytokeratin staining patterns, resulting in a poor sensitivity and specificity (191,192).

TABLE 2.12 MUC Gene Expression

![FIG. 2.81. Barrett esophagus stained with Alcian blue/periodic acid–Schiff at pH 2.5. Note that the goblet cells stain strongly blue and have a large distended mucous droplet. These cells contrast with the “columnar blues,” which stain much less intensely and do not have the prominent mucinous droplet.](Image)
MUC1  Intestinal goblet cells and enterocytes
MUC2  Intestinal goblet cells
MUC3  Intestinal enterocytes
MUC5AC  Gastric foveolar and mucous neck cells
MUC6  Gastric, antral, and fundic epithelium

Other markers that have been examined include reactivity with the antibody Das-1 (a monoclonal antibody raised against colonic epithelial cells) (185) and expression of colonic-type mucins such as MUC2 (193), CDX2 (194) villin, sucrase isomaltase (195), intestinal-type alkaline phosphatase (196), and dipeptidyl peptidase IV. At least 12 MUC genes, (MUC1 to 12), have been identified, each of which encodes a specific mucin core polypeptide (197) that is differentially expressed in different portions of the normal gut (Table 2.12). A recent study using gene expression arrays suggest that BE is an incompletely differentiated epithelium with similarities to both gastric and squamous epithelium. In addition, there are several uniquely expressed genes (198). However, a criticism of this study is that the epithelia were not microdissected and as noted earlier, Barrett mucosa contains heterogeneous cell populations. At present writing, it does not appear that specific biomarkers can distinguish SSBE from intestinal metaplasia of the gastric (199).

Squamous Metaplasia in the Distal Esophagus

Squamous metaplasia develops in the distal esophagus following treatment of BE. It appears as a normal-appearing neosquamous epithelium or as a multilayered immature squamous metaplasia. The neosquamous epithelium appears in areas previously occupied by BE, often appearing as squamous islands surrounding the Barrett epithelium. These squamous cells largely arise from a progenitor cell that differs from the cells responsible for self-renewal of the Barrett epithelium, although occasionally it arises from a stem cell that gives rise to either the squamous cells or the Barrett epithelium (199a).

Squamous metaplasia resembling that seen in the uterine cervix develops at the GEJ in patients with BE (200). It usually appears as a pseudostratified epithelium; cilia are often present on the luminal surface (201). The epithelium has morphologic and cytochemical characteristics of both squamous and columnar epithelium and may be a precursor of BE (200). It is possible that a multipotential stem cell is stimulated to differentiate toward a columnar phenotype after passing through an intermediate multiepithelial-layered phase.

Multilayered epithelium typically consists of four to eight cell layers (Fig. 2.82). The basal cells contain a small round to oval nucleus with a small centrally placed nucleolus and abundant eosinophilic cytoplasm, features similar to those of normal basal or suprabasal esophageal squamous cells. Nuclear pseudostratification is common. Intercellular bridges are absent. The suprabasal and superficial layers of the multilayered epithelium show increasing degrees of columnar differentiation characterized by cells with clear or slightly bubbly cytoplasm and a basally oriented nucleus having an appearance like that of basal cells. Most cases contain rare superficial columnar cells with distended cytoplasm similar in appearance to goblet cells. The epithelium expresses cytokeratin patterns characteristic of both stratified squamous and columnar epithelium (202). Ultrastructurally the surface cells show features of both squamous and columnar cells (200). This multilayered epithelium often lies contiguous to the mucosal gland duct epithelium. The multilayered epithelium shows a high proliferative capacity as demonstrated by Ki67 immunoreactivity and the strong expression of growth factors such as TGF-α and EGFR. This epithelium may also serve as a potential source of multipotential cells for the development of both the multilayered epithelium and BE. Others suggest that it is a metaplastic change and that the mature form of this change may be ciliated pseudostratified epithelium with an immunophenotype that resembles that of the bronchial mucosa (201).
FIG. 2.82. Multilayered epithelium. The surface of this biopsy from the gastroesophageal junction shows columnar epithelium on the right side of the figure. The area underlying the arrow is an example of the multilayered epithelium.

Pathology of Treated Barrett Esophagus

The aim of therapeutic strategies for BE is to eliminate the abnormal epithelium, thereby removing the risk of progression to malignancy. Regression occurs following both surgical treatment and treatment with proton pump inhibitors and is more common in patients with SSBE than LSBE (203). Newer techniques for eradicating BE include photodynamic therapy, laser therapy, and endoscopic mucosal resection. Biopsies are often taken after these therapies to evaluate their effectiveness. Restoration of squamous epithelium may occur if the established columnar tissue is ablated and the acid secretion is reduced while the esophageal epithelium heals. The histologic changes following treatment show partial squamous re-epithelialization of the previously metaplastic columnar epithelium. Squamous re-epithelialization results from the ingrowth of contiguous squamous epithelium, extension of epithelium from the submucosal glandular ducts, and growth of progenitor stem cells within the glandular mucosa. When regression occurs, one may see squamous epithelium overlying columnar epithelium, especially near the area of the squamocolumnar junction. The mucosa may also show evidence of scarring and mucosal hyperplasia with acanthosis. Many cases show intestinal-type epithelium underlying the squamous islands (Fig. 2.83). The Barrett epithelium under squamous islands shows a significantly lower Ki67 proliferative index and a lower degree of cyclin D and p53 positivity compared to adjacent areas of BE, perhaps due to decreased exposure to the luminal contents (204). This raises the question as to the subsequent risk of neoplasia in the buried metaplastic epithelium. However, low-grade (Fig. 2.84) and high-grade dysplasia may be present in these buried regions (204). Patients with dysplasia in the Barrett epithelium under squamous islands often have coexisting dysplasia in other areas of the esophagus. In addition, adenocarcinomas arising in the esophageal wall and presenting as unresectable or metastatic cancers have been reported following argon plasma coagulation (205), photodynamic therapy (206), or laser treatment (207). All techniques using chemical or thermal measures to ablate the epithelium make it virtually impossible to detect occult carcinoma buried beneath the squamous epithelium during endoscopic surveillance. Residual glandular mucosa, both nonneoplastic and dysplastic, underlying the squamous epithelium may require histologic examination of deep biopsies in order to rule out the presence of the buried neoplastic glands (208). Because of the cancer risk, endoscopic mucosal resections are becoming more popular, particularly if the BE is associated with high-grade dysplasia or early invasive carcinoma.
FIG. 2.83. Treated Barrett esophagus (BE). The Barrett epithelium lies under a parakeratotic squamous lining. The majority of the epithelium is nonneoplastic BE. However, there is a central area of low-grade dysplasia indicated by the arrows.

FIG. 2.84. Higher magnification of the area indicated by the arrows in Figure 2.83 shows glands with hyperchromatic, overlapping nuclei, some of which have irregular contours.

Tumor Development
Patients with BE develop hyperplastic polyps, squamous papillomas, dysplasia, and rarely adenomas. However, the major importance of BE lies in its propensity to develop into an adenocarcinoma (see Chapter 3). The management of patients with Barrett esophagus includes careful examination of endoscopic biopsies for evidence of dysplasia. Cytology may also have a role in assessing Barrett metaplasia in terms of monitoring it for the development of neoplasia. Cytology, however, should not be relied on without biopsy confirmation since one cannot assess either the exact location or the extent of the lesion using only cytology.

Esophageal Varices
Varices are portosystemic collaterals formed from pre-existing vascular channels that have become dilated by portal hypertension. The esophageal submucosal venous plexus, part of the portacaval collateral system, receives blood from the left coronary gastric vein; it drains chiefly through the azygous, although some vessels may drain through the inferior thyroidal veins into the superior vena cava. Typically, this plexus remains closed but it fills in response to increased portal venous pressure. The longer the duration is of the portal hypertension, the greater the risk is of developing large varices (209). In portal hypertension the number of lamina propria veins increases (210). The veins also enlarge with increasing flow resistance. Portal hypertension also triggers overexpression of mucosal nitric oxide synthase, and this combined with the thinness of the muscularis mucosae and the epithelium may facilitate the development and rupture of esophageal varices (211). Venous stasis and subsequent anoxia also produce

epithelial necrosis and ulceration, thereby increasing the risk of a variceal bleed. An increase in intravariceal pressure leads to an expanding diameter so that the variceal wall thickness decreases. Bleeding occurs when the expanding force is no longer counterbalanced by the variceal wall tension. Varices almost always rupture on the unsupported luminal side of the varix (212).
Chapter 2

Varices usually remain asymptomatic until they rupture, at which time they produce massive hematemesis. Variceal hemorrhage accounts for 10% to 30% of all upper GI bleeds (213).

Variceal hemorrhage occurs in 25% to 35% of patients with cirrhosis and accounts for 80% to 90% of bleeding episodes in these patients (214). Thirty-four percent of initial bleeding episodes are fatal; as many as 70% of survivors have recurrent bleeding after the first hemorrhage (214). If patients survive the initial episode, their probability of remaining alive for 1 year remains about 30%. If bleeding from esophageal varices occurs, it usually stops spontaneously, at least temporarily, in up to two thirds of patients. However, 30% to 40% of these patients remain at risk for rebleeding within 2 to 3 days, and 60% rebleed within 1 week.

Variceal rupture may occur without an apparent triggering event. However, many patients have an antecedent history of vomiting. In some patients, the bleeding arises from concomitant gastritis, esophageal lacerations (Fig. 2.85), or peptic ulcer disease. Endoscopic predictors of bleeding include large varices and endoscopic red signs (215). Prolonged tube placement may weaken the esophageal wall, precipitating ulcer formation, and eventually leads to fistula development. Masses of varices may also produce esophageal pseudotumors (216).

Varices are endoscopically visible as areas of telangiectasia, cherry-red spots, red color signs, wale markings, minivaries, or varices. Red wale markings generally measure about 1 to 2 mm in diameter and, if present, lie on top of the large dilated subepithelial or submucosal vessels, which are usually >5 mm in size (215). Well-developed varices appear as bluish, sinuous, linear mucosal elevations that are most prominent below the aortic arch, especially as one approaches the distal esophagus. Occasionally, the vascular channels appear ruptured. Varices may be difficult to detect at the time of pathologic examination (autopsy or resection) because they collapse unless special efforts are made to keep them blood filled or to fill them with a plastic or gelatin-containing solution. In some cases, transillumination highlights their presence.

The dilated deep intrinsic veins displace the superficial venous plexus and assume a subepithelial position. Histologically, varices present as dilated intraepithelial or subepithelial blood-filled channels (Figs. 2.86 and 2.87). Vessels deeper in the esophageal wall may appear massively thickened and sclerotic. Thrombosis is rare but perivenous edema and necrosis of the adjacent epithelium are often present, as are hemorrhage and submucosal inflammation. Evidence of old thrombosis, hemorrhage, hemosiderin deposition, inflammation, or fibrosis suggests previous rupture. Epithelial necrosis occurs over extremely dilated superficial submucosal varices. Patients who survive eventually develop fibrosis and re-epithelialization of the ulcerated surface. Eventually, severe stenosis with stricture formation results.

Patients are often treated with sclerosing agents that are introduced perivascularly to incite inflammation, thrombosis, and fibrosis. Sclerotherapy results in severe necrosis initiated by venous thrombosis, particularly in the submucosa. This results in extensive superficial injury and less extensive deep tissue necrosis. Patients usually develop ulceration within the first week. The ulcers usually remain limited to the submucosa, but transmural ulcerations do occur. The organized thrombi can be difficult to identify by H&E stains, but their presence can be highlighted by the use of elastic tissue stains. Fibrosis occurs late and is often transmural. Destruction of neural plexuses may lead to subsequent esophageal dysmotility, and reduced LES tone predisposes the patient to GERD. Occasionally, one identifies the sclerosing agent within the tissues. Complications of sclerotherapy include esophagitis, necrosis, ulcer, tears (Fig. 2.88), perforations, and bacteremia.

Because of the high complication rate associated with sclerotherapy, endoscopic ligation offers an alternate therapy. In this therapy, varices are ligated and strangulated with small elastic “O” rings. Changes following band ligation vary, depending on the proximity to the time of the ligation procedure. Shortly after ligation, the appearance is that of a polyp with its base compressed by a band. Thrombosis is present by day 2, resulting in mucosal and submucosal necrosis and superficial ulceration without involvement of the muscularis propria. Varying degrees of ischemic necrosis of the polyp are present on days 0 to 5. If there is premature loss of the bands, the polyp becomes necrotic and dilated variceal vessels develop. After complete healing, submucosal fibrosis occurs (217).

Vascular Abnormalities

Esophageal vascular malformations, other than varices, are rare. They appear as an isolated, protruding, visible vessel in the middle or distal third of the esophagus covered by a normal-appearing surrounding mucosa (218). These are the esophageal counterpart of the Dieulafoy ulcer or caliber-persistent artery (see Chapter 4).

Ischemia

Esophageal ischemia (Fig. 2.89) is rare because the esophagus is well vascularized. However, ischemia may result from therapeutic agents used to treat varices, radiation, or manifestations of systemic diseases, such as atherosclerosis and anticardiolipin antibody syndrome. Esophageal small-vessel disease consists of submucosal arteriolar narrowing, a condition usually associated with advanced arteriosclerosis (Fig. 2.90). The vascular lumen may be reduced by a hypertrophic smooth muscle wall or by intimal proliferation and fibrosis. Protein-rich edema fluid intermingles with fibrin in the adjacent connective tissue. Interstitial necrosis affects the epithelium from below, leading to local tissue necrosis and sloughing of the surface layers to expose the partially infarcted connective tissue stroma at the base of the shallow ulcers or erosions.
Chapter 2

FIG. 2.86. Prominent subepithelial vascular lakes are present.

The entity known as idiopathic acute esophageal necrosis is thought to have an ischemic basis. Most patients have severe underlying diseases (hyperglycemia, significant cardiac problems, hypoxia, and shock) (219). The average age at diagnosis is 65.2, with a range of 26 to 83; men are much more likely to be affected than women (220). Grossly, the esophagus appears erythematous with a friable, denuded mucosa; whitish exudates; and superficial ulcers. The changes may progress to a black esophagus with blood clots on the surface. In severe cases, one sees full-thickness necrosis of the esophageal wall, absence of stratified squamous epithelium, necrotic tissue, and deranged muscle fibers. The differential diagnosis includes severe reflux disease, exogenous dye ingestion, lye ingestion, malignant melanoma, melanosis, pseudomelanosis esophagi, and ischemia (219).

Vasculitis

A primary vasculitis, such as periarteritis nodosa, may produce esophageal vascular disease. The extent of the mucosal damage depends on the severity of the lesion. The pathologic features resemble those seen in the intestine (see Chapter 13). Behçet syndrome most commonly affects the terminal ileum or cecum. Exceptionally, it affects the esophagus; when it does it may cause a severe esophagitis with multiple small erosions, ulcers, and strictures involving the midesophagus (221). Esophageal ulcers can tunnel under the mucosa. Strictures and perforations may also develop (221). If biopsied, most cases show no distinctive features with only necrosis and inflammation. Vasculitis may be present (221). Granulomas are usually absent. The features of Behçet disease are discussed further in Chapter 6.

Nutritional and Metabolic Disorders

Amyloidosis and diabetes affect the esophagus, but since they largely alter esophageal motility they are discussed further in Chapter 10. Iron pigment becomes deposited in the submucosal glands of the esophagus in patients with advanced hemochromatosis. Dyskeratotic, degenerative epithelial alterations with nuclear enlargement and extreme vacuolar degeneration within, between, and beneath the epithelium develop in uremia. Necrobiosis leads to ulceration. Following this, the entire epithelial layer desquamates. A fibrinous exudate with neutrophils covers the ulcer. Granular eosinophilic degeneration suggests partial submucosal hydrolysis and necrosis. Hydropic degeneration and cytoplasmic zonation affecting the smooth muscle cells develop. Vascular ectasia with focal incomplete thrombosis of the capillaries and veins occurs. The damage results from circulating metabolites in the uremic patient.
**FIG. 2.87.** Vascular ectasia in esophageal varices. *A:* Low-power magnification demonstrating the presence of a “polyp” of residual esophageal tissue. A central area of organizing fibrin is identified. *B:* Higher magnification demonstrating the organizing blood clot and vascular dilation.

**FIG. 2.88.** The mucosa overlying the varices is eroded because of rupture of the dilated vessels. *Small arrow* shows a small tear, whereas a large tear is near the *larger arrow.*

**Inflammatory Bowel Disease**

Esophageal *Crohn disease* is rare and it is difficult to distinguish the esophageal lesions from other forms of esophagitis (Fig. 2.91), especially if one is unaware that the patient has Crohn disease. Rarely, Crohn disease manifests initially in the esophagus; intestinal disease becomes apparent later. Grossly or endoscopically one or more erosions, aphthous ulcers, ulcers, inflammation, fistulas, or strictures are present. Histologically, one may see acute and chronic inflammation, ulcers, sinus tracts, and possibly granulomas (222). The granulomas should be compact sarcoidlike granulomas without necrosis. They may have inflammatory cells infiltrating them. If present, esophageal granulomas should prompt a differential diagnosis of possible etiologies so as not to miss specific, and perhaps rare, lesions. One must perform special stains for fungi and acid-fast bacilli to exclude the possibility that the granulomas result from an infectious process. Muscular hypertrophy and neural hyperplasia are also often present. In some cases only granulomas are seen. Many patients only show focal nonspecific inflammation deep in the esophageal wall, and it may be impossible to make a definitive diagnosis. Irregular stenotic esophageal segments may mimic esophageal carcinoma.
FIG. 2.89. Infarction of the gastroesophageal junction. A: A well-demarcated area of hemorrhagic mucosa contrasts with the intact squamous and glandular mucosa on either side. B: Appearance of an acute infarction in the fresh state as compared to the fixed state shown in A.

FIG. 2.90. Small muscular artery in the submucosa with thickened intima caused by arteriolosclerosis. A submucosal gland and duct are also present.

Patients with ulcerative colitis may have esophagitis, but this is usually the result of coexisting GERD.

Sarcoidosis

Sarcoidosis may involve the esophagus and is in the differential diagnosis of granulomatous esophagitis. Intrinsic esophageal involvement shows characteristic noncaseating epithelioid granulomas usually in the lamina propria or submucosa. If sarcoid is suspected, the biopsy must be deep enough to sample the submucosa. However, esophageal sarcoid is extremely rare and other causes of granulomas within the esophagus should be excluded first.

FIG. 2.91. Multinucleated giant cells (arrowhead) in the lamina propria are seen in this example of Crohn disease of the esophagus. (Courtesy of Dr. D. Schmutz-Moorman, Klinikum der Phillips Universität, Marburg, West Germany.)

Dermatologic Conditions Involving the Esophagus

A number of primarily dermatologic disorders affect the esophagus (Table 2.13), a fact not surprising since both the skin and mucous membranes are lined by squamous epithelium. These disorders include epidermolysis bullosa, drug-induced conditions such as Stevens-Johnson syndrome, and various forms of antibody-mediated pemphigoid and pemphigus. In some patients, esophageal disease develops in the absence of dermatologic evidence of the disease.
Pemphigus

Desmogleins (DSGs), glycoprotein components of the core regions of desmosomes in the squamous epithelium, represent the target antigens in the various forms of pemphigus (Fig. 2.92) (222). Antibodies against them interfere with their adhesive functions. The various forms of pemphigus can be distinguished by the autoantibody type as well as the clinical and histologic features. Antibodies in pemphigus foliaceus (PF) and pemphigus vulgaris (PV) are directed at the extracellular domains of DSG-1 and DSG-3, respectively (223). As stem cells migrate from their origin in the basal layer and move toward the surface, the epithelium forms, breaks, and reforms tight desmosomal connections with its neighbors while simultaneously undergoing a process of differentiation that culminates at the surface. This scaffolding of squamous cells is disrupted via impaired desmosomes due to the anti-DSG antibodies. Bullae develop from the fluid that accumulates in the mucosal gaps. Levels of circulating autoantibodies correlate with disease activity.

TABLE 2.13 Dermatologic Diseases Involving the Esophagus

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td>Behçet syndrome</td>
</tr>
<tr>
<td>Benign mucous membrane pemphigoid</td>
</tr>
<tr>
<td>Darier disease</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td>Erythema multiforme</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
<tr>
<td>Pemphigus</td>
</tr>
<tr>
<td>Scleroderma</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (Lyell disease)</td>
</tr>
<tr>
<td>Tylosis palmaris et plantaris</td>
</tr>
</tbody>
</table>

Pemphigus Vulgaris

PV, the most common type of pemphigus, predominates in middle-aged and elderly Jewish patients and is characterized by the formation of flaccid blisters and/or erosions. PV is an autoimmune disease as noted above, but it may also be induced by drugs, including D-penicillamine and angiotensin-converting enzyme inhibitors (224). All patients with PV initially have antibodies against DSG-3, but they may also develop antibodies against DSG-1 (225). Esophageal involvement is uncommon. Patients develop flaccid dermal and mucosal bullae. The latter involve various mucosae, including the esophagus (226). Typical esophageal lesions include exfoliative erosions, ulcers, and blisters. Esophageal bleeding, webs, strictures, and formation of epithelial casts may develop. The mucosa becomes acantholytic, causing the cells to separate from each other and form bullae.
resulting in a suprabasal cleft (Fig. 2.93). Eosinophilic spongiosis may also be present. Direct immunoelectron microscopic examination of esophageal biopsies discloses immunoglobulin (Ig) G and C3 localized to desmosomes on the free surfaces of acantholytic cells (227).

**FIG. 2.93.** Pemphigus vulgaris. *A:* Hematoxylin and eosin–stained section demonstrating the presence of mucous membrane that has lost the overlying layers due to the acantholysis and dissolution of the epithelium. *B:* Antibodies localize to the intracellular areas between the keratinocytes antibodies.

**Pemphigus Foliaceous**

PF, or superficial pemphigus, is also a disease of the middle-aged and elderly, but it does not preferentially affect Jewish persons. These patients develop antibodies to DSG-1 (225). Some cases result from exposure to sulfhydryl-containing drugs such as penicillamine (228). An endemic form known as fogo selvagem occurs in Brazil, Columbia, and Tunisia (229). The endemic and nonendemic forms of the disease are clinically, histologically, and immunologically similar (228). Features unique to the endemic form include the geographic, temporal, and familial clustering of cases; a higher frequency of cases among children and young adults; and an association with specific HLADR alleles (229). Antibodies to DSG-1 are high among normal subjects living in endemic areas, suggesting that antibody production is initiated by exposure to some environmental agent (229). The most characteristic lesions of PF are scaling and crested plaques. Intact blisters are uncommon. Mucosal involvement in PF is rare.

**Pemphigus Vegetans**

Pemphigus vegetans may affect the esophagus, presenting as severe odynophagia. Multiple white plaquelike lesions are present with erythematous bases in the esophageal mucosae. Biopsies from the mucosal esophageal layer show rounded epidermal cells with large nuclei and numerous inflammatory cells, including eosinophils.

**Paraneoplastic Pemphigus**

Paraneoplastic pemphigus (PNP) is an atypical form of pemphigus that shows features of PV and erythema multiforme but is clinically distinct from both. It associates with various malignancies and with Castleman disease (230). The autoantibodies are directed against desmoplakin 1, a protein common to the cytoplasmic plaque of desmosomes in all epithelia (230). Patients with PNP also develop antibodies to DSG-3 as well as several members of the plakin family of desmosomal plaque proteins. Features that characterize PNP include (a) painful mucosal erosions and a polymorphous skin eruption; (b) intraepidermal acantholysis, basal cell vacuolization, keratinocyte necrosis, and vacuolar interface reaction; (c) deposits of IgG and C3 along the epidermal basement membrane zone; (d) serum autoantibodies that bind to skin and mucous epithelium in a pattern characteristic of pemphigus and bind to simple columnar and transitional epithelia; and (e) immunoprecipitation of a complex of four proteins from keratinocytes by the autoantibodies (231).

**Pemphigoid**

Pemphigoid is a heterogeneous group of blistering disorders characterized by bullae and ulcers affecting mucous membranes and skin. Two types of pemphigoid are identified: Bullous pemphigoid and cicatricial (mucous membrane pemphigoid). Patients with bullous pemphigoid typically have skin lesions; approximately one third have mucosal lesions. All patients with cicatricial pemphigoid have mucosal lesions and one third have skin lesions. The disorder is rare and tends to affect the elderly. It affects men twice as frequently as women. Bullae form as the result of complement activation following IgG binding to basement membrane areas (232,233). The target protein is BP, a 180- to 230-kd protein associated with basilar membranes of basal keratinocytes (234). Eosinophils, neutrophils, and mast cells have all been implicated in the pathogenesis of bullous pemphigoid.
Chapter 2

The mean age of onset of bullous pemphigoid is approximately 60 years, with most cases presenting between ages 41 and 80 (235). Esophageal lesions appear suddenly and may persist for days. They reappear at the same site, often following mild trauma induced by food ingestion. Gross findings include bullae, webs, and dense strictures, usually in the upper esophagus. Histologic findings are relatively nonspecific and include inflammation and multiple subepithelial bullae and basement membrane deposits of IgG and complement. In some cases, epithelial sloughing occurs. Patients with cicatricial pemphigoid have significant IgA in addition to IgG circulating anti–basement membrane antibodies.

**Epidermolysis Bullosa**

Epidermolysis bullosa (EB) is a heterogeneous group of heritable mechanobullous blistering diseases manifesting with fragility of the skin and mucous membranes. Gastrointestinal tract involvement is observed in different forms of EB, including esophageal involvement in dystrophic EB (DEB) or pyloric stenosis in junctional epidermolysis bullosa (JEB) (236). Even mild trauma splits off the mucosa from the underlying submucosa, resulting in severe scarring and chronic nonhealing wounds. EB associates with mutations in at least ten different genes, encoding proteins that form the basement membranes of skin and mucous membranes. These proteins include keratin intermediate filaments, laminin 5, collagen VII, and plectin (236,237).

**Dystrophic epidermolysis bullosa** is an inherited disorder caused by a structural abnormality in type VII collagen that prevents proper assembly of collagen and anchoring fibrils (238). Esophageal bullae develop at sites of trauma by food at the proximal and distal ends of the esophagus and at the level of the carina. The bullae develop in childhood. They lead to dysphagia, poor oral intake, and malnutrition. Both the skin and mucosal lesions heal by fibrosis, leading to mummification and recurrent esophageal strictures (239). Endoscopy is contraindicated because it can cause new bullae to form. Instead, the disease is diagnosed from skin manifestations and esophagograms. Dilation carries a high risk of perforation.

**Junctional epidermolysis bullosa** is a clinically and genetically heterogeneous autosomal disorder in which the phenotype depends on the specific gene/protein system affected as well as on the type and combination of genetic defects within these genes (237). Three major variants of JEB have been recognized (237): (a) the classic, lethal type of JEB, which is associated with mutations in both alleles of one of the three genes LAMA3, LAMB3, or LAMC2 encoding the x3j and T2 polypeptides of laminin 5; (b) a rare variant of JEB presenting with neonatal blistering together with congenital pyloric atresia (JEB-PA) (239) associated with genetic lesions in the plectin and x6 and x4 integrin genes (237,238); and (c) a generalized atrophic benign epidermolysis bullosa, a relatively rare nonlethal variant of JEB associated with widespread atrophic skin changes, alopecia, nail dystrophy, and dysplastic teeth in addition to skin fragility. The latter is inherited as an autosomal recessive disorder, and mutations in collagen type XVIII, a transmembrane component of hemidesmosomes, is found in most patients. They may also show mutations in the LAMB3 gene (237).

**Epidermolysis bullosa acquisita (EBA)** is characterized by the presence of autoantibodies to type VII collagen. The disease primarily affects the skin. Esophageal disease results from bulla formation followed by ulceration and edema. This eventually predisposes to severe stricture or web formation (240). Perforation may also result (241).

**Erythema Multiforme**

Erythema multiforme is an acute, benign, self-limited mucocutaneous eruption associated with underlying infections, particularly HSV. It is preceded or accompanied by a low-grade fever, malaise, and symptoms suggesting upper respiratory tract infection. Erythema multiforme also results from drug reactions. Mucosal involvement is referred to as Stevens-Johnson syndrome. Diffuse erythema, friability, and whitish plaques that can be mistaken for candidiasis are seen endoscopically. The lesions may resemble peptic esophagitis. Esophageal disease ranges from mild to severe, with the severity of esophageal lesions corresponding to the severity of dermal disease. Keratinocytes become necrotic, containing a homogeneous pink cytoplasm and pyknotic nuclei. Biopsies reveal marked inflammation in the lamina propria, eosinophilia, and subepithelial stromal changes, and atrophy of the basement membrane. The mean age of onset of bullous pemphigoid is approximately 60 years, with most cases presenting between ages 41 and 80 (235). Esophageal lesions appear suddenly and may persist for days. They reappear at the same site, often following mild trauma induced by food ingestion. Gross findings include bullae, webs, and dense strictures, usually in the upper esophagus. Histologic findings are relatively nonspecific and include inflammation and multiple subepithelial bullae and basement membrane deposits of IgG and complement. In some cases, epithelial sloughing occurs. Patients with cicatricial pemphigoid have significant IgA in addition to IgG circulating anti–basement membrane antibodies.

**Lichen Planus**

Lichen planus is a common disease of unknown etiology that often affects the oral cavity. Esophageal disease is very rare. The lesion begins in adulthood; about two thirds of patients are women. Medications such as gold, thiazides, and antimalarials can induce the lesions (242). Patients develop dysphagia and odynophagia. The gross features include esophageal erythema, papules, ulcers, erosion, strictures, or webs. The lesions may appear as subtle papules involving the distal third of the esophagus; occasionally the entire esophagus is involved. A submucosal bandlike CD3+ T-cell–rich lymphocytic infiltrate develops with vacuolization, degeneration of the basal epithelium, and superficial parakeratosis (243). The squamous epithelium is variably atrophic or acanthotic with elongation of the rete pegs. Fibroinflammatory exudates and granulation tissue indicate the presence of coexisting ulcers or erosions. Immunofluorescence examination shows dense fibrillar fibrinogen in the upper lamina propria (243).

**Acanthosis Nigricans**

Acanthosis nigricans is a distinctive dermatosis characterized by hyperpigmented velvety plaques. The lesions involve the skin and mucous membranes. Histologically the squamous epithelium displays hyperkeratosis, papillomatosis, and slight and irregular acanthosis in the valleys between the papillae. Esophageal lesions are usually not pigmented (244).

**Graft Versus Host Disease**

Graft versus host disease (GVHD) typically affects the skin, liver, and GI tract. Severe acute GVHD occurs after mismatched allogenic transplants, after discontinuation of drugs such as cyclosporin and tacrolimus, or following allogeneic donor lymphocyte infusions. Chronic GVHD damages the esophagus, but the presentation of chronic GVHD is more subtle than that of acute GVHD. Esophageal symptoms include dysphagia, retrosternal pain, and aspiration. Acute GVHD may present as mucosal shedding ulcers or strictures. GVHD usually affects the upper third of the esophagus, producing focal or diffuse mucosal friability, vesicles, bullae, mucosal sloughs, ulcers, webs, and strictures (Fig. 2.94) (245). GVHD may also result in esophageal casts (246). The diagnosis is based on the history and presence of single cell necrosis (apoptosis) as well as the failure to identify specific infectious agents, although superinfection may be present. The mucosa becomes infiltrated with CD8+ T lymphocytes. Submucosal fibrosis may develop. Despite the fact that these findings are typical of the disorder, often all one sees is nonspecific inflammation and/or granulation tissue.

**Melanosis**

Melanocytes lie in the epithelial–stromal junction in 4% to 8% of normal esophageal specimens examined at the time of autopsy, 21% of consecutive upper endoscopies, and 29.9% of surgical cases with esophageal...
melanomas (247,248). They are more common in Asians than in Western populations and in patients with carcinomas. The latter may result from some factor induced or produced by tumors that stimulate melanocytic hyperplasia (Fig. 2.95) (248). Single or multiple, discrete, 1- to 3-mm, circular or oval, brown, or brown-black mucosal patches or linear streaks are present, usually in the midesophagus. The melanotic areas consist of increased numbers of melanocytes in the basal mucosa as well as an increased number of melanosomes in individual melanocytes and increased melanin transfer to keratinocytes, stromal macrophages, and fibroblasts. The pigment is positive with melanin stains.

FIG. 2.94. Graft versus host disease (GVHD). A: Biopsy from a patient who underwent a bone marrow transplant. Single-cell necrosis is evident in the basal cell layer. B: The esophageal mucosa appears desquamated, inflamed, hyperemic, and edematous in this severe case of GVHD. (Case donated by Drs. Sale, Myerson, and Schulman, Fred Hutchinson Cancer Center, Seattle, WA.)
FIG. 2.95. Melanosis of the esophagus. A: Low-power magnification demonstrating the presence of prominent pigmentation at the basal layer. In the areas of acanthosis, the pigmentation is particularly prominent as it is in the cross sections through the acanthotic extensions. B: Higher magnification showing the presence of the melanin within the basal portion of the epithelium. Melanophages are also present in the underlying stroma.

White Sponge Nevus

White sponge nevus is a rare benign disorder of mucous membranes, with an autosomal dominant inheritance pattern (249). Most lesions exist at birth or have their onset in infancy, childhood, or adolescence. The condition usually affects Caucasians of either sex. It is characterized by the presence of a thickened, deeply folded mucosa with a creamy white appearance. The mucosa is fragile and bleeds when touched. The lesions appear small and wartlike or large, moist, and white, resembling *Candida*. They increase in size and number after puberty and then stabilize. The lesions are characterized by irregular acanthosis with spongy hydropic squamous cells at all mucosal levels except for the uninvolved basal layer. Mitoses may be present but there is no nuclear atypia. The finding of parakeratotic plugs appears to be pathognomonic. Surface fragmentation leads the superficial squamous cells to appear shaggy (249). Inflammation is absent.

Nevi

Nevi are melanocytic lesions composed of dendritic melanocytes and subepithelial stromal tissue. They may develop in the esophagus (250), where they appear as linear patches of bluish pigmentation. Elongated, sometimes finely branched S100+ melanocytes are present in the lamina propria. They have long, dendritic processes and cytoplasmic brownish melanin granules. Chronic inflammation, fibrosis, and granulation tissue are also present. The overlying esophageal epithelium does not show melanin deposits. The differential diagnosis includes charcoal deposits following lye ingestion, pigmentation caused by hemosiderin, pseudomelanosis, heavy metal deposition, and melanosis.

Wegener Granulomatosis

Wegener granulomatosis is characterized by granulomatous vasculitis, renal disease, and upper and lower respiratory tract disease. Esophageal involvement may present with severe odynophagia, secondary to severe necrotizing and erosive esophagitis due to the underlying vasculitis (251). Necrotizing granulomatous inflammation is present, as is necrotizing inflammation of the walls of small and medium-sized vessels. Variable numbers of multinucleated giant cells are present. Affected vessels may be occluded by organizing thrombi.

Benign Polyps

Polypoid lesions of the esophagus and GEJ are uncommon and include giant fibrovascular polyps; squamous papillomas; polypoid mesenchymal tumors such as lipomas and smooth muscle tumors; fibroid polyps; pyogenic granulomas; and hyperplastic/inflammatory polyps. Mesenchymal lesions are discussed in Chapter 19.

Inflammatory Polyps

Inflammatory polyps are the most common esophageal polyps, often complicating reflux esophagitis. Most affect men, reflecting their relationship to reflux esophagitis. Similar lesions occur at anastomotic sites, following irradiation or in any severe erosive or ulcerative esophagitis. They may be single or multiple and usually consist of granulation tissue. When they re-epithelialize, they resemble mucosal tags. These lesions bleed easily when eroded by the passage of food. They may be covered by squamous or glandular mucosa depending on the circumstances in which they arise. Some inflammatory polyps develop a pseudosarcomatous stroma. The presence of large, pleomorphic, atypical cells in the stroma can be quite alarming. However, they are strongly positive for vimentin and negative for cytokeratin, CD34, CMV, S100, and HMB45.
**Inflammatory Fibroid Polyps**

Inflammatory fibroid polyps (IFPs) complicate GERD (252) or HIV infections. These lesions are almost always single and the symptoms depend on lesional location. They present as solitary raised, often eroded or ulcerated lesions with a pedicle, often with a prominent submucosal component. The lesions may measure up to 5 cm in maximum diameter. Microscopically, the lesions appear variably cellular (Fig. 2.96), edematous, and highly vascular. IFPs contain fibrous tissue, proliferating blood vessels and inflammatory cells, fibroblasts, myofibroblasts, and histiocytes. They resemble their gastric counterparts, which are more common (see Chapter 4). These lesions must be differentiated from sarcomatoid carcinoma (see Chapter 3).

**Giant Fibrovascular Polyps**

Giant fibrovascular polyps account for 0.5% to 1% of all esophageal tumors. Seventy-five percent of patients are male, usually between the ages of 40 and 70. They are pedunculated, slow-growing, intraluminal tumorlike lesions usually arising in the upper esophagus (253), just below the upper esophageal sphincter. The clinical differential diagnosis includes carcinoma and intramural myoma. The lesions vary in size with an average length of 15 cm. Fibrovascular polyps consist of a core of mature fibrous tissue with an occasionally myxoid stroma that contains scattered, thin-walled vessels and variable amounts of fat covered by nonkeratinizing squamous epithelium. These are resected to avoid complications of obstruction of either the upper airway or the esophagus.

**Hyperplastic Polyps**

Hyperplastic polyps most typically complicate GERD and therefore usually arise in the distal esophagus and GEJ. They are usually associated with ulcers or erosive esophagitis. There is a moderate male predominance reflecting the fact that most lesions develop in patients with GERD. Other potential etiologies include medications, infection, anastomotic or polypectomy sites, vomiting, and photodynamic therapy. The lesions represent a regenerative response to surrounding mucosal injury (254). Average patient age is 53.9 years, although the lesion may occasionally be seen in children. Hyperplastic polyps may be single or multiple and they are typically <1 cm in size, but they may measure up to 3 cm. They are characterized by a proliferation of hyperplastic gastric-type foveolar epithelium, hyperplastic squamous epithelium, or admixture of these two mucosal types. Most contain variably inflamed predominantly cardiac mucosa; mixed types are the least common. These lesions frequently resemble their gastric counterparts. Intestinal metaplasia and low-grade dysplasia can be seen in a small number of cases.

**Glycogen Acanthosis**

Glycogen acanthosis appears as discrete raised, nodular, white plaquelike esophageal lesions usually measuring <1 cm in diameter (Fig. 2.97). They rarely measure more than 3 mm in diameter. When extensive, they coalesce into larger plaques. The presence of diffuse esophageal glycogen acanthosis represents an endoscopic marker of Cowden disease (see Chapter 12), and it is a characteristic component of the syndrome.
Glycogen acanthosis may also be associated with celiac disease (255). The lesions appear as small, round, mucosal elevations, representing focal thickening of the squamous epithelium. The mucosa contains a collection of hyperplastic enlarged squamous cells containing increased amounts of intracellular glycogen (Fig. 2.98) distributed along the longitudinal ridges. The lesion can be accentuated by the use of PAS reactions since the cell cytoplasm contains abundant glycogen. There is no inflammation and no basal cell hyperplasia.

**FIG. 2.97.** Glycogen acanthosis. Everted esophagus showing characteristic pale-tan raised nodules of glycogen acanthosis. These lesions may be confused with the inflammatory pseudomembranes of candidiasis. They are unrelated to leukoplakia and have no malignant potential.

**Xanthelasma/Xanthoma**

Xanthelasmas, also known as *xanthomas or lipid islands*, are asymptomatic incidental lesions sometimes encountered during upper GI endoscopy. They most commonly develop in the stomach (see Chapter 4), but they can occur in the esophagus where they are quite rare (256). They appear as yellow-white well-demarcated single or multiple mucosal nodules or plaques. They consist of collections of large foamy histiocytes containing cholesterol and lipoproteins. They may be surrounded by chronic inflammatory cells. The cells have small central or slightly eccentric nuclei.
FIG. 2.98. Glycogen acanthosis. The lesion consists of thickened epithelium caused by both an increased number of squamous cells and an increased glycogen content of individual cells.

Abnormalities Associated with Surgical Procedures

Esophageal replacement surgery is unavoidable in patients with long-gap esophageal atresia, esophageal resection, or severe esophageal strictures resulting from caustic or peptic injury. The small intestine and colon are favored organs for use for the interposition, although the stomach is also occasionally used. The transplants are placed in a subcutaneous or retrosternal location or in the left chest. Tissue-engineered esophagus created from esophagus organoid units, mesenchymal cores surrounded by epithelial cells, represents an attractive alternative for replacement of the native esophagus, since it can maintain normal histology (257). Complications relate to luminal patency, conduit integrity, hemorrhage, ulceration, anastomotic leaks, fistula formation, strictures, and ischemia. The transplant may develop ischemic necrosis. The histology of the transplanted segment demonstrates the presence of normal, inflamed, or infarcted colonic or small intestinal histology. When the grafts are followed prospectively with mucosal biopsies, minimal histologic changes are found in uncomplicated patients. There may be congestion and neutrophil infiltrates in the distal third. They may show a proliferation of fibrous tissue with reactive blood vessels and inflammatory cells that include histiocytes, lymphocytes, neutrophils, and eosinophils mixed with notable numbers of fibroblasts. The regional lymph nodes may show reactive hyperplasia.

References


P.81


file:///F|/GastroChapter%202%20oesoph.htm (88 of 93)2/4/2009 2:04:43 PM
Chapter 2


183. Watson C, Van De Bovenkamp NH, Korteland-Van Male AM, et al: Barrett's esophagus is characterized by expression of gastric-type mucins (MUC5AC, MUC6) and TFF peptides (TFF3 and TFF2), but the risk of carcinoma development may be indicated by the intestinal-type mucin, MUC2. Hum Pathol 2002;33:660.


Chapter 3
The Neoplastic Esophagus

Esophageal tumors arise in any of the tissues comprising its four layers: The mucosa, submucosa, muscularis propria, and adventitia. Many types of carcinoma arise in the esophagus, but >70% to 95% are either squamous cell carcinomas (SCCs) and their variants or gastroesophageal junction (GEJ) adenocarcinomas arising in the setting of Barrett esophagus (BE). This chapter focuses on epithelial tumors. The World Health Organization (WHO) classification of epithelial tumors is shown in Table 3.1 (1). WHO staging for esophageal carcinomas is shown in Table 3.2. Mesenchymal tumors are discussed in Chapter 19. Hematologic tumors are discussed in Chapter 18. Neuroendocrine tumors are discussed in Chapter 17. Esophageal epithelial neoplasms are more likely to be malignant than benign. Esophageal squamous carcinomas are the eighth most common cancer worldwide and the sixth most common cause of cancer-related deaths (2). Adenocarcinomas at and proximal to the GEJ are less common, but are increasing in frequency in North America (3) and Europe (4).

Benign Squamous Papillomas

Squamous papillomas are benign exophytic esophageal tumors that fall into two major types: Those associated with human papillomavirus (HPV) infection, often referred to as condylomas, and those unassociated with HPV, usually referred to as squamous papillomas. Their prevalence ranges from 0.01% to 1% (5,6). Squamous papillomas may arise on a background of esophagitis due to reflux or other causes. Some result from the synergistic action of mucosal irritation (as from gastric acid reflux) and HPV infection (7). Evidence of HPV infection is most likely when the papillomas demonstrate a condylomatous histology (5,8,9). In this setting, HPV 16 is most commonly present followed by HPV types 18, 6b, and 11.

Esophageal squamous papillomas may be asymptomatic or present with dysphagia, heartburn, or hematemesis. Patients range in age from 2 to 86 years, with a male:female ratio of 24:9. Esophageal papillomatosi affects children with laryngeal papillomatosis, and is usually related to HPV infection (10). HPV-related esophageal papillomas are rare in adults. Acanthosis nigricans, a rare hereditary condition, associates with multiple esophageal papillomas and late-onset hyperkeratosis (tylosis) of the palms and soles.

Squamous papillomas usually arise in the lower esophagus where they are generally single, exophytic, multilobulated, soft, semipedunculated, pinkish-white lesions with smooth or slightly rough surfaces. They measure from 0.2 to 1 cm in diameter with an average size of 0.4 to 0.5 cm (5,11). Some patients have multiple lesions, numbering from 2 to more than 20 (5). Benign, proliferating, hyperplastic (thickened and acanthotic) stratified squamous epithelium covers inconspicuous connective tissue cores containing stromal cells and thin-walled vessels (Fig. 3.1). The squamous cells demonstrate orderly cellular maturation from the basal layer toward the surface (Fig. 3.2). The basal cells may appear prominent but they lack significant cytologic atypia. The squamous epithelium of distal papillomas may exhibit the characteristic features of reflux esophagitis.

Esophageal papillomas demonstrate several distinct architectural patterns (5). Exophytic lesions have smooth, fingerlike, papillary, and acuminate configurations with central fibrovascular cores extending to the surface of the papillae (Fig. 3.1). Endophytic lesions consist of benign squamous cell proliferations with an inward or papillomatous proliferation of the surface epithelium. The spiked type has a spiked surface configuration and invariably demonstrates a prominent granular cell layer and marked hyperkeratosis. These different histologic patterns exist alone or intermingle with one another (5).

Esophageal condylomas demonstrate the cytologic changes characteristic of HPV infection, including giant cells, multinucleated cells, superficial koilocytosis, and anisonucleosis (Fig. 3.3). Disturbances in squamous cell maturation and keratinization are present, including hyperkeratosis, acanthosis, papillomatosis, and dyskeratosis. Papillomas are benign lesions with little or no malignant potential.

Papillomatosis

Papillomatosis consists of multiple minute esophageal squamous papillomas. It involves any part of the esophagus, most frequently affecting the distal esophagus. The lesion is rare, appearing in <1% of endoscopic examinations. The papillomas appear as multiple, small, irregular, wartlike mucosal projections. Their histology resembles that seen in isolated papillomas. Esophageal papillomatosis results from chronic inflammation from HPV infection, gastroesophageal reflux, prolonged nasogastric intubation, or the use of esophageal self-expanding metal stents. One unusual patient had multiple polyps showing synchronous HPV-16 and -33 infections. She also had a gastric carcinoma and once the gastric carcinoma was resected, the esophageal polyps completely regressed (12).

| TABLE 3.1 World Health Organization Classification of Esophageal Epithelial Tumors |
|-----------------|----------------------------------|
| **Epithelial tumors** | **Squamous papillomas** |
| **Intraepithelial neoplasia** | **Squamous** |
| | **Glandular** |
| | **Flat** |
| | **Adenoma** |
| **Carcinomas** | **Squamous cell carcinoma** |
| | **Verrucous (squamous) carcinoma** |
| | **Basaloid squamous carcinoma** |
| | **Spindle cell (squamous) carcinoma** |
| | **Adenocarcinoma** |
| | **Mucoepidermoid carcinoma** |
| | **Adenoid cystic carcinoma** |
| | **Small cell carcinoma** |
| | **Undifferentiated carcinoma** |
### TABLE 3.2 TNM Classification of Esophageal Carcinomas

<table>
<thead>
<tr>
<th>T—Primary Tumor</th>
<th>N—Regional Lymph Nodes</th>
<th>M—Distant Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 No evidence of primary tumor</td>
<td>NX Regional lymph nodes cannot be assessed</td>
<td>MX Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>N0 No regional lymph node metastases</td>
<td>M0 No distant metastases</td>
</tr>
<tr>
<td>T1 Tumor invades lamina propria or submucosa</td>
<td>N1 Regional lymph node metastases present</td>
<td>M1 Distant metastases present</td>
</tr>
<tr>
<td>T2 Tumor invades muscularis propria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 Tumor invades adventitia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumor invades adjacent structures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Stage Groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2 or T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T1 or T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IVa</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
</tr>
<tr>
<td>IVb</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
</tr>
</tbody>
</table>
Squamous Cell Carcinoma and its Precursors

Globally, esophageal SCC is the sixth most common cancer in males and the ninth most common in females (2). Esophageal SCCs show marked geographic (13) and ethnic differences. Esophageal SCC is relatively uncommon in the United States (3) and Western Europe. Its annual incidence is 2.2 per 100,000 among white men in the United States compared to 13.2 among black men (3); 18.2 per 100,000 in Normandy, France (13); and 8.2 per 100,000 in Shanghai, China and 183.8 per 100,000 in Linxian, China (13). The most prominent cluster of elevated cancer rates occurs in north central China on the border of Henan, Hebei, and Shanxi provinces. Northeast China is the eastern pole of the Asian belt of SCC that begins in eastern Turkey and extends through the southern states of the former Soviet Union, Iran, and Iraq (14). Other high-risk areas include Chile, the Transkei region of South Africa, Japan, and Brazil (13). Because many risk factors interact with one another, their individual effects are difficult to weigh; however, antecedent esophagitis is common to all patients with esophageal carcinoma. Migrants from high-risk to low-risk countries retain their high risk through the first generation, but fall to the level of the host country in the second generation (15). This decline in rates may be attributed to diminished exposure to the environmental carcinogens peculiar to the country of origin. The persistence of risk in first-generation migrants, however, suggests that the anatomic changes induced by these carcinogens are not reversed in the new environment.
The male:female ratio varies from 1.5:1 in Linxian, China, to 17:1 in Normandy, France (13). In the United States, the age-adjusted incidence of esophageal cancer is highest among blacks (15 per 100,000) and Hawaiians (5.8) and is lowest among Filipinos (2.9) (16). The incidence of esophageal cancer increases with age and peaks in the 6th decade in high-risk areas (13). Patients 35 years or younger constitute approximately 7.4% of esophageal cancers in high-risk populations such as China. Time-trend studies show that incidence rates for SCC are stable or decreasing in most populations. For example, there has been a decrease in SCC incidence among U.S. blacks of 5.8% per year between 1992 and 2001 (17), while the rates of SCC in U.S. whites have fallen below that of esophageal adenocarcinoma (3). A decrease in smoking in Western countries (18), combined with an increased consumption of fresh fruits and vegetables, may account for this decline (19).

The incidence of esophageal SCC closely correlates with a low socioeconomic status whatever the level of risk in any population (20); childhood economic status is a predictor of SCC risk in the adult (14). This suggests that increased tobacco consumption (21) and poor nutrition associated with poverty are common denominators in the genesis of this cancer. The increased incidence in U.S. black males has been attributed to increased tobacco and alcohol use, but the deleterious effects of these agents are amplified by the absence of the protective effects of fruits and vegetables (19).

**Etiology**

Both genetic and environmental factors play a role in the genesis of esophageal SCC. Environmental factors associated with esophageal SCC and adenocarcinomas are summarized in Table 3.3.

**Alcohol and Tobacco**

Heavy consumption of strong liquors, such as whiskey and calvados, shows a dose-dependent increased SCC risk (19,22). The combined use of alcohol and tobacco incurs a multiplicative increase in the risk of SCC. In Brittany, the relative risk is 49.6 for nonsmokers with the highest alcohol intake, 7.8 for nondrinkers with the highest tobacco use, and 155.6 for men at the maximum consumption level of both substances (23). Persons at high risk for SCC due to alcohol and tobacco consumption and poor nutrition may be vulnerable to field cancerization of the entire upper aerodigestive tract (UADT), including the esophagus (24). The frequency of developing a second UADT SCC in the 10 years following treatment of an index cancer is estimated to be from 5% to 40% (25). A prospective family study found the 10-year standardized incidence rates for esophageal cancer to be elevated after the diagnosis of an index cancer in the UADT (8.24) and lung (2.0) (26). Half of the multicentric cancers are synchronous. Most metachronous cancers develop within 3 years.

**TABLE 3.3 Environmental Risk Factors for Esophageal Carcinoma**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Squamous Cell Cancer</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol intake</td>
<td>Yes</td>
<td>Maybe</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HPV infection</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Inadequate intake of fruits and vegetables</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>High intake of nitrate and nitroso compounds</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thermal injury</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Caustic injury</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Achalasia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Barrett esophagus</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Chapter 3

#### Dietary/Personal Factors

Patients with esophageal SCC can be divided into two overlapping risk groups: Those who smoke and consume large amounts of alcohol and those whose diets lack green, leafy vegetables, citrus fruits, micronutrients, and trace elements (27). The missing trace elements include molybdenum, manganese, zinc, iron, silicon, barium, titanium, and magnesium. Mineral deficiencies in the soil lead to increased fungal invasion and mycotoxin food contamination. Calcium, riboflavin, vitamin A, and vitamin C deficiencies may also play a role in esophageal carcinogenesis, since these vitamins play a role in maintaining mucosal integrity and normal epithelial differentiation. Deficiencies in these substances render the esophageal mucosa vulnerable to carcinogens in foods, such as mycotoxins in the Transkei (28) and N-nitroso compounds in China (29).

The influence of dietary supplements on SCC cancer risk has been studied among high-risk Chinese communities. These micronutrients have included β-carotene, vitamin E, selenium, molybdenum, retinol, riboflavin, and vitamin C. Overall, the evidence shows that these supplements cause a small, or borderline, reduction in the SCC risk (27). Since exposure to dietary carcinogens begins in childhood, it is not surprising that micronutrient supplements show only modest protection from this cancer in the adults in high-risk populations.

Thermal injury from hot drinks including hot tea in East Asia and maté consumption in South America has long been identified as a risk factor for SCC (27,30). It is difficult to separate the effects of thermal injury from the constituents of tea and maté, but the many studies strongly suggest that hot drinks do impose a risk of developing SCC (27).

The nitrosamine content of foods varies widely in high- and low-risk areas of China. Fermented, moldy, pickled food that contains high levels of nitroso compounds is a dietary staple in high-risk areas (27). The low molybdenum content of the soil in these high-risk areas yields crops with a high nitrate content that may be converted to potentially carcinogenic nitroso compounds. Nitrosamines are potent alkylating agents that can produce various alkyl DNA adducts, particularly involving O6-methylguanine, which can preferentially mispair with thymine rather than cytosine, causing GC to AT mutations (31). O6-methylguanine-DNA methyl transferase (MGMT) is a primary defense against alkylase-induced carcinogenesis. Some SCC patients have MGMT inactivation via aberrant promoter methylation (32). Vitamin C inhibits this conversion.

The dietary factors that increase or decrease the SCC risk vary from culture to culture. Thus, heavy chili consumption is an independent risk factor for SCC in India (33). Capsaicin, the active component of chili and its metabolites, may be a proximate carcinogen/mutagen. In contrast, a Mediterranean diet would appear to lower the risk of SCC, even when associated with moderate to high alcohol consumption (34).

#### Environmental and Genetic Interactions

Genetic polymorphisms in enzymes that metabolize alcohol render some individuals vulnerable to its deleterious effects. Acetaldehyde, the first metabolite of alcohol, is eliminated by aldehyde dehydrogenase-2 (ALDH2) (35). ALDH2 polymorphisms influence blood acetaldehyde concentrations after drinking (36). An inactive mutant allele, ALDH2*2, is common in Orientals and is associated with increased circulating acetaldehyde levels, inducing painful facial flushing among occasional alcohol consumers (37). Alcoholics with this mutant allele develop tolerance to this reaction and the presence of this less active genotype in alcoholics enhances their SCC risk (38). The influence of alcohol on SCC risk may also be modified by an XRCCI polymorphism at codon 399. The XRCCI protein facilitates base excision repair or single-strand break repair. The odds ratio (OR) for SCC among alcoholics with the Arg/Arg XRCCI genotype compared to the Gln/Gln or Gln/Gln genotypes is 2.78 (1.15 to 6.67) (39). Recent data suggest that individuals with low selenium intake and ALDH2 Lys/Lys and XRCC1 399 Gln/Gln genotypes associate with an increased risk of developing SCC, especially in the presence of exposure to tobacco and alcohol (40).

Aromatic hydrocarbons in tobacco smoke require metabolic activation by phase I enzymes (CYP450s), and are then subject to detoxification by phase II enzymes (GSTM1) (41). Patients with the Val/Val CYP1A1 genotype are at increased risk of SCC (OR = 6.63, 95% confidence interval [CI], 1.86 to 23.7); this risk is enhanced when associated with increased circulating acetaldehyde levels, inducing painful facial flushing among occasional alcohol consumers (37). Alcoholics with this mutant allele develop tolerance to this reaction and the presence of this less active genotype in alcoholics enhances their SCC risk (38). The influence of alcohol on SCC risk may also be modified by an XRCCI polymorphism at codon 399. The XRCCI protein facilitates base excision repair or single-strand break repair. The odds ratio (OR) for SCC among alcoholics with the Arg/Arg XRCCI genotype compared to the Gln/Gln or Gln/Gln genotypes is 2.78 (1.15 to 6.67) (39). Recent data suggest that individuals with low selenium intake and ALDH2 Lys/Lys and XRCC1 399 Gln/Gln genotypes associate with an increased risk of developing SCC, especially in the presence of exposure to tobacco and alcohol (40).

#### Occupational Factors

Certain occupations associate with an increased risk for SCC. These include warehouse workers and workers in miscellaneous food industries as well as those with occupational exposure to asbestos, metal dusts, vulcanization products, asphalt, petrochemical products, and textile products (44). Persons engaged in the production and distribution of alcoholic beverages also have an increased SCC risk as seen in the Calvados region of France (45).

#### Radiation Exposure

Radiation therapy increases esophageal SCC in patients treated for various malignancies. As an example, the risk following treatment for breast cancer increases starting 5 years after exposure (46). Most radiation-induced cancers arise in the upper and midesophagus and the tumors may be multifocal in nature.

#### Infections

HPV DNA may be found in invasive SCC, areas of carcinoma in situ, the hyperplastic epithelium surrounding cancers, and histologically normal cells near these cancers (47). The areas with the highest incidence of HPV infections include China, Japan, and parts of South Africa. Although HPV types 6, 7, 9, 11, 13, 16, 18, 24, 30, 33, 51, 52, 57, and 73 have all been identified, HPV 16 is the most common (47). A p53 codon 72 polymorphism significantly (p = 0.001) associates with HPV-related esophageal cancers in northern China (48). Fifty-three percent of patients with HPV positive were Arg/Arg carriers, compared to 26% of HPV-negative cancers and 23% of controls. The presence of HPV infection may be suspected in cytology preparations, as shown in Figure 3.3.

Fungi frequently contaminate the grains and foodstuffs consumed in high-risk geographic areas. The fungi belong to many genera, but Fusarium and Aspergillus are the two most common and their respective mycotoxins, fumonisin B1 and aflatoxin, act as carcinogens. They are found on maize (corn), millet, and other cultivated grains in Linxian and on pickled vegetables. The fungi reduce nitrates to nitrites and promote the formation of nitrosamines (22).

#### Inherited Risk Factors

<table>
<thead>
<tr>
<th>Prior radiotherapy</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>HPV, human papilloma virus.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The autosomal dominant familial syndrome palmoplantar keratoderma (PPK) (tylosis) predisposes patients to the development of esophageal SCC. PPK results in defective mucosal keratinization (50) and altered mucosal integrity, increasing susceptibility to environmental mutagens. The mean age of onset for esophageal malignancies in these patients is 61 years. Members of PPK families have a 50% risk of developing esophageal cancer by age 50 and a 90% to 95% risk of developing esophageal cancer by age 65 (50). These patients also have an increased risk of melanoma, breast and lung cancer, leukemia, hepatomas, malignant lymphomas, and colorectal adenomas (50,51). The presence of multiple carcinomas involving the oral cavity, tongue, oropharynx, and stomach suggests that exposure to a common environmental agent contributes to the genesis of all of the tumors. PPK patients who smoke are particularly likely to develop SCC (51). PPK results from a mutation in the tylosis in esophageal cancer (TOC) region of chromosome 17q25 (52). Loss of heterozygosity (LOH) of polymorphic microsatellite markers located near the TOC locus also occurs in sporadic esophageal cancers (52,53). PPK patients develop chronic esophagitis, followed by dysplasia, carcinoma in situ, and invasive carcinoma. Other histologic changes include abnormal keratinocyte maturation, the presence of basophytic inclusions, and surface keratinization (54). The neoplastic squamous cell lesions that develop resemble those arising in the absence of tylosis.

The recessive form of dystrophic epidermolysis bullosa due to a type VII collagen mutation is a less common source of inherited esophageal SCC (55). This condition is most common among people of Northern European origin.

**Predisposing Diseases**

Chronic esophagitis is the most common SCC precursor (56). The esophagitis has many causes, as discussed in Chapter 2. SCC arising in association with GERD originates in the mucosa bordering the upper limits of BE (57). The SCC associated with caustic burns emerges 30 to 45 years after the initial injury, usually in the midesophagus (58). Motility disorders that increase the risk of SCC include achalasia and scleroderma. Patients with achalasia develop esophagitis due to postprandial retention of solid foods (59). Food retention also increases the risk of SCC in diverticula, including Zenker (60) and the epiphrenic diverticula. The achlorhydria that accompanies autoimmune atrophic gastritis associates with an elevated SCC risk (61), as does the multifocal gastritis caused by CagA-positive Helicobacter pylori. This effect is strongest among patients with gastric atrophy, as measured by low pepsinogen group I levels (62). The association is supported by the parallel decline in the incidence of esophageal SCC and H. pylori–induced stomach cancer in migrants from Japan to the United States (63). The esophagitis that accompanies Plummer-Vinson syndrome also associates with an increased risk of SCC in the hypopharynx and cervical esophagus (64). There is also an association with celiac disease (64).

**Dysplasia**

Esophageal SCC passes through the sequence of chronic esophagitis, low-grade and high-grade dysplasia (also known as intraepithelial neoplasia), and invasive carcinoma. As a result, histologic or cytologic specimens may contain a constellation of histologic abnormalities, including normal, or near-normal esophageal mucosa, atrophy; esophagitis; parakeratosis; dyskeratosis; basal cell hyperplasia; simple hyperplasia; mixed basal spinous hyperplasia; variable degrees of dysplasia; and invasive cancer. In general, the epithelium increases in thickness and the papillae elongate as the process evolves (Figs. 3.4 and 3.5). Dysplasia, defined as the presence of unequivocally neoplastic squamous cells that are confined to the mucosa above the basement membrane, is the immediate precursor lesion for SCC. Dysplasia was traditionally classified into mild, moderate, and severe degrees. However, since interobserver agreement in distinguishing the three grades is generally poor, most favor a two-tier system of low-grade and high-grade dysplasia. The latter classification scheme includes epithelial changes previously classified as carcinoma in situ. The higher the grade of dysplasia, the greater is the likelihood that the lesion will evolve into an invasive cancer.
FIG. 3.4. Squamous dysplasia. A: Low-grade dysplasia. The changes are more severe on the right-hand side of the photograph. Note the beginning of irregular budding to the left of the arrows and the disorderly arrangement of the epithelium. B: Mild dysplasia. Disorderly atypical squamous epithelial cells localize to the basal epithelium. C: Moderate dysplasia. Dyskeratotic cells and cells with enlarged nuclear-to-cytoplasmic ratios and prominent nucleoli are present. D: Severe dysplasia. The atypical cells extend almost to the free surface.


The following facts support the concept that dysplasia is a step in SCC development. The frequency of dysplasia correlates with the level of risk. For example, endoscopically screened subjects in high-risk Linxian, China, show high-grade dysplasia in 7.9% of men and 9.8% of women. This contrasts with 2.4% and 2.5% in intermediate-risk Argentinian men and women, respectively, and 0% of screened subjects in low-risk areas of China (14). The age distribution of dysplasia and cancer supports a continuous progression from mild dysplasia to severe dysplasia to invasive carcinomas. Follow-up studies show that invasive cancers develop in areas of dysplasia. When assessed prospectively, 20% of 500 Chinese people with high-grade dysplasia progressed to carcinoma, compared with only 0.12% of 11,011 individuals with a normal mucosa (14). Areas of dysplasia share similar molecular abnormalities with the invasive cancers adjacent to them.

As in other tumors, there is a sequential acquisition of molecular abnormalities as the lesions progress from early precancerous lesions to invasive carcinoma (1). Those that are thought to be important are shown in Figure 3.6. A biopsy study from Chinese patients with dysplasia found genetic instability, including LOH and microsatellite instability (MSI) in the precursor lesions (65). LOH was identified at ten different markers on chromosomes 3p, 5q, 9p, 9q, 13q, 15q, and 17p. This study also found MSI in both low-grade and high-grade dysplasia, with its frequency increasing with the severity of the process. p53 mutations can be found in dysplasia and in situ cancer (66). The same mutations are present in the adjacent invasive cancer, indicating that p53 mutations are an early event in esophageal carcinogenesis. A Japanese study of field carcinogenesis found different p53 mutations in synchronous multicentric SCCs, but the identical p53 mutations were found in the dysplastic epithelium adjacent to each invasive cancer (67,68). p53 mutations may also be found in areas of transitions from esophagitis to dysplasia and are among the earliest changes seen in the development of esophageal SCC (1).

FIG. 3.6. Diagram of the progressive acquisition of molecular abnormalities as the epithelium progresses from normal to invasive cancer.

Areas of dysplasia generally remain symptomless, and it takes 3 to 5 years for carcinoma in situ to progress to more advanced stages of the disease. Up to 25% of patients with squamous dysplasia will develop cancer within 8 years. Because of the stepwise progression of SCC, cytologic esophageal screening has proven to be cost effective in asymptomatic patients in the high-risk areas. Cytology examination of 12,877 subjects in a high-risk Chinese population found high-grade dysplasia in 6% of cases and carcinoma in 3% (69). Population-based screening programs for esophageal cancer are not applicable to low-risk areas, such as North America or Europe. Selective cytologic screening
Chapter 3

than in reactive lesions. Dysplasia from reactive changes. While this test is by no means specific, the presence of large numbers of p53 immunoreactive cells (as opposed to only isolated positive cells) is much more likely to be present in areas of dysplasia.

It corresponds to the treatment recommendation of local tumor ablation.

This difference may contribute to widely variant incidence rates and predictions of prognosis. In an effort to address these differences, the Vienna Classification was developed (Table 3.4) (73), although it has not been widely adopted.

The dysplasia is considered to be low grade when the abnormal cells are limited to the middle third of the mucosa and high grade when they extend to the upper third of the epithelium or involve the full mucosal thickness and show more epithelial atypia than low-grade lesions. In carcinoma in situ (the high end of the spectrum of high-grade dysplasia), atypical cells extend through the full thickness of the epithelium without evidence of surface maturation. Dysplastic cells may also extend into the underlying submucosal glands and ducts. While ductal extension predisposes to deeper penetration (71), this finding by itself does not constitute invasion. Dysplastic squamous cells may also spread in a pagetoid manner into the adjacent normal esophageal mucosa. The pagetoid cells stain positively with low-molecular-weight keratin, do not stain for mucus, and have a high proliferative index. Acanthotic epithelial buds containing atypical epithelial cells occur in both low-grade and high-grade dysplasia. They appear regular and the same size or vary in size, shape, length, and width (Fig. 3.5). Irregular buds are most common in areas of severe dysplasia adjacent to invasive cancer (72) and microinvasive cancer tends to develop from their tips. Dysplasia associated with HPV infection shows koilocytotic changes. Lymphocytic infiltrates in the surrounding lamina propria are common and correlate with the severity of the dysplasia.

Histologic examination is necessary to diagnose dysplasia. Dysplasia is characterized by both architectural and cytologic abnormalities. A disorderly proliferation of immature cells with hyperchromatic nuclei, abnormally clumped chromatin, and pleomorphic nuclei is present (Fig. 3.4). The cells typically have an increased nuclear:cytoplasmic ratio and demonstrate loss of polarity. The nuclei are frequently overlapping. Mitoses are frequent and are often abnormal. The dysplasia is considered to be low grade when the abnormal cells are limited to the middle third of the mucosa and high grade when they extend to the upper third of the epithelium or involve the full mucosal thickness and show more epithelial atypia than low-grade lesions. In carcinoma in situ (the high end of the spectrum of high-grade dysplasia), atypical cells extend through the full thickness of the epithelium without evidence of surface maturation. Dysplastic cells may also extend into the underlying submucosal glands and ducts. While ductal extension predisposes to deeper penetration (71), this finding by itself does not constitute invasion. Dysplastic squamous cells may also spread in a pagetoid manner into the adjacent normal esophageal mucosa. The pagetoid cells stain positively with low-molecular-weight keratin, do not stain for mucus, and have a high proliferative index. Acanthotic epithelial buds containing atypical epithelial cells occur in both low-grade and high-grade dysplasia. They appear regular and the same size or vary in size, shape, length, and width (Fig. 3.5). Irregular buds are most common in areas of severe dysplasia adjacent to invasive cancer (72) and microinvasive cancer tends to develop from their tips. Dysplasia associated with HPV infection shows koilocytotic changes. Lymphocytic infiltrates in the surrounding lamina propria are common and correlate with the severity of the dysplasia.

Histologic examination is necessary to diagnose dysplasia. Dysplasia is characterized by both architectural and cytologic abnormalities. A disorderly proliferation of immature cells with hyperchromatic nuclei, abnormally clumped chromatin, and pleomorphic nuclei is present (Fig. 3.4). The cells typically have an increased nuclear:cytoplasmic ratio and demonstrate loss of polarity. The nuclei are frequently overlapping. Mitoses are frequent and are often abnormal. The dysplasia is considered to be low grade when the abnormal cells are limited to the middle third of the mucosa and high grade when they extend to the upper third of the epithelium or involve the full mucosal thickness and show more epithelial atypia than low-grade lesions. In carcinoma in situ (the high end of the spectrum of high-grade dysplasia), atypical cells extend through the full thickness of the epithelium without evidence of surface maturation. Dysplastic cells may also extend into the underlying submucosal glands and ducts. While ductal extension predisposes to deeper penetration (71), this finding by itself does not constitute invasion. Dysplastic squamous cells may also spread in a pagetoid manner into the adjacent normal esophageal mucosa. The pagetoid cells stain positively with low-molecular-weight keratin, do not stain for mucus, and have a high proliferative index. Acanthotic epithelial buds containing atypical epithelial cells occur in both low-grade and high-grade dysplasia. They appear regular and the same size or vary in size, shape, length, and width (Fig. 3.5). Irregular buds are most common in areas of severe dysplasia adjacent to invasive cancer (72) and microinvasive cancer tends to develop from their tips. Dysplasia associated with HPV infection shows koilocytotic changes. Lymphocytic infiltrates in the surrounding lamina propria are common and correlate with the severity of the dysplasia.

Japanese and Western pathologists differ in their diagnostic criteria for esophageal squamous cell lesions. Invasion is the most important diagnostic criterion for a diagnosis of carcinoma for Western pathologists, whereas nuclear and structural features are more important for Japanese pathologists. In Japan, esophageal squamous cell carcinomas are diagnosed based on nuclear grade, and include cases judged to be noninvasive, low-grade dysplasia in the West. This difference may contribute to widely variant incidence rates and predictions of prognosis. In an effort to address these differences, the Vienna Classification was developed (Table 3.4) (73), although it has not been widely adopted. It corresponds to the treatment recommendation of local tumor ablation.

There are several diagnostic pitfalls with respect to early squamous neoplasias. Dysplasia must be distinguished from regenerative changes or areas of pseudopitheliomatous hyperplasia. Herpes esophagitis, chemotherapy, or radiotherapy and areas of regeneration adjacent to ulcers may induce histologic changes that may be mistaken for early squamous neoplasia. The differences between regenerative and neoplastic changes are summarized in Table 3.5. Inflammation or ulceration, if extensive, may help identify the epithelium as regenerative in nature. However, caution must be exercised because dysplastic epithelium may become ulcerated or inflamed. If one is unable to distinguish between a truly dysplastic lesion and one that is regenerative in nature, one can use the term indefinite for dysplasia to diagnose the changes that are present. Subsequent biopsies, particularly those obtained once the inflammation has been treated, often help clarify the nature of the underlying process. Immunostaining for p53 may also help distinguish dysplasia from reactive changes. While this test is by no means specific, the presence of large numbers of p53 immunoreactive cells (as opposed to only isolated positive cells) is much more likely to be present in areas of dysplasia than in reactive lesions.

### TABLE 3.4 Vienna Classification

<table>
<thead>
<tr>
<th>Category 1: Negative for dysplasia/neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 2: Indefinite for dysplasia/neoplasia</td>
</tr>
<tr>
<td>Category 3: Noninvasive neoplasia: Low grade (low-grade dysplasia)</td>
</tr>
<tr>
<td>Low-grade dysplasia or adenoma includes mild and moderate dysplasia</td>
</tr>
<tr>
<td>Category 4: Noninvasive neoplasia: High grade (high-grade dysplasia)</td>
</tr>
<tr>
<td>a. High-grade adenoma/dysplasia (severe dysplasia)</td>
</tr>
<tr>
<td>b. Noninvasive carcinoma (carcinoma in situ)</td>
</tr>
<tr>
<td>c. Suspicious for invasive malignancy</td>
</tr>
<tr>
<td>Category 5: Invasive neoplasia</td>
</tr>
<tr>
<td>a. Intramucosal carcinoma: Invades the lamina propria</td>
</tr>
<tr>
<td>b. Invasion into the submucosa or beyond</td>
</tr>
</tbody>
</table>

### TABLE 3.5 Features Useful in Distinguishing between Reactive and Neoplastic Squamous Epithelium
Reactive Changes Neoplastic Changes
Basal cell hyperplasia Highly atypical cells
Glycogen depletion Keratinizing epithelium
Vesicular hyperchromatic nucleoli Bizarre cell shapes
Increased N:C ratios
Normal or increased N:C ratio Prominent heterochromatin
Prominent nucleoli Irregular nuclear outlines
Increased mitotic activity
Basophilic cytoplasm
Presence of inflammation
Presence of causative agent (i.e., HSV, etc.)
Nonkeratinizing epithelium
Epithelial edema
Vascular congestion
HSV, herpes simplex virus; N:C, nuclear:cytoplasmic.

Both radiation and/or chemotherapy, particularly in the setting of neoadjuvant therapy, may induce mucosal changes that mimic dysplasia. Individual cells may have irregular contours and contain hyperchromatic nuclei as well as abnormal mitotic figures. Often the latter have a ring shape, a feature not found in neoplastic cells, which helps avoid overdiagnosing dysplasia or carcinoma in this setting.

A final pitfall in the diagnosis is the examination of biopsies that are not representative of the mucosal changes. This generally results from superficial biopsies that do not contain lamina propria so that areas of invasive carcinoma cannot be excluded and very superficial biopsies that may miss pagetoid spread of a tumor along the basal part of the mucosa.

**Early Esophageal Cancers**

The term *early esophageal cancer* is used by the Japanese and Chinese to designate a neoplastic process that is confined to the mucosa or submucosa, regardless of the nodal status. For these pathologists, early esophageal cancers include both areas of dysplasia and superficially invasive cancer with and without nodal metastases. The small proportion of early cancers that become symptomatic and/or have abnormal radiographic features are most likely to be protruding lesions. The prognosis in early lesions is good and progression to advanced cancer is slow (74). It takes a little more than 1 year to progress from mucosal involvement to submucosal invasion, 6.6 ± 3.2 months to progress from submucosal invasion to advanced disease, and 21.1 ± 6.8 months to progress from mucosal to advanced disease (75).

Early cancers may be multicentric or consist of large fields of invasive or microinvasive cancer associated with varying degrees of epithelial dysplasia. Several macroscopic types of early carcinoma are recognized: Flat, coarse, verrucous, polypoid, and ulcerating infiltrating (76). Most appear as areas of redness, plaques, or maplike erosions. The frequency of multicentric esophageal SCC ranges from 7% to 28% (76,77). Flat, early lesions may be difficult to detect endoscopically or in resected specimens. Lugol staining of the specimen highlights the abnormal areas and allows one to assess the extent of the disease and to detect the presence of multiple lesions. Several histologic patterns of early esophageal cancer exist: (a) conventional SCC, (b) SCC with basaloid features and expansile growth, and (c) SCC with spindle cell features (76,78). Tumor cells invading the submucosa appear larger than the dysplastic cells. Areas of dysplasia often surround the invasive foci. Basaloid tumors tend to show prominent peripheral nuclear palisading and the invasive cells tend to appear smaller than those of ordinary SCC. Basaloid tumors tend to be superficial and lack metastases, thus having a better prognosis than other histologic types (78). The earliest invasive lesions appear to drop off the base of the mucosa. The overlying mucosa may or may not be involved by full-thickness replacement by intraepithelial neoplasia (Fig. 3.7). Progression from noninvasive to invasive disease associates with an increased lymphocytic reaction (Fig. 3.7).

Identifying superficially invasive cancers in resection specimens is usually not a diagnostic problem. However, the interpretation of small endoscopic biopsies may be challenging. The distinction of malignancy from pseudoeosinophilic hyperplasia in regenerating squamous epithelium in the setting of esophagitis poses the greatest difficulty. Regenerating squamous cells generally do not show abnormal mitoses or loss of polarity.
When a cancer is superficial and not associated with nodal metastases, endoscopic mucosal resection (EMR) may be the treatment of choice since it incurs less morbidity and a smaller risk of mortality than esophagectomy. This procedure is now widely used in Japan. Single or multiple areas of the mucosa unstained by iodine identify resection targets. Recurrence after EMR varies from 2% to 4%, but may be treated by repeat EMR. Patient survival with SCC correlates with the extent of the tumor, and there are several systems used to assess the stage of this disease. The different systems shown in Table 3.6 have been used to stage the SCCs and each has advantages in certain situations. The T (tumor) N (node) M (metastasis) system is used by the American Joint Committee for Cancer Staging and End Results (AJCC) (79) and the WHO classification (1). When preceded by a lowercase “p”, the TNM values are based on pathology findings. When preceded by lowercase “yp”, the TNM values represent pathology review of a tumor that has been previously treated (80). A simplified system used by the Surveillance, Epidemiology, and End Results (SEER) registries is frequently used in epidemiologic studies of incidence and mortality since it generates data comparable to those from the large, population-based international registries that are published by the International Agency for Cancer Research (13). Tachibana et al. (81) proposed a modified Dukes system to bypass international variations in the use of the TNM system. One variable not included in these systems is tumor size even though this is an independent predictor of 1- and 2-year survivals among patients with node-negative cancers (82). The number of involved lymph nodes also correlates with mortality (82).

### TABLE 3.6 Comparison of Staging Systems for Esophageal Squamous Cell Cancer

<table>
<thead>
<tr>
<th>AJCC (6th ed.)</th>
<th>Modified Dukes</th>
<th>SEER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 TisN0M0</td>
<td>A</td>
<td>Localized</td>
</tr>
<tr>
<td>Stage I T1N0M0</td>
<td>A</td>
<td>Localized</td>
</tr>
<tr>
<td>Stage IIA T2N0M0</td>
<td>A</td>
<td>Localized</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>B</td>
<td>Localized</td>
</tr>
<tr>
<td>Stage IIB T1N1M0</td>
<td>C1</td>
<td>Regional</td>
</tr>
<tr>
<td>T2N1M0</td>
<td>C1</td>
<td>Regional</td>
</tr>
<tr>
<td>Stage III T3N1M0</td>
<td>C1</td>
<td>Regional</td>
</tr>
<tr>
<td>T4 Any N M0</td>
<td>CII (.31Nodes)</td>
<td>Regional</td>
</tr>
<tr>
<td>Stage IV Any T Any N M1</td>
<td>CII (.31Nodes)</td>
<td>Distant</td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee for Cancer; SEER, Surveillance, Epidemiology, and End Results.


In countries such as China and Japan, where a large proportion of SCCs are diagnosed at an early stage, a more discriminating assessment of prognosis of early cancers is achieved by dividing them into three levels of mucosal and submucosal penetration (Fig. 3.8) (83). The deeper the penetration, the greater the probability is of lymph node metastases, as shown by Araki et al. (84), who found nodal spread in 35.7% of sm3 cancers, compared with 8.3% of sm1 lesions. This staging system is commonly used to evaluate EMR specimens. Other Japanese studies have also found lymph node metastases in approximately 30% of tumors that penetrate to the submucosa (84).
Multivariate analysis indicates that factors that increase the relative risk of recurrence with submucosal cancer are intramural metastases, vascular invasion, and nodal metastases (85). The postresection 5-year survival rates of patients with submucosal SCC vary from 44% to 96%, with the most favorable prognosis occurring in patients without vascular invasion, intramural metastases, or nodal involvement. Patients with all three of these have the least favorable prognosis (85). If metastases are found in a patient with esophageal high-grade dysplasia, or if one detects vascular and/or lymphatic vessel invasion, an undetected invasive cancer is likely to be present. Resection specimens should be extensively sampled to find the invasive focus. If none is found the possibility remains that an invasive focus remains in the patient.

**Superficial Spreading Carcinoma**

Superficial spreading carcinoma is defined as a tumor >5 cm in length consisting mainly of intraepithelial carcinoma with or without limited submucosal invasion. The tumor can measure up to 14 cm in length and is frequently located in the midesophagus. Like other early squamous cell lesions, the lesions may be superficial and flat, slightly elevated, slightly depressed, or superficial and distinctly depressed (86). These tumors may show well-differentiated or moderately differentiated squamous cell histologies or may be basaloid in appearance. Superficial spreading carcinomas are likely to be multicentric. These lesions are important to recognize due to the difficulty in establishing clear resection margins at the time of esophagectomy (87). The mean age of patients with superficial spreading esophageal squamous carcinoma is 56 to 63 years, with the lesion being most common in females.

**Advanced Squamous Cell Carcinoma**

Clinical Features

Esophageal SCC usually grows slowly. The patients may remain asymptomatic with invasive disease because the esophagus is highly distensible and tumors can grow to a considerable size before the lumen becomes sufficiently narrowed to produce symptoms. Symptomatic esophageal SCC presents with dysphagia, odynophagia, weight loss, coughing, choking, pain, and dehydration (88). Frequently patients do not complain of dysphagia, but make subtle changes in their eating habits without realizing it. Other symptoms include fever, anemia, hematemesis, melena, hoarseness, or the sensation of food “becoming stuck in the throat.” A persistent hiccup may indicate the presence of laryngeal nerve paralysis or aspiration, ominous signs of advanced disease. Local tumor extension beyond the esophagus often leads to substernal or high back pain. Aortic erosion results in rapid exsanguination. Aspiration of esophageal contents through a tracheoesophageal fistula is a common cause of death in patients with advanced SCC. Palpable lymph nodes in the cervical or supraclavicular regions may be noted.

Patients may also develop various paraneoplastic syndromes. Tumor-induced hypercalcemia is common (89). It results from the release of calcium from the bones due to tumor production of parathyroid hormone–related protein (PTHrP) (90). The presence of hypercalcemia is a poor prognostic sign (91). A hypertrophic osteoarthropathy affects some patients with esophageal SCC (92), but this may result from concomitant chronic obstructive lung disease, which shares an association with heavy tobacco consumption. An acute vasculitis developed in a patient with stage II SCC, a phenomenon attributed to circulating immune complexes or tumor-associated antigens (93). The vasculitis went into remission after tumor resection. The AJCC divides the esophagus into three compartments (79). The cervical esophagus extends from the pharyngoesophageal junction to the thoracic inlet, approximately 18 cm from the incisors. The middle esophagus extends from the thoracic inlet to a point 10 cm above the GEJ, approximately 31 cm from the incisors and at the level of the lower edge of the eighth thoracic vertebra. The lower esophagus extends from this point to the GEJ, or approximately 40 cm from the incisors. Carcinomas may develop in both the hypopharynx and cervical esophagus in men who are heavy consumers of alcohol and tobacco. SCCs complicating the Plummer-Vinson syndrome arise in the area of the cricopharyngeus muscle in women (male:femal ratio = 1:10) with a median age of 45 to 50 years. Cancers that appear after radiation therapy for breast cancer usually develop in the upper and midesophagus. Most SCCs in high-risk populations develop in the middle and lower thirds of the esophagus.

Pathologic Features

Esophageal SCCs appear as fungating, ulcerating, infiltrating, or stenotic lesions. Mixed gross growth patterns also occur. Advanced tumors may measure up to 10 cm in length. Fungating cancers present either as large, intraluminal, variably ulcerated masses with raised, everted margins or less commonly as polypoid, irregular, bulky tumor masses (Fig. 3.9).

The lesions may have sharply defined borders; intramural submucosal extension may be grossly inapparent. The extent of tumor infiltration at the tumor base varies and does not necessarily reflect the size of the protruding mass. Ulcerating cancers have irregular, noninverted, and sometimes serpiginous edges, and a shaggy, hemorrhagic central crater. The ulcers lie along the longitudinal esophageal axis and the tumors may extend into the surrounding visera. Infiltrating carcinomas cause esophageal wall thickening. The esophagus appears rigid with slitlike areas of stenosis. The proximal esophagus dilates. Rarely, the pattern resembles the linitis plastica pattern seen in gastric carcinoma. Papillary or verrucous lesions usually develop in the proximal esophagus. Their differential diagnosis includes a papilloma, sarcomatoid carcinoma, and verrucous carcinoma.
FIG. 3.10. Well-differentiated keratinizing squamous cell carcinoma. A: Note the infiltrating nests with prominent central keratinization. B: The high nuclear-to-cytoplasmic ratio is appreciated.

Biopsies cannot determine the extent of invasion, but they yield a positive diagnosis in 81% to 100% of cases, depending on the number of biopsies obtained. Endoscopic ultrasonography (EUS) may identify tumor penetration to the submucosa or muscularis propria in up to 80% of early cases (94). EUS is most useful in identifying the superficial lesions that are best treated by surgery alone. Detection of nodal involvement is more accurate with EUS than with tomography (95). Fine needle aspirations enhance the ability of EUS to detect nodal disease, yielding an accuracy of more than 90% (96).

SCCs arise from areas of pre-existing dysplasia and invade through the basement membrane into the lamina propria or deeper tissues. Histologically, ordinary SCCs show varying grades of differentiation ranging from a well-differentiated keratinizing carcinoma containing well-formed squamous cell nests and keratin pearls to undifferentiated tumors without recognizable keratin or prickle cells. The tumors are classified into well-, moderately, and poorly differentiated lesions based on how closely they resemble mature nonneoplastic squamous cells (Figs. 3.10, 3.11, and 3.12). As the lesions become less mature, they show progressive degrees of pleomorphism and loss of keratinization and intercellular bridges. The degree of keratinization and the prominence of intercellular bridges inversely correlate with the degree of cytologic atypia and nuclear pleomorphism, although one occasionally sees marked keratinization of highly atypical cells. Most tumors are well- to moderately differentiated lesions. Well-differentiated keratinizing carcinomas have a high proportion of large differentiated squamous cells (Fig. 3.10) and a low proportion of small basal-type cells, which are typically located at the periphery of the tumor cell nests. The tumors contain squamous cell nests, dyskeratotic cells, and keratin pearls. Less well-differentiated tumors consist of cellular masses containing polygonal, round, fusiform, or, rarely, small nonkeratinizing cells. Poorly differentiated carcinomas typically contain an abundance of basaloid cells and the degree of differentiation often varies throughout the tumor. Most poorly differentiated SCCs contain some foci of squamous differentiation such as dyskeratotic epithelial nests, keratin pearls, or intercellular bridges. They generally appear as invasive sheets of cells with prominent areas of central necrosis. Occasionally, areas of individual cell necrosis in poorly differentiated tumors produce a pseudoacinar pattern, but mucicarmine stains are negative. Typically the degree of differentiation varies throughout the tumor. In undifferentiated lesions, one may not recognize keratin or prickle cells, and one has difficulty identifying the tumor as squamous in nature. Most tumors contain at least focal histologically identifiable squamous differentiation with evidence of epithelial nests, pearls, or intercellular bridges. Cytokeratin 14 immunostains may help identify a tumor as being squamous cell in origin (97).
FIG. 3.11. Moderately differentiated invasive squamous cell carcinoma. Note the absence of marked atypia, keratinization, and pearl formation.

FIG. 3.12. Poorly differentiated invasive squamous cell carcinoma. Note the high degree of atypia and the brisk mitotic index.
FIG. 3.13. Moderately differentiated squamous cell carcinoma involving the regional lymphatics and lymph node. A: The lymph node has become secondarily involved with a moderately to poorly differentiated tumor. The nerve outside of the lymph node is also surrounded by tumor (arrow). B: Tumor within lymphatic spaces.

As the tumor cells infiltrate the esophageal wall, they may form sheetlike nests with rounded margins or they may have an asteroid shape with spiculated margins. Tumors with an asteroid configuration are more likely to show deep penetration, lymphatic permeation, nodal metastases, and desmoplasia and have a worse prognosis than those with rounded borders (98). Tumors with downward penetration are more likely to show vascular and lymphatic invasion (Fig. 3.13).

Patients treated preoperatively with chemotherapy or chemoradiation may show complete tumor ablation, partial regression with a reduced tumor:stroma ratio, or residual unaltered tumor cells, sometimes resulting in a stricture (Figs. 3.14 and 3.15). Tissues examined within 3 to 6 days of preoperative treatment show pronounced apoptotic changes, with or without necrosis. Most tumor cells appear extensively degenerated. The tumor may completely disappear, creating a partially re-epithelialized ulcer containing granulation tissue heavily infiltrated by lymphocytes. Calcification may be present. Fibrosis in the muscularis propria causes shrinkage of the muscle bundles. Tumor regression can be graded (99), although this is not commonly done.
Chapter 3

FIG. 3.14. Esophagus following radiotherapy. A: Low-power magnification showing the presence of a recurrent tumor (arrows) deep in the wall of the esophagus. The superficial tissues have become markedly sclerotic. The overlying epithelium is hyperplastic but nonneoplastic. B: Higher magnification shows the presence of the dense, sclerotic, submucosal tissues with atypical stellate-shaped radiation fibroblasts.

Cytologic Features

Cytologic evaluation of the esophagus is important as noted above. Exfoliated malignant cells from intraepithelial squamous cell carcinomas may be obtained by means of esophageal washings. These cells resemble those of carcinoma in situ of the cervix without evidence of keratinization. Abundant cell samples are usually obtained from SCCs. Paradoxically, large fungating growths frequently associate with inadequate material; false-positive results are rare in this setting. Well-differentiated carcinomas shed highly atypical and partly keratinized cells with bizarre shapes, anisocytosis, and hyperchromatic nuclei (Fig. 3.16). Malignant pearl formations may be observed. Moderately and poorly differentiated squamous cell carcinomas exfoliate single or clustered immature atypical cells with increased nuclear:cytoplasmic ratios and either pale nucleoli or dark angulated nuclei containing large amounts of heterochromatin (Fig. 3.17).

Tumor Spread

SCC spreads within the esophageal wall, invading the muscularis propria and extending into the periesophageal tissues. Mediastinitis, pleural fistulas, and empyema may develop. Depending on tumor location, invasion into the trachea, bronchi, aorta, pleural cavity, lung, thyroid, lymph nodes, pericardium, major vessels, and/or nerves occur. Malignant tracheoesophageal fistulas develop in up to 28% of patients (100). Eventually the tumors become fixed to surrounding structures, including the diaphragm, mainstem bronchi, aortic arch, or the great veins of the neck. At this point, the lesion is unresectable.

Intramural intralymphatic vascular spread is common; lymphatic extension produces submucosal nodules distant from the main tumor in up to 16% of esophageal carcinomas (85). The esophageal lymphatics drain into the mediastinal lymphatics leading to regional spread early in the disease. In Western populations, up to 61% of patients show local extension and nodal involvement at the time of diagnosis (101). Cervical nodes become involved in 19% to 60% of cases, mediastinal nodes in 21% to 64%, and abdominal nodes in 47%. Tumors of the cervical region metastasize to infraclavicular, peritracheal, supraclavicular, paraesophageal, and posterior mediastinal lymph nodes. Tumors of the upper and midesophagus commonly involve the paraesophageal, posterior, and tracheobronchial nodes. Lower esophageal tumors disseminate to paraesophageal, celiac, and splenic and hepatic artery lymph nodes. However, the distribution of nodal metastases does not always reflect the site of the primary tumor, since 40% of cervical esophageal tumors metastasize to abdominal nodes; 38% of lower esophageal carcinomas metastasize to cervical nodes (101). Extrathoracic nodal metastases represent distant metastases. The number of positive nodes is higher in distal cancers than in upper or midesophageal cancers. Simultaneous metastases to lymph nodes in the neck.
mediastinum, and abdomen occur far more commonly in lower esophageal cancers than in upper and midesophageal cancers. In some cases, the appearance of a supraclavicular, cervical, or abdominal metastasis may precede detection of the primary tumor.

Hematogenous metastases occur late in the disease, usually following nodal metastases. The most common metastatic sites include liver (35% to 72%), lungs (20% to 60%), adrenals (35%), kidneys (25% to 26%), bones (9% to 20%), adrenal gland (5%), peritoneum (2%), and, rarely, the central nervous system (2%) (101).
FIG. 3.15. Squamous cell carcinoma (SCC) following radiotherapy. *A:* Most of the tumor appears viable, although the cytoplasm is vacuolated and some nuclei appear pyknotic. *B:* Biopsy of a stenotic area in a patient several years after radiotherapy for SCC. The tissue fragments contain squamous epithelial cells and a highly cellular stroma. *C:* Higher magnification of the epithelial component of the tumor shows marked cytologic atypia and a disorderly architecture. *D:* The stroma contains infiltrating squamous cell nests as well as atypical stromal cells secondary to the radiation.

Molecular Alterations

SCC induction and progression result from genetic and epigenetic changes in genes controlling cell cycling, cell growth, DNA repair, and tumor dissemination (see Fig. 3.18). A brief summary of immunostains that may be useful in the diagnosis of dysplasia and in determining the prognosis of esophageal SCC follows. Abnormalities in p53 expression are common in esophageal SCCs occurring early in tumor development (102). A significantly greater frequency of p53 expression occurs in high-grade dysplasia versus low-grade dysplasia and in low-grade versus normal esophageal mucosa (103). p53 expression had no influence on survival in one study (104), was a marker for radioreistance in another study (105), and in another had no predictive value in patients receiving either chemoradiation therapy or radiation alone (106). Cyclin D overproduction or production at the wrong time may stimulate inappropriate cell division. Tumors showing cyclin amplification tend to invade deeply (107). Cyclin D overexpression increases in frequency from 22% in well-differentiated cancers to 54% in poorly differentiated tumors (107), but is not a useful prognostic marker. Cyclin B1 expression, however, associates with poor prognosis in both univariate and multivariate analyses (108).

FIG. 3.16. Well-differentiated squamous cell carcinoma of the esophagus. *A–D:* Variably shaped cells are found singly and in small groups.

Expression of epithelial growth factor receptor (EGFR), c-erbB2, Int-2, transforming growth factor-alpha (TGF-α), and human stomach cancer transforming factor (HST-1) has prognostic significance for SCC. EGFR overexpression occurs in 40.65% to 71% of esophageal SCC (109) (Fig. 3.18) and correlates with nodal metastases and depth of invasion. Immunoreactivity for TGF-α in esophageal SCC ranges from 35% to 78% (109,110) and associates with lower survival than seen in TGF-α–negative cancers (p <0.01). Survival is poorest with cancers that overexpress both EGFR and TGF-α (111). Amplification of HST-1 affects approximately 50% of SCCs, associating with hematogenous spread (112). Expression of vascular endothelial growth factor (VEGF), a selective mitogen for endothelial cells, correlates with microvessel density adjacent to the tumor. Shortened survival has been observed in VEGF-positive esophageal SCCs in most studies (113), but not all (114).

Degradation of extracellular matrix components by matrix serine proteinases (MSPs) is essential for tumor invasion. Esophageal SCC trypsin (an MSP) production correlates with the depth of invasion, TNM stage, and probability of recurrence (115). Matrix metalloproteinases (MMPs) also play a role in this process. Trypsin activates matrilysin, an MMP. Expression of both proteinases increases the probability of recurrence and mortality. Cytoplasmic overexpression of heparinase, an enzyme that cleaves the carbohydrate chains of heparin sulfate proteoglycans, associates with poor survival (116). Its expression is related to the depth of invasion, the TNM stage, and nodal metastases.

Prognostic Factors

The prognosis of esophageal SCC is influenced by patient age and gender (117); nutritional status (118); tumor location, size, and stage; proliferative rate (119); histologic differentiation; growth pattern; tumor resectability (120); and the presence of micrometastases, as determined by immunohistochemistry.
Esophageal SCCs in young adults are significantly larger and more likely to associate with nodal metastases when compared to older patients. Patients undergoing esophagectomy for SCC have a less favorable long-term prognosis than those with adenocarcinoma, experience higher postoperative mortality, and have more frequent lymph node metastases in early-stage tumors. In one study approximately 68% of esophageal cancers were resectable. Of these, 30.3% of SCCs were 5-year survivors, compared to 42.3% of adenocarcinomas.

**FIG. 3.17.** Moderately to poorly differentiated squamous cell carcinoma of the esophagus. A: Two large hyperchromatic cells: one has ingested an erythrocyte. B: Cluster of hyperchromatic cells (May-Grunwald-Giemsa). C: Poorly differentiated squamous cell carcinoma.

**Tumor stage** is an important prognostic factor. Most esophageal SCCs in Western countries are detected at an advanced stage and have a very poor prognosis. The SEER registries note that only 23% of men and 29% of women with esophageal SCC have localized disease; only 7% of men and 10% of women are 5-year survivors. The 5-year survival rate exceeds 95% for stage 0 disease and is 50% to 80% for stage I, 30% to 40% for stage II A, 10% to 30% for stage III, and 10% to 15% for stage III disease. Patients with stage IV disease treated with palliative chemotherapy have a median survival of <1 year. Tumors that completely infiltrate the esophageal wall or extend beyond it have a very poor prognosis. Patients with a malignant tracheoesophageal fistula have a median survival time of 1.4 months after the development of the fistula.

Disease-specific survival also correlates with the presence and number of nodal metastases. The 5-year survival is 92.2% for node-negative patients compared to 58.4% for patients with one to four positive nodes and 21.3% for those with five or more positive nodes. In one study, 31.7% of esophageal SCCs originally classified as node-negative by routine histopathologic examination exhibited micrometastases when the nodes were examined immunohistochemically. Immunohistochemically detected micrometastases exhibit the same poor prognosis as those in which the metastases are detected by hematoxylin and eosin (H&E) stains. Gastric involvement affects 8% of patients and has an extremely poor prognosis.

Tumor growth patterns also affect patient prognosis. Papillary lesions are less aggressive and present at a lower stage than other squamous cell carcinomas. Their 5-year survival rate is 71% compared to 11% for other growth patterns. The frequency of aneuploidy ranges from 42% to 72%. Sixty-two percent of patients with diploid tumors are 5-year survivors, compared to 34% of those with aneuploidy tumors. Tumors with heterogeneous DNA patterns exhibit more frequent nodal metastases than those with homogenous DNA patterns. Ploidy also correlates with histologic grade, distant metastases, mitotic activity, and the presence of other genetic aberrations.
FIG. 3.18. Prognostic markers. A: Squamous cell carcinoma (SCC) stained for the epidermal growth factor receptor (EGFR). The tumor is strongly positive, especially at the tumor–stromal junctions. B: EGFR immunoreactivity of a poorly differentiated SCC present within vessels. C: p53 immunostain showing numerous immunoreactive cells. D: Fluorescence in situ hybridization for cyclin D showing the presence of multiple copies of the gene in the neoplastic cells. The nuclei are stained with propidium iodide and appear red. The cyclin D is labeled with a fluorescent probe and appears yellow. More than two copies (yellow spots) are seen in many cells.

Treatment

The only therapy that can potentially cure esophageal SCC is complete surgical resection, including removal of the regional lymph nodes (133). Depth of tumor invasion and nodal status determine tumor resectability. Key findings that preclude esophagectomy are aortic and/or tracheobronchial invasion. Local invasion of the pericardium, diaphragm, or stomach does not preclude surgical resection in some medical centers (134). Advanced tumors with early infiltration of the tracheobronchial system may benefit from preoperative radiation to reduce tumor burden (135). Early postoperative mortality is about 10% (136) resulting from respiratory complications, pyothorax, surgical dehiscence, and hemorrhage.

In evaluating treatment data, it is important to recognize that esophagectomy with extended lymph node resection as performed in Japan differs significantly from that performed
in other countries. This has implications both in terms of outcome and assignment of tumor stage. An extended lymph node dissection involving the neck, mediastinum, and abdomen (137) results in better detection of metastatic lesions. As a result, some recommend adding cervical lymph node status to the N category and combining stages IIA and IIB. The survival in the N stages can then be divided into N1 and N2 based on the number of involved lymph nodes (138).

The presence of systemic disease accounts for most treatment failures after esophagectomy. Supplemental adjuvant and neoadjuvant chemoradiation therapy may improve on the results of surgery alone. A review of 34 randomized controlled trials and six metaanalyses evaluating these approaches concluded that for patients with resectable esophageal cancer for whom surgery is appropriate, surgery alone (i.e., without neoadjuvant or adjuvant therapy) is appropriate (139). Preoperative cisplatin-based chemotherapy trials show conflicting results (140,141). Chemotherapy may reduce SCC metastases (142). Shrinkage of the tumor by at least 50% may occur in 15% to 30% of patients treated preoperatively with fluorouracil, taxane (paclitaxel or docetaxel), or irinotecan (125). Similar results have been found in 35% to 55% of patients treated with cisplatin combined with these agents (143). While chemotherapy can palliate the symptoms in many patients, the response typically only lasts for a few months and survival is usually short.

Tumor recurrence is the most frequent cause of death in patients with resectable disease. The carcinoma may recur locally, in lymph nodes, or at distant sites or disseminate throughout the thorax and/or abdomen (144). Factors favoring recurrence include male sex, moderate to poor differentiation, presence of nodal metastasis, stage IIB or worse disease, and incomplete resection. A common reason for inadequate resection is the failure to recognize the extent of the submucosal spread. Submucosal extension to the resection margins associates with an increased risk of anastomosis dehiscence, a potentially fatal complication. Therefore, surgeons usually place the resection line well beyond the margins of visible carcinoma. Even with this approach, as many as 35% of patients have residual cancer in the tumor margins. For this reason, many surgeons monitor resection margins with frozen sections to detect unsuspected submucosal tumor extension.

Special Variants of Squamous Cell Carcinoma

There are several squamous cell carcinoma variants (Table 3.7).

Undifferentiated Carcinoma

Undifferentiated carcinomas lack definitive light microscopic features of differentiation, although some ultrastructural and immunohistochemical features of squamous differentiation may be present (1). The tumors constitute up to 20% of esophageal cancers (145) and belong in the group of poorly differentiated SCCs (Fig. 3.19). Undifferentiated cancers tend to be large tumors that penetrate to the esophageal adventitia, spread to regional nodes, and associate with poor survival. The immunohistochemical profile of these cancers is consistent with their highly malignant properties and include reduced expression of cell–cell adhesion molecules (E-cadherin, thrombomodulin), high expression of Ki-67, and no expression of p21 (146). Poorly differentiated carcinomas may coexpress keratin and vimentin, desmin, or neurofilament proteins (147), especially after chemoradiation.

<table>
<thead>
<tr>
<th>TABLE 3.7 Histologic Variants of Squamous Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional squamous cell carcinoma</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
</tr>
<tr>
<td>Basaloid carcinoma</td>
</tr>
<tr>
<td>Carcinoma with lymphoid stroma</td>
</tr>
<tr>
<td>Carcinoma associated with Epstein-Barr virus</td>
</tr>
<tr>
<td>Adenoacanthoma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
</tr>
</tbody>
</table>
FIG. 3.19. Undifferentiated squamous cell carcinoma (SCC). An undifferentiated SCC dissects beneath the more or less normal squamous epithelium above it.

FIG. 3.20. Verrucous carcinoma. Note the multiple warty outgrowths of the tumor. Part of the lesion was a spike condyloma.

Verrucous Carcinoma

Verrucous squamous cell carcinoma is a distinct, well-differentiated SCC variant. This very rare tumor typically associates with chronic esophagitis, usually developing in the distal esophagus (148). Associated medical conditions include achalasia, gastroesophageal reflux disease, caustic injury, and esophageal diverticula. Because of its slow growth, symptom onset is insidious and there is usually a long delay between development of dysphagia and detection of the lesion. Grossly these tumors appear as exophytic warty, papillary, spiked, or cauliflower-like masses (Fig. 3.20). The tumors consist of very well-differentiated keratinized squamous epithelium with cytologic atypia that may be so
minimal that the pattern mimics benign squamous proliferations (Fig. 3.21). The tumors exhibit a pushing rather than an infiltrating margin. Superficial biopsies show only nonspecific acanthosis, para-keratosis, and hyperkeratosis, making it very difficult to make the correct diagnosis. Invasion of the wall of the esophagus is its distinguishing feature and may be detected by ultrasonography. A fully resected specimen may be needed to confirm this. Morbidity and mortality result from local invasion. The tumors have a very low potential for metastases.

**FIG. 3.21.** Verrucous carcinoma. *A:* The lesion shows a well-differentiated squamous cell carcinoma (*left*) that arose in a condylomalike lesion (seen at the *right* of the picture). *B:* The metastases in regional lymph nodes are less well differentiated.

**Squamous Cell Carcinoma with Lymphoid Stroma**

SCC with lymphoid stroma is a rare variant of esophageal SCC and some tumors contain Epstein-Barr virus (EBV) DNA sequences (149). The tumors are poorly differentiated, penetrate into the muscularis propria, and may be focally necrotic (Fig. 3.22). Broad inflammatory cell infiltrates containing lymphocytes, plasma cells, neutrophils, macrophages, and eosinophils separate individual tumor cell nests. The infiltrating lymphocytes consist of a large number of T cells around tumor cell nests and a small number of B cells (149). Well-formed lymphoid follicles with and without germinal centers are present at the periphery. It may be difficult to distinguish the neoplastic epithelium from the lymphoid stroma without immunostains for epithelial and/or lymphocytic differentiation. These tumors resemble medullary carcinomas of the stomach.

**Squamous Cell Carcinoma in Barrett Esophagus**

SCCs may arise in the squamous mucosa just above Barrett esophagus (150), often in areas of high-grade squamous dysplasia. The invasive SCC and the squamous cell dysplasia are separated from the Barrett mucosa by normal squamous epithelium. These tumors resemble other SCCs.

**Spindle Cell Carcinoma**

Synonyms for spindle cell carcinoma include polypoid carcinoma with spindle cell features, pseudosarcoma, spindle cell carcinoma, carcinosarcoma, metaplastic carcinoma, carcinoma with mesenchymal stroma, and sarcomatoid carcinomas.

**FIG. 3.22.** Invasive carcinoma with lymphoid stroma. An invasive poorly differentiated squamous cell carcinoma is present. It is associated with large numbers of inflammatory cells.
Some tumors arise on a background of BE. Most patients with spindle cell carcinomas present with slowly developing dysphagia and weight loss. Vomiting, regurgitation, and epigastric or retrosternal pain frequently occur. Because of their polypoid growth, they become symptomatic early and therefore present at a lower stage than typical SCCs. An unusual patient presented with leukocytosis and granulocytic hyperplasia due to high serum levels of granulocyte–colony-stimulating factor (G-CSF) produced by both the epithelial and sarcomatous components of the cancer. The peripheral white count and cerebrospinal fluid (G-CSF) levels reverted to normal after removal of the tumor (154).

Spindle cell carcinomas are typically polypoid, with 7% developing in the upper third and 82% to 93% arising in the middle and lower third of the esophagus. Most lesions are large lobulated masses with mucosal erosions (Fig. 3.23). They range in size from 1 to 15 cm (151,153). The tumors may have a broad base or, less frequently, are attached by a slender pedicle, measuring up to 2 cm in length. Occasionally, they may be flat with surface ulceration resembling a more typical esophageal SCC (153,155). Multiple satellite nodules may lie in the adjacent mucosa (155). On cut section, the tumors appear gray-white, soft, and fleshy. At the time of diagnosis, 80% are confined to the esophageal wall. Metastases of the regional lymph nodes, liver, and skin occur late in the disease (153).

Characteristically, spindle cell carcinomas have a clearly identifiable squamous cell component consisting of invasive SCC and/or squamous cell dysplasia in the adjacent mucosa. However, surface necrosis or tumor growth may erode any residual intraepithelial neoplasia. The invasive SCC may appear well- to poorly differentiated. Other types of carcinoma may be present, including those with basaloid, neuroendocrine, glandular, adenoid cystic, or undifferentiated growth patterns (151,155). The epithelial components of spindle cell carcinoma are best seen at its base and in the adjacent mucosa. Mitotic activity in different areas of the tumor can be quite brisk. The spindle cell component typically forms the majority of the tumor mass (Figs. 3.24, 3.25, and 3.26). It varies from a bland proliferation of spindle-shaped cells with little or no pleomorphism to areas showing marked pleomorphism with bizarre giant cells similar to those seen in malignant fibrous histiocytomas. Mitoses are frequent. Some tumors show cartilaginous, osseous, or rhabdomyoblastic differentiation. Multinucleated cells resembling osteoclasts may also be present (153). The epithelial areas are often sharply demarcated from the more spindled areas. Transition zones between the two cell populations are frequently present. An edematous, myxoid, or collagenized stroma may be admixed with inflammatory cells and prominent blood vessels. There is a greater level of proliferation and a higher level of aneuploidy in the sarcomatous components than in the epithelial components, giving the sarcomatous phenotype a growth advantage, allowing it to become the predominant part of the tumor (156).
FIG. 3.24. Sarcomatoid carcinoma.  

A: Polypoid pedunculated lesion of the lower thoracic esophagus.  
B: Nests of squamous cell carcinoma (SCC) within a cellular moderately atypical stroma.  
C: Epithelial cell nest positive for keratin. Note the negativity of the stroma.  
D: Intraepithelial SCC adjacent to the tumor mass.

The squamous component typically expresses high-molecular-weight cytokeratin (Fig. 3.26), whereas the spindle cells variably express cytokeratin, vimentin (Fig. 3.26), desmin, and smooth muscle actin. Cytokeratin positivity is present in 50% to 65% of the spindle cell areas. Cytokeratin staining may be strong and diffusely positive, or may be scattered and faint. Vimentin antibodies strongly stain the sarcomatoid areas and sometimes stain the epithelial areas. E-cadherin is expressed in the epithelial cells and is absent from the spindle cells (159).
FIG. 3.25. Sarcomatoid carcinoma. A: The recognizable epithelial component shows varying degrees of differentiation. B: Areas of tumor cells show mesenchymal cell features with marked cytologic atypia. An epithelial component is on the left. C: In this area the sarcomatous component resembles a fibrosarcoma. D: Here the sarcomatous component resembles a malignant fibrous histiocytoma.

The differential diagnosis includes true sarcomas, malignant melanoma, and inflammatory pseudotumors. Diffuse strong staining for myogenous markers supports a diagnosis of leiomyosarcoma, although smooth muscle tumors can sometimes stain with antibodies to cytokeratin and some sarcomatoid carcinomas may express muscle antigens. Malignant melanoma markers include melan-A, HMB45, and S100. Inflammatory pseudotumors lack cytologic anaplasia and the abnormal mitotic figures that characterize sarcomatoid carcinomas.

The prognosis of patients with spindle cell carcinoma resembles that of patients with pure SCCs. The tumor metastasizes to regional lymph nodes and the lung, liver, brain, and adrenal glands. The metastases may consist of only sarcomatoid or epithelial elements or a mixture of the two (151).

Basaloid Carcinoma

Basaloid carcinoma is a rare SCC variant, being more common in the upper aerodigestive tract. This pattern occurs in approximately 0.3% to 4.5% of primary esophageal malignant tumors (156,157) and is more common in men than in women (male:female ratio = 7:1). It often presents in the 6th decade, but does have a wide age range from 27 to 88 years with a mean of 62 years. Dysphagia is the most common presenting symptom. The gross and endoscopic features resemble those of typical SCC. The tumors arise throughout the esophagus (156). These tumors are frequently fungating, but they may also be ulcerative and infiltrative. The tumors range in size from 10 to 90 mm (156).

Early lesions resemble submucosal tumors since they are frequently covered by normal epithelium, a feature that makes their diagnosis difficult by endoscopic biopsy. These invasive tumors arise from totipotent stem cells in the basal layer of the squamous epithelium (158). The intermediate and superficial cells show normal maturation in noninvading areas, a feature that distinguishes basal cell intraepithelial neoplasia from squamous cell intraepithelial neoplasia. The palisading pattern that characterizes normal basal cells is retained in areas of invasion. The mitotic index is high (15 to 40 mitoses/10 high-powered field [hpf]). The lobular pattern is characterized by comedonecrosis and interlobular desmoplasia. The cribriform form is characterized by glandlike squamous hyalinosis and associates with

the presence of basement membrane substance positive for collagen 4 and laminin (157). Comedonecrosis affects the intraepithelial component as well as its invasive nests. The lobules and nests have smooth rounded margins. Small nests tend to be solid, but large lobules frequently show central comedonecrosis. The nuclei demonstrate an open chromatin pattern and contain small nucleoli. Occasional serpentine or ribbonlike arrangements of the tumor cells remind one of neuroendocrine differentiation. The presence of squamous cell dysplasia, carcinoma in situ, or invasive cancer in the contiguous mucosa is common (158), but adenocarcinomatous or small cell carcinomatous components may also be present. Each component is usually clearly distinguishable from the others, and they metastasize separately.
Chapter 3

FIG. 3.26. Sarcomatoid carcinoma. A: Malignant epithelial (left) and stromal components (right). B: Antikeratin antibody stains single cells within stromal area. C: Antivimentin antibody localizes to more stromal cells and is also present in the epithelial cells.

<table>
<thead>
<tr>
<th>TABLE 3.8 Basaloid Carcinoma Versus Adenoid Cystic Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finding</strong></td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Clinical duration</td>
</tr>
<tr>
<td>Myoepithelial cells</td>
</tr>
<tr>
<td>Cytologic features</td>
</tr>
<tr>
<td>Mitoses</td>
</tr>
<tr>
<td>Coexisting dysplasia</td>
</tr>
</tbody>
</table>

Antibodies to a wide range of molecular-weight cytokeratins, such as AE1/AE3 and AE1, may show heterogeneous staining patterns with some areas being strongly positive and others being negative (78). CK14 stains 90% of the tumors (159). There is extensive to moderate neuron-specific enolase (NSE) reactivity when a small cell component is present (160), but chromogranin and other neuroendocrine markers are negative. The differential diagnosis of basaloid carcinoma includes small cell carcinoma. Both neoplasms may coexist with a squamous component and both are thought to arise from pluripotent stem cells or basal cells with multidirectional differentiating capabilities. The distinction between basal cell SCC and small cell undifferentiated carcinoma is important because of the therapeutic implications (157).

There is confusion between adenoid cystic carcinomas and the basaloid variant of SCC. These lesions may be separated from one another by the features shown in Table 3.8. Basaloid cancers are aggressive tumors with a prognosis similar to that of SCC (156). They form large tumors with lymph node metastases and commonly spread hematogenously to the lungs and liver (160). The poor prognosis of these tumors relates in part to their advanced clinical stage at the time of diagnosis. Their metastases may show only the basaloid component or may have basaloid and squamous components in different lymph nodes. The metastasis may consist only of the small cells if the small cell...
component is predominant in the main tumor (156).

Adenocarcinoma of the Gastroesophageal Junction

It may be impossible to determine whether a cancer straddling the GEJ arose from the gastric cardia or the distal esophagus. Cancers in both sites associate with gastroesophageal reflux disease (GERD) and BE. Cardia cancer shares the same secular trends, epidemiologic backgrounds, and molecular profiles as BE-associated adenocarcinoma (161,162,163) and differs in these respects from noncardiac gastric cancer (164). The following discussion bundles cardia cancer together with BE-associated esophageal adenocarcinoma as cancer at the GEJ.

Adenocarcinomas usually arise in the distal esophagus from BE. BE-associated cancers account for more than 90% of esophageal adenocarcinomas. The remainder arise from heterotopic rests or submucosal glands. The origin and morphology of BE are discussed in detail in Chapter 2. Not all GEJ cancers are of esophageal origin. Some arise from the gastric cardia or involve the esophagus by proximal extension from more distal gastric cancers. The presence of dysplasia in BE helps identify a cancer as originating in the esophagus, but this may be impossible to identify in advanced adenocarcinomas that replace the pre-existing BE.

Siwertel et al separated GEJ cancer into three subgroups based on their relationship to the proximal end of the gastric folds: adenocarcinoma of an esophagogastric junction (AEG I) = cancers of the distal esophagus; AEG II = cancers of the true cardia; and AEG III = cancers of the subcardia (165). Types AEG II and III are categorized as gastric adenocarcinomas in this treatment-based classification. However, as noted above, we believe that BE-associated cancers (AEG I) and cardia cancer (AEG II) are so similar with respect to patient characteristics (obese, middle-aged white men with reflux disease and no H. pylori gastritis), secular incidence trends, and molecular profiles that they are essentially the same cancer.

Epidemiology

The incidence of GEJ adenocarcinoma has increased by more than 350% in the United States since the mid-1970s (3). The increase has shown marked gender, geographic, and ethnic differences. The 3-year average incidence of this cancer among white males in the period 1996–1998 was 4.0 compared to 0.5 for women. A survey of 11 SEER registries found that white male rates in Seattle increased 800% from 1974–1975 to 1996–1998, compared to only 300% in Utah during the same timeframe (166). Black males had a small but significant increased incidence. The 3-year average incidence of this cancer among blacks is 0.8 compared to 4.0 among whites. A similar increased incidence occurred in Britain (167), and there was a 10-fold increased incidence in Finland since the 1970s. However, Finnish rates (1.1 per 100,000) are low compared to those in the United States or Britain (168). In contrast to Western countries, GEJ adenocarcinoma incidence rates have been stable over the past 40 years in Japan, where these tumors constitute only 0.67% of all esophageal cancers (169).

Predisposing Factors

The degree of GERD is more severe in BE patients with cancer than in those without it (170), and antireflux therapy does not decrease the cancer risk (171). The risk of cancer increases with the duration of GERD (172). This may explain a 10-fold increased risk of GEJ cancer among adults whose birth weights were <2,000 g (173), since GERD is very common in preterm infants. The presence and size of a hiatal hernia also directly correlates with the presence of both BE and adenocarcinoma (174). The presence of bile acids in the refluxate is thought to be critical to the generation of BE-associated adenocarcinomas (175,176). Obesity consistently associates with esophageal adenocarcinoma (177), possibly due to the increased risk of GERD in this setting (178). Recent studies, however, found an independent positive association of obesity with GEJ cancer in patients without GERD (177,179). The association between the body mass index (BMI) and GEJ cancer is dose dependent in males (180), and in 17% of cases the BMI exceeds the value that defines the highest decile of the control population (181). Smoking and alcohol are consistently and directly related to GEJ cancer (247,248,251), but the risk is not as strong as that for SCC and in some studies does not reach statistical significance (172,177,181,182).

It has been proposed that interactions between salivary nitrite and gastric refluxate can activate mutagenic nitroso compounds within the Barrett mucosa (183). On entering the Barrett segment there is a substantial fall in nitrite levels, indicating a reduction of nitrite to nitric oxide (NO) at this site. High luminal NO concentrations exert nitrosative and oxidative stress, damaging DNA and inhibiting DNA repair. The decreased risk of GEJ carcinoma associated with a high intake of antioxidants (184) may result from suppression of this process (185). H. pylori is a well-established risk factor for gastric cancer distal to the cardia (see Chapter 5). In contrast, H. pylori inversely correlates with GERD and GEJ cancer (186,187). As the frequency of distal gastric cancer decreased in Western countries, there was a reciprocal increase in GEJ cancers (3). The decreased gastric acidity resulting from H. pylori-induced gastritis prevents GERD development and its metastastic P.110

and neoplastic consequences (188). Successful eradication of the H. pylori infection doubles the frequency of GERD when compared to untreated patients (189).

Medications that promote GERD through relaxation of the esophageal sphincter, such as anticholinergics, may increase the risk of esophageal adenocarcinoma (190), while medications that inhibit prostaglandin synthesis and block prostaglandin-induced immunosuppression may protect against BE-associated cancer (191).

Genetic Factors

It appears that there may be a genetic susceptibility to the development of carcinomas arising in the setting of BE. The fact that these cancers develop almost exclusively in white males suggests the involvement of an as yet unknown genetic factor in the development of the disease. In addition, there are familial forms of the disease that appear to have an autosomal dominant mode of inheritance (192,193). Genetic polymorphisms may also play important roles in determining the risk of developing this tumor. An association has been shown for polymorphisms in glutathione S-transferase P1 (GSTP-1) and BE-associated adenocarcinoma (194). GSTP-1 is responsible for the detoxification of various carcinogens, and inherited differences in carcinogen detoxification may play an important role in the develop of BE and its associated carcinoma. There is also an association between the MTHFR 677TT variant and esophageal adenocarcinoma (43). A number of genetic alterations characterize the development of neoplasia in areas of BE. Among the most common and earliest are p53 and p16 alterations (195,196). Other alterations are listed in Table 3.9.

Dysplasia

Because dysplasia often lies adjacent to areas of invasive carcinoma, the presence of dysplasia represents both a marker of increased risk for the subsequent development of esophageal adenocarcinoma and a potential marker for the coexistence of an invasive carcinoma. The risk level correlates with the extent of high-grade dysplasia (197), but a recent study indicated that invasive cancer is as likely to accompany focal high-grade dysplasia as extensive diffuse dysplasia (198). Dysplasia is found in 5% to 10% of patients with BE (199), and increases in frequency as BE is followed over time. A cohort study of patients with BE followed for 20 years found the rate of cancer to be 1 in 274 patient-years in the presence of dysplasia, compared to 1 in 1,114 patient-years in patients without dysplasia (197). The diagnosis of dysplasia is a decisive factor in the management of patients with BE (199).

### Table 3.9 Genes and Genetic Products Involved in Barrett-associated Carcinogenesis

<table>
<thead>
<tr>
<th>Gene/Genetic Product</th>
<th>Function/Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTP-1, GSTM1, GSTT1</td>
<td>GLUTATHIONE S-TRANSFERASES</td>
</tr>
<tr>
<td>TP53, CDKN2A, APC</td>
<td>TUMOR SUPPRESSOR GENES</td>
</tr>
<tr>
<td>ATM, BRCA1, BRCA2</td>
<td>DNA REPAIR GENES</td>
</tr>
</tbody>
</table>

Note: This table is a simplified representation of the genetic factors involved in Barrett-associated carcinogenesis. The actual list of genes and genetic products may vary and include additional or more specific variations.
Tumor Suppressor Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>Commonly mutated in dysplasia and invasive carcinoma</td>
</tr>
<tr>
<td>p16</td>
<td>Hypermethylated in dysplasia</td>
</tr>
<tr>
<td>FHIT</td>
<td>Altered in dysplasia</td>
</tr>
<tr>
<td>APC</td>
<td>Mutations occur late in the dysplasia–carcinoma sequence</td>
</tr>
<tr>
<td>Rb</td>
<td>Loss in invasive carcinoma</td>
</tr>
</tbody>
</table>

Cell Cycle Regulatory Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclin D1</td>
<td>Frequently overexpressed in invasive adenocarcinomas</td>
</tr>
<tr>
<td>MDM2</td>
<td>Overexpression and/or amplification affect many invasive carcinomas</td>
</tr>
</tbody>
</table>

Growth Factor Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Overexpressed in &gt;75% of invasive carcinomas</td>
</tr>
<tr>
<td>TGF-A</td>
<td>Overexpressed in invasive carcinoma</td>
</tr>
<tr>
<td>c-erbB2</td>
<td>Amplified in invasive carcinomas; prognostic factor</td>
</tr>
</tbody>
</table>

Cell Adhesion Molecules

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-cadherin</td>
<td>Loss of expression in dysplasia and invasive carcinoma</td>
</tr>
<tr>
<td>P-cadherin</td>
<td>Up-regulated in invasive carcinoma</td>
</tr>
<tr>
<td>α-Catenin</td>
<td>Loss of expression in invasive carcinoma</td>
</tr>
<tr>
<td>β-Catenin</td>
<td>Nuclear expression in invasive carcinoma</td>
</tr>
</tbody>
</table>

Proteases

<table>
<thead>
<tr>
<th>Protease</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPA</td>
<td>Prognostic factor in invasive carcinoma</td>
</tr>
</tbody>
</table>

Problems in establishing a diagnosis of dysplasia include difficulties relating to sampling error, the distinction between reactive changes and dysplasia, differences in observer interpretation of the diagnosis of dysplasia, and difficulties in differentiating high-grade dysplasia from invasive carcinoma. Dysplasia has no specific gross or endoscopic features unless there is a mass lesion. Flat dysplasia is more common than a polypoid lesion. The dysplastic mucosa may be slightly raised, with or without areas of ulceration. Usually, the dysplastic foci cannot be distinguished grossly from the surrounding BE or from gastric-type mucosa. Therefore, multiple random biopsies are usually required for its detection. A protocol proposed by Levine et al (200) requires the endoscopist to obtain quadrant biopsies from three levels of the BE. However, this will sample only 3.5% of the affected mucosa, assuming that jumbo biopsy forceps are used and that a 2-cm segment of BE has a surface area of 14 cm² (201). It is therefore not surprising that reports of the prevalence of unsuspected invasive cancer found in resections for high-grade dysplasia esophagus vary from 0% to 75% (202).

The sampling problem is compounded by the lack of interobserver agreement on the histologic diagnosis of dysplasia, especially of low-grade dysplasia (see below). Since cytologic atypia is the defining characteristic of dysplasia, some endoscopists supplement biopsies with cytologic smears. Unfortunately, cytology may miss BE-associated adenocarcinomas that drop off the base of the mucosa in a manner analogous to that seen in ulcerative colitis. Because of the difficulty in recognizing dysplasia, newer imaging methodologies have been developed. These include high-resolution endoscopy, which enhances the ability to target small lesions for biopsy, and chromoendoscopy and optical coherence tomography (OCT), which are analogous to ultrasound but measure echo time delay of light rather than sound (203).

As noted, interpretation of dysplastic lesions can be quite difficult because the histologic and cytologic abnormalities form a continuous spectrum that extends from relatively mild atypia to overt dysplasia to invasive cancer. The boundaries separating negative and low-grade dysplasia, low-grade and high-grade dysplasia, and high-grade dysplasia and invasive cancer are therefore not always sharply definable. Histologically, dysplasia is defined as a benign neoplastic epithelial change that is confined within the basement membrane. The classification of dysplasia resembles that used for inflammatory bowel disease, with dysplasia being divided into high-grade, low-grade, and indefinite categories. The levels of inter- and intraobserver agreement are poor for the low-grade and indefinite categories. Although the level of agreement is better for high-grade dysplasia, substantial differences remain (204). Supplemental immunohistochemical (IHC) procedures may increase the ability to identify dysplastic mucosa (see below). However, IHC may not distinguish between low-grade and high-grade dysplasia, but may identify patients who require re biopsy and/or careful follow-up.

A large cohort study found incidental cancer to be uncommon with BE, but the risk was significantly higher in men with low-grade dysplasia (205). Patients with low-grade dysplasia were free of cancer or high-grade dysplasia in 90% of cases at 6 years and in 80% of cases at 10 years. This suggests that there is no urgency in making a definitive diagnosis, and that careful follow-up may resolve doubts created by diverging interpretations. Inadequate sampling may result in underdiagnosis of the degree of dysplasia. Approximately one third of resections for high-grade dysplasia have a previously unsuspected invasive cancer, even when the biopsy samples are taken according to recommended guidelines. The frequency of underdiagnosis with low-grade dysplasia cannot be determined because this diagnosis does not mandate resection. The diagnosis of low-grade dysplasia therefore establishes a need for long-term follow-up. A diagnosis of high-grade dysplasia is of critical importance. Overdiagnosis in an older, obese male (the usual BE patient) could generate substantial, but unnecessary, operative morbidity and mortality, while underdiagnosis could allow a cancer to progress from an early treatable stage to an inoperable one.
FIG. 3.27. Low-grade dysplasia in Barrett esophagus. A: Most of the glands are dysplastic. Some residual nondysplastic cells are seen in the lower right-hand corner. The dysplastic nuclei extend approximately halfway toward the lumen. B: Higher magnification of a different lesion showing loss of nuclear polarity and dysplastic goblet cells.

A diagnosis of dysplasia is based on both cytologic and architectural changes, including varying degrees and combinations of epithelial disarray, cytologic atypia, and architectural distortion. While both architectural and cytologic abnormalities characterize dysplastic areas, one or the other usually predominates (Figs. 3.27 and 3.28). The dysplastic epithelium may be tubular or villiform, and it may contain glands with papillary infoldings, irregular contours, or back-to-back configurations. Dysplastic crowded cells show decreased mucous secretion with nuclear irregularity, enlargement, hyperchromasia, and chromatin clumping. Increased nuclear:cytoplasmic ratios, abnormal mitotic figures, and nuclear stratification are also present. As low-grade lesions progress to high-grade dysplasia, architectural and cytologic abnormalities increase. A description of the specific lesions follows.

Negative for Dysplasia

Reactive metaplastic glands in BE may appear irregular in size and position with expanded proliferative zones containing cells with enlarged crowded nuclei and prominent centrally located nucleoli and numerous mitoses. Since a gradient of cellular differentiation extends from the base of the gland to the surface, the abnormalities remain confined to the lower part of the glands while their upper portions show few abnormalities and the surface cells usually appear normal. However, it is important to note that when extreme cytologic atypia is present in the glandular bases and not at higher levels, a diagnosis of dysplasia is still warranted (see below). A diagnosis of dysplasia should not be made on the basis of villiform transformation or glandular branching since these changes may be present in either reactive or dysplastic lesions.
**Indefinite for Dysplasia**

Chronic reflux-induced inflammation generates overlapping inflammatory, regenerative, and dysplastic changes in BE. Therefore, it may be difficult to distinguish reactive changes from low-grade dysplasia in this setting, especially if ulceration has occurred, since both cytologic and architectural alterations may be present. The term *indefinite for dysplasia* describes the uncertainty engendered by these changes. Villiform hyperplasia with mild atypia may superficially resemble villous adenomas, creating diagnostic confusion, especially when mucus-depleted foveolar cells resemble intestinal absorptive cells. There may also be an expansion of the proliferative zone. The glands usually show a differentiation gradient as the surface is approached in regenerative epithelium that contrasts with a shift of the proliferative zone to the surface in dysplastic lesions. However, in the face of proliferation that involves the full length of the crypt, it may be impossible to tell whether the proliferative cells are extending upward (as in regeneration) or downward (as in dysplasia). When doubt exists as to the true nature of the lesion, a diagnosis of indefinite for dysplasia is made and a repeat biopsy is performed following a course of antireflux therapy. Features that favor a reactive lesion over a dysplastic one are listed in Table 3.10.

**Low-grade Dysplasia**

Low-grade dysplasia is characterized by minimal or no architectural abnormalities, but the cells appear more atypical than in BE. The nuclei become elongated and stratified, but the nuclei do not reach the apical surfaces, remaining limited to the lower three fourths of the cells. The enlarged nuclei are crowded and hyperchromatic. Goblet cell mucus is usually diminished and goblet cell dystrophy may be present (Fig. 3.27). (Goblet cell dystrophy does not, by itself, constitute a diagnosis of dysplasia.) Since the mucosa of the distal esophagus often resembles gastric mucosa, the lower portions of the glands normally exhibit a back-to-back configuration. When intestinal metaplasia involves these pre-existing glands, they will present a back-to-back appearance, which, when combined with reactive changes (increased mitoses and hyperchromatic nuclei), may prompt an erroneous diagnosis of high-grade dysplasia. This is less worrisome than a back-to-back configuration involving the upper mucosa where the mucous neck region and glandular crypts are normally separated by a loose stroma. The dysplasia often resembles early colonic tubular adenomas.

---

### TABLE 3.10 Reactive Versus Dysplastic Epithelial Features

<table>
<thead>
<tr>
<th>Features shared by reactive and dysplastic epithelia</th>
<th>Features that favor reactive changes</th>
<th>Features that favor dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased mitoses</td>
<td>Round to oval nuclei</td>
<td>Cellular pleomorphism</td>
</tr>
<tr>
<td>Nuclear enlargement</td>
<td>Smooth nuclear contours</td>
<td>Irregular nuclear contours</td>
</tr>
<tr>
<td>Hyperchromasia</td>
<td>Evenly spaced and nonoverlapping nuclei</td>
<td>Variable hyperchromasia</td>
</tr>
<tr>
<td>Decreased intracellular mucin</td>
<td>Granular chromatin</td>
<td>Nuclear stratification, overlapping, and crowding</td>
</tr>
<tr>
<td>Expanded proliferative zone</td>
<td>Uniform nucleolar appearance among the cells</td>
<td>Loss of nuclear polarity</td>
</tr>
<tr>
<td></td>
<td>Nearby active inflammation</td>
<td>Atypical mitoses</td>
</tr>
</tbody>
</table>

---

**FIG. 3.28.** High-grade dysplasia. *A:* Polypoid area of dysplasia resembling a colonic adenoma. It arises on a broad area of Barrett metaplasia. Note the villiform transformation on the right side of the figure. *B:* Higher magnification of the dysplastic part of lesion shown in *A.* Note the prominent nuclear stratification. *C:* Severe dysplasia affects the cells at the upper mucosa. The cells are beginning to lose their polarity and the glands are beginning to fuse with one another. *D:* Dysplastic glands on the left and Barrett esophagus on the upper right. Note the disorganized architecture.
Since dysplasia usually affects the mucosal surface, mitotic figures and Ki-67–labeled cells are characteristically present in this area (Fig. 3.29). p53 immunostaining may also be useful in identifying dysplasia if more than a few isolated cells are positive (Fig. 3.29).

**High-grade Dysplasia**

One may diagnose high-grade dysplasia by cytologic or architectural criteria, or both, since the cells have the features of malignancy. Nuclear stratification reaches the luminal surface and the nuclei lose their normal polarity. As a result, the long axis of the nucleus no longer remains perpendicular to the crypt basement membrane. Nuclear enlargement, hyperchromasia, variations in size and shape, nucleolar prominence, increased nuclear:cytoplasmic ratios, and increased numbers of abnormally shaped mitoses develop. Metaphases may exhibit horizontal rather than the usual vertical orientation relative to the cytoplasmic luminal surface. Goblet cells and mucous cells are usually absent. These abnormalities extend to the mucosal surface (Fig. 3.28). Architectural distortion may be quite marked, consisting of branching and lateral budding of the crypts, villiform configuration of the mucosal surface, or intraglandular epithelial bridging to form a cribriform back-to-back glandular pattern (Fig. 3.30). The architectural distortion of high-grade dysplasia may be so marked that it may be hard to distinguish from an invasive carcinoma. The pattern that usually prompts this diagnostic dilemma consists of back-to-back glands closely packed together or ill-defined glands present in the lamina propria. In this setting, one can make the diagnosis “high-grade dysplasia, cannot rule out an invasive carcinoma.” Intramucosal carcinoma is recognized by the presence of single cells, small irregular cluster cells, or sheets of neoplastic cells infiltrating the lamina propria. Examination of multiple biopsies increases the chance of detecting invasive foci.

**Crypt Dysplasia with Surface Maturation**

We have seen a number of cases, especially among our consult material, in which the cells at the bases of the crypts display features consistent with those that are present in areas of dysplasia (Table 3.10) and yet the cells mature as they approach the mucosal surface. These areas occur in the absence of acute inflammation, ulcers, or erosions. The most common features of these basal cells include nucleomegaly, loss of nuclear polarity, marked variation in cell size and shape, overlapping of the nuclei, increased mitotic activity, and goblet cell dystrophy.

**FIG. 3.30.** Well-differentiated carcinoma. *A:* The lesion illustrated in this figure could represent either carcinoma in situ or severe dysplasia. Note the absence of desmoplasia surrounding the lesion. The glands are highly atypical and have lost their polarity. *B:* An infiltrating well-differentiated carcinoma surrounded by a desmoplastic stroma. The glands have acquired irregular shapes and back-to-back glandular formations. *C:* Microglandular pattern (*upper right corner*) of an invasive carcinoma.
Similar lesions have been recently evaluated by Lomo et al, who termed the changes basal crypt dysplasialike atypia (BCDA). They found that this change had a prevalence of 7.3% and it was commonly associated with high-grade dysplasia, a high percentage of p53 immunoreactivity, a high proliferative rate, and aneuploidy (206). These authors concluded that BCDA is a possible variant of dysplasia that warrants further study. It is our practice to diagnose these lesions as at least low-grade dysplasia due to the nature of the cytologic changes, even though surface maturation does occur.

Adenomas (Polypoid Dysplasia)

Polypoid dysplasia is uncommon. Its precise frequency is unknown since most GEJ adenomas have been described as individual case reports. One retrospective study found only five adenomas among 250 cases of BE-associated dysplasia, corresponding to a prevalence of 2% in a highly selected population (207). Instances of multiple polyps have been reported (208). As in the colon, the polyps display a tubular, tubulovillous, or villous architecture; show varying degrees of dysplasia (Fig. 3.31); and may contain areas of invasive carcinoma.

Natural History of Dysplasia

The progression to malignancy in BE is a multistep process involving the transition from metaplasia to low-grade dysplasia to high-grade dysplasia to invasive carcinoma. The development of infiltrating carcinoma is rare in patients initially diagnosed as negative for dysplasia. This contrasts with the up to 60% of patients who have or will develop invasive carcinoma if their biopsies disclose the presence of development of high-grade dysplasia. Thus, high-grade dysplasia is the proximate precancerous lesion but it need not progress to full-blown invasive adenocarcinoma, and predicting which case will evolve into cancer is difficult. In some cases, high-grade dysplasia persists for years without progressing (209). The risk increases if high-grade dysplasia associates with a mass lesion (210). High-grade dysplasia found in biopsies associates with concurrent adenocarcinoma in approximately one third of cases; the presence of the associated invasive cancer may not be suspected until a resection specimen is examined (202,210). This is particularly true of well-differentiated tubular carcinomas. The glands forming these neoplasms may be so "benign" in appearance and rarely show tumor cell dissociation, even at the invasive front, that the only way to correctly diagnose the lesion is to see it invading into the lamina propria and beyond.

Early invasive adenocarcinoma may develop anywhere throughout the length of BE. The presence of high-grade dysplasia is an indication for surgical intervention, but there is no consensus as to how patients with high-grade dysplasia should be treated (211). Most agree that immediate rebiopsy should be performed to determine whether there is coexistent carcinoma. If a diagnosis of high-grade dysplasia with unassociated carcinoma is made, the diagnosis should be confirmed by a pathologist familiar with the changes in the setting of BE and with extensive experience in this area.

Patients with high-grade dysplasia or early cancer arising in BE have the best chance of cure if handled in a careful multidisciplinary team approach involving the surgeon, gastroenterologist, and pathologist. The surgical procedure is determined by the length of the BE. Some individuals develop a second carcinoma following resection for the first one. The second tumor usually develops in the residual BE. These findings suggest that if the patient does undergo a resection, all of the BE should be resected to avoid the future development of another cancer.

Ancillary Techniques for Evaluating Dysplasia

Because of the difficulties in distinguishing regenerative changes from dysplasia and because not all individuals with dysplasia develop carcinomas, numerous adjunctive tests have been developed to predict which lesions are most likely to evolve into carcinomas. Some of the more promising are discussed below.

At least three cell cycle abnormalities develop in the dysplastic mucosa. These include mobilization of cells from the G0 into the G1 compartment of the cell cycle, loss of control of the G1/S-phase transition, and accumulation of cells in the G2 phase (212). Cell proliferation shifts from the lower parts of the glands into the upper mucosa and mucosal surface. Markers of cell proliferation, such as PCNA and Ki67, highlight this shift toward the superficial mucosa (Fig. 3.29).

Flow cytometric abnormalities correlate well with the presence of dysplasia and carcinoma (210). DNA aneuploidy increases as the severity of the neoplastic process increases (212). However, even specimens histologically negative or indefinite for dysplasia may contain aneuploid cells (213). Careful mapping studies demonstrate that early carcinomas arise within a single aneuploid population (212). An abnormal DNA pattern in a small biopsy may change a diagnosis from indefinite for dysplasia to frank dysplasia, or may prompt rebiopsy.

P.116

p53 immunoreactivity may help diagnose areas of dysplasia since its overexpression increases as dysplasia progresses toward invasive cancer. Patches of strongly positive cells occur in 9% of low-grade dysplasia, 55% of high-grade dysplasia, and 87% of adenocarcinomas (214). The nonneoplastic mucosa may only show an isolated positive cell. p53 immunoreactivity may predict progression from low- to high-grade dysplasia (215).

Recently, it has been suggested that α-Methylacyl-CoA racemase (AMACR), which is overexpressed in a number of cancers, has a high sensitivity in its ability to detect areas of dysplasia, especially high-grade dysplasia (216). It is not yet clear how useful this marker will be in discriminating between reactive lesions and those that are truly dysplastic.

Distinguishing High-grade Dysplasia from Invasive Cancer

It can be difficult to distinguish an invasive cancer from dysplasia in small biopsies. The complex glandular arrangement that characterizes either low-grade or high-grade dysplasia may resemble that seen in invasive cancer. If BE becomes ulcerated, individual glands may drop into the ulcerated areas and mingle with the reduplicated muscularis mucosae, making it difficult to determine whether or not invasion has occurred. The presence of a mass in the esophagus is suggestive of an underlying carcinoma, even if none is demonstrated histologically.

Surveillance and Management of Patients with Barrett Esophagus

The object of surveillance programs is to identify adenocarcinomas at an early stage. BE-associated cancers of patients in surveillance programs are diagnosed at an earlier stage and have a better prognosis than cancers found because they are asymptomatic. In one study the stage of surveillance cases versus symptomatic cases was as follows: stage 0 or I: 76% versus 15%; stage II: 17% versus 35%; stage II or IV: 6% versus 50% (p <0.001). The 3-year survival of surveillance cases was 80% versus 31% of symptomatic cases (p = 0.008) (217), confirming similar findings in other studies (218). Therefore, it is now generally agreed that surveillance of BE patients helps detect adenocarcinomas at an early stage. The surveillance protocol recommended by the American Gastroenterological Association (AGA) (219) is as follows:

- A program of regular endoscopic surveillance for dysplasia and early carcinoma is recommended for patients with BE unless contraindicated by a comorbidity.
- Random biopsies should be taken from the involved segment of the esophagus with four sites sampled every 1 to 2 cm, with additional biopsies from endoscopically detectable lesions.
- Patients without dysplasia or identifiable lesions on their initial evaluation should be re-examined again in 1 year to decrease the chance of sampling errors. If the second set of surveillance biopsies shows no evidence of dysplasia, the patient should be re-evaluated in 5 years.
- If high-grade dysplasia is detected, treatment with either surgical resection or endoscopic mucosal resection is recommended.
- Patients with multiple foci of high-grade dysplasia should undergo surgical resection of all of the esophagus that is lined by columnar epithelium. Surveillance may be offered to such patients if they are willing to undergo endoscopy every 3 months with at least eight random biopsies taken every 2 cm.
- Surveillance should only be practiced if the patient is anticipated to have a reasonable life expectancy and can tolerate treatment for high-grade dysplasia or invasive cancer.

The recommendations of the American Society of Gastrointestinal Endoscopy (220) differ from these in the following respects:

- For BE patients with no dysplasia in the first two examinations, follow-up examinations are recommended at 3-year, rather than 5-year, intervals.
- Patients with low-grade dysplasia should be followed at 12-month intervals as long as dysplasia persists.
- When the degree of dysplasia is indefinite and there is evidence of acute inflammation, repeat biopsy should be performed after 8 weeks of acid-suppression therapy.

Various endoscopic ablative modalities are utilized to treat dysplasia in the setting of BE. These include photodynamic therapy, argon plasma coagulation, Nd-YAG laser, multipolar electrocoagulation, and EMR. In addition, other modalities such as cryotherapy and radiofrequency ablation are also currently in clinical trials (203). All of these methodologies, except for EMR, basically destroy the lesion without yielding a pathologic sample to evaluate the completeness of the ablative technique.

Invasive Adenocarcinoma at the Gastroesophageal Junction

The symptoms of patients with GEJ cancer typically relate to those caused by the underlying GERD. The dysphagia becomes progressive as tumors develop. Patients with advanced disease develop weight loss, bleeding, fatigue, chest pain, and vomiting. Most tumors arise distally and extend into the stomach at the GEJ. The cancer may arise anywhere within BE, although early Barrett carcinomas are often contiguous with both the specialized BE mucosa and the squamous epithelium (Fig. 3.32), suggesting that the mucosa at the squamocolumnar border is most vulnerable to cancer development. The majority of GEJ cancers are found at an advanced stage unless patients are in a surveillance program. Advanced lesions may be flat, ulcerated.

P.117
polypoid, or fungating. A diffusely infiltrative form resembling linitis plastica may also be present. Tumors vary in size, measuring up to 10 cm in greatest diameter.
FIG. 3.32. Papillary esophageal adenocarcinoma. A: Exophytic papillary tumor at the gastroesophageal junction. The squamous mucosa is recognized by the pearly-white mucosal surface. B: Higher power shows numerous papillary fronds. C: A large fungating lesion occupies almost the entire circumference of the esophagus. The patient has a relatively short amount of Barrett esophagus, which appears beefy red and lies above the termination of the gastric folds. This lesion is difficult to see but is more easily appreciated by palpation of the specimen. D: Flat ulcerating lesion lies near the junction of the normal squamous epithelium with the Barrett epithelium. It is present on a large field of Barrett esophagus.

Histologically, cancers arising in the setting of BE and those arising in the gastric cardia are virtually identical in terms of growth pattern (expansile or infiltrative), degree of differentiation, and extent of spread at the time of surgery. As in the stomach, the cancers may be either intestinal or diffuse in type. In the former, a tubular (Fig. 3.33), papillary (Fig. 3.34), or colloid microscopic pattern prevails. Well-differentiated intestinal-type carcinomas often mimic intraepithelial neoplasia on their surface and the diagnosis is determined by examining the base of the lesion. Poorly differentiated tumors often grow as solid sheets of cells without obvious glandular differentiation (Fig. 3.34). Diffuse cancers that produce a linitis plastica growth pattern infiltrate the esophageal wall and cause luminal stenosis (221). Signet ring cells predominate in diffuse cancers and associate with a desmoplastic stroma. Occasional tumors show a mixed intestinal and diffuse histology.

In contrast to carcinomas occurring in the gastric cardia, adenocarcinomas arising in BE may be multifocal and pleomorphic and may be accompanied by dysplasia in the contiguous BE (222). The surrounding epithelium may show a spectrum of premalignant epithelial changes ranging from hyperplasia, regeneration, and dysplasia of varying degrees, including adenocarcinoma in situ. Some tumors show extensive mucin production and occasional cases contain areas of squamous or endocrine differentiation. Squamous cell carcinomas may arise in BE, either alone or separate from the adenocarcinoma. These arise from residual squamous islands in the BE or from squamous epithelium immediately proximal to the squamocolumnar junction (223). Some tumors are so well differentiated that they are only recognized as carcinomas by their submucosal invasion. GEJ cancers may produce various hormones including gastrin, bombesin, substance P, somatostatin, and serotonin; somatostatin and serotonin are the most commonly detected (224).

FIG. 3.33. Well-differentiated adenocarcinoma. A: The surface epithelium has become villous in architecture. A well-differentiated carcinoma drops off the bottom of the mucosa. Some glands are so well differentiated that making a cancer diagnosis would be difficult except for the obvious invasion into the esophageal wall. B: Extension of well-differentiated adenocarcinoma under the acanthotic hyperplastic squamous epithelium above it. C: Higher magnification of the well-differentiated areas shown in A. Note that desmoplasia surrounds individual glands. D: Higher magnification of another focus of the invasive carcinoma with more glandular crowding, cytologic atypia, and loss of polarity.

The tumors may arise underneath the squamous epithelium (Fig. 3.35) in patients who have been previously treated with various endoscopic ablative techniques. These tumors may not be grossly visible on the mucosal surface, since the squamous epithelium may be intact. They may be suspected by seeing or palpating a submucosal mass.

If ulceration occurs, exuberant granulation tissue containing prominent endothelial or mesenchymal cells may simulate an invasive cancer. Cytokeratin stains used to distinguish between invasive cells and mesenchymal cells can be misleading, since mesenchymal cells occasionally stain with these antibodies. Repeat esophageal biopsies after healing of the ulcer may show resolution of reactive atypia.

The histologic appearance of a GEJ cancer may be altered if the patient was treated prior to resection. Neoadjuvant chemoradiation may completely destroy a GEJ cancer leaving only a dense acellular stroma, or it may have little impact on its histologic appearance. The presence of small islands of very bizarre tumor cells embedded in a dense stoma is a commonly encountered neoadjuvant effect (Fig. 3.36). Acellular mucous lakes in regional lymph nodes may mark the sites of no longer viable metastases from a mucoid carcinoma (Fig. 3.36). If the acellular lakes fail to contain viable cells, after examination at several levels the tumors are staged as ypN0.
Chapter 3

FIG. 3.35. Adenocarcinoma arising beneath the squamous epithelium.

Cytologic preparations may be useful in identifying the neoplastic changes associated with BE. Cells derived from esophageal adenocarcinomas usually form groups and clusters (Fig. 3.37) and are recognizable if the primary tumor appears well differentiated and sheds papillary fragments. Less well-differentiated adenocarcinomas exfoliate cells that may be indistinguishable from poorly differentiated squamous cell carcinomas. Malignant cells from adenocarcinoma in situ of the esophagus do not differ morphologically from those of invasive adenocarcinoma. However, cytology has the advantage of obtaining diagnostic material safely from regions difficult to sample.

BE-associated adenocarcinomas may also contain areas of yolk sac and trophoblastic differentiation (225,226). These rare tumors appear as large, bulging, hemorrhagic, and necrotic masses (225). Choriocarcinomas usually contain both cytotrophoblasts and syncytiotrophoblasts. Areas of yolk sac differentiation exhibit glandular and papillary structures lined by columnar epithelium. Mucin is absent in these areas but diastase-resistant periodic acid–Schiff (PAS)-positive cytoplasmic globules are present. Choriocarcinomatous areas produce both human placental lactogen and human chorionic gonadotropin (hCG). Areas of yolk sac differentiation produce α-fetoprotein. hCG production by carcinomas is not limited to choriocarcinomas. hCG production also occurs in squamous cell carcinomas, usually in the most infiltrative areas of the tumors where poorly differentiated and pleomorphic cells predominate.

Adenocarcinomas extensively infiltrate the esophageal wall and often show perineural invasion (Fig. 3.38), lymphatic (Fig. 3.39) and vascular invasion, and direct extension through the esophageal wall. Lymph node metastases are present in 51% to 74% of cases (227). The frequency of nodal metastasis correlates with the depth of tumor invasion. A study of 90 early cancers found no metastases among 36 mucosal tumors, 3 of 29 cancers that involved the muscularis mucosae or superficial submucosa (10%), and 9 of 25 cases that penetrated to the deep submucosa (36%; p < 0.001) (228). In another study, nodal metastases were present in 67% of intramural and 89% of transmural carcinomas (229). The paracardiac lymph nodes have the highest frequency of metastases (40%), followed by nodes along the lesser curvature of the stomach (29%), and splenic/pancreatic nodes in 11%. Intrathoracic nodes are involved in only 7% of cases (230). Metastases to distant sites, such as the celiac axis or upper mediastinum, almost exclusively affect patients with multiple positive regional nodes. Skipping of regional node occurs in <5% of cases (231).

Recurrences affect cervical (7.9%), mediastinal (21%), and abdominal lymph nodes (24%). Nodal recurrences develop at sites outside the resection margins in 60% of cases. The prognosis of patients with lymphatic metastases is enhanced if fewer than four nodes are involved (231). When a similar number of nodes show metastatic disease, patients with metastases limited to nodes within 3 cm of the primary cancer fare better than those with more distant nodal involvement (232).

The prognosis of BE-associated cancer correlates with tumor stage, the degree of differentiation, and the status of the lymphatics and other vascular structures. GEJ cancers are staged by the same systems used for esophageal SCC (Table 3.2). The deeper the penetration, the worse the prognosis is (229,233). The higher the tumor stage, the lower the survival rate is. The 3-year survival rates for stages 0, I, IIA, IIB, III, and IV tumors in one study were 100%, 85.7%, 53.6%, 45%, 25.2%, and 0%, respectively. The overall 5-year survival rate was 23.5% (171). Early cancers offer the best chance of cure. For example, the 5-year survival rates of patients with invasive tumors limited to the submucosa may be as high as 63% (234).

Patients under 55 years of age have a slightly poorer prognosis than the following 10-year cohort. After that, age shows an inverse relationship with survival (233). Other factors that unfavorably affect survival include the presence of vascular or perineural invasion and an infiltrative growth pattern. The chance of survival is enhanced if there is a Crohn-like lymphoid response and/or an intense peritumoral lymphoid...
response (233). Lymphatic invasion relates to poor prognosis of GEJ cancers and shows statistically different subsite variations in frequency (235). Cancers limited to the esophagus are less likely to show lymphatic invasion than are cancers that also involve the cardia and proximal stomach.

**FIG. 3.36.** Adenocarcinoma of the gastroesophageal junction treated with neoadjuvant chemoradiation. *A:* A small focus of invasive carcinoma remains. It and the overlying squamous epithelium show the effects of the chemoradiation. *B:* Higher magnification discloses the presence of isolated bizarre cells in a desmoplastic stroma. *C:* Higher magnification of the glandular areas. *D:* Acellular mucinous lake in a regional lymph node.

There are now many immunohistochemical procedures that help pathologists identify the phenotype of a GEJ tumor and assess its prognosis. Many genes are altered in GEJ cancer (Table 3.9; Fig. 3.40). The literature on this subject is vast and expanding. A short, and necessarily incomplete, review of the subject follows.

A diagnosis of BE or BE-associated cancer requires identification of intestinal metaplasia in the affected tissue. Several markers fill this need, including two brush-border proteins: villin (236) and sucrase-isomaltase (SI) (237). Poorly differentiated cancers arising in BE are more likely to retain villin expression than SI (237). Cdx2, a homeobox gene regulating intestine-specific gene transcription, is uniformly expressed in the BE nuclei (238,239). As with villin and SI, progression to dysplasia and undifferentiated cancer is characterized by cases that express this marker in the contiguous epithelium, suggesting that Cdx2 transcription is an early step in the generation of metaplasia. Cytokeratin 7/20 and mucin core protein (MUC) have been proposed as markers to distinguish between cancers arising in the distal esophagus from those arising in the proximal stomach, but they yield inconsistent results among different investigators (240,241). Invasive GEJ adenocarcinomas that express EGFR are more likely to be poorly differentiated and show more rapid progression than EGFR-negative cancers (242,243). Increasing cyclooxygenase (COX)-2 expression is a feature of BE progression to dysplasia and carcinoma (244,245). It significantly correlates with local recurrence ($p = 0.05$) and distant metastases ($p = 0.02$) (246).

The response is unrelated to the expression of the protein in the tumor and does not associate with EGFR mutations (249).
FIG. 3.37. Recurrence of esophageal adenocarcinoma at the esophagogastric anastomosis. A: Cancer cells with large nuclei and eccentrically placed granular cytoplasm. Mitoses are evident. B: Group of cancer cells with granular cytoplasm and uniform nuclei. C: Same case stained with May-Grünwald-Giemsa.

FIG. 3.38. Perineural invasion by a gastroesophageal junction adenocarcinoma.

**Proximal Adenocarcinoma of the Esophagus**

Developmental anomalies may be the sites of a small minority of adenocarcinomas in the proximal esophagus. The heterotopic gastric epithelium present in an inlet patch (see Chapter 2) may undergo metaplastic changes and may develop areas of dysplasia or invasive carcinoma (250,251). Adenocarcinoma can also arise in tracheobronchial rests in the upper esophagus (252).
FIG. 3.39. Extension of carcinoma arising in a Barrett esophagus into the lymphatics (arrows).

Tumors Arising from Submucosal Glands

Submucosal Adenomas

Submucosal adenomas arise from the ducts of submucosal glands independent of BE (253). They present as an esophageal polyp and are often covered by an intact squamous epithelial mucosa. The adenomas have a globoid shape and measure about 1 cm in diameter. Histologically, they retain the lobular architecture of submucosal glands but the acini appear hyperplastic and they may become cystic. Such lesions are sometimes termed serous cystadenomas.
because of their resemblance to pancreatic lesions. Histologically, they may show mild atypia (254).

### Adenoid Cystic Carcinoma

Adenoid cystic carcinomas are rare esophageal neoplasms that resemble similar tumors that develop in salivary glands. However, they are more aggressive than their salivary counterparts. Less than 50 cases have been reported (255, 256, 257, 258). The tumors are more common in women than men. Progressive dysphagia and obstruction are common presenting symptoms and are typically present for 2 weeks to 6 months. The tumors have a high rate of distant metastases at the time of diagnosis, and the median survival is only 9 months following diagnosis. However, exceptions exist in which long-term survival has been reported. Such patients present early when the tumor is small and more localized. Additionally, such tumors tend to be better-differentiated lesions.

Most commonly, adenoid cystic carcinomas arise in the middle third of the esophagus (63%), less often in the lower third (30%), and rarely in the upper third (7%). They are typically fungating or polypoid lesions, although ulcerative and infiltrative growth patterns are sometimes seen. The histology of adenoid cystic carcinoma resembles that of analogous salivary tumors. They contain two cell types: Duct-lining epithelial cells and myoepithelial cells (257, 258). The tumor has expansile or infiltrating margins. The tumors are subclassified based on their histologic pattern into tubular, cribriform, solid, or basaloid variants (Fig. 3.41). The tubular pattern is characterized by ductlike structures or large cellular masses dispersed around microcystic spaces with a lacelike pattern. This pattern is more common than the cribriform pattern usually found in salivary gland lesions. The microcystic spaces are not true glandular lumina, but rather they consist of replicated, eosinophilic, PAS-positive, diastase-resistant basement membrane material. One may see coexisting squamous cell carcinoma in situ in the overlying epithelium. The esophageal tumors tend to show more cellular pleomorphism and a higher mitotic index than those arising in salivary glands.

### Mucoepidermoid Carcinoma

This uncommon esophageal cancer consists of a diffuse mixture of squamous and mucin-secreting cells (259) and most commonly arises in the middle and upper two thirds of the esophagus. Less than 100 cases of this type had been reported through 2000. These aggressive cancers uniformly express CEA. The infrequency of this cancer limits comparative studies of its prognosis, but published reports suggest that its prognosis is similar to SCC with 1-, 2-, and 5-year survival rates of 46%, 39%, and 0%, respectively (260). Mucoepidermoid carcinomas are usually well-differentiated tumors and should not be confused with adenocarcinomas with squamous metaplasia (adenoacanthomas). A second diagnostic difficulty results from the inability to classify the tumor correctly on the basis of a small unrepresentative biopsy. Because the esophageal tumor is so commonly solid or basaloid, a small biopsy may suggest the diagnosis of a small cell carcinoma or undifferentiated carcinoma unless the more cribriform or tubular areas are also present.

### Adenosquamous Carcinoma

Adenosquamous carcinomas are rare and the differential diagnosis includes mucoepidermoid carcinoma. Adenosquamous cancers may arise in esophageal submucosal glands or ducts, and in some cases, one can identify ductal epithelial origin. They may also arise as a result of multipotential cellular differentiation in BE. The tumor contains a mixture of adenocarcinoma and squamous cell carcinoma. Mucin stains show the histochemical profile of esophageal glands when they arise from these structures (261). These tumors are highly malignant, especially when poorly differentiated, and they can spread in a pagetoid fashion. They behave more aggressively than mucoepidermoid carcinomas, warranting a distinction between them (262). Several characteristics separate these two tumor types: (a) adenosquamous carcinoma tends to spread throughout the mucosal surface; (b) prominent separate foci of squamous cell carcinoma, often containing focal mucin production, occur in adenosquamous carcinomas (Fig. 3.43); (c) keratinization, a characteristic feature of adenosquamous carcinoma, is rarely present in mucoepidermoid carcinomas; (d) invasive and metastasizing glandular formations with abundant mucin production occur in adenosquamous carcinoma, although mucin production is not a requirement for the diagnosis of adenosquamous carcinoma in the presence of well-formed glands; and (e) severe nuclear pleomorphism characterizes adenosquamous carcinomas.
FIG. 3.42. Mucoepidermoid carcinoma. A: Nests of malignant cells with glandular and squamous differentiation. Pearl formations and intraluminal mucinous material are shown. Kreyberg stain. B: Intramural spread by two nests, one composed of squamous cells and the other having glandular features.

Paget Disease

Pagetoid spread accompanies squamous cell carcinoma, adenocarcinomas arising in Barrett esophagus (Fig. 3.44), adenosquamous carcinoma, or, more rarely, proximal spread of a gastric cancer. The pagetoid cell nests can extend away from the main tumor for considerable distances and may even involve the ducts of submucosal glands. Grossly, the lesions may appear as mucosal irregularities. Alternatively, Paget disease may arise as an intraepithelial neoplasm of the ducts of the submucosal glands. The cells grow singly or in clusters in the lower part of the epithelium and, unlike malignant melanoma, single cells usually do not appear in the upper mucosa. The tumor cells may contain mucin- or CEA-positive material if the primary tumor contains glandular or mucinous differentiation. The tumor cells may attach to neighboring keratinocytes by short, poorly formed desmosomes. Detection of Paget disease in a specimen indicates that an invasive carcinoma is likely to be present in the nearby mucosa.

FIG. 3.43. Adenosquamous carcinoma. Foci of well-differentiated squamous metaplasia in an adenocarcinoma.

Malignant Melanoma

Esophageal malignant melanomas represent 0.1% to 0.5% of primary malignant esophageal neoplasms (263,264), and approximately 0.5% of malignant melanomas originate in the esophagus (265). Cutaneous malignant melanomas metastatic to the esophagus are more common than primary esophageal malignant melanomas (266). Slightly more males are affected than females (267). Mean patient age is 60 years with a wide age range from 7 to over 80 years (268). The disease almost exclusively affects whites. Patients with esophageal melanoma usually complain of dysphagia and weight loss. Primary esophageal melanomas are most common in the lower and middle thoracic segments; mean tumor diameter is 7 cm (267). They usually appear as a polypoid intraluminal mass in a dilated esophageal segment. The tumors often appear gray or black in color. Satellite nodules are relatively uncommon. Esophageal malignant melanomas resemble their cutaneous counterparts. The tumor cells vary in size and shape, both from neoplasm to neoplasm and within a given tumor. The tumor contains a mixture of variably pigmented epithelioid, spindle-shaped, and bizarre cells (Fig. 3.45) (267). Spindle cells arranged in fascicles may impart a sarcomalike pattern to the tumor. Occasional tumors show marked pleomorphism with numerous bizarre cellular forms. Small cell, signet ring cell, and balloon cell features may also be present. The inflammatory host response is usually mild. A peripheral in situ lentiginous growth pattern often surrounds the main lesion. It is important to distinguish between primary and metastatic melanoma. Melanosis
(Fig. 3.46), a nesting growth pattern and junctional change in the contiguous squamous mucosa, suggests the diagnosis, but absence of these changes does not exclude a primary esophageal malignant melanoma (269). If the tumor has overgrown these premalignant features, it may be extremely difficult to establish the fact that the tumor represents a primary esophageal neoplasm, even if a careful examination has been made of the skin, other mucosal membranes, and the eyes.

FIG. 3.44. Pagetoid spread. A: Intramucosal extension of an adenocarcinoma into the surrounding squamous epithelium. Tumor is also present in the underlying submucosa. B: Periodic acid–Schiff (PAS) stain of a biopsy showing the presence of atypical cells that are PAS positive within the upper layers of the squamous epithelium.

When contemplating the diagnosis of malignant melanoma, several antibodies are useful in confirming the diagnosis. These include melan-A, HMB45, and S100. Melan-A is specific for melanocytic lesions and is more sensitive than HMB45, but it has less value than S100 in detecting spindle cell and desmoplastic melanomas (270). Prognosis is extremely poor and not much different from that of esophageal squamous cell carcinoma. The prognosis is worse than that seen in cutaneous melanoma perhaps due to the rich esophageal vascular and lymphatic supply. Esophageal melanomas are usually treated by esophagectomy and excision of any identifiable paraesophageal lymph nodes or regional metastases. Melanomas are radioresistant. Unfortunately, these distinctly uncommon neoplasms tend to present as advanced tumors with aggressive biologic behavior and a dismal prognosis. Survival after surgery averages about 8 months. The best survival rates appear to be those following radical surgical resection with 5-year survivals of 4.2%.

Other Primary Tumors

Primary malignant nonepithelial esophageal tumors constitute only 0.4% to 0.99% of esophageal tumors. These include mesenchymal tumors as described in Chapter 19 and hematologic tumors as described in Chapter 18.

Collision Tumors

Collision tumors occur when two tumors that have arisen independently lie adjacent to one another. One makes the diagnosis of a collision tumor when the component tumors are phenotypically different and there is clear separation of the two components. If both tumor types metastasize, the two types of growth also remain clearly separated in the metastasis. At the early stage of their evolution, the two components may appear as separate dual noncolliding carcinomas. With further growth, the tumors may become more intimately admixed with one another. Collisions occur between squamous cell carcinomas and/or adenocarcinomas, and with sarcomas, lymphomas, melanomas, or metastases (271,272). However, the simultaneous occurrence of mesenchymal and epithelial tumors in the esophagus is quite rare.

Spagnolo and Heenan proposed the following guidelines for diagnosing collision tumors: (a) two distinct topographically separate sites of origin for the two components must be present (e.g., squamous cell carcinoma arising from esophageal squamous epithelium and adenocarcinomas arising from the gastric mucosa), (b) there must be at least some separation of the two components so that despite intimate mixing at points of juxtaposition, the dual origin can be recognized, and (c) at the areas of the collision, in addition to intimate mixing of the two components, some transitional patterns may be seen such as a mucoepidermoid appearance as in the case of collisions between squamous carcinomas and adenocarcinomas (272).

Costa (273) proposed three possible explanations for collision tumors: A carcinogen could theoretically interact with two neighboring histologically distinct tissues causing tumors to arise in them both. This would be more likely to occur in patients suffering from inherited predispositions to tumors or from exposures to some agent that causes cancer in several tissue types. A second possibility would result from the phenomenon known as horizontal recruitment, which describes those tumors composed of host cells that are induced to become malignant adjacent to a pre-existing tumor. A third possibility is that the growth of one tumor creates circumstances that directly or indirectly favor the genesis of the second lesion. In addition, one lesion may represent a primary lesion and the second a metastasis.

Secondary Malignant Tumors

Secondary carcinomas involve the esophagus, either by direct extension or by metastasis. Carcinomas originating in the lungs, pharynx, larynx, thyroid, or stomach may extend directly into the esophagus. Breast, kidney, testes, prostate, and pancreas tumors can all metastasize to the esophagus. Breast carcinoma, in particular, may be responsible for strictures (274) or concentric stenosis of the esophageal wall with an intact mucosa, due to the permeation of submucosal lymphatic vessels showing the typical picture of the so-called carcinomatous lymphangitis. Metastatic breast cancer can also present as achalasia. Melanoma metastasizes to the gastrointestinal tract in 43.5% of patients (248).
FIG. 3.46. Melanosis of the esophagus in an area adjacent to a malignant melanoma. The underlying submucosa also contains a malignant melanoma of the small cell type.

Tumorlike Conditions

There are a number of esophageal conditions that create variably sized masses that may clinically or endoscopically mimic neoplasms (Table 3.11). These are discussed in Chapter 2.

Handling Esophageal Resection Specimens

Esophagectomy specimens should be opened longitudinally. The prosector should describe all lesions, including tumors, ulcers, or areas of Barrett esophagus or other discolorations. The distance of a tumor from the proximal, distal, and radial margins should be measured. The depth of invasion should be estimated and extension beyond the esophagus should be documented, if present. A comment should be made as to whether or not the nodes appear to be grossly involved. It is a common practice to remove a fresh piece of tumor and normal mucosa for future research if this does not interfere with the pathology assessment. This should be in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. If there is an interest in studying SCCs and their precursor lesions, the esophageal mucosa may be sprayed with a Lugol iodine solution or dipped in a Lugol solution so as to highlight areas of mucosal abnormality. This approach may allow one to detect small lesions that remain unstained by the Lugol iodine and that may represent areas of dysplasia or multicentric carcinomas. On completion of the gross examination the esophagus should be pinned out flat on a cork board and floated upside down in 10% formalin, and fixed overnight.

| TABLE 3.11 Tumorlike Conditions of the Esophagus |
Inflammatory fibroid polyps
Granuloma pyogenicum
Cysts/duplications
Pseudoepitheliomatous hyperplasia
Pancreatic metaplasia
Congenital rests producing masses
Heterotopic tissues (pancreatic, gastric, sebaceous, thyroid)

Once the resection specimen is handled for sectioning, attention should be given to documenting the size, appearance, and anatomic relationship of any lesions that are present. Blocks should be obtained to evaluate the nature and extent of those lesions. The gross evaluation should include measurements of tumor size, since this measurement helps determine prognosis. Specimen palpation helps delineate full tumor extent. The status of the resection margins, including the soft tissue (especially the submucosa) as well as proximal and distal margins must be established. Painting the margins with India ink can be useful in making these determinations. Lymph nodes should be carefully sought in the adipose tissue adjacent to the esophagus and cardia, and the distance of harvested nodes from the tumor should be identified. It is important that when sections are submitted, the origins of each section be noted in the gross description.

When dealing with squamous cell lesions, it is important to document the presence of multiple lesions, including areas of coassociated carcinoma in situ. The margins should be examined not only for the presence of invasive disease, but also for the presence of intramucosal disease or evidence of pagetoid spread.

With respect to adenocarcinomas, one should describe the extent of the tumor. If the Barrett epithelium is present in the resection margin, this should also be documented, since it is subject to the risk of subsequent development of carcinoma.

If the patient has been treated with preoperative radiation and/or chemotherapy, the presence of residual cancer may not be obvious and one may need to block an entire suspicious area in order to find remnants of tumor.

EMR specimens require special handling in order to determine whether the resection margins are microscopically complete. Intact specimens should be stretched and pinned to a block. Deep and lateral margins should be marked with India ink. The specimen should be sectioned longitudinally at 2-mm intervals after fixation for 24 hours in formaldehyde. Piecemeal resections should be handled in a similar way, although it is generally not possible to pin out the individual tissue pieces. A resection may be classified as being complete for neoplasia if the deep and lateral margins are negative, and complete for BE if the margins are composed of nonmetaplastic mucosa.

References

P.130

Chapter 3


162. Fuchte U, Steinborn E, Alem V, et al: Immunoreactivity of cytokines (CK7, CK29) and mucin peptide care antigens (MUC1, MUC2, MUC5AC) in adenocarcinomas, normal, and metaplastic tissues of the distal esophagus,
Chapter 3


Histopathology


Int J Surg Pathol


Chapter 4
The Nonneoplastic Stomach

Embryology

The stomach develops from a fusiform foregut swelling at approximately 4 weeks' gestation. It originates in the neck and descends into the abdomen during the next 8 weeks. The enlarging thoracic contents push the stomach caudally. The gastric curvature develops during the 6th to 7th fetal week. Simultaneously, the dorsal stomach rotates to the left. In the ninth week, a diverticulum appears in the upper stomach, which subsequently merges with and lengthens the greater curvature. The stomach rotates 90 degrees so that the greater curvature lies on the left, and the distal end becomes anchored by a short ventral mesentery, the bile duct, and the vitelline artery (1).

Gastric development is more complex than other parts of the gut due to the different epithelial types that populate different areas of the stomach. These areas constitute a complex epithelial system organized in a highly structured, continually renewing architecture. Embryonal differentiation is regulated via several signaling cascades, an important one of which starts with the transcription factor Sonic hedgehog (Shh), which binds to its receptor Patched (Ptc). The Shh signaling system helps maintain normal gastric glandular architecture (2). Shh is expressed in parietal cells and its receptor Ptc is present in chief cells (3).

The stomach is initially lined by stratified or pseudostratified epithelium; later, cuboidal cells replace it. As secretions accumulate, droplets and vacuoles coalesce to form the gastric lumen. The first differentiated cell type to appear is the mucous neck cell, which acts as a progenitor for the other cell types. Gastric pits are well developed by 5 to 7 weeks. Gastric glands begin to develop at 11 to 14 weeks (1); they grow by progressively branching, a process that continues until birth. Parietal cells appear by 9 to 11 weeks (Fig. 4.1). Endocrine cells begin to appear at the second week of fetal life; a full spectrum of endocrine cells is present by week 11. Mesoderm surrounding the stomach differentiates into the gastric connective tissue and the muscularis propria by the end of the second fetal month. The muscularis mucosae forms by the 20th week.

Gastric Physiology

The stomach exhibits major motor, secretory, digestive, hormonal, and mucosal barrier functions, some of which will be briefly summarized here.

**Mucosal Barrier**

One of the incredible facets of gastric physiology is that the acid-containing stomach is able to withstand the detrimental effects of its intraluminal contents. In order to do this, a complex mucosal cytoprotection system has evolved that protects the stomach without inhibiting gastric acid secretion. Mucosal defenses include pre-epithelial, epithelial, and postepithelial mechanisms (Fig. 4.2). Adherent mucus provides a stable unstirred layer that supports surface neutralization of acid by mucosal bicarbonate and acts as a permeability barrier to luminal pepsin (4). (Surface mucus is hydrophobic and water repellent.) Surface-active phospholipids are produced by mucous neck cells and parietal cells. Parietal cells pump one HCO3- ion across the basal membranes for every H+ they secrete into the canaliculi (5). HCO3- is picked up by mucosal capillaries and carried to the basal part of surface foveolar cells. The bicarbonate ions are then secreted into the overlying mucous layer, where they are trapped by glycoproteins in the mucus, increasing the pH in the unstirred layer from approximately pH 2.0 in the gastric lumen to approximately 7.0 at the mucosal surface. This creates a pH gradient that traps and neutralizes most hydrogen ions as they enter the unstirred mucous layer (6). Maintenance of the pH gradient depends on both the secretion rate of bicarbonate and the thickness of the mucous gel layer (6). Mucus also lubricates the stomach facilitating food movement along the gastric lining, without causing mucosal abrasions. Its glycoproteins play a major role in resistance to injury by maintaining the viscoelastic and permeability properties of the mucous gel. Foveolar cells secrete lipid into the mucus that coats the epithelium lining the gastric lumen with a nonwettatable surface, protecting the mucosa against the action of water-soluble H+ and pepsin (7). (Pepsin can destroy the polymeric structure of this glycoprotein layer, solubilizing the surface...
mucous gel and liberating degraded glycoprotein subunits into the gastric lumen.)

An adequate mucosal blood flow is critical to maintaining the mucosal barrier since it brings oxygen and nutrients to the luminal surface and removes hydrogen ions from the same region (8). The autonomic nervous system, peptidergic nerves (8), nitric oxide (9), prostaglandins (10), epidermal growth factor (EGF), and transforming growth factor-alpha (TGF-α) all regulate mucosal blood flow. Interruption of the mucosal blood flow (as occurs in stress gastritis) results in decreased intramucosal pH and ulceration. Junctional complexes, basolateral membranes, and the basal lamina are also major structural components of the gastric mucosal barrier (11). Cytoprotectants (prostaglandins, immunoglobulins, sulfhydryl donors such as glutathione, and neuropeptides) are also naturally present in the gastric mucosa (10,12). Prostaglandins aid in mucosal protection (10) by mediating mucus and bicarbonate secretion, inhibiting acid secretion, regulating mucosal blood flow, maintaining surface-active phospholipids, and mediating the protective actions of EGF and TGF-α (13). Prostaglandins also modulate the inflammatory response by inhibiting release of tumor necrosis factor (TNF) from macrophages (14) and TNF plus other inflammatory mediators from mast cells (15).

**FIG. 4.1.** Gastric mucosa of a 10-week-old fetus. *A:* Medium power showing the presence of a well-defined lumen lined by columnar epithelial cells with primitive glands. The muscularis mucosae is just beginning to form. *B:* Higher magnification showing the presence of parietal cells (*arrows*).
FIG. 4.2. Mucosal defenses. A mucous layer that contains a pH gradient overlies the surface epithelium. Bicarbonate ions are pumped into this layer along with lipids secreted by the lining epithelium. The epithelium is bound together by intercellular tight junctions. The epithelial cells lie on intact basement membrane and produce the epidermal growth factor (EGF) and transforming growth factor-α (TGF-α). The underlying blood supply in the lamina propria brings bicarbonate to the surface-lining cells from the parietal cells where it was produced. The mucosal blood flow also brings oxygen and nutrients. Prostaglandins (PGs) are made within the stroma. The stroma contains antioxidants such as glutathione. Pep, pepsin.
Chapter 4

FIG. 4.3. Mucosal renewal. The mucous neck region contains stem cells and is the generative zone. From here, foveolar cells begin to differentiate and migrate toward the surface to be exfoliated. Other cells developing in this area migrate downward to form the epithelium of the oxyntic, cardiac, and antropyloric glands. These glandular cells die by apoptosis.

Another aspect that protects the gastric mucosa is its ability to proliferate and rapidly replace damaged surface epithelial cells. The gastric epithelium maintains a dynamic equilibrium between cell production and cell loss (Figs. 4.3 and 4.4) (16). The surface epithelium is renewed every 4 to 8 days. Gastrointestinal and nongastrointestinal hormones, growth factors, neural
mediators, secretions, luminal food, and absorbed nutrients all modulate gastric mucosal growth (17). EGF, TGF-α and insulinlike growth factor directly stimulate gastric mucosal growth (17,18). EGF is ideally suited to participate in gastric repair because it is acid stable and stimulates epithelial migration, DNA synthesis, and gastric mucus production. TGF-α shares 35% homology with EGF and mimics its mitogenic effects (19). EGF and TGF-α also modulate parietal cell function and inhibit gastric hydrochloric secretion (20).

Cell progenitors reside in the mucous neck region giving rise to multiple cell types. One type migrates toward the luminal surface and differentiates into foveolar cells. Other cell lineages migrate downward from the mucous neck region slowly differentiating into parietal, chief, mucous, and endocrine cells (Fig. 4.3). Mature parietal cells and chief cells do not divide. Parietal, chief, and endocrine cells turn over more slowly than surface cells, renewing themselves every 1 to 3 years.

**Acid and Pepsin Secretion**

Three separate pathways stimulate acid secretion: (a) a neural pathway, which delivers transmitters such as acetylcholine; (b) an endocrine pathway, which delivers hormones such as gastrin; and (c) a paracrine pathway, which delivers tissue factors such as histamine (Fig. 4.5) (21). Potentiating interactions between two or three gastric secretagogues amplify oxyntic secretory responses. Histamine released from lamina propria mast cells and from enterochromaffinlike (ECL) cells binds to H2 receptors on oxyntic cells, resulting in up-regulation of cholinergic and gastrin receptors, making them more sensitive to subsequent stimulation by their respective secretagogues. ACH binds to muscarinic cholinergic receptors on oxyntic cells, stimulating acid secretion. ACH in the antral mucosa inhibits somatostatin production, a peptide that inhibits gastrin release (22).

![FIG. 4.4. Proliferative zone of the gastric mucosa highlighted by Ki-67 immunostain.](image)
G cells are central to parietal cell secretion. The G cell is positively influenced by acetylcholine release and gastrin-releasing peptide from the vagus as well as from cytokines and growth factors in the gastric mucosa. Mucosal neuroendocrine cells also produce gastrin-releasing peptide, positively influencing the G cell. Vagal stimulation releases acetylcholine, negatively influencing D cells, suppressing somatostatin function. Somatostatin negatively regulates G-cell activity, suppressing gastrin production. G cells, once stimulated, act directly on parietal cells through release of gastrin or indirectly through enterochromaffinlike cells that produce histamine. Histamine released from mast cells or neuroendocrine cells positively influence parietal cells to secrete acid. Somatostatin has a negative influence on acid secretion and forms part of the feedback loop in which acid secretion by parietal cells enhances D-cell function.

Antral G cells release gastrin when the antrum becomes alkalinized, stimulating acid secretion via gastrin receptors on parietal cells and histamine release from ECL cells (23). Vagal stimuli also liberate gastrin-releasing peptide, prompting G cells to produce gastrin and stimulating ECL cells to release histamine. Pepsinogens synthesized by gastric chief cells (24) have no digestive capacity until they are broken down into pepsin, a reaction that maximally occurs in an acid environment. The stomach produces two immunologically distinct pepsinogens: Pepsinogen 1 (PG1) and pepsinogen 2 (PG2). PG1 is only present in fundic chief and mucous neck cells, whereas PG2 is produced by chief cells, fundic mucous neck cells, cardiac and pyloric glands, and Brunner glands (25). Serum levels of PG1 and PG2 reflect the volume of the cells that produce them. PG1 levels below 20 mg/dL indicate a profound loss of fundic gland volume, as occurs in autoimmune gastritis.

**Gastric Motor Functions**

In addition to its secretory, digestive, hormonal, and mucosal barrier functions, the stomach has three specific motor functions:
(a) storage and volume adaptation, (b) mixing of gastric contents, and (c) forward propulsion of its contents, or gastric emptying. When empty, the stomach is at its smallest possible size. Filling the stomach with fluid or food increases the gastric luminal volume without increasing gastric pressure. Gastric motility is regulated by the extrinsic nerves and by the intrinsic myenteric plexus, which contains cholinergic nerves, adrenergic nerves, and nonadrenergic, noncholinergic nerves.

**Anatomy**

The stomach lies intraperitoneally, extending from the lower end of the esophagus at the Z line at the level of the 11th thoracic vertebrae, crossing to the right of the midline, and ending in the duodenum. The opening that connects the esophagus to the stomach is known as the *cardiac orifice*; the opening from the stomach to the intestine is known as the *pyloric orifice*. The stomach has two curvatures: The greater curvature, the inferior border of the stomach, is convex in shape, extending from the gastroesophageal junction to the duodenum. It is more freely movable than the lesser curvature. The concave lesser curvature is the upper margin of the stomach. The size and shape of the usually J-shaped stomach (Fig. 4.6) depends on body position and the degree of filling. Its anterior surface abuts the abdominal wall and the inferior surface of the left lobe of the liver. Posteriorly, it abuts the pancreas, splenic vessels, left kidney, and adrenal gland. The lesser curvature is suspended from the inferior aspect of the liver by the hepatogastric ligament and the lesser omentum. The greater omentum extends caudally from the greater curvature. The gastric fundus touches the dome of the left diaphragm and the upper left margin of the greater omentum rests against the spleen to which it is attached by the gastrosplenic ligament.

The stomach has four layers: Mucosa, submucosa, muscularis propria, and serosa (Fig. 4.7). The gastric wall is slightly firm but pliable and, with the exception of the pylorus, usually does not measure more than 0.5 cm in thickness. The stomach is often divided into four anatomic regions: Cardia, fundus, body, and antropyloric region (Fig. 4.8). The cardia, a narrow, ill-defined region, is not grossly distinctive and is identified histologically by the presence of cardiac glands. Its anatomy is discussed in Chapter 2. The fundus is that portion of the gastric body that protrudes over a horizontal line drawn from the esophagogastric junction (Fig. 4.8). It blends into the gastric body, which constitutes most of the stomach. The body is demarcated from the distal portion, called the pyloric antrum, by a notch in the lesser curvature, the incisura angularis. Numerous longitudinal, grayish pink mucosal folds (called rugae) lie parallel to the lesser curvature (Fig. 4.9) and characterize the mucosa of the gastric body.

**FIG. 4.6.** Unopened stomach demonstrating its classic J shape. Esophagus and duodenum is also present.
The triangularly shaped antrum occupies the distal third of the stomach proximal to the pyloric sphincter extending further along the lesser curvature (5 to 8 cm) than along the greater curvature (6 cm), often almost reaching the cardia (26). The antrum is more firmly anchored to the underlying submucosa than the remainder of the stomach. A greatly thickened distal muscular wall forms the pyloric sphincter. A narrow lumen passes through the pyloric sphincter. The pyloric canal, or pyloric channel, measures 2.5 cm in length. The various gastric zones are not fixed anatomic entities; their extent varies between individuals, with age, and with disease processes.

The gastric muscularis propria differs from that of the rest of the gastrointestinal (GI) tract in that it consists of muscle fibers oriented in three different directions: The outer longitudinal, the middle circular, and the inner oblique layer. Only the middle circular layer is complete. It is the strongest of the three muscle layers and it becomes hypertrophic proximally and distally at the sphincters. The pyloric musculature consists of two layers: A thick inner circular layer and a thin outer longitudinal layer. The muscularis mucosae consists of two or three muscle layers.
**FIG. 4.8.** Diagram of the four anatomic and three histologic regions of the stomach. The depths of the gastric pits (red) and the glandular composition are different in the various areas of the stomach. The color of the glands corresponds to the color of the anatomic regions. The histology of the glands differs in the pink, green, and blue areas. The gastric pits are similar (red) throughout the entire stomach.

**FIG. 4.9.** Gastric rugae. When the normal stomach is opened the rugae appear as coarse folds of the mucosa.

The stomach has a rich blood supply that derives from the celiac, hepatic, and splenic arteries. Mucosal capillaries lie beneath the epithelium. The capillary networks drain into subepithelial venules, which converge into submucosal veins. Venous drainage is through the portal system to the liver. Right and left gastric veins drain the lesser curvature. The left gastric vein arises on the anterior and posterior gastric surfaces. Esophageal veins enter before it reaches the portal vein. Venous drainage from the anterior and posterior surfaces of the antropyloric region forms the right gastric vein, which empties directly into the portal vein. The abundant blood supply explains why gastric ischemia is unusual and why gastric hemorrhages are so life threatening. Gastric lymphatic distribution resembles that of the colon. Lymphatics are absent from the superficial mucosa but are present in the deep interglandular region (27). They converge into thicker channels piercing the muscularis mucosae and enter the larger submucosal plexus. From there, they drain into the lymphatic plexus between the inner and outer layers of the muscularis propria (27). The lymphatic distribution generally follows that of the main arteries and veins. Gastric lymphatics drain into numerous lymph nodes situated in chains along the greater and lesser curvatures, the cardia, and the splenic hilum. There are four drainage areas. The largest drainage area comes from the lower esophagus and most of the lesser curvature (Fig. 4.10). It follows the left gastric artery and drains into the left gastric lymph nodes. The pylorus drains to the right gastric and hepatic lymph nodes (Fig. 4.10). Lymphatics from the cardia drain into pericardial lymph nodes surrounding the gastroesophageal junction, and efferent channels from the left gastric lymph nodes drain into the celiac lymph nodes. The proximal greater curvature drains into the pancreaticosplenic lymph nodes in the splenic hilum. The distal greater curvature drains into right gastroepiploic lymph nodes in the greater omentum and to the pyloric lymph nodes at the pancreatic head. The pyloric portion of the lesser curvature drains into the right gastric lymph nodes, which then drain into hepatic nodes located along the course of the common hepatic artery. Efferents from all four lymph node groups ultimately pass to the celiac nodes around the main celiac axis.
The stomach is innervated by sympathetic and parasympathetic components of the autonomic nervous system as well as by the peptidergic neural system. The parasympathetic nerve supply derives from the vagus and its branches. Numerous neuropeptides produced and released from nerve fibers in the stomach wall regulate gastric function (28).

A thin translucent serosa (the visceral peritoneum) invests the outer portion of the stomach. The serosa normally appears pink-tan, smooth, and glistening.

**Normal Gastric Histology**

Histologically, the stomach contains three major epithelial compartments: The gastric pits and surface lining, the mucous neck region, and the glands. The nature and relative thickness of the glands and pits (Fig. 4.8) defines each gastric zone. Foveolar (or surface) epithelium lines the entire gastric surface and short, straight, narrow gastric pits (foveolae) that lie parallel to one another. Gastric glands empty into the bottom of the pits. The stomach is divided into the cardiac, oxyntic, and pyloric areas based on its glandular components. The oxyntic mucosa, which secretes acid and pepsinogen, occupies the proximal 80% of the stomach, including the mucosa of the body and fundus. It is thicker than the cardiac and pyloric mucosa due to the presence of specialized acid-secreting glands. Fundic gastric pits are shorter than elsewhere, occupying only 25% of the mucosal thickness (Fig. 4.8). The antropyloric mucosa constitutes the distal 20% of the stomach and contains mucous-secreting glands and endocrine cells. Cardiac mucosa extends distally from the lower esophagus. Transitional zones between the different areas are gradual and junctional mucosa showing mixed histologic features commonly measures up to 1 cm in width. Each of the gastric epithelial cell types produces a specific cell product (Table 4.1).

<table>
<thead>
<tr>
<th>TABLE 4.1 Gastric Epithelial Cells and Their Products</th>
</tr>
</thead>
</table>

file:///F|/Gastro/Chapter%204%20non-neoplastic%20stomach.htm (11 of 159)2/4/2009 2:05:06 PM
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface cells</td>
<td>Mucin, carbonic anhydrase, TGF-α, EGFR</td>
</tr>
<tr>
<td>Mucous neck cells</td>
<td>Mucin, pepsinogens, weak lipase, TGF-α</td>
</tr>
<tr>
<td>Parietal cells</td>
<td>HCl, intrinsic factor, carbonic anhydrase, TGF-α, cathepsins</td>
</tr>
<tr>
<td>Chief cells</td>
<td>Pepsinogen, carbonic anhydrase, lipase</td>
</tr>
<tr>
<td>Endocrine cells</td>
<td>Numerous hormones (see Chapter 17)</td>
</tr>
<tr>
<td>Cardiac and antral cells</td>
<td>Mucin, proteinases, cathepsins, lysozymes</td>
</tr>
</tbody>
</table>

EGFR, epithelial growth factor receptor; TGF-α, transforming growth factor-α.

**FIG. 4.11.** Mucus-secreting foveolar cells cover the gastric surface and line the upper gastric pits.

**Surface Epithelium (Foveolar Epithelium)**

Tall, columnar, foveolar epithelium covers the entire gastric mucosa. It consists of a single layer of mucus- and bicarbonate-secreting cells with irregular, basally situated nuclei and a single inconspicuous nucleolus (Figs. 4.11 and 4.12). Ovoid, spherical, mucin-containing, membrane-bound granules pack the supranuclear cytoplasm. The mucin stains strongly with the periodic acid–Schiff (PAS) stain (Fig. 4.13); it is negative or only weakly positive with mucicarmine stains. Numerous spot desmosomes and gap junctions maintain intercellular communication between the surface mucous cells, regulate cell differentiation (29), and help maintain mucosal barrier integrity. The surface mucous cells are produced in the mucous neck region, migrate upward, and extrude from the surface.
FIG. 4.12. Lining of the gastric pits. Variably mature foveolar cells populate the pits. The mucinous contents increase in size as the cells progress toward the surface. Foveolar epithelia characteristically have basal nuclei with supranuclear mucin collections.
Gastric Glands

The three types of gastric glands are fundic, cardiac, and pyloric glands. Cardiac and antral glands contain mucin and are compared in Table 4.2. The cardiac mucosa is discussed in detail in Chapter 2. Both cardiac and pyloric glandular cells have ill-defined borders and a bubbly vesicular cytoplasm containing neutral mucin (Figs. 4.14 and 4.15). Unlike foveolar cells, the mucin fills the basal cytoplasm displacing and flattening the nuclei. Pyloric glands contain two major cell types: Tall columnar cells, which secrete neutral mucin, and scattered endocrine cells. Rare parietal and chief cells may also be present. The oxyntic mucosa characteristically contains long, tightly packed oxyntic glands and short foveolae. In contrast to cardiac and pyloric glands, oxyntic glands are straight rather than coiled. Up to three gastric glands empty into the base of a gastric pit. Oxyntic mucosa contains six different cell types: Surface foveolar cells, isthmus mucous cells, parietal cells, mucous neck cells, chief cells, and endocrine cells (Figs. 4.16 and 4.17). The gland neck contains undifferentiated, mucous neck, and parietal cells; the glandular bases contain parietal, chief, and endocrine cells.

<p>| Table 4.2 Comparison of Antral and Cardiac Glands |</p>
<table>
<thead>
<tr>
<th></th>
<th>Cardiac</th>
<th>Antral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contents</td>
<td>Neutral mucin</td>
<td>Neutral mucin</td>
</tr>
<tr>
<td>Structure</td>
<td>Coiled, occasionally branched, loosely packed</td>
<td>Coiled, extensively branched, more compact than cardiac glands</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>Abundant</td>
<td>Less abundant than cardiac glands</td>
</tr>
<tr>
<td>Cell types</td>
<td>Tall columnar mucinous cells, some endocrine cells</td>
<td>Tall columnar mucinous G cells, enterochromaffin cells</td>
</tr>
<tr>
<td>Cystic dilation</td>
<td>May be present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Gastric pits</td>
<td>Length variable up to 50% of mucosa</td>
<td>One third of the mucosal height</td>
</tr>
</tbody>
</table>

### Mucous Neck Cells

Mucous neck cells reside in the neck and isthmic region of the gastric glands (Fig. 4.18). They are continuous with, and resemble, foveolar epithelium, but they contain fewer cytoplasmic mucous granules. They derive from mitotically active stem cells in the neck region. These tall, irregularly shaped cells with basal nuclei produce acid glycoproteins, which differ from the neutral mucins secreted by foveolar epithelium. Mucous neck cells may be difficult to recognize in routine sections but they can be highlighted using a PAS stain. The major function of mucous neck cells is mucosal proliferation and regeneration. However, mitoses are rare unless regeneration is occurring.

![FIG. 4.14. Low magnification showing the junction of the esophagus bracketed by the band labeled E and cardiac glands bracketed by the band labeled S. Submucosal glands lie both underneath the esophageal-lining epithelium and the gastric-lining epithelium. The esophageal lining has been denuded, although major ducts remain. Note that the glandular configuration underlying the S resembles those underlying the E.](image)

### Parietal Cells

Parietal cells constitute approximately one third of the cells in oxyntic glands. They arise from progenitor cells in the lower isthmus and slowly migrate down into the deeper parts of the gland. Intermediate forms exist between immature and mature
parietal cells. Parietal cells are easily identifiable by their large size, pyramidal shape, central nuclei, and intensely eosinophilic or clear cytoplasm. Their tapered apical ends tend to bulge into the glandular lumen, whereas their broader basal surfaces rest against the basement membrane (Fig. 4.19). Parietal cells produce hydrochloric acid, intrinsic factor, TGF-α, and cathepsins B and H. In the nonsecretory state, an extensive closed system of smooth membranes, the tubulovesicular system, occupies the cytoplasm adjacent to intracellular canaliculi. Stimulation of acid secretion causes the tubulovesicles to fuse with the canaliculi and the apical secretory membrane, resulting in up to a 40-fold expansion of the apical membrane area. The microvilli become more prominent (30). The canaliculi derive from the smooth endoplasmic reticulum and contain the hydrogen ion pump, a unique H⁺,K⁺-ATPase that exchanges H⁺ for K⁺ across the apical membrane (31). When acid secretion is inhibited, the situation reverses. The canaliculi collapse, the microvilli recede, and cytoplasmic tubulovesicular structures become prominent again as the cell returns to its resting state.

The basolateral membranes of parietal cells carry receptors for histamine, gastrin, and acetylcholine (Fig. 4.20). Ligand binding to these receptors stimulates hydrogen ion secretion into the lumen and bicarbonate ions into the interstitium. There is a simultaneous appearance of pathways for K⁺ and Cl⁻ movement coordinated with exchange of H⁺ for K⁺ powered by the proton pump located in the membranes. Basolateral uptake of chloride by parietal cells is mediated by an HCO₃⁻ Cl⁻ anion exchange mechanism (31).

Chief Cells
Chief (zymogenic) cells arise from isthmic stem cells. These triangular low columnar cells contain a coarsely granular, pale gray-blue, basophilic cytoplasm with one or more small nucleoli. Chief cells constitute 20% to 26% of oxyntic glands lying deep within them (Fig. 4.19). The basal cytoplasm contains an extensive rough endoplasmic reticulum, which appears as a striated basophilic region. Chief cells produce lipase and pepsinogen, the pepsin precursor. Pepsinogen secretion is stimulated by the same agents that stimulate acid secretion. Secretory granules form in the Golgi complex and are released by exocytosis. Zymogenic cells degenerate via necrosis or apoptosis. Apoptotic cells are phagocytosed by neighboring zymogenic cells or by lamina propria macrophages that break through the basement membrane of oxyntic glands.
FIG. 4.15. Normal antral glands. A: Low magnification of a normal antrum. B: Higher magnification showing the mucous glands.
FIG. 4.16. Normal oxyntic mucosa. The bottom portion of the photograph contains densely packed oxyntic glands containing chief cells, parietal cells, and endocrine cells.
FIG. 4.17. Oxyntic gland showing its base ($b$), neck ($n$), and isthmus ($i$).
FIG. 4.18. Mucous neck cells. A: High magnification of the mucous neck region showing the presence of tall cells lacking the differentiated features of either foveolar epithelium or underlying glandular epithelium. Mitoses are absent. B: Ki-67 immunostaining showing the proliferative nature of this region.

FIG. 4.19. Normal oxyntic glands. A: The plump eosinophilic cells are parietal cells, and the chief cells are basophilic. Note the prominent capillaries lying beneath the parietal cells (arrow). B: Oxyntic mucosa stained with Giemsa. The parietal cells (P) are particularly prominent.
FIG. 4.20. Parietal cells have various receptors along their basolateral membranes. These include those for histamine, prostaglandin, acetylcholine, and gastrin. Ligands bind their respective receptors and activate protein kinase through cyclic adenosine monophosphate (cAMP). The process involves calcium ions. These events result in cellular secretion of H⁺ ions. ATP, adenosine triphosphate.

**Antral and Pyloric Glands**

In the antral and pyloric region, the pits occupy approximately 40% of the mucosa. These branch and may not always lie perpendicular to the surface. The deep mucosa contains coiled tubular glands that are lined by faintly granular mucin-secreting cells, often resembling mucous neck cells.

**Endocrine Cells**

The stomach contains a prominent and diverse endocrine cell population that is discussed further in Chapter 17.

**Gastric Transitional Zones**

Gastric transitional zones are the junctional zones between the different types of mucosae: Antral/body, body/cardia, and antrum/duodenum. They are dynamic areas that involve a gradual merging of mucosal types so that it may be difficult to determine the exact location of each of the transitional zones. The antral/body transitional zone is usually located approximately two fifths of the way along the lesser curvature; on the greater curvature it is closer to the pylorus (26). The most useful criteria to determine when one crosses from body into antrum are the absence of chief cells and the change from single tubular glands in the body to branched glands in the antrum (32). It may be difficult to determine the site of origin of the gastric mucosa, particularly when it is altered by inflammation, atrophy, and/or metaplasia. In particular, it may be difficult to differentiate between a nonatrophic antral gastritis and an atrophic body gastritis with pyloric metaplasia.

**Lamina Propria and Mononuclear Cells**
The surface, pits, and glands are supported by a well-developed lamina propria that contains a fine reticulin meshwork with occasional collagen and elastic fibers condensed beneath epithelial basement membranes and blood vessels. The lamina propria is more abundant in the superficial mucosa between the pits than in the lower mucosa. It contains numerous cell types including fibroblasts, macrophages, plasma cells, and lymphocytes. The lymphocytes are predominantly immunoglobulin (Ig) A–producing B cells. IgG- and IgM-secreting cells are also present. Intraepithelial T lymphocytes are present but they are much less frequent than in the small bowel. These may have a perinuclear halo superficially resembling endocrine cells. There are also a small number of lamina propria T cells, neutrophils, and mast cells. Lymphoid follicles suggest the diagnosis of chronic gastritis. The lamina propria also contains capillaries, arterioles, and nonmyelinated nerve fibers. Lymphatics appear in the deep lamina propria adjacent to and within the muscularis mucosae. The upper and mid–lamina propria lacks lymphatics. In contrast, the entire mucosa contains a rich supply of capillaries, many of which lie adjacent to the basal lamina of the gastric glands and surface epithelium.

**Neuromuscular Relationships**

The muscularis mucosae varies from 30 to 200 µm in thickness. It becomes hyperplastic and extends into the overlying mucosa in certain conditions as discussed later. The muscularis propria consists of smooth muscle cells and contains nerve fibers and a myenteric plexus. There are also interstitial cells of Cajal (ICC), which have contacts with each other and with the smooth muscle cells and nerve endings in the muscularis propria (33). They lie in the myenteric plexus and in the circular muscle (33). They serve as gastric pacemakers.

**Serosa**

The serosa, the outermost gastric layer, consists of connective tissue and a mesothelial lining continuous with the peritoneum.

**Structural Abnormalities**

**Duplications**

Gastric duplications constitute only 3.8% to 10% of all gastrointestinal duplications (34). They affect females more commonly than males. Sixty-five percent of patients present during the first year of life, often with respiratory distress or as an intrathoracic or extragastric mass (34). Occasionally, the lesions present in adults (35). Thirty-five percent of patients have associated developmental anomalies (Table 4.3) (36). Complications include ulceration, bleeding, rupture, fistula formation, and, rarely, carcinoma (37). Distal duplications cause gastric outlet obstruction, pain, vomiting, fever, weight loss, or hemorrhage (34).

Gastric duplications appear as intramural cylindrical or cystic masses ranging in size from 1.3 to 12 cm. They share a common blood supply with the rest of the stomach; a common musculature invests them. Most duplications occur on the greater curvature (34); one third affect the distal stomach. They may be complete or incomplete, communicating or noncommunicating. Alimentary mucosa lines gastric duplications. This lining resembles and/or differs from that of the normal stomach. Gastric and small intestinal epithelium may coexist within a single duplication. Pancreatic tissue may also be present, as may respiratory mucosa, cartilage, or submucosal glands.

**Dextrogastria**

In patients with situs inversus, the stomach lies to the right of the midline, a condition known as dextrogastria. The esophageal diaphragmatic hiatus also lies on the right side; the first part of the duodenum lies on the left side. Dextrogastria affects approximately 1 of every 6,000 to 8,000 births (38). Situs inversus affecting only the stomach and duodenum (with the remainder of the thoracic and abdominal viscera lying in their normal positions) is extremely rare (38). The stomach either lies completely behind the liver or above it. Although abnormally positioned, gastric structure and function are normal.

**Gastroschisis**

The incidence of gastroschisis increased from 0.006 per 1,000 in 1968 to 0.089 per 1,000 in 1977. Young, socially
disadvantaged women have the highest risk of giving birth to a child with gastroschisis (39). Gastroschisis presumably results from vascular injury to the abdominal wall causing defective somatopleural mesenchymal differentiation during the 5th to 11th fetal weeks (40). Gastroschisis may complicate premature atrophy or abnormal persistence of the right umbilical vein (40). Portions of the stomach, small intestine, and colon herniate through an abdominal wall defect lateral to the umbilicus. Since no peritoneal sac or sac remnant covers the eviscerated abdominal contents, the herniated organs are exposed to amniotic fluid leading to gastric wall thickening, serosal edema, and fibrinous exudates.

<table>
<thead>
<tr>
<th>TABLE 4.3 Lesions Coexisting with Gastric Duplications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal duplications</td>
</tr>
<tr>
<td>Heterotopic pancreas</td>
</tr>
<tr>
<td>Gastrointestinal malrotations</td>
</tr>
<tr>
<td>Meckel diverticulum</td>
</tr>
<tr>
<td>Thoracic vertebral anomalies</td>
</tr>
<tr>
<td>Pulmonary sequestration</td>
</tr>
</tbody>
</table>

**Congenital Hiatal Hernia**

A congenital periesophageal gap or congenital elongated esophageal hiatus can result in a congenital hiatal hernia with invagination of abdominal contents into the thorax (Fig. 4.21). The defect results from failure of the pleuroperitoneal folds to develop or from failure of the pleuroperitoneal canal to close. Urinary tract abnormalities are common in patients with congenital posterolateral diaphragmatic defects including renal agenesis, dysplasia, hypoplasia, or hydronephrosis.

**Acquired Hiatal Hernia**

The freely movable stomach can prolapse through natural and surgically created diaphragmatic defects, coming to lie in the thoracic cavity. Clues that a biopsy may come from the area of a hiatal hernia include the presence of variably inflamed cardiac or oxyntic mucosa with edema, lymphatic dilation, and pronounced muscle hyperplasia, splaying, or stranding. Squamous metaplasia may be present.
FIG. 4.21. Congenital right diaphragmatic defect. The small intestine has herniated into the right thoracic cavity with partial collapse of the right lung and deviation of the trachea to the left. A large thymus overlies the trachea.

Diverticula

Congenital Diverticula

Gastric diverticula are rare, ranging in incidence from 0.02% to 0.18% (41). Most arise on the posterior wall, in a juxtacardiac position (41). Congenital diverticula appear as solitary, sharply defined, round, oval, or pear-shaped pouches communicating with the gastric lumen via a narrow or broad-based mouth (Fig. 4.22).

Acquired Diverticula

Acquired diverticula almost always originate in the distal stomach as a complication of antral inflammation. Fibrosis following acute inflammation causes traction on the tissues and mucosa herniates through the gastric wall. Therefore, antral diverticula should be carefully evaluated to exclude the presence of an underlying pathologic process such as gastritis, peptic ulcer disease, or neoplasia.

Atresia, Webs, and Diaphragms

Congenital gastric outlet obstruction due to a membranous antral web is extremely rare with an incidence of 0.0001% to 0.0003% of live births (42). A high incidence of associated extraintestinal anomalies and a strong familial history for pyloric atresia support the theory that atresias and webs result from underlying genetic alterations. Polyhydramnios affects more than 50% of cases. Gastric atresia may associate with trisomy 21, epidermolysis bullosa, or esophageal and anal atresia (43,44). Hereditary multiple gastrointestinal atresias affect the GI tract from the pylorus to the rectum and are inherited in an autosomal recessive fashion. They may associate with immunodeficiency syndromes (44,45).
Most patients with gastric atresia present in the first few days of life with bile-free vomiting and abdominal distention. Type 1 gastric atresia (the most common type) consists of an internal web or diaphragm that completely separates the stomach from the duodenum. Type 2 atresia (the rarest type) consists of a thin, fibrous cord that connects a blind gastric pouch to a distal blind small intestinal segment. Type 3 atresia consists of a blind gastric pouch and a blind distal intestinal pouch without intervening tissue.

A variably inflamed distal antral mucosal fold with a central aperture measuring from 1 to 10 mm in diameter lies perpendicular to the long axis of the antrum. The serosa may appear indented at the level of the diaphragm. Antral mucosa lines both sides of the diaphragm covering a submucosal core. Heterotopic pancreatic tissue sometimes lies within webs and diaphragms. In adults, diaphragms and webs complicate inflammatory conditions.

**Pyloric Stenosis**

Pyloric stenosis affects both children and adults and assumes several forms.

**Infantile Hypertrophic Pyloric Stenosis (Congenital Pyloric Stenosis)**

This disorder is discussed in Chapter 10 since it is primarily a motility-related disorder.

**Acquired Pyloric Stenosis**

Adult forms of hypertrophic pyloric stenosis result from inflammation associated with antral gastritis and/or peptic ulcer disease, or from inherent neuromuscular abnormalities. Partial gastric obstruction leads to an increased stomach size and weight due to localized or diffuse gastric muscular hypertrophy and hyperplasia, increased mucosal thickness, and G-cell hyperplasia. The pyloric deformity leads to bile reflux and secondary alkaline reflux gastritis.
Torus Hyperplasia

The very rare condition known as focal pyloric hypertrophy (torus hyperplasia) appears as a localized area of circular muscle hypertrophy affecting the lesser curvature near the pyloric torus. The lesion may represent a form of acquired pyloric stenosis or it may represent persistence of congenital pyloric stenosis into adulthood. Some speculate that the lesion results from chronic gastritis or from repeated spastic pyloric contractions (46).

![Image](file:///F|/Gastro/Chapter%204%20non-neoplastic%20stomach.htm)

**FIG. 4.23.** Pancreatic metaplasia versus heterotopic pancreas. *A:* Pancreatic metaplasia consists of pancreatic acini that merge with the surrounding gastric mucosa. *B:* Heterotopic pancreas usually involves the submucosa and may contain pancreatic lobules, islets, and ductules (not shown).

**Heterotopias**

Normal tissues lie in abnormal locations due to a congenital heterotopia or secondary to a metaplasia. Congenital heterotopias differ from metaplastic (acquired) lesions in that they usually retain a normal organizational structure, whereas metaplastic processes tend to consist of a single cell type lacking normal tissue patterns (Fig. 4.23). Congenital heterotopias result from cellular entrapment during embryonic morphogenetic movements. The congenitally displaced tissues then differentiate along the lines of normal organs in response to the local environment.

**Heterotopic Pancreas**

Heterotopic pancreas is the most common gastric heterotopia. It accounts for 25% to 30% of all pancreatic heterotopias (47). It is usually an incidental finding, commonly found in the antrum, and followed by the pylorus, greater curvature, and esophagogastric junction. If a tumor or pancreatitis develops, the heterotopic tissue may become symptomatic. Heterotopic pancreas usually appears as a solitary submucosal, hemispheric, umbilicated mass measuring 0.4 to 4.0 cm in diameter. The entry of single or multiple ducts into the gastric lumen produces a symmetric cone or short, cylindric, nipplelike projection (Fig. 4.24). Heterotopic pancreas may also present as large submucosal mucinous cysts. Multiple or pedunculated pancreatic heterotopias are uncommon. Approximately 75% of pancreatic heterotopias lie in the submucosa (Fig. 4.25), with the remainder involving the muscularis propria. Cross section of larger lesions reveals the typical tan, lobulated tissue characteristic of eutopic pancreas. The deeper the lesion, the more disordered it tends to appear. The pancreatic lobules contain variable mixtures of pancreatic acini, ducts, islets, glands resembling Brunner glands, and hypertrophic smooth muscle
fibers. The islets contain variable numbers of pancreatic polypeptide and insulin-producing cells (48). If only pancreatic acini are present, the lesion may represent foci of pancreatic metaplasia (see below), especially if the cells lie within the mucosa. Sometimes one sees both heterotopic pancreatic and gastric tissue lying side by side in the submucosa (Fig. 4.26).

Heterotopic pancreatic tissue does not pose a diagnostic problem when both pancreatic acini and ducts are present. However, lesions containing only smooth muscle and/or pancreatic ducts have been misinterpreted as adenomyomas. A clue that the lesion represents heterotopic pancreatic tissue, rather than an adenomyoma, is the finding of hypertrophic circular and longitudinal smooth muscle cells arranged circumferentially around the ducts in a more or less normal fashion (Fig. 4.25). Secondary changes such as pancreatitis, cyst formation, or neoplasia (islet cell tumors, ductal dysplasia [Fig. 4.27], and adenocarcinoma) may also cause confusion, particularly when they distort the underlying tissue (49). Dilated ducts forming submucosal mucin pools containing epithelial clusters and variable degrees of inflammation, without obvious pancreatic tissue adjacent to the mucin, may suggest a diagnosis of colloid carcinoma. One should not make a diagnosis of invasive cancer in the absence of significant cytologic atypia and stromal desmoplasia.

**FIG. 4.24.** Heterotopic pancreas. The heterotopic pancreas produces a well-defined submucosal mass that is visible endoscopically (A) as well as grossly (B). The submucosal mass distorts the gastric folds (arrow) and appears as a hemispheric lesion with a central umbilication. C: Cross section of the gastric wall demonstrating the presence of a whitish, firm mass lying within the submucosa as indicated by the arrows.

**Heterotopic Gastric Glands**
Diffuse or localized submucosal gastric heterotopias occur in up to 14% of stomachs (50). These are either congenital in origin or represent areas of gastritis cystica profunda (discussed below). Congenital gastric heterotopia usually contains oxyntic mucosa with foveolar epithelium arranged in a normal architectural pattern.

**Heterotopic Brunner Glands**

Heterotopic Brunner glands can accompany heterotopic pancreas, or the heterotopia may contain only Brunner glands and smooth muscle. The heterotopic glands lie in the pylorus and gastric antrum and histologically resemble duodenal Brunner gland hyperplasia (see Chapter 6).

**Double Pylorus**

Double pylorus is an acquired condition in patients with peptic ulcer disease. Prepyloric ulcers penetrate the pyloric wall, perforate into the duodenum, and create a new mucus-lined channel. Rare examples of congenital double pylorus also exist (51).

**Pyloric Mucosal Prolapse**

Antral mucosa may prolapse into the duodenum, sometimes forming a mushroom-shaped duodenal or gastric pseudopolyp (Fig. 4.28). It occurs sporadically or complicates gastritis or previous gastric surgery. Submucosal edema (as the result of an underlying inflammation) predisposes to mucosal prolapse. As the edema increases, the tissues fail to return to their normal position; progressive gastric outlet obstruction develops. Patients with mucosal prolapse usually develop crampy abdominal pain, delayed gastric emptying, or vomiting due to the gastric outlet obstruction. The prolapsed mucosa appears variably inflamed, edematous, and necrotic, depending on the duration and severity of the obstruction and the degree of vascular compromise. Pit hyperplasia, pit distortion with cystic serrated branched villiform surfaces, a hyperplastic muscularis mucosae with a muscular lamina propria, erosions, ulcers, glandular atrophy, and variable inflammation may all develop.

**Volvulus**

Gastric volvulus, also known as gastric torsion, affects both children and adults, usually in the presence of a left P.151 diaphragmatic abnormality (52,53). It presents acutely or chronically. Acute presentations include hemorrhage, ischemia, and infarction (52,53). Most patients are elderly with a chronic form of the disease. They have recurrent epigastric pain, vomiting, and occasional hematemesis.
**FIG. 4.25.** Heterotopic pancreas. *A:* A lobulated submucosal glandular structure with a central duct. Delicate strands of fibrovascular tissue separate individual lobules. *B:* Higher magnification of the duct and pancreatic acini on either side of the duct. Prominent smooth muscle fibers also surround the duct.
FIG. 4.26. Heterotopic pancreas combined with heterotopic gastric tissue. A: Low-power magnification demonstrating the side-by-side arrangement of heterotopic pancreatic tissue (P) (arrow) and gastric foveolar epithelium (G) (arrow). B: Higher magnification demonstrating the histologic features of the gastric epithelium.

Gastric volvulus occurs in several forms. The most common type, organoaxial volvulus, accounts for approximately 60% of cases. The stomach twists around the longitudinal axis of its lesser curvature, causing the stomach to turn upside down (Fig. 4.29), producing both proximal and distal obstructions. Anterior rotation is more common than posterior rotation. Mesenteroaxial volvulus represents 30% of cases. It occurs around a line that runs from the center of the greater curvature to the porta hepatitis. Mesenteroaxial and organoaxial volvulus can coexist. The stomach can also twist about the vertical axis of the gastrohepatic omentum producing torsion rather than a true volvulus. As a volvulus develops, the stomach progressively distends, due to accumulated secretions that cannot pass forward or be regurgitated because the volvulus produces both distal and proximal obstruction. Death results from the sequence of obstruction, strangulation, and ischemic necrosis, the latter resulting from compression of the gastric vasculature.
**FIG. 4.27.** Heterotopic pancreas with dysplastic epithelium. *A:* Numerous cystic structures lie within the gastric wall. Some are lined by flattened epithelium and contain prominent mucinous collections. Others are lined by benign neoplastic epithelial cells. *B:* Higher magnification of one of the glands showing the junction of more or less normal epithelium with basal nuclei above the *arrows* with the benign neoplastic hyperchromatic epithelium with an increased nuclear:cytoplasmic ratio and prominent nucleoli beneath the arrows. *C:* Higher magnification of the neoplastic epithelium showing cytologic atypia, nuclear stratification, and prominent nucleoli. *D:* Another area with a more complicated glandular architecture. Note the absence of invasion into the surrounding tissues and the absence of a desmoplastic response. The glands are still surrounded by intact smooth muscle fibers.
Microgastria

Microgastria, a rare congenital anomaly, often coexists with other anomalies such as midgut malrotations, cardiac abnormalities, and asplenia (54). The underdeveloped lower esophageal sphincter becomes incompetent and gastroesophageal reflux develops. Symptoms appear in infancy and include failure to thrive, vomiting, and recurrent aspiration pneumonia. Barium swallows demonstrate a small tubular stomach. Histologically, the gastric wall appears hypoplastic (55). The stomach is small, often nonrotated without a clear definition of the various zones. The disorder may result from failed development of the mesogastrium.

Mucosal Biopsy

Endoscopic examination with mucosal biopsy and/or cytologic sampling is regularly employed for the initial identification and monitoring of patients with various gastric conditions including gastritis, gastric atrophy, peptic ulcer disease, and neoplastic proliferations. Gastric biopsies are also commonly used to evaluate the stomach for the presence or absence of Helicobacter pylori (HP). Routine gastric biopsies may also show special forms of gastritis (eosinophilic, lymphocytic, and granulomatous), giant fold disease, or polyps. Gastric biopsies can provide information about the grade, extent, and topography of gastritis-related and atrophy-related lesions, information that provides the opportunity to assess the patient's risk for developing gastric carcinoma. As noted previously, gastric histology varies from area to area and since many gastric diseases are patchy in their distribution, an adequate evaluation often requires examining biopsies from the body, antrum, and any endoscopically visible lesions. The Sydney system requires that biopsies be obtained from five locations in the stomach (the greater and lesser curvature in the antrum, the greater and lesser curvature in the corpus, and the incisura) (56), although this seldom happens in...
Typically gastroenterologists take a couple biopsies from the antrum and a couple from the corpus. Ideally these should be submitted in separate containers, although this does not always happen either.

It is important to note that endoscopic procedures may cause variable degrees of edema, vascular dilation, focal lamina propria hemorrhage, and surface cell flattening. These changes are usually easily distinguishable from mucosal disease because of the absence of both epithelial degeneration and acute inflammation. A systematic examination of gastric biopsies facilitates the diagnosis of various gastric diseases and provides the discipline of establishing a differential diagnosis so that specific diagnostic entities are considered and important entities are not overlooked. One should determine where the biopsy comes from by looking at various mucosal components. However, it may be difficult to determine the precise location of a biopsy because of the presence of atrophy and/or metaplasia. Gastric epithelium may appear in the duodenum in peptic duodenitis; intestinal metaplasia occurs in the setting of gastritis and Barrett esophagus, and pyloric glands develop in the proximal stomach in certain forms of gastritis.

One can broadly divide gastric inflammatory diseases into gastritis and gastropathy. The major distinction between the two is the presence of inflammation in gastritis and its absence in gastropathies. Gastritis typically results from infections, autoimmune or hypersensitivity reactions, or drugs. Determining whether gastritis is a pangastritis or affects only the antral or corpus, whether it is focal or diffuse, and whether it is superficial or occupies the entire mucosal thickness helps distinguish among these etiologies. Other changes that may be assessed include a determination of whether any of the following are present: Surface epithelial damage, superficial stromal hemorrhage, metaplasia (intestinal, pancreatic, or antral), endocrine cell hyperplasia, intraepithelial lymphocytosis, granulomas, apoptosis, or microorganisms. Gastropathies result from hypovolemia, stress, ischemia, drug or alcohol ingestion, chronic congestion, or alkaline reflux from the duodenum. Diagnostic approaches we find useful are shown in Figures 4.30 and 4.31. We do not believe that it is necessary to routinely order special stains to determine whether *HP* infections or intestinal metaplasia are present, a view shared by others (57). A more detailed evaluation can be used by applying the Sydney system as discussed further in a later section.
FIG. 4.30. Diagnostic algorithm. One can use this approach once one has determined the subsite localization for the changes that are present. One makes an assessment as to whether or not inflammation is present and, if so, what type and where it is. If inflammation is absent, then one might consider a chemical injury.

FIG. 4.31. Diagnostic approach to interpreting gastric biopsies. In this approach, one starts by identifying the portion of the stomach that is primarily affected because different entities preferentially affect the antrum and corpus. One then goes through a decision tree based on the character of the inflammation and whether the mucosa appears normal, atrophic, or hyperplastic and contains other cell types. IM, intestinal metaplasia.

TABLE 4.4 Causes of Acute Gastritis

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Radiation</th>
<th>Acute alcoholism</th>
<th>Multiorgan failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremia</td>
<td>Certain foods</td>
<td>Severe burns</td>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Ischemia</td>
<td>Sepsis</td>
<td>Alkaline refluxa</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Shock</td>
<td>Trauma</td>
<td>Bile refluxa</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Corrosive agents</td>
<td>Certain infections</td>
<td>Major surgery</td>
<td>Increased intracranial pressure</td>
</tr>
</tbody>
</table>

aAcute inflammation uncommon.
Chapter 4

Acute Gastritis

Acute gastritis (accompanied by acute mucosal injury) results from many disorders with multifactorial etiologies and diverse histologic patterns (Table 4.4). The clinical symptoms, endoscopic findings, and histologic features rarely correlate with one another due to the nonspecificity of the symptoms, the diverse etiologies, and the diffuseness (or focality) of the process. Acute gastritis appears hemorrhagic, nonhemorrhagic, erosive, or nonerosive.

**Acute Hemorrhagic, Erosive Gastritis (Stress Gastritis)**

Acute erosive gastritis complicates major physiologic disturbances including sepsis, extensive burn injury, head injury, severe trauma, and multiorgan failure. It also develops following ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or alcohol. Acute gastritis often presents as abdominal discomfort, pain, heartburn, nausea, vomiting, and hematemesis. Bleeding begins 3 to 7 days following a stressful event. It ranges from occult blood loss to massive hemorrhage that originates from innumerable foci of mucosal damage to smaller, more discrete ulcers (Fig. 4.32). Curling ulcers develop in severe burn patients within 24 to 72 hours, predominantly in the proximal stomach.

Pathophysiology

Major factors implicated in the development of stress ulcers include hyperchlorhydria and decreased mucosal protection. The latter results from decreased mucus secretion, mucosal blood flow, and DNA and prostaglandin synthesis, and mucosal barrier breakdown. Indeed, mucosal ischemia is the common denominator of stress-associated injury. Cardiac dysfunction, hemorrhage, shock, and sepsis redistribute blood flow away from the subepithelial capillaries, causing mucosal hypoxia. The hypoxia may persist after recovery from the initial injury, especially as mucosal arterioles contract, further reducing tissue oxygenation (58). An adequate microcirculation that provides nutrients and removes waste products, particularly oxygen-free radicals, is required to maintain the mucosal barrier. A damaged mucosal barrier allows back-diffusion of acid, resulting in tissue acidosis, vascular compromise, mucosal congestion, and necrosis. The mucosal injury increases significantly during the reperfusion that follows ischemia due to the production of toxic oxygen-free radicals (59) by infiltrating neutrophils (60). In addition, activated leukocytes release mediators that reduce mucosal blood flow and increase vascular permeability (61,62). The oxygen-free radical-induced injury is further enhanced by mucosal depletion of the endogenous antioxidant reduced glutathione (GSH) (63). The GSH oxidation/reduction cycle, catalyzed by glutathione peroxidase, reduces H₂O₂ and breaks the chain reaction that generates highly reactive hydroxyl radicals. GSH acts as a natural scavenger whose superoxide anion protects proteins against oxidation. GSH also plays a major role in restoring other free radical scavengers and antioxidants such as vitamins E and C to their reduced state (64). Prostaglandins limit the initial injury (65). Oxidative stress leads to epithelial growth factor receptor (EGFR) phosphorylation and increased production of its ligands, EGF and amphiregulin (66). A mucoid cap promotes mucosal restitution by protecting the lamina propria from luminal acid, limiting the extent of the injury (65).
Various factors contribute to the repair of acute gastric mucosal injury. Re-epithelialization requires epithelial migration across an intact basal lamina. This occurs within minutes to hours of the injury to ensure quick restoration of surface epithelial continuity and inhibiting acid back-diffusion (65). In addition, cells in the mucous neck region migrate out of the proliferative zone and progressively differentiate into mature foveolar cells. Gastric mucosal blood flow increases (65). If this is inhibited, mucosal cytoprotective events fail and the mucosal injury progresses with deeper ulceration than would otherwise result from the initial injury.

**Pathologic Features**

Erosive gastritis and stress ulcers typically appear as multiple lesions located anywhere in the stomach, although they tend to predominate in the oxyntic mucosa (Fig. 4.32). When severe, they extend to the antrum. Stress ulcers tend to be superficial and usually measure <15 mm in diameter. The ulcer bases appear grayish yellow and hemorrhagic with slightly raised, congested, regenerative margins. The intervening gastric mucosa appears diffusely congested and contains numerous small petechial hemorrhages. Alternatively, the mucosa is diffusely hemorrhagic without discrete areas of damage. Early lesions center around intensely congested blood vessels, which leak blood into the surrounding tissues (Fig. 4.33). Extensive hemorrhagic mucosal erosions or ulcers develop in more severe cases. Rare cases present with deep linear ulcers coexisting with more discrete, round, superficial lesions. Curling and Cushing ulcers tend to be deep and single.
Chapter 4

**FIG. 4.33.** Close-up gross photograph of the gastric mucosa in a patient who died of multiorgan failure. Note the intensely congested vessels as well as the areas of neovascularization. Pinpoint hemorrhages extend from vessels of all sizes contributing to the diffuse leakage of blood from the gastric surface.

<table>
<thead>
<tr>
<th>TABLE 4.5 Pathology of Acute Erosive Gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute phase</strong></td>
</tr>
<tr>
<td>Vascular engorgement</td>
</tr>
<tr>
<td>Lamina propria hemorrhage</td>
</tr>
<tr>
<td>Superficial necrosis</td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes in pits and glands</td>
</tr>
<tr>
<td>Ulcers and erosions</td>
</tr>
<tr>
<td>Superficial fibrin deposits</td>
</tr>
<tr>
<td><strong>Healing phase</strong></td>
</tr>
<tr>
<td>Epithelial regeneration with nuclear enlargement</td>
</tr>
<tr>
<td>Pit elongation</td>
</tr>
<tr>
<td>Mucus depletion</td>
</tr>
<tr>
<td>Numerous mitoses</td>
</tr>
</tbody>
</table>

The histologic features depend on the severity and duration of the underlying insult; they are often not as dramatic as the gross features. Features associated with acute gastritis are listed in Table 4.5. Mucosal changes range from hyperemia, surface erosions, and acute inflammation to massive mucosal necrosis (Fig. 4.34), sloughing, and eventual scarring. Lesions seen in biopsies are typically early. More severe changes are usually seen at the time of autopsy. Mild stress gastritis may be difficult to distinguish from biopsy trauma. More severe disease shows extreme vascular congestion with dilation and hemorrhage into the superficial lamina propria (Fig. 4.34) often associated with acute inflammation (Fig. 4.34). Erosions appear as discrete, superficial oval or circular areas of mucosal necrosis and tissue loss that do not extend deeper than the muscularis mucosae and have sharply defined, often raised edges; edema; and superficial epithelial necrosis (Fig. 4.34). Numerous neutrophils infiltrate the gastric pits and glandular lumina (Fig. 4.35). The inflammation usually spares the deepest glands. True granulation tissue is absent. Rather, the eroded cavity contains an exudate of proteinaceous fluid, debris, neutrophils, and red cells. The mucosa contains superficial fibrin deposits (Fig. 4.34). Chronic inflammation is absent in...
the acute phase. Only a minimal reparative fibroblastic response occurs when the injury is minor. Healing occurs in days to weeks following removal of the causative factor(s).

The healing phase (Table 4.5) is characterized by proliferation of pluripotential stem cells in the mucous neck region, pit elongation, a pseudostratified or syncytial appearance of the superficial epithelium, and vascular congestion (Fig. 4.35). The stem cells differentiate into foveolar cells above and specialized glandular epithelial cells below, reconstituting a normal mucosal architecture within a few days. Proliferating mucous neck cells contain abundant basophilic cytoplasm, increased mitoses, and an increased nuclear:cytoplasmic ratio, and appear mucin depleted. Despite their potentially alarming cytologic features (Fig. 4.35), the nuclei of the regenerating epithelium retain a basal orientation and contain vesicular chromatin and a prominent solitary eosinophilic nucleolus. The nuclear pleomorphism and atypical mitoses characteristic of neoplasia are usually absent. Residual clusters of neutrophils may reside within the pits and the surrounding lamina propria may be inflamed. One must be careful not to mistake regenerative changes for carcinoma. Atypical regenerative epithelium still retains a normal glandular architecture. If one can line the glands up parallel with one another in a regular fashion, perpendicular to the mucosal surface, if there is acute inflammation and if lamina propria separates the glands, one should be extremely cautious before making a diagnosis of malignancy, even in the face of extreme epithelial atypia.
FIG. 4.34. Early changes of acute erosive gastritis. A: The earliest changes consist of vascular dilation in the superficial lamina propria. The overlying epithelium remains intact. B: Small thrombi develop (arrow) and the superficial lamina propria becomes increasingly edematous. C: With further disease progression, the tops of the gastric surface become eroded with loss of the surface epithelium. D: In larger lesions, extensive areas of transmucosal necrosis are present. E: Portions of the superficial epithelium degenerate, forming amorphous pinkish fibrinous debris on the surfaces of the mucosa. The glands become widely dilated and the surrounding lamina propria is infiltrated with extravasated red cells. F: Higher magnification of the extravasated red cells.
FIG. 4.35. Evolving erosive gastritis. A: The mucosal surface is eroded and as a result mucous neck regions become hyperchromatic and appear regenerative. B: With further disease progression, one sees a marked expansion of the mucous neck region with the regenerative cells showing significant reparative atypia. C: The surface cells acquire a syncytial appearance. D: Eventually, the entire surface becomes re-epithelialized, although the epithelium appears immature and has a large nuclear:cytoplasmic ratio. Some residual syncytial knots remain.

Superficial erosions usually heal completely, without evidence of scarring, providing the inciting agent disappears. In patients with deeper lesions, complete regeneration of the gastric glands rarely occurs. Rather, mild mucosal scarring results (Fig. 4.36).

**Ethanol-Induced Gastritis**

The extent of alcohol-induced injury results from the quantity of alcohol ingested as well as its mucosal contact time (67). Injury usually requires gastric alcohol concentrations >10%. The presence of a concurrent *HP* infection may augment the alcohol-induced injury. Alcohol contacting the superficial gastric mucosa impairs mucus synthesis and secretion and damages epithelial cells, causing them to become necrotic and slough, leaving the underlying mucosa exposed to the alcohol and to gastric luminal acid (68). Acid back-diffusion increases mucosal blood flow, capillary permeability, and acid secretion. Increased capillary permeability leads to interstitial edema. Vasoactive mediator release from mast cells, endothelial cells, and neutrophils triggers venoconstriction and plasma transudation. The neutrophils generate superoxide anion and hyperchlorous acid in a manner similar...
to that seen in stress gastritis (69). Arterial and arteriolar dilation rapidly follow, leading to marked congestion, edema, hemorrhage, cellular translocation, ischemia, and cell membrane damage sufficient to cause local edema, hypoxia, hemorrhage, and cellular necrosis (Fig. 4.37). Alcohol penetration into the congested tissues causes hemolysis, vascular congestion, protein precipitation, vascular stasis, thrombus formation, and capillary leakage (70). Neuropeptides stimulated by the alcohol affect blood vessels, leukocytes, and epithelium, and aid in activating inflammatory mediators (71).

FIG. 4.36. Healed erosion. A: A focal area of fibrosis of the lamina propria distorts the glands. B: This figure shows more extensive lamina propria fibrosis and collagenization with only a few atrophic glands remaining. The surface has not re-epithelialized in this particular specimen, indicating the presence of both acute and more chronic recurrent damage.
Actively drinking alcoholics predominantly show multiple areas of subepithelial hemorrhage, prominent mucosal edema in the adjacent nonhemorrhagic mucosa, and only mild inflammation. The edema may be severe enough to extend into the submucosa (72). The foveolar epithelium overlying the lamina propria hemorrhage may appear mucus depleted and show focal loss of nuclear polarity. Tiny erosions may be present in some patients, especially those consuming large quantities of alcohol in a short period of time. These resemble the lesions seen in stress gastritis and predominantly involve the proximal stomach. In these patients there may be focal necrosis of the foveolar epithelium along with focal neutrophilic infiltrates in the gastric pits. Chronic ethanol ingestion increases mucosal expression of EGF and other growth factors (68) leading to increased cell proliferation. Differentiation of cells in the proliferating mucous neck region replaces the damaged cells.

**Drug-Induced Gastritis and Gastropathy**

Many drugs produce gastric erosions, hemorrhage, and necrosis, the most common of which are NSAIDs and aspirin. The pathogenesis of the injury varies. Some drug-induced and stress-induced ulcers share common pathogenetic events, but the factors that lead to the initial cellular damage may differ. The fact that many drugs produce similar changes whether administered intravenously or orally suggests that mucosal contact need not occur to produce the damage.

**Aspirin/Nonsteroidal Anti-Inflammatory Drugs**

The nature of aspirin-related injury depends on whether the drug ingestion is acute or chronic. One-time aspirin ingestion causes subepithelial hemorrhages within an hour, and regular intake over a 24-hour period leads to gastric erosions in many individuals. Chronic ingestion often results in less severe damage than acute ingestion because mucosal adaptation occurs, making the mucosa resistant to injury. The adaptive response involves decreased neutrophilic infiltration and extensive epithelial proliferation (73). Aspirin-induced damage results from its toxic effects as well as by decreasing mucosal defenses (74). The physicochemical property of aspirin aids in its rapid absorption, mucosal accumulation, and mucosal barrier breaking effects. Salicylates in aspirin become trapped inside gastric epithelia interfering with ATPase-dependent processes and
leading to increased membrane permeability. Eventually osmotic swelling and cell death develop. Additionally, small aspirin fragments may become embedded in the mucosa. These produce circular erosions or ulcers surrounded by hemorrhagic zones. Adjacent erosions become linked by linear mucosal cracks. The aspirin particles then fall into the cracks and become walled off in mucus until they dissolve.

**Nonsteroidal Anti-Inflammatory Drugs**

NSAIDs are a common cause of grossly visible gastric injury and are responsible for some of the most severe drug injury seen in the United States (75). Gastric injury typically complicates the use of NSAIDs prescribed by physicians. However, consumption of high-dose over-the-counter NSAIDs also causes significant gastrointestinal injury (76). Gastroduodenal lesions develop in 31% to 68% of patients on chronic therapy; up to 25% have gastric ulcers (77). The vast majority of individuals utilizing NSAIDs are 60 years of age or older. These patients are particularly susceptible to develop GI hemorrhage and gastric ulcers, in part due to the fact that mucosal prostaglandin levels decrease in the elderly (78).

NSAIDs cause direct local mucosal toxicity and inhibit hydrogen sulfide generation (79) and cyclooxygenase enzymes. The latter leads to reduced prostaglandin synthesis. As noted earlier, prostaglandins are critical to maintaining the integrity of the mucosal barrier. Most NSAIDs are weak organic acids and in the highly acidic stomach, are un-ionized so that they are lipid soluble and diffuse freely into the epithelium elevating intracellular pH. The damaged mucosa becomes leaky allowing acid back-diffusion, peptic injury, erosions, hemorrhage, and other damage to occur. Coexisting *HP* infections increase mucosal susceptibility to NSAID-mediated damage and increase the risk of ulceration and bleeding (80).

NSAIDs produce acute mucosal lesions within 7 days of administration by the mechanisms shown in Figure 4.38. Altered blood flow and increased leukocyte–endothelial interactions in the gastric microcirculation occlude microvessels, further reducing mucosal blood flow. The inflammatory cells also release various procoagulants, inflammatory mediators, proteases, and oxygen-free radicals that further damage the endothelium and the underlying connective tissue (81). NSAID effects are summarized in Table 4.6 (74).

NSAIDs cause several types of injury: Acute hemorrhagic gastritis, erosions, chemical gastropathy (discussed in a later section), ulcers, and perforation. Because of the direct local toxicity caused by NSAIDs, the damage is patchy and is increased in areas of mucosal contact. Thus, injury is more common in dependent parts of the stomach (antrum and body along the greater curvature). Gastric ulcers are of greater clinical significance than erosions because of their chronicity and their potential for perforation and significant bleeding.

The acute hemorrhagic gastritis is characterized by a damaged surface epithelium with edema, hemorrhage into the superficial lamina propria, and variable inflammation, resembling stress gastritis. The degree of inflammation tends to be minimal. However, neutrophilic infiltrates are present if erosions or ulcers develop. The hemorrhagic erosions usually heal within a few days. Prominent eosinophilia may also be present, as may increased epithelial apoptosis. Biopsies taken of antral lesions thought to be erosions by endoscopists are frequently areas of chemical gastropathy with moderate to marked capillary dilation. The epithelium may appear very atypical (Figs. 4.39 and 4.40). The diagnosis of NSAID-induced gastritis can be problematic in the absence of a history of NSAID ingestion, but the presence of changes resembling stress gastritis, or a chemical gastropathy, especially if increased eosinophils are present, may suggest the diagnosis.
Following NSAID absorption, there is uncoupling of mitochondrial oxidative phosphorylation leading to reduced adenosine triphosphate (ATP) levels, which in turn result in the loss of intercellular junctional integrity and increased mucosal permeability. Also as a result of the mitochondrial oxidative phosphorylation uncoupling, an efflux of calcium and hydrogen ions from mitochondria occurs, further depleting ATP stores and promoting oxygen radical damage. The damaged cell releases arachidonic acid, but the conversion of arachidonic acid to prostaglandins is prevented by the NSAID inhibition of cyclooxygenase. As a result, the damage of the gastric mucosa is more prolonged than would ordinarily be the case. As a result of the damage, the mucosa becomes vulnerable to luminal aggressive factors, which include acid, pepsin, bile, and Helicobacter pylori.

**Proton Pump Inhibitors**

Proton pump inhibitor (PPI) therapy may induce changes in G cells, ECL cells, and parietal cells. Mild G-cell and ECL-cell hyperplasias (but not carcinoid tumors) occur and may be diffuse, linear, or micronodular (82). The micronodular hyperplasia is more likely to occur in patients with HP infections. Parietal cell changes include increases in cell size and number, leading to swelling (Fig. 4.41) and convex bulging of the apical cell membranes into the glandular lumens, which imparts a serrated appearance to the normally round or tubular glandular lumens (83). This change affects over 90% of patients treated for 1 year with daily doses of 20 to 40 mg of omeprazole. The parietal cell protrusions appear to be related to the hypergastrinemia (83,84). For this reason, parietal cell protrusions are not specific for PPI therapy. They can also be seen in patients with HP gastritis, gastric ulcers, morbid obesity, Zollinger-Ellison syndrome, or gastric cancer (83).

**TABLE 4.6 Nonsteroidal Anti-inflammatory Drug Effects**

- [Link to Table 4.6]
Break gastric mucosal barrier
Alter cell membrane permeability, allowing H⁺ back-diffusion
Increase acid secretions
Concentrate in epithelial cells due to ion trapping
Alter transmural electrical potential differences
Cause surface cell damage and loss
Alter cell junctions
Inhibit gastric mucosal secretions
Increase pepsin-mediated proteolysis of mucin
Increase permeability of mucus to H⁺
Inhibit active bicarbonate secretion
Alter surface phospholipids
Alter mucosal blood flow
Inhibit prostaglandin synthesis
Reduce surface hydrophobicity

Patients on long-term treatment may develop tiny fundic gland polyp (FGP)-like lesions. They contain glandular cysts measuring between 0.25 and 7 mm in diameter (Fig. 4.41). These are lined by flattened parietal and chief cells; they may also contain foveolar cells. The lesions may disappear after PPI therapy is withdrawn and reappear after the reintroduction of the therapy (85). While there appears to be a relationship between FGPs and PPIs, the data are inconsistent and not all patients develop the polyps. Additionally, some PPI-associated fundic gland cysts lack superficial foveolar dilation, a hallmark of FGPs. PPIs also slightly increase the number of apoptotic bodies in the antral mucosa (86).

**Steroids**

The association between peptic ulcer disease and corticosteroids has been debated for years. There appears to be a small increased risk of gastric ulceration and bleeding in steroid users; the concomitant use of steroids and NSAIDs associates with an up to 10-fold increased risk of an upper GI bleed. Steroids stimulate G-cell hyperplasia (87), indirectly increasing acid production by parietal cells. They also decrease epithelial turnover and mucin secretion, thereby impairing mucosal barrier protection. There may be acute inflammatory cells in the lamina propria and apoptotic debris in the glandular lumens (Fig. 4.42).

P.162
FIG. 4.39. Nonsteroidal anti-inflammatory drug (NSAID) damage. *A:* A gastric biopsy from the body region of a patient on NSAIDs. The patient showed endoscopic evidence of multiple petechial hemorrhages. The biopsy shows that the changes mainly affect the superficial mucosa with edema, telangiectasia, and little or no inflammatory infiltrate. *B:* The mucosa appears regenerative with loss of glands and irregularity of the remaining pits.

FIG. 4.40. Nonsteroidal anti-inflammatory drug (NSAID) injury. *A:* The regenerative changes that develop following NSAID-induced injury can be cytologically alarming. The atypia primarily affects the cells in the mucous neck region. A clue to their regenerative, nonneoplastic nature is evidence of maturation in the foveolar cells. *B:* When the biopsy is fragmented without the ability to see the foveolar cell maturation, the diagnosis is more difficult.

FIG. 4.42. Patient with aplastic anemia treated with steroids. There is acute inflammation in the lamina propria and the gland, and the glands contain apoptotic debris.

FIG. 4.43. Chemotherapy-associated gastric changes showing increased mitotic activity and enlarged atypical cells. The nuclear:cytoplasmic ratio is not increased.

Chemotherapy
Patients undergoing chemotherapy develop many complications due to direct mucosal injury, vomiting (leading to potential esophagogastric tears), drug-induced immunosuppression, and thrombocytopenia. Cisplatin, doxorubicin, nitrosoureas, and vincristine are notorious for inducing nausea and vomiting. Chemotherapy-induced immunosuppression can lead to multiple gastric infections. Hepatic arterial infusion chemotherapy (HAIC) can produce gastric ulcers and alarming epithelial regenerative atypias easily confused with carcinoma (88,89) because of the presence of binucleated or multinucleated cells containing massive nuclei (Fig. 4.43). Features of the atypia of HAIC and neoplasia are compared in Table 4.7. The presence of ring mitoses, which are not characteristic of neoplasias, suggests drug injury. Floxuridine causes epithelial necrosis with the inflammation and epithelial regeneration (90). The epithelial cytoplasm becomes vacuolated and foamy. Other drugs causing severe epithelial atypia include combinations of 5-fluorouracil (5-FU) with either leucovorin or mitomycin. These drug-induced atypias become most difficult to accurately diagnose in superficial gastric mucosal brushing specimens. Vinorelbine predisposes to bezoar formation (91), probably due to toxic myenteric plexus damage.

| TABLE 4.7 Comparison of Hepatic Arterial Infusion Chemotherapy (HAIC) and Neoplasia |
|---------------------------------|----------------|----------------|
| **Feature**                     | **HAIC**       | **Neoplasia**  |
| Cytologic features              | Bizarre enlarged cells | Uniform anaplasia |
| Nuclear:cytoplasmic ratio       | Low            | High           |
| Mitoses                         | Few or none    | Many           |
| Location of the atypia          | Glands         | Mucous neck region and foveolae |
| Atypia in granulation tissue    | Yes            | No             |
| Atypia in stromal cells         | Yes            | No             |
| Glandular architecture          | Preserved      | Distorted      |
| Cytoplasmic vacuolization       | Present        | Absent         |

**Iron Pill Gastritis**

Acute gastritis develops in individuals consuming large amounts of oral iron. Iron supplements may cause erosions, ulcers, an almost infarctlike gastric mucosal necrosis, and strictures as the ulcers heal. Grossly, grayish or bluish mucosal patches may be present. Superficial edema, inflammation, and necrosis characterize the histologic changes. A layer of brownish pigment that stains positively with iron stains (Fig. 4.44) may cover the epithelial surface and extend into the superficial gastric pits. Some of the pigment may appear crystalline. The majority of the iron that is present is in an extracellular location. Iron pigment may lie in granulation tissue, on the top of damaged epithelium, in the glands or lamina propria, or in the submucosa (Fig. 4.45) (92). Focal epithelial or stromal cell deposition is less common than deposits in the lamina propria and surface unless the patient has also had transfusions or has alcoholic liver disease. Features of chemical gastropathy may also be present (93). The changes differ from those seen in hemosiderosis in that patients with hemosiderosis or hemochromatosis lack significant inflammation (unless there is a coexisting gastritis) and the iron predominantly localizes within cells, especially the epithelium of deeper glands. Erosions are not present.
Chapter 4

**FIG. 4.44.** Changes associated with high-dose iron ingestion. *A:* Note the superficial damage and edema of the lamina propria. A layer of iron is deposited on the surface of the gastric mucosa as well as extending into the upper portions of the gastric pits. *B:* Prussian blue stain of the same biopsy at a lower magnification showing the prominent coating of the gastric mucosa with iron and extension into the pits.

**Prostaglandin Therapy**

Prostaglandin E infusions, used to treat congenital heart disease and other neonatal and adult disorders, induce gastric outlet obstruction secondary to foveolar hyperplasia and elongation of the gastric pits that results in marked antral hyperplasia (94).

**Cocaine Use**

Cocaine abuse can cause gastric injury with the newer forms being more toxic than cocaine hydrochloride (95). Affected patients tend to be young males. Cocaine causes intense vasoconstriction, focal ischemia, and perforation (95,96). Granulomas may be present, presumably due to cutting the drugs with foreign materials (Fig. 4.46).

**FIG. 4.45.** Iron-pill gastritis. Note the prominent iron deposits in the submucosa.

**Gastric Mucosal Calcinosis**

Rare patients have crystalline deposits in the superficial gastric mucosa that consist of aluminum, phosphorus, calcium, and...
chlorine. They occur in transplant patients on long-term aluminum-containing antacid therapy or sucralfate therapy (97). The deposits lie just below the foveolar epithelium, sometimes rimmed by macrophages. They show variable degrees of calcification and often appear refractile (Fig. 4.47). There may be coexisting gastritis.

**Other Drugs**

*Kayexalate resin crystals* can be present in the stomach in patients treated for hyperkalemia. Sodium cations are released from the resin and exchanged for hydrogen ions in the gastric acid milieu. As the resin passes through the intestines, hydrogen is exchanged for potassium, which is then eliminated in the feces along with the remainder of the altered resin, thereby lowering serum potassium levels. The crystals have a characteristic refractile crystalline mosaic pattern that resembles fish scales that distinguishes Kayexalate crystals from cholestyramine crystals, which they resemble (98,99). This pattern is faintly seen in hematoxylin and eosin-stained sections and is better demonstrated with acid fast, Alcian blue, or Diff-Quik stains. The crystals do not polarize. The crystals are always located in a luminal location, either adherent to intact surface epithelium or admixed with inflammatory exudates in patients with ulcers or erosions (98,99). In some cases, Kayexalate crystals aggregate with mucous secretions and clotted blood to form gastric bezoars.

Some patients on *colchicine* develop gastritis or antral erosions. The most discriminating feature indicating colchicine damage is the presence of abundant epithelial mitotic figures in metaphase arrest (100), particularly in the proliferative zone in the mucous neck region. Metaphase mitoses appear as enlarged epithelial cells with condensed chromatin in a ring formation in the center of the cell (ring mitoses). These changes are accompanied by marked foveolar cell hyperplasia resulting in crowded, enlarged, distorted epithelial cells; epithelial pseudostratification; and loss of cellular polarity. However, in contrast to the large size of the cells, the nuclei are small, hyperchromatic, and compressed to the cellular periphery. The changes are more prevalent in the gastric antrum than in the gastric body (100).
FIG. 4.47. Mucosal calcinosis. A: Low-magnification photograph of the gastric mucosa showing the presence of superficial aggregates of deeply pigmented crystalline material (arrows) that were positive with Von Kossa stains. B: Higher magnification showing the details of these mucosal deposits (arrows).

Ticlopidine sometimes causes lymphocytic gastritis, and methyldopa treatment sometimes leads to the development of autoimmune gastritis (101). Both interleukin-4 (IL-4) and tumor necrosis factor (TNF), agents used to treat patients with advanced cancer, cause acute gastric mucosal injury and hemorrhagic necrosis (102). Some drugs alter gastric motility, including anticholinergics, adrenergic agents, dopaminergic agents, narcotics, and erythromycin.

Acute Corrosive Gastritis

Extensive acute gastritis results from ingestion of corrosive agents (Fig. 4.48), be it accidental or suicidal. The types of agents that cause injury resemble those damaging the esophagus (see Chapter 2). Ingestion causes rapid and widespread gastric mucosal necrosis. The mucosal surface may appear black due to digested blood and mucosal necrosis. The damage often localizes to the prepyloric region, due to the stasis that occurs there allowing longer mucosal contact times with injurious agents than would otherwise exist. However, if only small quantities of the corrosive agent are consumed, then the injury may be more proximal in location. Initially there is mucosal hemorrhage and edema. The injury may extend deep into the gastric wall and patients with myonecrosis may perforate. Severe acute changes consist of coagulative necrosis (Fig. 4.49). The damage is patchy, with the most severe damage occurring in the areas of mucosal contact. Alkalis usually injure the esophagus more severely than the stomach; the reverse occurs with acids.

If the patient survives the acute event, fibrosis causes progressive stricturing. If the process progresses, complete obstruction
may result. Perforation, peritonitis, or massive hemorrhage complicates corrosive gastritis. One classifies corrosive gastritis into three grades, in a manner similar to that used for corrosive esophageal burns (Table 2.10).

**FIG. 4.48.** Corrosive gastritis from a suicidal ingestion of acid.

**Ischemic Gastritis**

While focal ischemia mediates many of the changes seen in acute (stress) gastritis, gastric infarction is rare because of the rich gastric vasculature. Severe, diffuse arterial sclerosis coupled with smoking and systemic hypertension (103) can lead to severe gastric damage and even gastric infarction (Fig. 4.50). Less severe ischemia develops secondary to vasculitis, bacterial gastritis, previous gastric surgery, disseminated intravascular coagulation (DIC), or volvulus (103). The features of ischemic gastritis include a coagulative necrosis (Fig. 4.50), the extent of which reflects the degree and duration of the ischemia. Transmural infarction is a rare and usually terminal event. The histologic features resemble those seen in the intestines and are discussed more extensively in Chapter 6.
**FIG. 4.49.** Lye ingestion in suicide attempt. *A:* Much of the stomach had become completely necrotic. The lesions were focally distributed throughout the gastric mucosa as seen in *A.* *B:* Higher magnification demonstrating the coagulative necrosis and edema of the gastric mucosa.

**FIG. 4.50.** Ischemic necrosis of the cardia and upper part of the fundus. *A:* This patient died of severe cardiovascular collapse. The patient was a known smoker, was hypertensive, and had previously undergone a surgical procedure. The death occurred during the postoperative period. *B:* Coagulative necrosis is seen affecting the gastric glands.

**Radiation Gastritis**

Patients receiving radiation in doses in excess of 4,000 rads demonstrate both acute and chronic gastritis with areas of epithelial necrosis and shallow ulcers (104). Gastric radiation injury assumes one of three forms:

- **Acute radiation gastritis** develops a few days to a few months following the radiation exposure. Inflammation is present early but it eventually diminishes. Extensive mucosal necrosis and superficial ulcers may be present. The endothelium swells, reducing vascular luminal caliber. Submucosal capillary ectasia is present. As the mucosa heals, it regenerates, but variable degrees of atrophy, fibrosis, edema, and endarteritis persist. The cytologic features may resemble those induced by many chemotherapeutic agents. Indeed, many cancer patients show the effects of
combined chemoradiation.

- One to two months following radiation exposure, some patients develop a deep acute ulcer, which usually wall off before perforation occurs. The ulcer represents the long-term effects of vascular damage and ischemia. Stigmata of radiation damage are histologically evident as evidenced by the vascular alterations and the presence of radiation fibroblasts in the surrounding fibrotic stroma (104).
- A month to several years following radiation exposure, a chronic ulcer, indistinguishable from a peptic ulcer, may develop. The only clues to its etiology are the clinical history, an unusually prominent antral fibrosis with oblitative endarteritis or foamy macrophages involving the submucosal blood vessels, and the presence of atypical hyperchromatic fibroblasts (“radiation fibroblasts”). The submucosa develops capillary telangiectasia and arterial wall hyalinization with intimal fibrosis. Patients may also develop severe atrophic gastritis. Even though mucosal regeneration occurs, gastric acid output remains reduced; many patients develop hypochlorhydia.

**Infectious Gastritis**

The stomach normally contains \(<10^3\) organisms/mL, with most coming from the oral cavity. Gastric pH determines the gastric bacterial content; pH levels below 4.0 kill most bacteria. If the pH is not at or below this level, the stomach does not sterilize itself and an abnormal flora may become established. Normal gastric motility and emptying also protect against bacterial infections. When dysmotility or pyloric obstruction develops, anaerobic organisms may accumulate. Not uncommonly one finds oral bacteria lying in the gastric lumen. They have a typical diplococcal or tetrad morphology and reach the stomach when swallowed with other oral contents or when they are carried there via the endoscope. These organisms have no clinical significance.

**Helicobacter Pylori**

**Transmission**

*HP* infections occur worldwide, although there are marked geographic variations in their incidence. The prevalence of *HP* infections in adults ranges from \(<15%\) in some populations to virtually 100% in less well-developed areas. There are also substantial variations among different ethnic groups in the same geographic locale (105). In developing countries, people become infected much earlier in life than in developed countries. The prevalence of *HP* infections correlates with lower socioeconomic status (106). The human stomach is the primary reservoir for the organism and it is transmitted via an oral–oral route and possibly via a gastric–oral and fecal–oral route (107). The infection is easily passed from one family member to another, particularly in areas of dense housing. Children under the age of 5 are most susceptible to *HP* infections. *HP* infections are present in gastric biopsies of 16.8% to 55% of children with abdominal pain, upper gastrointestinal symptoms, and histologic evidence of acute and/or chronic gastritis (106). The infection prevalence in developing countries can be as high as 75% by age 25. There has been a recent decline in the incidence of *HP* infections in the developed world, largely due to improved living conditions and a decrease in living density and family size. Even though the prevalence of *HP* infections is currently decreasing, at least 50% of the world population is infected with the organism (108).

Recurrent infections are usually a persistent infection rather than the acquisition of new infections. Infection with more than one *HP* strain can also occur (109). When AIDS patients become infected, the disease may exhibit particularly virulent characteristics and large numbers of organisms may be present.

**Pathogenesis**

*HP* is highly adapted to occupy a special ecologic gastric niche with unique features that allow it to enter the mucus of the mucosal barrier, attach to the epithelium, evade immune responses, proliferate, and colonize the gastric mucosa. The eventual outcome of *HP* infections reflects strain-specific, environmental, and host-related factors. After they are ingested, *HP* organisms must evade the bactericidal activity of the gastric lumen and enter the mucous layer. Corkscrewlike bacterial
movement and enzyme production (particularly urease and lipase) are important early in the infection (110,111). Bacterial proteases digest gastric mucin (194,195,196,197) facilitating bacterial movement and urease protects the HP from the luminal acid by creating an alkaline microenvironment around the bacterium (110,111).

HP bacteria normally reside in the unstirred layer of gastric mucus. They wind down to the epithelial surface, moving easily through the viscous environment above it, to attach themselves to the apical membranes of foveolar cells (Fig. 4.51). Bacterial adhesins recognize cell surface–specific proteins facilitating epithelial colonization. The best characterized adhesin, BabA, is a 78-kD outer bacterial membrane protein that binds to the fucosylated Lewis B blood group antigen (112). The Lewis blood group terminal carbohydrate structures are present on the ends of MUC1 carbohydrate side chains as well as on secreted mucins. MUC1 is highly polymorphic and evidence suggests that functional allelic differences affect infection susceptibility (113). HP bacteria also bind to MUC5AC, a major mucin produced by foveolar cells (114). The specificity of the binding, together with the limited distribution of the receptors, results in a restricted range of HP-colonized tissues. Bacteria unable to adhere to the epithelium are rapidly cleared from the mucosa. HP bacteria preferentially attach at or near intercellular junctions, penetrating the junctional complexes moving down along the lateral cell membranes. This disrupts intercellular tight junctions between viable cells, allowing luminal contents, including acid, to flow between the cells.

Most HP strains secrete the vacuolating cytotoxin VacA (115). The toxin inserts itself into the epithelial cell membrane and forms a hexameric anion-selective, voltage-dependent channel through which bicarbonate and organic anions can be released, possibly providing HP bacteria with their nutrients (116). VacA (117) also inhibits T-lymphocyte activation (118). Certain vacA gene variants produce more severe disease than others (119).

Most HP bacteria possess the cag pathogenicity island (cag PAI) that contains 29 distinct genes (120). Some of these genes facilitate translocation of the CagA protein into foveolar cells (121). Once in the cells, CagA is phosphorylated and binds to the SHP-2 tyrosine phosphatase (122), leading to host growth factor–like cellular responses, cytokine production, and cell proliferation (123). These cytokines mobilize leukocytes to areas of immune challenge. An EPIYA-repeat polymorphism influences the magnitude and duration of phosphorylation-dependent CagA activity (124). CagA also plays a major role in disruption of the apical junctional complexes (125). cagA-positive strains associate with increased epithelial cell apoptosis (126).

The oipA (outer inflammatory protein) gene encodes one of the outer membrane proteins and is an inflammation-related gene near, but not in, the CagA PAI. oipA functional status correlates with clinical presentation, HP density, and gastric inflammation. Cag PAI, babA2, and vacA status may

FIG. 4.51. Helicobacter pylori gastritis. Diff-Quik–stained section demonstrating spirally shaped bacteria intimately adherent to the surfaces of the epithelium as well as lying in the intercellular spaces. Both coccoid and spiral forms are present at the free surface.
be a surrogate marker for a functional oipA gene (127). OipA and the cag PAI are both necessary for full activation of the IL-8 promoter (128). Nitric oxidase synthase and cyclooxygenase-2 are induced by HP infections; these enzymes modulate the inflammatory responses.

Host Responses to *Helicobacter pylori*

*HP* infections cause gastric inflammation (gastritis) in almost all infected persons, although the severity of the changes varies among individuals. The injury results from both the infection and its associated inflammation. Bile reflux and dietary irritants may further enhance the deleterious bacterial effects. Additionally, anti-*HP* antibodies that cross-react with the gastric mucosa induce further damage (129). Some *HP*-infected patients develop an autoantibody response directed at the H+-K+-ATPase pump in parietal cells leading to atrophy of the corpus (129).

Initially neutrophils are recruited to the infected site, followed by the recruitment of T and B lymphocytes, plasma cells, and macrophages. The neutrophilic infiltrate and mononuclear phagocytic activation may be facilitated by bacterial urease production and induction of nitric oxide synthase and cyclooxygenase (130). *HP* infections generate significant cellular and humoral responses via antigenic stimulation of mucosal monocytes and T cells. The inflammatory cells produce numerous cytokines (TNF-α, interferon-γ, and interleukins 1, 6, and 8), prostaglandins, proteases, and reactive oxygen metabolites that cause epithelial necrosis and mucosal injury. IL-8, a potent neutrophil-activating chemokine expressed by gastric epithelium, plays a central role in the inflammatory response (127,128). *HP* bacteria containing the cag PAI induce a stronger IL-8 response than cag-negative strains (131). Some cytokines promote leukocyte adhesion to endothelial cells and others recruit additional leukocytes to the infected site. Mediators of local humoral responses, such as mucosal IgA, attract eosinophils, which then degranulate. Stimulated B cells differentiate into IgM, IgA, and IgG antibody–producing cells (132). IgA promotes complement-dependent phagocytosis and *HP* killing by polymorphonuclear neutrophils (PMNs). Secretory IgA synergizes with IgG to promote antibody-dependent cell-mediated cytotoxicity induced by PMNs, monocytes, and lymphocytes. High anti-*HP* IgG antibody levels correlate with severe antral gastritis and dense *HP* antral colonization (132).

*HP* infections result in hyposecretion, hypersecretion, or normal acid secretion, depending on disease stage. Hypochlorhydria develops when the gastritis extends proximally to involve (and destroy) the oxyntic mucosa. Acid secretion increases via several mechanisms (133). Patients with an increased parietal cell mass and hyperchlorhydria exhibit antral restriction of the gastritis because the high acid levels protect the corpus from bacterial adhesion and inflammation.

*Helicobacter pylori* Identification

*HP*, a Gram-negative, nonsporulated microaerophilic motile bacterium, measures 1 to 3 µm in length and 0.3 to 0.6 µm in width and has distinctive sheathed flagella that terminate in a bulbous disc structure. *HP* bacteria assume a curved, sinuous, or gently spiraled shape (Fig. 4.51). They lie freely in the mucous layer, are attached to surface foveolar cells, or lie between epithelial cells (Fig. 4.51). The faintly eosinophilic organisms closely resemble and may be obscured by mucus, contaminating oral flora or epithelial cell membranes. During treatment, *HP* bacteria may lose their typical spiral shape and assume new forms, including U shaped, circular, irregular rod shaped, or coccoid (134). Histologically, coccoid forms appear as solid, round, basophilic, dotlike structures ranging from 0.4 to 1.2 µm in diameter. They resemble nonpathogenic bacteria, fungal spores, and cryptosporidia (134), but can be correctly diagnosed using immunohistochemical stains.

Diagnostic tests for *HP* include microbial cultures, histologic or cytologic examination, rapid urease-based tests, and serologic studies. Histologic examination equals or even surpasses culture, especially when positive. However, the patchy nature of the infection requires examination of a minimum of two biopsies: One from the gastric antrum and one from the fundus. The greater the number of biopsies examined, the greater the diagnostic yield, especially in individuals with light infections. Mucosal biopsies have the advantage of allowing one to examine the mucosa for the presence of gastritis or other lesions. Careful examination of four specimens, two from the antrum and two from the corpus, has a high probability of establishing the correct diagnosis of the infection (135). *HP* bacteria are generally readily apparent on H&E-stained sections but the infection may be focal and patchy or there may be only sparse organisms, especially if intestinal metaplasia is present (136).
A number of special stains aid in HP detection including Dieterle silver, Warthin-Starry, Gram, toluidine blue, Giemsa, Wright-Giemsa, Brown-Hopps, acridine orange, or Diff-Quik stains. In addition, there are good immunohistochemical reagents that detect the organism. These are particularly useful in detecting the coccoid forms of the bacteria. Each laboratory has its favorite stain for detecting HP. While some laboratories routinely use special stains on most gastric biopsies to highlight the organism, we routinely only examine H&E-stained sections since the organism is generally readily appreciated, especially in heavy infections. Special stains only increase the diagnostic yield by 1% (137). If we use a special stain, we favor an immunohistochemical stain to detect the organism. We will use this if there is a chronic active gastritis and no organisms are seen in the H&E-stained section or if we are asked by the clinicians to specifically rule out an HP infection and HP bacteria are not seen in the H&E-stained preparation.

One can also identify HP in routinely prepared cytology specimens. Gastric mucosal brushings sample larger surface areas than a biopsy, thus serving as a useful adjunctive diagnostic test. HP bacteria are easily detected microscopically in smears stained with H&E, (modified) Giemsa, Papanicolaou (Fig. 4.52), and silver-based stains (Warthin-Starry and Steiner). The availability of an anti-HP polyclonal antibody allows immunohistochemical identification.

![Numerous Helicobacter pylori bacteria amidst naked nuclei in a gastric smear.](image)

Since culture, cytologic and histologic examination, and rapid urease-based examinations all require endoscopy, less expensive and noninvasive diagnostic tests have been developed; the most popular is the urea breath test. The HP bacteria produce urease following orally administered carbon-labeled urea. The urease activity releases carbon, which is absorbed into the blood and converted to bicarbonate and expired as radiolabeled CO₂. Such tests are rapid and reasonably easy to perform. They are indicated for the initial diagnosis of the infection and to follow patients for infection eradication. HP bacteria elicit antibody responses, allowing serologic testing. Serum enzyme-linked immunosorbent assays (ELISA) tests detect HP antibodies and indicate current or past infection. The test has a sensitivity of 80% to 100% and a specificity of 75% to 100% (138). There may be variations in the sensitivity based on strain differences. Serologic testing is not useful for detecting infection elimination. Stool antigen tests can be used to follow patients to determine if the infection has been eradicated if used after 8 weeks following treatment. They are particularly useful in children (139).

**Relationship of Helicobacter pylori to Gastric Diseases**

HP infection plays a significant role in the genesis of several gastric diseases (Table 4.8). The risk for developing gastric ulcers is highest in the nonatrophic forms of gastritis, whereas cancer associates with severe atrophic gastritis. Patient outcomes reflect differences in host susceptibility, organism virulence, or both. The development of gastritis, ulcer, and gastric cancer all involve an interplay between environmental, host, genetic, and microbial factors.
Gastritis

HP bacteria preferentially colonize the antrum, but they may infect any part of the stomach where they cause gastritis. When treated, the bacteria migrate from the antrum to the corpus with decreasing activity of the antral gastritis. Corpus gastritis is significantly more pronounced in patients with gastric cancer or a family history of gastric cancer (140). Infections with vacA-positive HP strains result in acute gastritis with cytoplasmic swelling and vacuolization, micropapillary changes, mucin loss, erosion of the juxtaluminal cytoplasm, and desquamation of surface foveolar cells. Regenerating cells form a multicellular layer with indistinct intercellular borders, creating syncytial polypoid excrescences (Fig. 4.53). Marked neutrophilic infiltrates appear in the mucous neck region (Fig. 4.54) and lamina propria in early acute gastritis; when severe, they aggregate in the pit lumens to form pit abscesses. The mucosa appears normal in thickness or even slightly expanded due to the lymphoplasmacytic cell infiltrate in the superficial lamina propria. At this point the lesion can be termed chronic active gastritis or active chronic gastritis. Eosinophils may also be present. The regenerative pit bases are characterized by mucin loss, cytoplasmic basophilia, increased mitoses, and hyperchromatic nuclei (Fig. 4.55) that are sometimes severe enough to mimic dysplasia. If the pits and glands appear parallel to one another with intervening lamina propria, one should be extremely hesitant before making a diagnosis of carcinoma, even in the presence of severe glandular or cellular atypia.

---

TABLE 4.8 Helicobacter pylori–related Diseases

<table>
<thead>
<tr>
<th>Acute gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic gastritis</td>
</tr>
<tr>
<td>Chronic active gastritis</td>
</tr>
<tr>
<td>Follicular gastritis</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
</tr>
<tr>
<td>Lymphocytic gastritis</td>
</tr>
<tr>
<td>Granulomatous gastritis</td>
</tr>
<tr>
<td>Gastric and duodenal ulcers</td>
</tr>
<tr>
<td>Some forms of autoimmune gastritis</td>
</tr>
<tr>
<td>Hyperplastic polypsa</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
</tr>
<tr>
<td>G-cell hyperplasia</td>
</tr>
<tr>
<td>Giant fold gastritis</td>
</tr>
<tr>
<td>Gastric adenocarcinoma</td>
</tr>
<tr>
<td>Gastric MALToma</td>
</tr>
<tr>
<td>Menetrier diseasea</td>
</tr>
</tbody>
</table>

*aUncommon.

MALT, mucosa-associated lymphoid tissue.
FIG. 4.53. Regenerating epithelium at the surface of an active chronic gastritis. This epithelium resembles that seen in an acute gastritis and occurs when chronic gastritis becomes active and loses the superficial epithelium.

FIG. 4.54. Active *Helicobacter pylori* gastritis. Large numbers of neutrophils infiltrate the mucous neck region causing pit abscesses and cytotoxic damage to the cells. *A:* Pits seen in longitudinal section. *B:* Pits seen in cross section.

Both the neutrophils and the HP destroy the epithelium, causing the mucous neck cells to proliferate in an effort to replace the
dying cells. Other changes in severe infections include epithelial cell dropout, microerosions, larger erosions, and ulcers. Erosions forming in the setting of HP infections typically lack the homogeneous eosinophilic necrosis seen in patients with stress ulcers or aspirin- or NSAID-related ulcers. One virtually never sees HP in individuals with a histologically normal gastric mucosa. However, it is not unusual to find significant quantitative differences in the amount of inflammation present relative to the number of HP bacteria that are present.

The acute foveolitis may associate with an epithelial alteration known as the “malgun” (clear) cell change. Malgun cells have enlarged euchromatic nuclei, abundant cytoplasm, and increased expression of proliferating cell nuclear antigen (PCNA) and cytokeratin 8, indicating that they are mitotically and metabolically active. Malgun cells may be morphologic indicators of genomic damage and repair (141).

**FIG. 4.55.** Regeneration in active chronic gastritis. The mucous neck region of the oxyntic mucosa demonstrates marked regeneration. The superficial surface has become completely eroded. An intense bandlike infiltrate of lymphocytes and plasma cells occupies the superficial mucosa. HP eradication causes rapid neutrophil disappearance. Eosinophils disappear more slowly. The surface changes reverse rapidly, and the epithelial cells acquire their normal shape and spatial organization within a few days of HP eradication. However, any atrophy that had developed remains, as do the lymphoid aggregates. These features become a permanent component of the once-infected gastric mucosa.

In *quiescent superficial gastritis*, the acute inflammation, edema, and vascular congestion disappear, and the epithelium returns to normal. However, the lamina propria contains increased numbers of mononuclear cells. Chronic superficial gastritis progresses to the next stage, chronic atrophic gastritis, over a period of 15 to 20 years (142). Since chronic gastritis develops as a patchy process, all stages in the evolution of chronic gastritis often coexist in a single stomach leading to the term *multifocal atrophic gastritis*, an entity discussed below with other forms of chronic gastritis. Lymphoid aggregates appear and sometimes lymphoid follicles develop. These are located deep in the mucosa, near the muscularis mucosae. When lymphoid follicles develop, with or without follicular centers (Fig. 4.56), the lesion is termed *follicular gastritis* (143). Antral lymphoid follicles can become quite prominent, sometimes causing mucosal nodularity, especially in children (144). The lymphoid aggregates represent an immune response to the bacteria. Their presence provides a useful marker for HP infections. Their number may decrease when the HP infections are treated. The features of HP-related mucosa-associated lymphoid tissue (MALT) lesions and the lymphomas that develop from them are discussed further in Chapter 18.
FIG. 4.56. Follicular gastritis. The gastric mucosa is infiltrated by mononuclear cells. The basal portion of the mucosa is expanded by a marked lymphocytic proliferation with the presence of prominent germinal centers.

Granulomatous gastritis develops in approximately 1% of HP-infected patients, usually in patients with small numbers of organisms. The small sarcoïd-type granulomas lie in the gastric lamina propria and HP bacteria can sometimes be found within them (145). The granulomas develop late in the disease, after the host has become sensitized to the organism. Antibody-coated bacteria ingested by macrophages may stimulate a histiocytic response (145).

Diffuse antral gastritis (DAG) is often considered to represent part of the peptic ulcer disease spectrum with antral and duodenal ulcers since it associates with increased gastrin, acid, and pepsin secretion (146). The hyperacidity creates a hostile environment for HP bacteria, restricting them to the antrum. The gastritis is characterized by an intense antral mononuclear infiltrate consisting of mature lymphocytes and plasma cells. Follicular gastritis is common. The epithelium may appear mucin depleted and there may be pit elongation.

Occasionally HP infections lead to the development of enlarged gastric folds in the gastric body, creating an endoscopic pattern suggestive of a hypertrophic gastritis/ gastropathy (147). The HP-induced mucosal fold thickening is termed giant fold gastritis. This differs from Menetrier disease (discussed in a later section) in that the mucosa is thinner in giant fold gastritis and there is less foveolar hyperplasia (148). Additionally, there are ultrastructural parietal cell alterations (148).

Gastric Ulcer

About 95% of patients with duodenal ulcer and 70% to 93% of patients with gastric ulcer have an HP infection (149). The mucosa, weakened by HP infection, becomes susceptible to peptic injury, especially in the face of increased gastric acid production, explaining the relationship between HP infection and peptic ulcer disease (149) as discussed further below.
Gastric Cancer

There is a well-established relationship between *HP* infection and gastric carcinoma, as discussed in detail in Chapter 5, and MALT lymphomas, as discussed in Chapter 18.

Gastroesophageal Reflux Disease

Some have suggested that *HP* infections may actually be beneficial to some humans. This assumption is based on the increased incidence of gastroesophageal reflux disease, Barrett esophagus, and adenocarcinoma of the esophagus following the eradication of *HP* in some countries. This aspect is discussed further in Chapter 2.

### TABLE 4.9 Comparison of *Helicobacter heilmannii* and *Helicobacter pylori* Infection

<table>
<thead>
<tr>
<th></th>
<th><em>H. heilmannii</em></th>
<th><em>H. pylori</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism differences</td>
<td>3.5–7.5 mm in length</td>
<td>3 mm in length/0.5 mm width</td>
</tr>
<tr>
<td></td>
<td>0.5 mm width</td>
<td>Curved or spiral</td>
</tr>
<tr>
<td></td>
<td>Up to 12 bipolar sheathed flagella</td>
<td>Four to six unipolar sheathed flagella</td>
</tr>
<tr>
<td></td>
<td>Tightly coiled, regular helical structure</td>
<td>Less tightly coiled</td>
</tr>
<tr>
<td>Urease producing</td>
<td>Urease producing</td>
<td>Urease producing</td>
</tr>
<tr>
<td>No in vitro culture available</td>
<td>Cultured under microaerophilic conditions</td>
<td></td>
</tr>
<tr>
<td>Location of the gastritis</td>
<td>Antrum/fundus</td>
<td>Antrum/fundus</td>
</tr>
<tr>
<td></td>
<td>No adherence to gastric epithelial cells</td>
<td>In gastric mucus/adherent to epithelium</td>
</tr>
<tr>
<td>Pathologic features</td>
<td>Mild chronic active gastritis</td>
<td>Chronic active gastritis</td>
</tr>
<tr>
<td></td>
<td>Seen with same stains as <em>H. pylori</em></td>
<td>Seen with silver staining, H&amp;E, Diff-Quik, Giemsa, immunostains</td>
</tr>
<tr>
<td>Host species</td>
<td>Dogs, cats, pigs, primates</td>
<td>Humans, ferrets, cats, dogs, pigs, rabbits</td>
</tr>
<tr>
<td>H&amp;E, hematoxylin and eosin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment

The goal of *HP* treatment is complete elimination of the organism. Triple therapy combines two or more antimicrobials with an antisecretory agent. The chief antimicrobials are amoxicillin, clarithromycin, metronidazole, tetracycline, and bismuth. However, some patients develop resistance to the antimicrobial drugs, with the frequency of this resistance differing depending on the drug that is used. Organism eradication is more difficult when a first treatment attempt has failed, usually due to the development of antibiotic resistance. Second-line therapy using quadruple therapies combines a proton pump inhibitor or *H₂*-receptor antagonist with a bismuth-based triple regimen therapy and high-dose metronidazole (150).
Other Helicobacter Infections

\textit{Helicobacter heilmannii}, previously known as \textit{Gastrospirillum hominis}, belongs to the \textit{Helicobacter} family (151) and is found in up to 1.1% of gastric biopsies (152). The infection may be acquired from pets (153). It is a Gram-negative, urease-producing bacterium that is twice as long as and more tightly coiled than \textit{HP} (154). The organisms tend to have five to eight prominent spiral turns making the organisms distinguishable from \textit{HP}. The features listed in Table 4.9 differentiate it from \textit{HP}. \textit{H. heilmannii} infections affect both children and adults, with a frequency of 0.3% to 0.7% (154,155). However, unlike \textit{HP} bacteria, which closely adhere to the gastric epithelium, \textit{H. heilmannii} bacteria usually lie freely in the lumen or deep in the gastric pits and necks of the pyloric glands with little or no epithelial attachment (Fig. 4.57). The organisms tend to be less numerous than in \textit{HP} infections and therefore, they can be easily missed. In one study, examination of touch cytology specimens had a higher rate of diagnosis than the examination of biopsy specimens (156). The organism produces a chronic active gastritis but it is usually milder than that produced by \textit{HP}. Prominent lymphoid aggregates may be present (157) and ulcers may develop. Gastric colonization is focal and restricted to the antrum. The organism is detectable with the same stains used to detect \textit{HP}. Other changes that may be present include foveolar hyperplasia, vascular congestion, and edema, changes mimicking a chemical gastropathy (156). The infection rarely results in gastric carcinoma or MALT lymphomas.

Suppurative Gastritis

Most cases of suppurative (phlegmonous) gastritis antedate the antibiotic era. The disease typically affects severely debilitated individuals. Patients present with dramatic episodes of nausea, vomiting, and severe, acute, noncolicky, epigastric pain. Commonly, peritonitis or pleural effusions develop. The clinical course resembles that of patients with a perforated viscus. The mortality rate approaches 100% unless the affected part of the stomach is resected. Some patients develop abscesses. The most common offending organisms belong to \textit{Streptococcus} species.

The stomach appears dilated and the wall is thickened, rigid, and purplish. Marked submucosal brawny edema leads to flattening of the rugal folds and hyperemia; fibrinous serous adhesions are also present. In some cases the mucosa contains focal necrosis; in others, a mucopurulent exudate completely replaces the mucosa. Acute inflammation with or without microabscesses and hemorrhage affects the submucosa. Widespread intravascular thrombosis involving the mural vessels results in secondary ischemic gangrenous necrosis with transmural inflammation. The muscularis propria appears variably inflamed and necrotic. A Gram stain demonstrates bacteria in the tissues.
Emphysematous Gastritis

Emphysematous gastritis, a form of suppurative gastritis, results from infections by gas-forming organisms, most commonly *Clostridium*, *Escherichia coli*, *Streptococcus*, *Enterobacter*, and *Pseudomonas aeruginosa* (158). Predisposing conditions include previous surgery, alcohol abuse, corrosive ingestion, pancreatitis, and cancer (158). Clinical features include an acute abdomen, systemic toxicity, and radiographic evidence of air bubbles in the gastric wall. Approximately two thirds of patients die of their disease; long-term complications include gastric fibrosis with stricture formation. The gastric wall feels crepitant due to the presence of numerous, variably sized, air-filled, intramural spaces. In advanced cases, the gastric wall appears thickened, gangrenous, and necrotic.

![FIG. 4.58. Emphysematous gastritis. Photograph of the gastric mucosa showing the presence of an inflamed, partially necrotic, gastric mucosa. Deep in the mucosa one sees large, dilated, air-filled spaces.](image)

The most prominent histologic findings consist of submucosal thickening, edema with transmural neutrophilic collections, a purulent serosal surface, patchy mucosal necrosis, and pneumatosis (Fig. 4.58). The infection rarely spreads to adjacent organs.

**Syphilis**

Syphilis affects the stomach in both its secondary and tertiary stages, but <1% of patients with syphilis develop gastric disease (159). Patients develop erosive gastritis or gastric ulcers with heaped, nodular edges. Erosions first develop in the pylorus, causing patients to present with gastric outlet obstruction. An infiltrative disease pattern causes thickened, edematous, rugal...
folds. Usually, the histologic features of H&E-stained slides are suggestive, but not diagnostic, of syphilis. One sees a diffuse gastritis containing a dense plasmocytic infiltrate, sometimes with prominent perivascular cuffing. Variable numbers of neutrophils and lymphocytes accompany the plasma cells. The lymphocytes may create lymphoepithelial lesions mimicking a MALToma. Neutrophils invade the gastric pits (Fig. 4.59). Variable degrees of glandular destruction and reactive atypia result. The inflammation extends into the submucosa with concomitant edema and fibrosis. A vasculitis is often present (160). However, the marked proliferative endarteritis or

proliferative endophlebitis typical of syphilitic lesions elsewhere is often absent. This may reflect the superficial nature of most gastric biopsies, which do not include the submucosa where these vessels are located. An ill-defined granulomatous process may be present. Silver stains (Fig. 4.59), dark-field examination, immunohistochemical stains, and polymerase chain reactions (PCRs) all demonstrate the spirochetes (161). The silver stains are not specific for the spirochetes since they also stain Helicobacter, but the morphology of the organisms is sufficiently different that they should not be easily confused.

FIG. 4.59. Syphilitic gastritis. A: The tissue appears to consist almost exclusively of inflammatory cells. There are rare residual glands (arrows). The inflammatory infiltrate consists of plasma cells and lymphocytes. B: Silver stain on this biopsy demonstrating numerous silver-stained spirochetes within the lamina propria. (Case courtesy of Dr. D. Schwartz, Department of Pathology, Emory University, Atlanta, GA.)

The lesions of tertiary syphilis appear infiltrative, ulcerative, or gummatous. In later-stage disease, the muscularis propria and submucosa become more severely involved and the stomach acquires a fibrotic, hourglass, or leather bottle (linitis plastica) appearance. Squamous metaplasia with the subsequent development of squamous cell carcinoma may complicate syphilitic gastritis (162).

**Tuberculosis**

Tuberculous gastritis occurs much less commonly in North America and Western Europe than it did decades ago. Less than
1% of individuals with pulmonary or disseminated disease (Fig. 4.60) develop gastric involvement. Primary gastric tuberculosis is even rarer (163). The relative rarity of gastric tuberculosis results from three factors: The scarcity of lymphoid follicles in the stomach, the high gastric acidity, and the rapid passage of organisms through the stomach.

Gastric tuberculosis produces multiple shallow ulcers and confluent caseating granulomas that cause local tissue destruction with little reactive fibrosis. The gastric wall becomes thickened and ulcerated, and fistulas develop. Tuberculosis usually affects the antrum and duodenum in a distribution similar to that seen in syphilis and Crohn disease. Rarely, extensive confluent granulomas thicken the pylorus, causing gastric outlet obstruction. The granulomas involve the mucosa, submucosa, or serosa. Perigastric lymph nodes frequently contain granulomas. The diagnosis rests on finding acid-fast organisms in the granulomas, although they may be very sparse. PCRs identify the bacterial DNA in cases that are negative on special stains.

**Viral Infections**

One can diagnose gastric viral infections histologically, cytologically, or by culture. Immunohistochemical reagents and genetic probes aid in their detection and specific diagnosis.

Patients previously exposed to *cytomegalovirus* (CMV) often maintain latent virus in many organs without evidence of tissue damage. The latent infections reactivate when patients age, develop serious disease, or become immunosuppressed. The infections are most common in transplant and AIDS patients. Infections affect children as young as 22 months (164). Patients present with epigastric pain, nausea, and vomiting. Complications include bleeding, ulcers, gastric outlet obstruction, and perforation. Unusual presentations include gastrocolic fistula (165) and pediatric forms of Menetrier disease (164). The stomach may appear normal or there may be an erosive gastritis. When severe, the gastric folds appear thickened and edematous with reduced antral distensibility simulating antral malignancy (166).

Gastric CMV infections display one of two major histologic patterns: Either a subtle infection or an obvious CMV gastritis. In more subtle forms of the disease, the mucosa appears almost normal with rare cells containing viral inclusions. CMV inclusions affect mucous neck cells and mesenchymal cells, including endothelial cells, macrophages, fibroblasts, and smooth muscle cells (Fig. 4.61). Usually one must examine multiple serial sections to find the viral inclusions. One can also routinely perform immunohistochemical stain in patients with a strong likelihood of having the infection. Patients with severe CMV infections demonstrate an obvious gastritis with inflammation and ulcers, and numerous prominent nuclear and cytoplasmic...
viral inclusions. Deep biopsies or resection specimens may disclose the presence of CMV-containing smooth muscle or ganglion cells; these patients may develop disordered gastric motility. *Herpes simplex virus* rarely infects the gastric mucosa, contrasting with frequent esophageal involvement. Herpetic gastritis presents as yellowish plaques or edematous mucosal nodules separated by criss-crossed ulcers. Biopsies from vesicle and ulcer bases disclose epithelial cells containing typical eosinophilic intranuclear inclusions and ballooning cytoplasm (Fig. 4.62). The infection remains restricted to epithelium; it does not affect mesenchymal cells. Herpes zoster may also infect the stomach.

**Fungal Infections**

Fungal infections often present as an acute gastritis, although some fungal organisms cause a granulomatous gastritis. Table 4.10 lists entities in the differential diagnosis of granulomatous gastritis. Death results from disseminated infection or from hemorrhage following fungal invasion of gastric blood vessels, especially in patients with peptic ulcer disease.

**Candida Infections**

*Candida* infections account for most cases of fungal gastritis. Infections develop in debilitated, immunosuppressed, alcoholic, or achlorhydric individuals (167). The infection grossly appears localized, sometimes presenting as discrete, gray-yellow, creamy, mucosal plaques, or it is seen in peptic ulcers (Fig. 4.63) where it represents either a *Candida* infection or secondary colonization of a peptic ulcer. Most often, fungi colonize superficial parts of ulcer beds, a finding with little clinical significance since the organism does not infect adjacent viable tissues. In healthy persons, the *Candida* disappears when the ulcer heals. Alternatively, the fungus aggravates the peptic ulcer by invading arterial walls in the ulcer base, causing arterial rupture and massive hemorrhage. In this situation, the fungus plays a significant role in patient morbidity and mortality.

**TABLE 4.10 Gastric Granulomatous Disorders**

<table>
<thead>
<tr>
<th>Foreign body granulomas</th>
<th>Food granulomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suture granulomas</td>
</tr>
<tr>
<td></td>
<td>Barium granulomas</td>
</tr>
<tr>
<td></td>
<td>Kaolin granulomas</td>
</tr>
<tr>
<td></td>
<td>Talc granulomas</td>
</tr>
<tr>
<td></td>
<td>Beryllium granulomas</td>
</tr>
<tr>
<td></td>
<td>Material used to cut drugs by drug addicts</td>
</tr>
<tr>
<td>Infectious granulomas</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium intracellulare</em></td>
</tr>
<tr>
<td></td>
<td>Whipple disease</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Mucor</td>
</tr>
<tr>
<td></td>
<td>South American blastomycosis</td>
</tr>
<tr>
<td></td>
<td>Anisakiasis</td>
</tr>
<tr>
<td></td>
<td><em>Helicobacter pylori</em></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Crohn disease</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Isolated granulomatous gastritis</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Associated with gastric carcinoma</td>
</tr>
</tbody>
</table>
Chapter 4

<table>
<thead>
<tr>
<th>Associated with gastric lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langerhans cell histiocytosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous disease of childhood</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
</tr>
<tr>
<td>Allergic granulomatosis and vasculitis</td>
</tr>
<tr>
<td>Plasma cell granulomas</td>
</tr>
<tr>
<td>Tumoral amyloidosis</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
</tr>
</tbody>
</table>

Histologic examination discloses the presence of fungal spores and/or pseudohyphae on the surface of peptic ulcers. The pseudohyphae invade the underlying tissues in invasive disease (Fig. 4.64). Grossly visible nodules result from microabscesses in which pseudohyphae invade and thrombose adjacent vessels and then coalesce to produce linear ulcerations presumably secondary to ischemia. Rarely, fungal bezoars develop. When diagnosing gastric Candida, a comment should be made as to whether the fungi invade the tissues or merely colonize the mucosal or ulcer surface and whether the organisms are spores, pseudohyphae, or both.

**Other Fungal Infections**

Other gastric fungal infections include Aspergillus, Mucor, Coccidioides, Histoplasma (168), Cryptococcus neoformans (169), Pneumocystis carinii (170), and Torulopsis glabrata. These organisms, like Candida, sometimes produce fungal bezoars. Zygomycotic gastric infections, formerly known as phycomycoses or mucormycoses, complicate chronic malnutrition. Gastric histoplasmosis complicates disseminated disease, producing a picture that mimics gastric carcinoma, gastric ulcer, polyps, or hypertrophic gastropathy. Vascular invasion causes hemorrhage and death. Both tumorlike nodules and perforated ulcers develop. The histologic features of these infections resemble those seen elsewhere.
FIG. 4.61. Cytomegalovirus (CMV) gastritis. A: Renal transplant patient with subtle CMV infection. A small intranuclear inclusion is noted in the mucous neck cells (arrow). B: Gastric biopsy in a patient who had undergone a liver transplant. Numerous CMV inclusions are present (arrows). These are both cytoplasmic as well as intranuclear. C: Gastric biopsy in a renal transplant patient demonstrating the presence of intranuclear inclusions within the endothelial cells (arrows). D: Subtle infection demonstrating the presence of a diffuse gastritis. Rare intranuclear inclusions are evident both in the epithelium as well as in the stromal cells (arrows).
FIG. 4.62. Herpes simplex viral inclusion (arrow) in a degenerating epithelial cell associated with chronic gastritis in a patient with AIDS.
FIG. 4.63. Gastric candidiasis. Three ulcers are present, each of which was colonized by the fungi. In addition, numerous whitish plaques were densely adherent to the mucosa. The arrows point to three of these. Note that prominent atrophy is present.

FIG. 4.64. Gastric candidiasis. Hyphae at the base of a necrotic gastric ulcer.

Parasitic Infections

Patients with parasitic gastric infections may exhibit mucosal eosinophilia or only a nonspecific gastritis. The diagnosis rests on demonstrating the specific organism.

Anisakiasis

Gastric anisakiasis develops in individuals consuming raw or poorly cooked fish (171) or pickled herring (172). The infected fish spend part of their time in freshwater and part in salt water, such as salmon, herring, cod, pollack, and mackerel. When people eat infected fish, the larvae penetrate the gastric, small intestinal, or colonic mucosa, causing acute focal inflammation. Patients present with intolerable abdominal pain, usually within 12 hours of larval ingestion. Unlike other worms, anisakiasis preferentially affects the stomach rather than the intestines. Gastric perforation may cause omental granulomas. Endoscopy allows removal of the larvae (173). Severe, acute infections appear phlegmonous and the gastric wall becomes infiltrated with numerous eosinophils, neutrophils, plasma cells, lymphocytes, histiocytes, and sometimes giant cells.
Other Parasitic Infections

Gastric cryptosporidiosis (Fig. 4.66) represents a legacy of the AIDS epidemic and the pathologic features resemble those seen in the intestines. *Ascaris lumbricoides* infects sites adjacent to the small bowel, including the stomach. Patients may
present with gastric outlet obstruction due to an antral roundworm mass (174). *Giardia* can be found in the gastric antrum in approximately 9% of patients with duodenal infections (175). Patients with gastric *Diphyllobothrium latum* infections present with megaloblastic anemia. The gastric mucosa shows variable degrees of chronic gastritis and atrophy. Other rare gastric parasitic infections include *Strongyloides* (Fig. 4.67), toxoplasmosis, schistosomiasis, and filaria.

**Rickettsial Infections**

Rickettsial infections affect the stomach in patients with generalized disease. The histologic changes are subtle and easily overlooked if one is unaware of the patient's condition. The mucosa develops petechial hemorrhages. A mild nonspecific chronic inflammatory response affects small vessels. The organism can be demonstrated within the endothelium ultrastructurally or by immunohistochemistry (176,177).

**Gastric Changes Present in AIDS Patients**

AIDS patients develop several gastric abnormalities, the most common of which is CMV gastritis. Patients with *HP* infections often have severe disease with a large number of organisms present. *HP* bacteria colonize cell surfaces and also the lamina propria, producing a prominent inflammatory response. The infection may also cause marked enlargement of the gastric folds. The inflammation resolves with treatment. Phlegmonous gastritis sometimes causes a fatal fulminant gastritis. Cryptosporidial or syphilitic infections of the antral mucosa cause isolated antral narrowing. Other rare infections of the stomach include those due to *Pneumocystis* and *Toxoplasma*.

*FIG. 4.67. Gastric Strongyloides in a patient with a widely disseminated infection.*

Some patients develop *AIDS gastropathy*, a disorder characterized by a reduction in parietal cell mass, gastric acid, and pepsinogen secretion and an increase in mucus secretion. The disease is mediated by the presence of antiparietal cell antibodies. Hypochlorhydria predisposes the patient to gastrointestinal bacterial infection.

**Chemical Gastropathies ( Reactive Gastropathies)**

Chemical gastropathy is the second most common diagnosis made on gastric biopsies (178). Chemical gastropathies result from surface-damaging agents in the gastric lumen. NSAIDs and alkaline reflux are its commonest causes. Endoscopically, gastritis is present, but there is little histologic evidence of inflammation. All chemical gastropathies resemble one another, making it impossible to determine the exact etiology in the absence of identifiable bile or a pertinent clinical history. Clues that suggest the presence of a chemical gastropathy are listed in Table 4.11. The most diagnostic features include gastric pit elongation and tortuosity, often with reactive changes and foveolar mucin depletion. There is only minimal chronic inflammation and no acute inflammation, unless that the patient has coexisting *HP* gastritis, NSAID-induced ulcers, or stress
gastritis.

**Uremic Gastropathy**

Uremic patients may develop gastric mucosal abnormalities since urea and other metabolites disrupt the mucosal barrier (179). Uremia preferentially stimulates differentiation of mucus neck region stem cells into parietal cells and ECL cells, leading to an increased parietal cell mass, decreased production of foveolar cells, a thinned mucous gel layer, and increased acid secretion. Abnormalities in bile salt formation and hypergastrinemia enhance the acid injury. The stomach contains intramucosal hemorrhages varying in size from petechiae to large ecchymoses. Uncommonly, gastric mucosal necrosis with superimposed active ulceration develops. The histologic features overlap with those seen in stress gastritis. Superficial gastritis, erosions, and ulcers may be present. Uremic patients may also have the Kayexalate crystals described earlier in the mucosa.

<table>
<thead>
<tr>
<th>TABLE 4.11 Clues That Suggest the Presence of a Chemical Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pit expansion</td>
</tr>
<tr>
<td>Superficial edema</td>
</tr>
<tr>
<td>No organisms</td>
</tr>
<tr>
<td>No polyps</td>
</tr>
<tr>
<td>Muscle fibers</td>
</tr>
<tr>
<td>Muscle fibers</td>
</tr>
</tbody>
</table>

Helicobacter pylori infection may be superimposed on a chemical gastropathy confounding the histologic features.

**Alkaline Reflux (Bile Reflux) Gastritis**

Alkaline reflux gastritis develops in patients with abnormal pyloric sphincter function, often resulting from previous surgical interventions, chronic alcohol ingestion, or aging. Both alkaline duodenal secretions and bile damage the gastric mucosa. Bile salts increase mucosal permeability to hydrogen ions (180), resulting in H⁺ back-diffusion. The most severe injury occurs in the antrum. The amount of reflux often correlates with symptom severity, but the endoscopic and histologic features rarely correlate with one another.

The histologic features of alkaline reflux gastritis are quite subtle and often overlooked. They include glandular elongation, tortuosity, and hypercellularity of the gastric pits; foveolar hyperplasia; and mucosal villiform transformation (Fig. 4.68).

The regenerative glands may appear more angular than usual. The foveolar cells show mild mucin depletion and vacuolization. Other changes include capillary congestion and vasodilation in the superficial lamina propria, edema, and increased numbers of smooth muscle fibers that sometimes extend quite high in the lamina propria. The number of chronic inflammatory cells and neutrophils is generally sparse (181). The lack of inflammation is in striking contrast to the degree of epithelial hyperplasia. Bile may be present on the luminal surface or within glands (Fig. 4.69). Glandular atrophy develops in patients who have had an antrectomy, due to loss of the gastrin-producing G cells in the antral mucosa. The output of gastric acid, however, remains unchanged (181). Intestinal metaplasia and/or atrophy may develop in longstanding disease.
FIG. 4.68. Alkaline reflux gastritis. Some patients develop prominent villiform transformation of the surface with foveolar hyperplasia that can be quite pronounced, as in this photograph. The hyperplastic epithelium almost appears adenomatous.
FIG. 4.69. Alkaline reflux gastritis. *A:* At first glance, the mucosa does not appear to be abnormal, although there might be a slight increase in the number of chronic inflammatory cells within the mucosa. *B:* Higher magnification of a different area of the same biopsy demonstrating the presence of an irregular gland containing bile crystals (*arrows*). The glandular epithelium appears regenerative both within the mucous neck region and at the free surface. The lamina propria contains a very mild increase in the number of mononuclear cells.

**Chronic Gastritis**

Nonspecific chronic gastritis has many etiologies (Table 4.12) that produce similar or overlapping histologic features. For this reason, the correlation between clinical symptoms, endoscopic features, and histologic evidence of chronic gastritis is poor. However, three distinct forms of chronic gastritis can be delineated: Diffuse antral, fundic, and multifocal (Fig. 4.70). Diffuse antral and multifocal gastritis are sometimes referred to as type B gastritis, and both share *HP* as an etiologic factor. The major difference between the two is that diffuse antral gastritis is nonatrophic, whereas multifocal gastritis progresses to atrophic gastritis. These forms of gastritis show specific histologic, clinical, epidemiologic, and etiologic parameters (Table 4.13) (182,183). Chronic gastritis can be further classified as active or quiescent depending on its histologic features.

Multifocal atrophic gastritis usually complicates longstanding *HP* infections, it although rarely complicates other conditions.

**TABLE 4.12 Etiology of Chronic Gastritis**

<table>
<thead>
<tr>
<th>Chronic alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Reflux of bile and alkaline secretions</td>
</tr>
<tr>
<td>Autoimmune injury</td>
</tr>
<tr>
<td>Hypersecretion</td>
</tr>
<tr>
<td>Gastric resection</td>
</tr>
<tr>
<td>Environmental factors including diet</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
</tr>
</tbody>
</table>

**TABLE 4.13 Fundic Versus Antral Gastritis**
### Fundic vs. Type B Antral

<table>
<thead>
<tr>
<th><strong>Fundic</strong></th>
<th><strong>Type B Antral</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundal, antral sparing</td>
<td>Antral, then spreads proximally</td>
</tr>
<tr>
<td>Immunologic factors</td>
<td>Dietary, intraluminal factors</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Pernicious anemia rare</td>
</tr>
<tr>
<td>Hypo- or achlorhydria</td>
<td>Hyperchlorhydria</td>
</tr>
<tr>
<td>Parietal cell antibodies</td>
<td>No parietal cell antibodies</td>
</tr>
<tr>
<td>Intrinsic factor antibodies</td>
<td>No intrinsic factor antibodies</td>
</tr>
<tr>
<td>Hypergastrinemia (due to antral sparing)</td>
<td>Gastrin levels low or normal</td>
</tr>
<tr>
<td>No familial tendency</td>
<td>Familial tendency</td>
</tr>
<tr>
<td>Parietal and chief cell destruction</td>
<td>No parietal and chief cell destruction</td>
</tr>
<tr>
<td>Tends to persist and progress</td>
<td>Progression less rapid</td>
</tr>
<tr>
<td>Gastric atrophy common</td>
<td>Peptic ulcers common</td>
</tr>
</tbody>
</table>

*Helicobacter pylori* does not play a role

### Helicobacter pylori–Associated Chronic Gastritis

Following *HP* infection the mucosa may become inflamed producing acute gastritis and then chronic active gastritis (Fig. 4.71). Early, the chronic inflammation remains confined to the superficial mucosa (Fig. 4.72). Superficial lamina propria lymphoplasmacytosis then extends for variable distances into the glandular compartment. With time, the inflammation

![FIG. 4.70.](image) The different forms of chronic gastritis show different gastric localizations. **A:** Autoimmune gastritis predominantly affects the fundus and body and spares the antrum. **B:** Hypersecretory gastritis predominantly affects the antrum and is associated with duodenal ulcers. **C:** Multifocal atrophic gastritis starts at the corpus–antral junction spreading proximally and distally. This form associates with gastric ulcers along the lesser curvature.
becomes confluent until it occupies the full thickness of the mucosa. T cells increase in number in both the epithelium and the lamina propria. Neutrophils, eosinophils, basophils, B cells, macrophages, monocytes, plasma cells, and mast cells infiltrate the mucosa resulting in mucosal damage. When the infection is treated, the mucosa regenerates and returns to normal; if the destroyed glands fail to regenerate, the space that they previously occupied in the lamina propria may be replaced by fibroblasts and extracellular matrix leading to an irreversible loss of functional mucosa and a change diagnosable as atrophy (Figs. 4.73 and 4.74). As atrophy develops, areas of intestinal metaplasia replace the native gastric mucosa. This may represent an adaptive response because HP bacteria cannot colonize the metaplastic cells since they lack the necessary bacterial adhesion factors discussed earlier. However, attachment of HP to areas of what appears to be incomplete intestinal metaplasia has been documented (184). These cells in fact represent a hybrid epithelium whose cells share characteristics of both gastric surface mucous cells and intestinal metaplastic cells (185). The intestinal metaplasia decreases the sites hospitable to the growth of the HP. However, the inflammation and its associated reparative processes continue in sites of persisting infection. As a result, the stomach acquires a mixed pattern of architecturally normal but inflamed areas (gastritis) alternating with expanding patches of atrophy and metaplasia producing multifocal atrophic gastritis (MAG) (186).

**FIG. 4.71.** Chronic active gastritis. The mucous neck regions appear hyperchromatic and are infiltrated with acute inflammatory cells.

MAG is the most common form of chronic atrophic gastritis among populations at high risk for developing gastric cancer, and it strongly associates with the presence of HP infections (187). A high intake of salt and nitrate and smoking contribute to its development (188,189). The development of atrophy determines the two main divergent outcomes of HP-related gastritis. Individuals who do not develop atrophy have an increased risk of duodenal ulcers but not of gastric cancer (187). Those who develop atrophy are at risk of gastric ulcers, mainly located on the lesser curvature around the incisura angularis, and they may develop intestinal metaplasia, dysplasia, and intestinal-type gastric adenocarcinoma (187). The progression of the gastritis to carcinoma involves a series of well-defined stages as discussed in detail in Chapter 5.
FIG. 4.72. Superficial gastritis. A: The superficial portion of the gastric mucosa is populated with a bandlike infiltrate of mononuclear cells. B: Higher magnification showing the presence of large numbers of lymphocytes and plasma cells.
FIG. 4.73. Atrophic gastritis in the setting of *Helicobacter pylori* infection. *A:* There is loss of pit, mucous neck, and glandular areas of the mucosa associated with a mononuclear and neutrophilic cell infiltrate. There is also a lymphocytic aggregate at the base of the mucosa. *B:* Higher magnification of the area of glandular destruction showing epithelial dropout.
FIG. 4.74. Atrophic gastritis. These three figures show varying degrees of atrophic gastritis. A: Active chronic gastritis with glandular dropout. The mucosa contains prominent lymphocytic collections. B: Higher magnification of the lesion shown in A demonstrating the intense infiltration of the lamina propria by mononuclear cells and active destruction of the mucous neck region by polymorphonuclear leukocytes. C: This biopsy comes from a stomach that has become so atrophic that gastric pits and glands have both disappeared and all that remains is a simple mucosal lining covered by foveolar epithelium.

MAG first appears on the lesser curvature at the incisura (187). Later, atrophic foci appear along the lesser curvature and on both sides of the antral–corpus junction in the shape of an inverted V. In untreated patients the atrophy may spread to the corpus. Histologically, MAG consists of superficial gastritis, regenerative epithelial changes, glandular loss, intestinal metaplasia, and atrophy.

Atrophic Gastritis

Gastric atrophy, a preneoplastic condition (56), especially in populations where gastric carcinoma is prevalent, develops following gastric injury induced by various factors. There are substantial geographic and ethnic variations in the prevalence and severity of atrophic gastritis and its distribution within the stomach. Its features differ, primarily determined by the clinical setting in which it arises, the lesion location, and etiologic, environmental, and host factors. One may also grade chronic atrophic gastritis as active or quiescent based on the presence or absence of acute inflammation.

Because extensive atrophy and metaplasia appear to increase the risk of gastric cancer, it is important to determine the severity of these lesions in biopsies (187). However, the definition of gastric atrophy is controversial and there is poor agreement in grading its severity, especially when it is only mild or moderate in nature (190). It is more difficult to appreciate minor degrees of atrophy in the antrum than in the corpus. This is due to the fact that in the antrum the gastric pits tend to be long and the antral glands normally lie in a loose connective tissue stroma. The interpretation is made more difficult due to the presence of an intense antral inflammatory infiltrate that typically complicates HP gastritis and expands the lamina propria. In contrast, the glands of the oxyntic mucosa are normally tightly packed and lined by a population of parietal and chief cells that occupy well-established positions from the neck zone to the deepest portion of the gland. In advanced atrophic gastritis, the glands disappear, the inflammation recedes, and the cellularity of the lamina propria returns to normal. Pre-existing reticulin fibers collapse on one another between the pits.

There is a large section of literature devoted to defining and quantifying gastric atrophy (56,186,191), particularly since atrophy is an early step in the carcinogenic process (187). It has been recommended that the term atrophic gastritis be restricted to those cases in which there is glandular loss that is replaced by extracellular matrix and fibroblasts, and/or when intestinal metaplasia is present (186). We agree with this approach.

P.186

TABLE 4.14 Definitions and Grading Guidelines for Each of the Histologic Features to Be Graded in the Sydney System
Chapter 4

Feature Definition Grading Guidelines

Chronic inflammation Increased lymphocytes and plasma cells in the lamina propria Mild, moderate, or severe increase in density

Activity Neutrophilic infiltrates of the lamina propria, pits, or surface epithelium Less than one third of pits and surface infiltrated = mild; one third to two thirds = moderate; more than two thirds = severe

Atrophy Loss of specialized glands from either antrum or corpus Mild, moderate, or severe loss

Intestinal metaplasia Intestinal metaplasia of the epithelium Less than one third of mucosa involved = mild; one third to two thirds = moderate; more than two thirds = severe.

*Helicobacter pylori* H. pylori density Scattered organisms covering less than one third of the surface = mild colonization; large clusters or a continuous layer over two thirds of surface = severe; intermediate numbers = moderate colonization

The revised Sydney classification for gastritis provides guidelines for grading different histopathologic changes in gastric biopsies (56). It aims to produce a standardized, consistent histologic interpretation of gastritis based on topography, morphology, and etiology and includes a morphologic component by which five histologic variables (chronic inflammation, neutrophil activity, glandular atrophy, intestinal metaplasia, and *HP* density) are graded (Table 4.14) (56). If one chooses to use this system, the pathology report should note the presence or absence of each variable and when present, each of these variables can be graded on a mild, moderate, or marked scale using the published visual guidelines (56). The *HP* density should be evaluated in nonmetaplastic areas.

![FIG. 4.75. Severe atrophic gastritis. A: The stomach has an almost complete loss of rugal folds. B: There is significant glandular loss and thinning of the mucosa. A few residual glands remain.](image)

The degree of atrophy can be graded as mild, moderate, or severe by estimating the thickness of the glands in relationship to...
the entire mucosal thickness. This is facilitated by examining properly oriented biopsies containing the muscularis mucosae. Increasing degrees of atrophy associate with glandular cystic dilation, epithelial atypia, and intestinal metaplasia. Loss of all the glands qualifies for the diagnosis of severe atrophic gastritis (Fig. 4.75). Intestinal and pyloric metaplasia commonly develop. A confident diagnosis of atrophy can be made when epithelial metaplasia and/or gastric gland loss affects at least 50% of the total area of gastric biopsy material (192), assuming that there has been adequate mucosal sampling as recommended by the updated Sydney classification (56). Three features, the ratio of the glandular

length to total mucosal thickness, the proportion of the secretory compartment area occupied by glands, and the number of glandular cross sections per 40× microscopic fields, consistently discriminate atrophic from nonatrophic lesions, particularly if one avoids areas of intestinal metaplasia and lymphoid follicles (191). Most patients with intestinal metaplasia have enough nonmetaplastic areas that the degree of atrophy can be evaluated. In patients in whom the entire stomach has been replaced by intestinal metaplasia, the patients are given the highest atrophy score (191). One factor that may call attention to the presence of atrophy is the presence of intestinal metaplasia, since the two lesions are commonly found together, but in its absence, mild or focal atrophy is easily missed.

Both antral and autoimmune gastritis show a marked inflammatory infiltrate consisting of plasma cells, lymphocytes, and variable numbers of eosinophils in all levels of the lamina propria. Initially, chronic inflammation fills the spaces left by glandular destruction and loss, thereby maintaining normal mucosal thickness. Plasma cells tend to lie superficially in the lamina propria, whereas lymphocytes lie deeper in the mucosa. Chronic progressive atrophy of the specialized epithelium results in an almost total loss of acid- and pepsinogen-secreting cells in the body of the stomach in autoimmune (type A) gastritis and of the antral glands in type B gastritis. As the mucosa thins and glands disappear, the bases of the pits come to rest on the muscularis mucosae. One must be careful not to mistake isolated residual cells seen in the setting of a gland-poor, stromal-rich mucosa, especially on a biopsy, as evidence of an early diffuse carcinoma.

**Autoimmune Gastritis**

The minority (approximately 20%) of cases of chronic gastritis fall into type A or autoimmune gastritis. Autoimmune gastritis results from immune-mediated destruction of parietal cells and is therefore restricted to the body and fundus. It shows a characteristic hypochlorhydria and an associated neuroendocrine cell hyperplasia discussed in Chapter 17. The classic form of the disease tends to affect individuals of Scandinavian or northern European descent. It is rare among other ethnic groups. The predilection for autoimmune gastritis to affect blue-eyed individuals with blood group A suggests a genetic predisposition to the disease.

Patients with autoimmune gastritis often have pernicious anemia and intrinsic factor autoantibodies and autoantibodies directed against other organs (Table 4.15) (193,194,195,196). Patients receiving methyldopa treatment may develop Parietal Cell Antibodies (PCAs) (101) and chronic autoimmune gastritis. The changes disappear upon cessation of the drug. Recently *HP* infections have been recognized as a cause of autoimmune gastritis. The majority of patients with *HP* infections have autoantibodies directed against the canalicular membranes of parietal cells or the luminal membrane of foveolar epithelium (129,197). The canalicular antibody targets the H⁺,K⁺-ATPase proton pump (197).

**TABLE 4.15 Autoimmune Diseases Associated with Autoimmune Gastritis**
Patients with autoimmune gastritis have PCAs, autoantibodies to intrinsic factor, and the gastrin receptor (198,199). The PCAs target the catalytic subunit of the H⁺,K⁺-ATPase proton pump. The antibodies against intrinsic factor are of two types. The most common inhibits the attachment of vitamin B₁₂ to intrinsic factor and the other binds the intrinsic factor–vitamin B₁₂ complex, interfering with its small intestinal absorption (200). Therefore, many patients with autoimmune gastritis develop pernicious anemia secondary to a vitamin B₁₂ deficiency.

**Pathologic Features**

Destruction of the oxyntic mucosa occurs over a period of years, ultimately leading to mucosal atrophy with hypo- or achlorhydria and decreased serum PG1 levels. PG1 levels below 20 mg/dL characterize the disease (201). Patients with severe disease often have mucosal flattening that stops abruptly at the antrum. Mucosal mononuclear cell infiltrates containing lymphocytes (both T and B lymphocytes), plasma cells, and eosinophils center around the oxyntic glands, eventually leading to their destruction (Fig. 4.76). Neutrophils are not a prominent component of the inflammation. The degree of parietal and chief cell loss and atrophy varies with disease stage. In the preatrophic phase of the lesion biopsies reveal cellular lamina propria infiltrates rich in plasma cells. T cells infiltrate the oxyntic glands resulting in lymphoepithelial lesions (202). The changes progress from a superficial gastritis to atrophic gastritis and eventually gastric atrophy. The patchy loss of parietal cells and chief cells is accompanied by an increased space between the glands that is readily appreciated when the atrophy is moderate or severe. As the oxyntic glands are lost, the lymphoepithelial lesions disappear and the lamina propria inflammation tends to be mild in nature. Eventually, the fundic mucosa becomes replaced by pyloric and/or intestinal glands (Figs. 4.77 and 4.78), foveolae may become hyperplastic (Fig. 4.77), and pancreatic metaplasia may develop. If the patient has coexisting untreated pernicious anemia, the epithelial cells may appear megaloblastic. Retention cysts may be present in the mucosa and superficial submucosa. In severe disease the entire gastric wall becomes atrophic, including even the musculature.

Patients with coexisting *HP* infections exhibit histologic features of both diseases.
FIG. 4.76. Autoimmune gastritis. A: Low-magnification photograph showing the presence of a gastric mucosa that exhibits lengthened pits and glandular loss. Focal intestinal metaplasia (arrow) is also noted. B: Higher magnification of the oxyntic mucosa demonstrating the loss of parietal cells. C: The mucosa also contains evidence of *Helicobacter pylori*–associated gastritis with the presence of dense lymphocytic aggregates arranged in a follicular pattern.

Gastric adenocarcinoma affects 1% to 3% of patients with autoimmune gastritis via intervening steps of intestinal metaplasia and dysplasia (Figs. 4.77 and 4.79) (203). Autoimmune gastritis also leads to G-cell hyperplasia, multifocal gastric ECL hyperplasia, ECL micronests, and multifocal carcinoid tumors as discussed in Chapter 17 (Fig. 17.12).
FIG. 4.77. Autoimmune gastritis. *A:* Patients often develop foveolar hyperplasia presumably in response to the gastrin secretion. A metaplastic gland lies to the right of the hyperplastic foveolae (*arrow*). *B:* Dysplasia (*arrows*) sometimes develops in the areas of intestinal metaplasia. A metaplastic gland is seen at the lower left-hand corner of the photograph.

**Juvenile Forms of Pernicious Anemia**

Juvenile pernicious anemia is rare and has three distinct forms. One occurs in late childhood and adolescence and appears to resemble the adult form of the disease in all respects except the age of patient presentation. So-called “true” juvenile pernicious anemia results from the failure of the parietal cells to produce intrinsic factor. The stomach is histologically normal and acid is produced by the parietal cells. The cause of the failure to produce intrinsic factor is not understood. The third type results from failed absorption of the vitamin B₁₂–intrinsic factor complex (204).
FIG. 4.78. Gastric body mucosa with focus of pyloric metaplasia (arrow). Villiform intestinal metaplasia makes up the remainder of the mucosa. Unless the location of this section is known, it would be difficult to identify it as body mucosa.

FIG. 4.79. Autoimmune gastritis with diffuse gastric dysplasia. A: Low magnification demonstrating the presence of extensive replacement of the glands by dysplastic epithelium. B: Higher magnification demonstrating the presence of dysplastic glands showing abnormally shaped nuclei with prominent nucleoli and numerous mitoses, some of which are atypical.

Atrophic Autoimmune Pangastritis

Atrophic autoimmune pangastritis is a distinctive form of antral and fundic gastritis associated with systemic autoimmune disease. This gastritis is characterized by intense mucosal inflammation that persists even into the phase of severe glandular atrophy. This differs from the other two major forms of chronic atrophic gastritis in which the inflammation tends to diminish as the mucosa becomes atrophic. The stomach shows a pangastritis with diffuse involvement of the body and antrum that is unassociated with either *HP* infections or the neuroendocrine cell hyperplasia associated with autoimmune gastritis. Patients range in age from 1 to 75 years and show a slight female predominance. All patients have systemic autoimmune diseases that include autoimmune enterocolitis, systemic lupus erythematosus, refractory sprue, autoimmune hemolytic anemia, and disabling fibromyalgia (205). The mucosal inflammation involves the mucosal thickness with a slight tendency to preferentially affect the deep glands, frequently accompanied by apoptotic bodies in a pattern resembling graft versus host disease (205). Glandular atrophy, lymphoplasmacytic infiltrates, and neutrophilic infiltrates diffusely involve the stomach. Microabscesses may be present in the gastric glands. There may also be areas of overt ulceration. These patients are not hypergastrinemic and do not develop neuroendocrine cell lesions.

Corpus Atrophy

Corpus atrophy also follows antrectomy. The loss of antral G cells results in a selective loss of parietal cells, atrophy, and pyloric and/or intestinal metaplasia.
**Metaplasias in Gastritis**

Morphologic, histochemical, and enzymatic patterns enable one to recognize five major types of metaplasia occurring in the stomach: Intestinal, pyloric, pancreatic, ciliated, and squamous. The first three types are the most common.

**Pyloric Metaplasia**

Pyloric metaplasia (also sometimes referred to as pseudopyloric metaplasia) most commonly occurs in the setting of autoimmune gastritis. It begins with loss of specialized cells in the oxyntic mucosa (Fig. 4.78). As the cells are lost, they are replaced by a simpler glandular epithelium. Ultimately, the metaplastic glands become indistinguishable from antral glands. Pyloric metaplasia first affects glands closest to the antral junction, producing antral expansion at the expense of the oxyntic mucosa. There is some debate whether the metaplastic cells are indeed metaplastic or are a novel cell lineage that develops in the stomach and other gastrointestinal sites following ulceration. The cells appear adjacent to the ulcers and are thus termed *ulcer-associated cell lineage* (UACL). The UACL produces EGF and trefoil peptides that promote mucosal proliferation and healing (206,207).

**Intestinal Metaplasia**

Gastric intestinal metaplasia (IM) is quite common. It is believed to represent a response to chronic injury, often caused by *Hp* infections. The risk factors for developing IM resemble those of gastric cancer in high-risk populations. Thus, IM is more frequent in smokers and in Asians than in other nationalities. Diets deficient in fresh fruits and vegetables combined with a high salt and nitrite content are common to both conditions (208). Thirteen percent of consecutive American Caucasians undergoing upper endoscopy and 50% of Hispanics and Blacks had evidence of gastric IM when routine protocol-mapping biopsies of the normal appearing mucosa were performed (209).

One of the more contentious issues is the significance of IM at the cardia. IM has been implicated in the development of both gastric and esophageal carcinoma. However, while gastric IM increases the risk of gastric cancer, with the increased risk being proportional to the extent of the metaplasia (208), the risk is much lower than Barrett esophagus (BE) progressing to cancer (210), at least in the United States. Thus, it is important to try to distinguish the IM of BE from the gastric type of IM. IM at the gastroesophageal junction is discussed in detail in Chapter 2.

As noted earlier, IM often complicates MAG. Over time, widened areas of gastric atrophy, often accompanied by gastric IM, replace the chronic active gastritis associated with *Hp* infections. IM begins at the antral–corpus junction in a patchy (Fig. 4.80), multifocal fashion, and then spreads both distally and proximally to involve the antrum and fundus. The areas of IM increase with patient age and often become confluent, replacing large areas of the gastric mucosa. This process can be highlighted by staining gastric resection specimens for alkaline phosphatase activity since only intestinal-type epithelium expresses the enzyme (Fig. 4.80). IM more frequently coexists with gastric cancer than with gastric ulcer, but it shows the same distribution when associated with either condition.

IM may result from mutations caused by nitrosative deamination of DNA by nitric oxide generated by inflammatory cells in stem cells in the replicating compartment of gastric glands in response to *Hp* infection (208). IM may also represent a change that raises gastric pH by replacing the oxyntic mucosa with an epithelium that favors the growth of bacteria capable of generating endogenous mutagens. Down-regulation of Sox2 and ectopic expression of Cdx2, an intestine-specific transcription factor belonging to the *caudal*-related homeobox gene family (211), are important in the development of IM (212). Cdx2 expression may lead to activation of intestine-specific gene transcripts, thereby directing intestinal epithelial development and differentiation in the metaplastic areas.

In IM the cells that normally line the gastric mucosa (surface epithelium, foveolar epithelium, and glands) are replaced by an epithelium resembling that of the small or large intestine. The earliest metaplastic changes consist of the appearance of mucin-negative absorptive enterocytes with a brush border alternating with Alcian blue–positive goblet cells (Figs. 4.81 and 4.82). In young individuals with less extensive IM, the metaplastic glands resemble normal small intestinal epithelium. Initially, only the epithelial type changes, but later the mucosal architecture acquires a small intestinal villiform architecture, often containing Paneth cells at the base of the pits (Fig. 4.83). Paneth cells in areas of IM do not have the same uniform distribution seen in the intestine. In some cases, they are limited to the antral corpus border and are lacking in IM in the distal stomach. They may
lie in the superficial portions of the metaplastic gland; ultrastructurally some Paneth cells contain both Paneth cell granules and mucinous vacuoles (208).

Goblet cells are easily seen on H&E-stained sections. However, an Alcian blue/PAS stain is commonly used to identify the goblet cells since it stains all acidic mucins blue-purple and neutral mucins magenta and is easy to perform and interpret. Some metaplastic cells exclusively secrete sialomucins and contain a “complete” set of normal small intestinal digestive enzymes (sucrase, trehalase, and alkaline phosphatase). This type of metaplasia is characterized by weak expression of (intestinal) MUC2 and absence of gastric (MUC1, MUC5AC, and MUC6) mucins and cytokeratin (CK) immunoreactivity (213). These cells have a complete switch in their differentiation program from a gastric to an intestinal phenotype, and they have been termed small intestinal, complete, or type I IM.
FIG. 4.80. Intestinal metaplasia. Both gastric specimens have been opened along the greater curvature and were stained with alkaline phosphatase to highlight areas of intestinal metaplasia. *A:* Note the inverted V-shaped configuration of the metaplastic process at the corpus–antral junction with areas of punctate staining as one moves away from this border. The duodenum also stains intensely with the enzyme. There is a benign gastric ulcer (*arrows*) at the junction zone of the metaplastic epithelium with the native oxyntic mucosa. *B:* A similar preparation in which the gastritis has extended far more proximally. Patchy metaplastic lesions are also seen in the antral region along the greater curvature. With the extensive replacement of the oxyntic mucosa, it is easy to see how hypo- or achlorhydria can develop. A polypoid carcinoma is present in the metaplastic area (*arrows*).

FIG. 4.81. Type I intestinal metaplasia. The brush border (*arrow*) of the absorptive cells is present, as are numerous goblet cells.
Later, as the disease becomes more extensive, the enterocytes disappear and are replaced by columnar cells containing abundant mucous droplets in their cytoplasm. These metaplastic cells lack a well-developed brush border and secrete both sialomucins and sulfomucins. They lack the complete set of digestive enzymes. This type of metaplasia has been termed enterocolonic, colonic, type II, or incomplete metaplasia. Incomplete metaplasia strongly expresses MUC1, MUC5AC, MUC6, MUC2, Das-1 (a large intestinal antigen), and CK 7. Incomplete IM shows a mixed gastric and intestinal phenotype reflecting aberrant differentiation programs that do not reproduce any phenotype occurring in normal adult gastrointestinal epithelia. Several types of metaplastic epithelium may develop within the same stomach. IM occurs concurrently with atrophic gastritis or independently. Incomplete IM frequently associates with areas of dysplasia and carcinoma.

The endocrine cell population in the different types of metaplasia changes with the phenotype of the nonendocrine cells. In patients with antral gastritis, the proportion of gastrin and somatostatin neuroendocrine cells decreases as the glands pass from a mixed gastric–intestinal phenotype to a pure intestinal phenotype. There is a corresponding increase in intestinal-type endocrine cells that produce glicentin, gastric inhibitory polypeptide, and glucagonlike peptide 1. Gastrin-positive cells emerge in the areas of pyloric metaplasia.

A distinct cellular subset consisting of groups of undifferentiated columnar cells lies on the interfoveolar crests of the gastric mucosa. These cells differ from both normal foveolar cells and metaplastic cells, and they show a close association with atrophic gastritis, particularly in the presence of sulfomucin-secreting IM. This lesion, termed gastric tip lesion, may provide a link between this type of metaplasia and the intestinal variant of gastric adenocarcinoma that develops in intestinalized areas.
Histologically the large, columnar, pseudostratified cells have central nuclei and lack the prominent cup-shaped mucus collection typical of foveolar cells. The cells cluster in groups of up to 25 cells and they show an abrupt transition with the adjacent normal foveolar epithelium.

There is no consensus on the role of the various IM subtypes and subsequent risk of developing carcinoma, and the question then arises as to what to do with a patient with a diagnosis of gastric IM. The answer to this depends on whether the patient has a family history of gastric cancer, has migrated from a high-risk geographic location, lives in a high-risk location, or is a member of an ethnic population with a high risk of developing carcinoma, and whether there is evidence of dysplasia on the biopsy. It can be assumed that any person with an increased cancer risk as defined by the factors noted in the previous sentence or those with extensive metaplasia is at high risk for gastric cancer and should be subject to periodic screening. The extent of the IM is probably more important than the metaplastic subtype (208). The prudent thing to do if IM is detected in a biopsy is to describe the type of metaplasia that is present, to make some estimate as to whether the process is focal or diffuse in nature, and to note whether or not dysplasia is also present. The guidelines of the Sydney System (56) can be used to grade the intestinal metaplasia. The relationship of IM to gastric cancer is discussed in greater detail in Chapter 5.

Ciliated Cell Metaplasia

Ciliated cells may develop deep to areas of intestinal metaplasia; in the mucosa of patients with gastric ulcers, dysplasia, or adenocarcinomas; and at sites away from the main lesion (Fig. 4.84) (217). The ciliated cells show some evidence of an antral phenotype, as demonstrated by their pepsinogen group II activity (208). The cilia in the cells often are structurally abnormal. The ciliated cells line cystically dilated glands, where they may represent an adaptive mechanism aimed at expelling semifluid viscous material and inflammatory cells from the cysts. As cysts enlarge, the intrinsic pressure of the retained mucus results in cellular atrophy and ciliary disappearance (217).

Pancreatic (Acinar) Metaplasia

Pancreatic metaplasia is present in 12% of patients with autoimmune gastritis, usually developing in the cardia and often coexisting with other types of metaplasia (218). Pancreatic acinar cells can also develop in the gastric antral mucosa in areas of IM or atrophy. The metaplastic foci contain single or multiple pancreatic nests and lobules measuring up to 1.7 mm in diameter (Fig. 4.85). The metaplastic tissue imperceptibly merges with the gastric glands. Less commonly, acinar cells lie scattered individually or in small cellular foci among the gastric glands. Larger lobules contain tubules or small cystic spaces reminiscent of dilated ductules. The layers of smooth muscle cells that circumferentially surround the ducts in heterotopic

FIG. 4.84. Ciliated metaplasia. Ciliated metaplastic cyst located near the muscularis mucosae. The cilia are difficult to see on hematoxylin and eosin stain.

Pancreatic (Acinar) Metaplasia

Pancreatic metaplasia is present in 12% of patients with autoimmune gastritis, usually developing in the cardia and often coexisting with other types of metaplasia (218). Pancreatic acinar cells can also develop in the gastric antral mucosa in areas of IM or atrophy. The metaplastic foci contain single or multiple pancreatic nests and lobules measuring up to 1.7 mm in diameter (Fig. 4.85). The metaplastic tissue imperceptibly merges with the gastric glands. Less commonly, acinar cells lie scattered individually or in small cellular foci among the gastric glands. Larger lobules contain tubules or small cystic spaces reminiscent of dilated ductules. The layers of smooth muscle cells that circumferentially surround the ducts in heterotopic
pancreas are absent. The acinar cells have a truncated pyramidal shape with a rim of deeply basophilic basal cytoplasm and numerous small, acidophilic, weakly PAS-positive, refractile granules in the mid- and apical cytoplasm. These granules contain trypsin, amylase, and lipase. The nuclei appear round, relatively small, and centrally or basally located, with a prominent nucleolus. Endocrine cells positive for somatostatin, gastrin, or serotonin intermingle with the acinar cells. Amphicrine cells containing both zymogen and neurosecretory granules are also present.

FIG. 4.85. Pancreatic metaplasia in autoimmune gastritis. A: This stomach shows the presence of prominent pancreatic metaplasia as well as cystic change. Numerous pancreatic lobules lie at the basal portion of the mucosa (arrows). B: Higher magnification of one of the metaplastic areas showing pancreatic acini-surrounded antropyloric glands.

The metaplastic cells probably result from aberrant stem cell differentiation (219). PDX-1, a homeodomain transcription factor, plays a key role in both endocrine and exocrine pancreatic differentiation and differentiation of endocrine cells in the gastric antrum. Therefore, it is of interest that both the pancreatic metaplasia and endocrine cell hyperplasia associated with atrophic corpus gastritis express PDX-1 (220).

**Granulomatous Gastritis**

Since gastric granulomas complicate many conditions (Table 4.10) (221), the diagnosis depends on the clinical presentation, the histologic appearance, and sometimes the use of special stains or other ancillary diagnostic techniques to determine whether the patient has a primary gastric granulomatous disease or some other entity. The granulomas contain epithelioid macrophages and lymphocytes with occasional giant cells, eosinophils, and neutrophils with or without necrosis. There are generally two types of granulomas in the stomach: Those that are a reaction to inert foreign material (like food) and those that form as part of a T-cell immune response to microorganisms. The products of activated T lymphocytes transform macrophages into epithelioid cells and multinucleated giant cells.

**Idiopathic Granulomatous Gastritis**

The diagnosis of idiopathic granulomatous gastritis is made when other entities associated with granuloma formation have been excluded. Symptomatic patients usually present over the age of 40 with epigastric pain, bleeding, weight loss, and vomiting secondary to pyloric obstruction. The histologic changes parallel those seen in sarcoid disease, so that a definitive morphologic diagnosis may be impossible. The predominant findings consist of antral narrowing and rigidity caused by transmural, noncaseating granulomas. The inflammation and fibrosis rarely extend beyond the mucosa. Ulcers similar to peptic ulcers may develop, but the slit-shaped ulcers and fissures typical of
Crohn disease are absent. In a third of cases, regional lymph nodes become involved. Controversy exists as to whether idiopathic granulomatous gastritis represents a distinctive entity or whether it represents an isolated or limited form of gastric sarcoid or Crohn disease. In the United States, most patients with gastric granulomas will eventually be shown to have inflammatory bowel disease (IBD) or sarcoid disease. The latter diagnoses may become evident over time.
**Crohn Disease**

Crohn’s patients with gastric involvement often also have duodenal disease. Endoscopic abnormalities, including mucosal nodularity with cobblestoning, aphthous ulcers, linear or serpiginous ulcers, thickened antral folds, antral narrowing, hypoperistalsis, and duodenal strictures, are present in patients with severe gastric Crohn disease (222). The diagnosis of gastric Crohn disease is easy in the presence of florid disease and in the setting of disease elsewhere in the gut. However, the diagnosis is more difficult if gastric involvement is the first disease manifestation. Well-developed gastric Crohn disease shows patchy, focal inflammation associated with acute inflammation in the pits (pit abscesses) or glands. Neural hyperplasia and lymphoid aggregates may be present (Fig. 4.86). A prominent lymphoplasmacytic infiltrate often surrounds the granulomas, contrasting with both sarcoid and isolated granulomatous gastritis, which tend to lack the associated nonspecific inflammation. Gastric Crohn disease is discussed further in Chapter 11.

**Sarcoidosis**

Gastric sarcoidosis is unusual and can only be diagnosed with confidence when gastric granulomas occur in the setting of documented sarcoid in other organs, such as in the liver, lungs, or hilar lymph nodes, and in the absence of microorganisms in the granulomas. Asymptomatic gastric involvement affects approximately 10% of sarcoid patients. Symptomatic patients present with gastric ulcers, hemorrhage, pyloric stricture, and gastric outlet obstruction. Endoscopic changes range from a distal gastritis with or without nodularity to ulceration and pyloric stenosis (223). The histologic features of the granulomas resemble those seen elsewhere in the body. They tend to associate with fewer lymphocytes and plasma cells than one sees in patients with Crohn disease, unless the patient has coexisting chronic gastritis (Fig. 4.87).
FIG. 4.87. Gastric sarcoid. A: Low magnification demonstrating the presence of several noncaseating granulomas within the gastric mucosa. Note that the mucosa lacks the intense infiltrate that surrounded the granulomas illustrated in Crohn disease in Figure 4.86. B: Another granuloma from a different patient in which almost no associated inflammation is present.

Food Granulomas

The presence of a gastric granuloma should always prompt the search for a foreign body. Foreign body granulomas form when mucosal defects allow small food particles or other substances access to the submucosa. These foreign body granulomas are usually easily distinguished from the granulomas seen in the disorders discussed above. They frequently have palisades of histiocytes and foreign body giant cells. Acid leads to necrosis, increasing the size of the mucosal defect, thereby allowing more food to enter. These food particles (particularly insoluble cereals) lying deep in the gastric wall elicit the granulomas (Figs. 4.88 and 4.89). They appear as amorphous eosinophilic masses, sometimes containing vegetable cells recognizable by their thick, bricklike cell walls. Palisading epithelioid histiocytes and foreign body giant cells surround the food particles. The granulomas may become fibrotic or calcified.
FIG. 4.88. Food granuloma in the muscularis propria. Note the presence of the bricklike architecture of the vegetable fiber in the center of the photograph surrounded by prominent multi-nucleated giant cells.
FIG. 4.89. Food granuloma. Granulomas demonstrating the presence of palisading epithelioid histiocytes and a thin eosinophilic line in the center of the lesion. This represents a dissolved material, which deposits in the granulomatous wall.

FIG. 4.90. Granulomatous gastritis complicating gastric carcinoma.

Other Granulomas

*Barium granulomas* also develop in the stomach. Collections of macrophages containing refractile, greenish gray, foamy
cytoplasm develop. Granulomas may also form around parasites. A marked granulomatous gastritis may also complicate gastric malignancies (carcinomas or lymphomas) (Fig. 4.90). The granulomas resemble sarcoid granulomas and may affect all levels of the gastric wall or the draining regional lymph nodes. The granulomas likely result from an immune response to the tumor.

**Eosinophilic Gastroenteritis**

Eosinophilic gastroenteritis, an uncommon condition, affects one or more gastrointestinal segments, commonly involving the stomach and small bowel (224). It usually presents between the 2nd and 5th decades of life. Seventy-five percent of patients present under age 50; some patients have an underlying connective tissue disorder (225) or an infection with *Eustoma rotundatum*, a parasite of North Sea herring (224). Many patients have a history of allergy, peripheral eosinophilia, asthma, eczema, or food sensitivity (226).

The eosinophilic infiltrates tend to affect specific layers of the bowel wall. They may involve only the mucosa, the submucosa (the most common location), the muscularis propria, or the serosa. Symptoms differ depending on the site and extent of involvement. Patients with predominantly mucosal disease experience postprandial nausea, vomiting, abdominal pain, and food intolerance. Disease predominantly affecting the muscular layer results in thickening and rigidity of the muscularis propria and gastric outlet obstruction. The least common disease pattern predominantly involves the serosa. Usually, one of these patterns predomimates; some patients have a mixed disease pattern. Patients often have a prompt response to steroid treatment.
FIG. 4.91. Eosinophilic gastroenteritis. Note the prominent number of eosinophils distributed throughout the lamina propria.

| TABLE 4.16 Gastric Eosinophilia |
|-------------------------------|--------------------------------|
| Allergic reactions            | Peptic ulcers                  |
| Drug reactions                | Crohn disease                  |
| Parasite reactions            | Foreign bodies                 |
| Allergic granulomatosis       | Adenomas                       |
| Chronic granulomatous disease | Carcinomas                     |
| Varioliform gastritis         | T-cell lymphoma                |
| Inflammatory fibroid polyp    | Eosinophilic gastroenteritis   |

Mucosal edema, capillary lymphatic dilation, and an intense but patchy eosinophilic infiltrate displace and destroy gastric pits and glands (Fig. 4.91). The infiltrate typically contains 10 to 50 eosinophils per high-powered field (hpf) (227). One often sees a concomitant increase in IgE-secreting plasma cells. Epithelial necrosis and degeneration develop, but ulcers are rare. Mucosal eosinophilic gastritis can be diagnosed in gastric biopsies, but due to its patchy distribution, multiple biopsies should be evaluated, including deeper biopsies that sample the submucosa, since each biopsy may show striking variations in the intensity of the eosinophilic, lymphocytic, and histiocytic infiltrates. The muscularis propria may show pronounced hyperplasia with the muscle fibers separated by dense eosinophilic aggregates. Charcot-Leyden crystals are present in areas of eosinophilic infiltrates. Some patients develop loose granulomas and acute vasculitis affecting small arteries, features characteristic of allergic granulomatosis (227). Postinflammatory strictures complicate muscularis propria involvement. Table 4.16 lists the differential diagnosis of gastric eosinophilia.

**Allergic Gastritis**

The stomach is commonly involved in food-induced hypersensitivity reactions, especially in children (228). It is usually a manifestation of a more extensive allergic gastroenteritis. Patients present with anorexia, nausea, vomiting, diarrhea, weight loss, peripheral eosinophilia, elevated serum IgE, a personal or family allergic history, and epigastric pain. Direct mucosal challenge with a specific antigen in allergic individuals produces gastric mucosal edema, erythema, and petechial hemorrhages (228). Mast cell degranulation recruits neutrophils followed by mononuclear cells (229). A diffuse eosinophilic infiltrate involving the lamina propria and the superficial and pit epithelium causes epithelial damage with focal denudation and erosions, mucin depletion, and concurrent regeneration. The mucosa surrounding the erosions shows foveolar hyperplasia (Fig. 4.92). Excessive histamine release can lead to gastric gland hyperplasia.

**Lymphocytic and Varioliform Gastritis**

A recently described form of gastritis consists of an intense T-cell infiltrate in the gastric pits and surface epithelium. The stomach may appear grossly normal, but in its most severe form *varioliform gastritis* is seen endoscopically (230). Lymphocytic gastritis affects 0.83% to 4.5% of individuals, mainly middle-aged and elderly men (230). The disorder complicates various diseases, including celiac disease, *HP* infections, Crohn disease, HIV infections, Menetrier disease, lymphocytic enterocolitis, inflammatory polyps, hypersensitivity reactions, autologous hematopoietic cell transplantation, ticlopidine use, lymphoma, and esophageal carcinoma (230,231,232,233,234,235). However, the change is most common in celiac disease and in patients with *HP* infections (235). In approximately 20% of cases, the etiology is unknown. Some
patients develop ulcers or hypoproteinemia (236). The stomach appears normal or it may present with thickened gastric folds, often with multiple discrete mucosal nodules, ulcers, erosions, or elevations measuring 3 to 10 mm in diameter. These are covered with mucus and have central umbilications surrounded by hyperemia, leading to the name varioliform gastritis (230,231). The mucosal elevations persist after the erosions heal, resembling sessile hyperplastic polyps. The disorder affects the entire stomach. Some patients develop hypertrophic lymphocytic gastritis.

Lymphocytic gastritis is characterized by an intraepithelial lymphocytosis with at least 25 lymphocytes/100 epithelial cells and mild foveolar hyperplasia (230,231). Usually the intraepithelial lymphocytosis is obvious so that counting the number of lymphocytes present is seldom required. The intraepithelial lymphocytes are small and round, sometimes surrounded by a clear halo. They infiltrate the basal part of the surface epithelium and the gastric pits (Fig. 4.93). The process spares the deeper glands. The lymphocytosis may be patchy so that different biopsies may vary in the intensity of the intraepithelial lymphocytosis. The intraepithelial lymphocytosis may be greater in the antrum in celiac disease, whereas it is greater in the corpus in HP infections (235). In patients with celiac disease, the number of gastric intraepithelial lymphocytes correlates with the histologic severity of small intestinal disease and gluten restriction results in a marked reduction in intraepithelial lymphocytes. An intense lamina propria lymphoplasmacytic infiltrate may accompany the intraepithelial lymphocytosis. The pits acquire a corrugated and dilated appearance and their lumina may contain abundant mucus admixed with neutrophils forming pit abscesses. Neutrophils are usually not present unless there are ulcers or erosions. Foveolar hyperplasia may create giant gastric folds. The intraepithelial lymphocytes cause the epithelium to appear vacuolated and acquire a clear cell appearance, particularly in the subnuclear region. Other entities that mimic this pattern include endocrine cell hyperplasia, dystrophic goblet cells, and fixation artifact. Immunohistochemical stains distinguish among these possibilities. Additionally, one must distinguish the lesions present in lymphocytic gastritis (particularly if lymphoepithelial lesions are present) and MALT lymphomas (see Chapter 18) (Table 4.17). The lack of cytologic atypia in lymphocytic gastritis and the fact that the cells are T cells readily differentiates lymphocytic gastritis from the B-cell lesion of MALT lymphoma.
**FIG. 4.92.** Allergic gastritis in a child.  
*A:* Low-power view of the focal destruction that has occurred as the result of the inflammation.  
*B:* Higher magnification showing the intense mucosal eosinophilia.
**FIG. 4.93.** Lymphocytic gastritis. *A:* Low-power magnification of this biopsy shows an intensely cellular mucosa. Increased numbers of cells are found both within the lamina propria and within the epithelium. *B:* Low-power magnification of another biopsy showing similar changes although less intensely inflamed. *C:* Higher magnification of *B* showing the details of the intraepithelial lymphocytic populations.

| TABLE 4.17 Lymphocytic Gastritis Versus Mucosa-associated Lymphoid Tissue (MALT) Lymphomas |
|---|---|---|
| **Feature** | **Lymphocytic Gastritis** | **MALT Lymphomas** |
| Lymphocyte number | Significantly increased | Significantly increased |
| Lymphocyte distribution | Single cells or linear arrangement in the epithelium | Clusters of three or more lymphocytes in the epithelium |
| Lymphocyte type | Mature T cells | Malignant B cells |
| Perilymphocytic halo | Common | Uncommon |
| Significant epithelial destruction | No | Yes |
| Cytologic atypia of the lymphocytes | No | Yes |
| Diffuse lamina propria infiltration and destruction by atypical lymphocytes | No | Yes |

**Graft Versus Host Disease**

Graft versus host disease (GVHD) follows allogeneic bone marrow transplant or transfusions, especially in immunocompromised patients (237). Upper gastrointestinal GVHD precedes lower gastrointestinal GVHD (238). Patients with isolated gastric GVHD present with nausea, vomiting, and upper abdominal pain without diarrhea. Early, the stomach appears endoscopically normal; 30% to 80% of patients have histologic evidence of GVHD after a normal endoscopy (237,238). In more severe disease, the stomach appears variably congested and atrophic. Histologically, the mucosa contains apoptotic cells (Fig. 4.94) predominantly in the mucous neck region; gland abscesses may also develop. The apoptotic bodies are present in both the antral and oxyntic mucosa and are small and less conspicuous than those seen in the colon (see Chapter 13). Sparse inflammation is present and granular eosinophilic material may be present in the glands. Even though apoptotic bodies may be present in small numbers, their presence is diagnostic of GVHD in the appropriate setting (237,239).
FIG. 4.94. Gastric graft versus host disease (GVHD). Single-cell necrosis (arrow) is the sine qua non of GVHD. (Case courtesy of Drs. Sale, Schulman, and Myerson, Fred Hutchinson Cancer Research Center, Seattle, WA.)

TABLE 4.18 Conditions Associated with Increased Apoptoses in the Gastric Mucosa

- Graft versus host disease
- Cytomegalovirus infections
- Severe T-cell immunodeficiency
- HIV infections
- Conditioning chemotherapy
- Cancer chemotherapy
- Radiation
- Crohn disease
- Proton pump inhibitors
- Nonsteroidal anti-inflammatory drugs

An interpretative problem complicating the diagnosis of GVHD results from the changes induced by the transplant cytoreduction regimen that can produce histologic features identical to those seen in GVHD. However, the changes due to the cytoreductive regimen are more diffuse than those typically seen in GVHD (237). Because of this confounding feature, it is prudent to avoid the diagnosis of GVHD early in the immediate posttransplant period. Another confounding feature is the use of PPI therapy, which can increase the number of apoptotic bodies seen in the antrum but not in the fundus (240). Table 4.18 lists entities associated with increased apoptotic bodies in gastric biopsies. GVHD may coexist with concurrent gastritis resulting from an HP or other infection and/or a chemical gastropathy.

Collagenous Gastritis

Collagenous gastritis is rare, affecting men and women, children and adults (241,242,243,244). The disease occurs as an
isolated disorder or it may coexist with collagenous colitis (245) and/or collagenous duodenitis, lymphocytic colitis (241), Sjögren syndrome (243), and ulcerative colitis (244). Patients range in age from 11 to 77 with a mean age of 40 (242). It appears that there are two subsets of patients with collagenous gastritis: (a) collagenous gastritis occurring in children and young adults who present with severe anemia, a nodular endoscopic pattern, and disease limited to the gastric mucosa; and (b) collagenous gastritis associated with collagenous colitis in adults with chronic watery diarrhea (242). Some patients present with vomiting or upper GI bleeding, whereas others are asymptomatic or have nonspecific symptoms. Rare patients improve on gluten-free diets (241). Other patients have slowly progressive disease (246). We have seen a patient with severe collagenous gastritis, duodenitis, and colitis who required total parenteral nutrition to maintain his nutritional requirements. The cause of collagenous gastritis is unknown, but it may result from immune-mediated processes. In the stomach, signs of local immune activation include epithelial overexpression of HLA-DR and increased numbers of CD3+ intraepithelial lymphocytes and CD25+ cells in the lamina propria (247).

Endoscopic abnormalities include erythema, mucosal hemorrhage, and mucosal nodularity involving the corpus and body and sparing the antrum. The stomach shows histologic changes resembling those present in collagenous sprue (in the small bowel) or collagenous colitis. The diagnostic criteria consist of a subepithelial collagen layer >10 \( \mu \text{m} \) in thickness, lamina propria lymphoplasmacytosis, intraepithelial lymphocytes, and epithelial damage (246). The distribution and thickness of the subepithelial collagen bands varies within and between biopsy specimens and can be highlighted by trichrome stains. Its thickness ranges from 13 to 96 \( \mu \text{m} \), averaging close to 40 \( \mu \text{m} \). It is discontinuous and irregular and contains entrapped dilated capillaries and mononuclear cells. Intraepithelial CD3+ T lymphocytes range from 14 to >30 per 100 surface epithelial cells with a mean of 20. A patchy chronic active gastritis may be present. The lamina propria contains variable numbers of neutrophils, eosinophils, and mast cells. Patchy epithelial damage with surface cell flattening, reactive epithelial changes, and focal sloughing are present. Rare abscesses form. The regenerative surface epithelial changes may be severe enough to warrant a diagnosis of indeterminate for dysplasia (246). The stomach may also show patchy glandular atrophy with shortening of the oxyntic glands. However, parietal and chief cells are still present. There may also be linear or micronodular endocrine cell hyperplasia in the corpus (246), a change that may result from treatment with proton pump inhibitors. In addition, intestinal metaplasia may develop in longstanding disease. Smooth muscle hyperplasia deep in the lamina propria increases over time with extension to the surface.

**Peptic Ulcer**

A “peptic ulcer” refers to any deep mucosal break resulting from exposure to gastric acid or pepsin. These ulcers develop adjacent to sites containing oxyntic mucosa. Rarely, they arise in the acid-secreting mucosa itself. Peptic ulcers fall into several major etiologic groups: Those resulting from acid hypersecretion, as in Zollinger-Ellison syndrome; those due to NSAIDs; and those associated with \( \text{HP} \) infection. Previously, most peptic ulcers resulted from \( \text{HP} \) infections. Urease and other factors produced by the \( \text{HP} \) break the mucosal barrier, allowing ulcers to develop. Not all \( \text{HP} \) infections lead to ulcer development. \( \text{VacA}- \) and \( \text{CagA}- \)positive \( \text{HP} \) are more likely to produce peptic ulcers than \( \text{VacA}- \) and \( \text{CagA}- \)negative \( \text{HP} \) (159,248). Specifically, colonization with \( \text{vacA2m2/cag A}- \)positive \( \text{HP} \) strains correlates with peptic ulcer disease (PUD) risk (249). Smoking also increases ulcer incidence. In Western countries the importance of \( \text{HP} \) in gastric PUD has declined and has been replaced by NSAID use.

Multiple environmental and genetic factors associate with peptic ulcer risk. The incidence of gastric ulcers varies depending on geographic locale, age, and sex. Evidence supporting a genetic contribution to gastric and duodenal peptic ulcers include increased family aggregation (more for blood relatives than spouses), twin studies (250), blood group studies, and elevated pepsinogen levels among relatives (251). A marked decline in peptic ulcers has resulted from decreased smoking (252), a decreased incidence of \( \text{HP} \) infections, and the widespread use of aggressive acid suppressive therapies. Today in Western countries, peptic ulcers tend to affect the elderly using NSAIDs. The probability of developing a peptic ulcer is highest in middle-aged men (age 41 to 60) with chronic antral gastritis or chronic pangastritis (253). Peptic ulcers also develop as sporadic lesions, in patients with gastrinomas or systemic mastocytosis (due to increased histamine
secretion), and in rare genetic syndromes including multiple endocrine neoplasia type 1 (MEN-1). A specific pepsinogen C gene polymorphism may predict gastric ulcer risk (254). Peptic injury may also complicate any disorder in which the mucosal barrier is compromised and mucosal ulcers form including infectious or drug injury.

Prepyloric and duodenal ulcers arise in the setting of increased acid secretion and antral gastritis, whereas gastric ulcers associate with decreased gastric acid secretion and diminished mucosal defenses (Fig. 4.95). There is a close association between the ulcer site and the severity of the gastritis. Antral ulcers most commonly develop along the lesser curve; with increasing severity of corpus gastritis, the ulcer location moves proximally. The further a gastric ulcer is from the pylorus, the more likely one is to find atrophic gastritis involving the body. This contrasts with duodenal and prepyloric ulcers, which associate with an antral-predominant gastritis without progressive body gastritis (255,256).

Episodic epigastric pain that is aggravated by meals or alcohol, often occurring at night, is the most prominent clinical feature of PUD. Bleeding develops in about 20% of patients and is massive in 5%. Bleeding is particularly likely in older individuals on NSAIDs (257). Endoscopic visualization of a bleeding vessel or other signs of recent hemorrhage predict further bleeding and increased mortality. Juxtapyloric ulcers cause obstruction due to coexisting edema and pyloric stenosis as the ulcer heals and fibrosis develops. Ulcer depth varies; it may perforate through the wall, extending into adjacent structures. The risk of perforation is increased in those who smoke and the risk correlates with the number of cigarettes smoked (258).

Gastric ulcers are usually solitary, although about 30% of patients have associated duodenal ulcers and 6% to 13% have multiple gastric ulcers (259). Gastric peptic ulcers arise anywhere in the stomach, but they typically develop on its lesser curvature, usually at the antral–corpus junction. The consequences of peptic ulceration include hemorrhage secondary to vascular erosion, perforation, ulcer penetration into contiguous structures, and pyloric outlet obstruction due to inflammation or scarring. Perforations typically appear as a round hole in the ulcer base. The serosal surface appears congested and fibrinous adhesions may be present. Occasionally, a large gastric ulcer high on the lesser curvature heals to produce a scarred, constricted, hourglass-shaped stomach (Fig. 4.96). Less commonly, gastric ulcers extend along the lesser curvature from the cardia to the incisura, forming a “trench ulcer” (260).
FIG. 4.95. Aggressive factors and etiology of peptic ulcer disease. A number of aggressive factors predispose the gastric mucosa to peptic damage. Two major causes involve infections with *Helicobacter pylori* or the use of nonsteroidal anti-inflammatory drugs (NSAIDs), both of which damage the mucosa by mechanisms discussed elsewhere. This leads to weakening of the intercellular junctions and foveolar damage that then allows pepsin and acid to diffuse into the underlying lamina propria. Prostaglandins (PGs) that play a major role in maintaining mucosal integrity are inhibited by the NSAIDs and therefore further predispose the mucosa to damage and failure to repair itself. Pep, pepsin.

FIG. 4.96. Gross photograph of an hourglass stomach.
Acute peptic ulcers are often deep, measure >0.5 cm in diameter, penetrate the muscularis mucosae, and have little fibrous tissue at their base. Those that measure >3 cm in diameter are sometimes referred to as giant gastric ulcers. These are more likely to penetrate than smaller gastric ulcers (261). Additionally, the risk of microscopic malignancy is significantly greater in giant ulcers than in the smaller ones (261). Chronic ulcers evolve from the acute ulcers. However, the acute stage is rarely seen unless a major blood vessel becomes eroded early in the disease, resulting in significant hemorrhage. Chronic ulcers that undergo repeated ulceration exhibit both acute and chronic features.

Benign ulcers are typically round to oval, sharply punched-out lesions with perpendicular walls (Fig. 4.97). The surrounding congested, edematous mucosa overhangs the ulcer margin, sometimes forming a lip and giving the ulcer a flask-shaped appearance. This lip should not appear rolled or heaped up. The mucosa away from the ulcer also often appears atrophic with flattened mucosal folds (Fig. 4.98). Ulcer bases appear smooth, cream colored or pearly gray, and clean, and are surrounded by thick fibrous tissue (Fig. 4.99) unless hemorrhage has occurred. Scarring at the ulcer base causes puckering of the surrounding mucosal folds, causing them to radiate away from the ulcer in a spokelike fashion (Fig. 4.98).

Four zones characterize chronic ulcers: (a) polymorphonuclear leukocytes, (b) coagulation necrosis, (c) granulation tissue, and (d) fibrosis of the ulcer base (Figs. 4.100 and 4.101). The latter often disrupts the muscularis mucosae and the submucosa, and can be highlighted using a trichrome stain. The vessels at the ulcer base may show endarteritis obliterans; the extent of this change governs the magnitude of hemorrhage should the vessels become eroded (Fig. 4.102).

The muscularis propria may be interrupted by the acute inflammation and tissue loss or by scar tissue. Candida may colonize the ulcer base. If the organism does not invade the underlying tissues, it has no clinical significance.
Acute peptic ulcers do not contain the four zones described above. A polymorphonuclear exudate replaces the epithelium and moderate amounts of granulation tissue fill the ulcer center. The remaining mucosa appears regenerative with immature cells and occasional mitotic figures. Scarring is absent. These are seldom examined histologically unless an acute bleed has resulted in death or surgical resection. Histologic examination of bleeding gastric ulcers usually reveals a small eroded artery in the ulcer crater. The mean diameter measures 0.7 mm with a range of 0.8 to 3.4 mm. The larger the size of the eroded artery, the more likely that death will result (458). The vessels may show aneurysmal dilation, intense arteritis, and/or endarteritis obliterans.
Peptic ulcers begin to heal by epithelial migration from the ulcer margin over the vascular granulation tissue of the ulcer base with mucosal replacement by the inward migration of a single epithelial layer at the ulcer edge (Fig. 4.103). The proliferating mucosa grows downward and extends over the ulcer surface. This single cell layer can extend to cover the entire surface of smaller ulcers (<2 cm). Epithelial migration is stimulated by multiple factors, including spasmolytic polypeptide, EGF, and TGF-β and by inhibition of E-cadherin expression (262). Simple mucous glands and areas of pyloric metaplasia develop. As noted earlier, the pyloric metaplasia may not be a metaplastic process at all, but rather the development of a novel cell lineage from stem cells called ulcer associated cell lineage, the cells of which produce a number of products that promote mucosal healing and repair (207). The cells grow in proliferating cell buds until they reach the mucosal surface (207). A number of genes are up-regulated following ulcer development, leading to the production of an integrated cascade of gene products that promote vasculogenesis, mucosal restitution, and healing (263). Later, other growth factors produced by the stromal cells stimulate epithelial proliferation and differentiation.

The cell cycle is suppressed in the migrating cells until they meet cells from the opposite side of the ulcer, at which time there is a proliferative spurt coinciding with a downward penetration of new glands. Mucosal islands may become entrapped in areas of submucosal fibrous or granulation tissue, and may be mistaken for an invasive carcinoma. Away from the ulcer, the mucosa appears normal or exhibits chronic gastritis (Fig. 4.104). There may also be prominent collections of chronic inflammatory cells (a Crohn-like reaction) associated with neural hyperplasia (Fig. 4.105) in a pattern that could suggest a diagnosis of Crohn disease, if one were unaware of the presence of an old ulcer.
Chapter 4

FIG. 4.100. Four zones characterize the histology of chronic gastric peptic ulcers. The first layer consists of debris and neutrophils. Underlying this is an area of coagulation necrosis followed by granulation tissue and then fibrosis.

FIG. 4.101. Histologic section of gastric ulcer. A: Edge of the ulcer demonstrating gastritis and regenerative epithelium. B: Base of ulcer demonstrating the typical four zones seen in most peptic ulcers: (+) fibrinopurulent debris, (-) inflammatory layer, (×) granulation tissue, and (4) fibrosis.
**FIG. 4.102.** Large artery penetrating an ulcer base. *A:* Large gastric ulcer eroding into gastric artery (arrow) causing massive gastrointestinal bleeding. *B:* Endarteritis obliterans is present, and there is fibrin clot at the surface.

**FIG. 4.103.** Healing gastric ulcer. *A:* Ulcers heal by the migration and ingrowth of epithelium from the ulcer edges. In this photograph, one can see the single layer of epithelial cells extending from the mucosa on the right-hand portion of the picture overlying the muscle and extending toward the inflammatory debris. *B:* Further progression of the healing process demonstrates an almost completely intact lining at the base of the ulcer. The acute inflammation has disappeared but the surrounding mucosa appears edematous and congested.

The serosa underlying a peptic ulcer often appears fibrotic, demonstrates fat necrosis, or shows mesothelial hyperplasia. The fibrosis and fat necrosis thicken the gastric wall. Adhesions develop and one may see extensive areas of mesothelial hyperplasia trapped within the inflammatory process. These can mimic a carcinoma, but the lack of cytologic atypia and...
positive immunostains for calretinin provide the correct diagnosis. Regional lymph nodes become enlarged and reactive in appearance.

**FIG. 4.104.** Gastritis surrounding a gastric ulcer. The ulcer is not shown.
FIG. 4.105. The wall of the stomach in areas remote from peptic ulcers often demonstrate secondary changes, including collections of chronic inflammatory cells, fibrosis, and neuromuscular hyperplasia. The neuromuscular changes may lead to motility abnormalities.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Length of history</td>
<td>Long, may be short</td>
<td>Short, may be long</td>
</tr>
<tr>
<td>Ulcerlike symptoms</td>
<td>Usually present</td>
<td>May be present</td>
</tr>
<tr>
<td>Location</td>
<td>Antrum or lesser curvature 100% benign</td>
<td>Cardiac and body 50% malignant</td>
</tr>
<tr>
<td>Radiologic appearance</td>
<td>Ulcer base outside gastric wall</td>
<td>Ulcer base inside gastric wall</td>
</tr>
<tr>
<td>Gastric pH</td>
<td>Tends to be low</td>
<td>Variable</td>
</tr>
<tr>
<td>Gross appearance</td>
<td>Punched out with overhanging edges</td>
<td>Bowl shaped with sloping edges</td>
</tr>
<tr>
<td>Rugal folds</td>
<td>Terminate in ulcer</td>
<td>Do not terminate in ulcer</td>
</tr>
</tbody>
</table>

**Histologic Distinction of Gastric Ulcers from Gastric Cancer**
Ulcerated carcinomas tend to be shallow, irregular, bowl-shaped lesions with rolled or heaped-up sloping borders and a necrotic base that often flattens out and distorts the rugal folds in such a way that they do not converge toward the ulcer or, if they do, they terminate short of it. Table 4.19 compares the gross features of benign and malignant gastric ulcers. One of the most difficult tasks facing the pathologist is to distinguish malignant cells from the regenerative atypia invariably present in areas of gastritis adjacent to ulcers. Marked desmoplasia at the base or sides of a chronic ulcer crater can distort regenerating glands suggesting invasion from a carcinoma. In these circumstances it is imperative that one recognize classic cytologic hallmarks of malignancy before one makes a diagnosis of cancer.

When one cannot unequivocally distinguish regenerative epithelium from a carcinoma in a biopsy specimen, a rebiopsy, once the inflammation subsides, may be warranted if a strong clinical suspicion for cancer exists. However, if the clinical features suggest that the lesion is benign and reactive, the patient can be treated medically for 4 to 6 weeks, then re-evaluated and additional biopsies taken at that time. A useful rule of thumb is that any chronic ulcer that has been histologically diagnosed as benign should be followed by the gastroenterologist until ulcer healing is complete.

The use of cytokeratin immunostains may help to determine whether or not individual cells have invaded into the lamina propria. However, one must be careful in interpreting these because isolated nonneoplastic cells can remain entrapped from necrotic glands in the granulation or fibrous tissue at the base of gastric ulcers. Alternatively, residual epithelial remnants from the associated gastritis may be present. Additionally, cytokeratin positivity is occasionally found in nonepithelial cells, especially near the peritoneal surface, due to the presence of subserosal mesothelial cells. These cytokeratin-positive spindled submesothelial cells do not communicate with the gastric mucosa and usually fail to show other epithelial features, such as epithelial membrane antigen (EMA) immunoreactivity. The mesothelial cells are also vimentin and calretinin immunoreactive.

The distinction between chronic ulcers and ulcerating cancers can be further facilitated by examination of the muscularis propria. Deep ulcers and their scars result in fibrous replacement of the muscle layer, whereas the muscularis propria deep to a cancer usually remains intact and nonfibrotic, and may even become accentuated.

**Hypertrophic Hyperplastic Gastropathies**

The gastric mucosa contains two epithelial compartments: The superficial foveolar epithelium and gastric pits and a deeper glandular compartment that contains the specialized epithelium unique to each gastric region. If the mucosa measures >1.5 mm in thickness, it is considered to be hypertrophic or hyperplastic. Diffuse mucosal expansions result in giant rugal folds (hypertrophic gastropathies) producing dramatic gross (Fig. 4.106) abnormalities. In contrast, localized expansions produce discrete polypoid lesions. Hyperplasia may affect either or both mucosal compartments. When a single component becomes hyperplastic, the remaining compartment may appear normal, hyperplastic, or atrophic. Thus, the surface can appear hyperplastic with concomitant glandular hyperplasia, atrophy, or normal numbers of glands (Fig. 4.107). Similarly, the glands may appear hyperplastic beneath normal, hyperplastic, or atrophic pits (Table 4.20). Gastric mucosal expansions are classified by the compartments that are expanded and by whether the expansion appears diffuse or localized.

Four well-defined hypertrophic gastropathies exist: Classic Menetrier disease with protein loss and hypochlorhydria, hypertrophic hypersecretory protein-losing gastropathy, hypertrophic hypersecretory gastropathy, and hypersecretory hypergastrinemia with protein loss (Zollinger-Ellison syndrome). Distinct clinical features often define the underlying process, but individual patients may exhibit incomplete manifestations of a particular syndrome. Other patients have classical clinical or laboratory findings but discordant histologic features. Additionally, some patients with hypertrophic gastric folds are not easily classified.
The surgical pathologist plays a limited role in the diagnosis of gastric giant fold diseases because most patients present with a classic clinical syndrome as detected by laboratory (264), radiographic, and endoscopic examinations. Mucosal biopsies document the presence or absence of classic forms of one of the diseases and rule out the presence of tumors that may expand the gastric wall. However, gastric biopsies are inadequate for complete diagnosis because all giant fold disorders share an expanded mucosae and it is difficult to obtain a full-thickness mucosal biopsy unless giant forceps are used. Usually in Menetrier disease either a biopsy contains pure foveolae, suggesting focal foveolar hyperplasia or the top of a hyperplastic polyp, or the mucosa appears normal. In Zollinger-Ellison syndrome or hypertrophic/hypersecretory gastropathy, the biopsy may appear normal because the pits are likely to be normal and the expanded glandular component is not easily appreciated. The only hint of Zollinger-Ellison syndrome is the finding of hyperplastic parietal cells high in the mucosa even near the surface, a phenomenon not usually observed in other conditions.

TABLE 4.20 Morphologic Clinical Manifestation of Giant Gastric Folds
<table>
<thead>
<tr>
<th>Condition</th>
<th>Surface Mucous Cells</th>
<th>Body Glandular Component</th>
<th>Gastrin Ulcers</th>
<th>Protein Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal variants</td>
<td>Normal</td>
<td>Normal</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zollinger-Ellison syndrome</td>
<td>Normal</td>
<td>Hyperplastic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertrophic hypersecretory gastropathy</td>
<td>Hyperplastic</td>
<td>Hyperplastic</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Menetrier disease</td>
<td>Hyperplastic</td>
<td>Atrophy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertrophic hypersecretory protein-losing gastropathy</td>
<td>Hyperplastic</td>
<td>Hyperplastic</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Normal Variants of the Gastric Mucosa**

Hypertrophic, but otherwise well-formed, rugae may occur in some individuals. When these are examined histologically, one finds that the gastric folds consist of prominent submucosal cores covered by a normal mucosa without evidence of hyperplasia or inflammation.

**Menetrier Disease**

Menetrier disease usually affects men in the 4th through 6th decades of life (265). Some cases are familial in nature (266). Exceptionally, the lesion coexists with colonic and gastric juvenile polyposis. Menetrier disease begins insidiously and gradually becomes increasingly symptomatic. Symptoms including epigastric pain, bloating, anorexia, vomiting, weight loss, anemia, and peripheral edema wax and wane. Diffusely enlarged gastric folds and marked mucus hypersecretion are present. Severe hypoproteinemia; hypoalbuminemia; hypochlorhydria, even to the point of achlorhydria; and a tendency to develop peripheral edema may all be present. Not all manifestations are present at the same time. Eosinophilia affects up to 61% of adults. In adults, Menetrier disease may resemble lymphocytic gastritis (265), especially since about one third of patients with lymphocytic gastritis present with weight loss, anorexia, protein loss, and peripheral edema. Extraintestinal phenomena include severe or recurrent pulmonary infections and pulmonary edema. Some patients have premature thrombotic cardiovascular disease, predisposing them to myocardial infarcts, pulmonary emboli, small bowel infarcts, and venous thromboses. Other associations include coexisting esophageal or gastric cancer.
Menetrier disease may affect children and young infants, although it is rare in infants (267). The pediatric form associates with CMV infection, allergies, and autoimmune reactions (268). Proteins, such as cow's milk, sometimes precipitate the disease. Children with CMV infections develop atypical lymphocytosis and transient hepatosplenomegaly, and have CMV demonstrable in the blood, urine, and gastric tissues (269). In young children, the disease is usually self-limited with spontaneous reversal of the protein loss, contrasting with the adult form of the disease, which is generally so prolonged and severe that it may require gastrectomy. Marked peri orbital or facial edema affects 88% of children with the disease. Vomiting (78% of cases), abdominal pain (45% of cases), and anorexia are other common symptoms. Frank upper GI bleeding develops in only 12% of children, contrasting with an incidence of 20% to 40% in adults. Eosinophilia may also develop, presumably due to mucosal allergen penetration following viral damage.

A bulky, thickened gastric wall characterized by marked enlargement of the mucosal folds is present in all cases. The enlarged folds vary from 1 to 3 cm in height and resemble cerebral convolutions with an occasional nodular or polypoid appearance (Fig. 4.108). The disease mostly affects the body and greater curvature, generally sparing the antrum, except in children where the reverse is true. The enlarged gastric folds can occur in both a localized and a diffuse form.

The most striking histologic feature of Menetrier disease is foveolar hyperplasia and glandular atrophy. Foveolar cells line elongated, tortuous, and dilated hyperplastic gastric pits. Excessive mucus spills onto the luminal surface. Mucus-secreting cells replace the glands and the elongated pits extend to the base of the mucosa, where they become cystic (Fig. 4.109). They may also extend into the superficial submucosa creating gastritis cystica profunda. The cysts further increase the mucosal thickness. The expanded mucosa covers lengthened submucosal cores. There is also superficial edema and variable lamina propria inflammation. The inflammatory infiltrate consists of neutrophils, eosinophils, lymphocytes, and occasional plasma cells. The muscularis mucosae becomes hypertrophic and hyperplastic, sending smooth muscle extensions into the lamina propria. Protein loss correlates with the pit hyperplasia, edema, and superficial inflammation. As the disease runs its course, mucosal atrophy develops with loss of the superficial inflammation and edema. Progressive hypochlorhydria results from gradual replacement of the glandular compartment by expanding pit compartments, thereby compromising the parietal cell mass and resulting in decreased acid secretion. Intestinal metaplasia occurs uncommonly and dysplasia is rare. Gastric adenocarcinoma complicates Menetrier disease, but the frequency of this event is hard to estimate.
Chapter 4

FIG. 4.109. Resection from a patient who clinically had Menetrier disease. A: Elongated foveolae characterize the tissue. Cysts are present in the glandular portions of the stomach. B: The cysts extend into the submucosa.

Mucosal biopsies confirm the foveolar hyperplasia and exclude other causes of enlarged rugae. Biopsies from the tips of the expanded folds show pit hyperplasia and pit distortion, as well as superficial inflammation. However, the presence of the hyperplastic mucosal cells is not sufficient to establish the diagnosis of Menetrier disease since foveolar cell hyperplasia occurs in other settings (Table 4.21). For this reason, it is important to correlate the histologic and clinical findings.

TGF-α overexpression in Menetrier disease leads to up-regulation of the antral transcription factor Pdx-1 in the gastric fundus. Pdx-1 is expressed in the cells of the affected glands and scattered gastrin cells appear, suggesting a reprogramming of the oxyntic mucosa to a more antral pattern (220). A disorder resembling Menetrier disease is seen in TGF-α transgenic mice and TGF-α overexpression induces Pdx-1 expression (270). These findings are of interest because of the report of a patient treated by EGFR blockade who went into disease remission with re-emergence of parietal cells (271).

Zollinger-Ellison Syndrome

Gastric mucosal hypertrophy and acid hypersecretion secondary to hypergastrinemia characterize Zollinger-Ellison syndrome (ZES), the prototypic hypersecretory gastropathy. The hypergastrinemia often results from a gastrin-secreting tumor (gastrinoma) located either in the pancreas or in the bowel wall (272). Five percent of patients with ZES have gastric G-cell hyperplasia rather than a true hyperplasia (272). For a further description of gastrinomas and G-cell hyperplasia, see Chapter 17. The increased gastrin levels stimulate acid secretion as well as the growth of parietal cells, peptic cells, ECL cells, and foveolar epithelium.

TABLE 4.21 Causes of Foveolar Hyperplasia
ZES affects 0.1% of all patients with duodenal ulcer disease and has an incidence of between 0.2 and 0.4 case per million population per year. The disease affects patients ranging in age from 7 to 90 (272), with most patients being diagnosed between the 3rd and 5th decades of life. There is no major gender predominance. The most common presenting symptom is abdominal pain. Diarrhea develops in 33% to 75% of patients. Some patients lack all features of ZES. Peptic ulcers may be absent, and diarrhea with steatorrhea may be the only clinical manifestation. The acid hypersecretion may be mild and indistinguishable from that seen in ordinary duodenal ulcer.

ZES causes profound alterations in the oxyntic mucosa, including mucosal hyperplasia with formation of prominent rugal folds, and an increased number and total mass of parietal and proliferation of ECL cells, potentially leading to the development of carcinoid tumors, especially in patients with MEN-1 (see Chapter 17). Giant rugal folds cover the body and fundus and spare the antrum. The surfaces of the folds appear uniformly exaggerated, coarsely granular, or finely cobblestoned. Ulcers, particularly multiple ulcers, may be present. Histologic examination of the hypertrophic gastric folds reveals substantial glandular lengthening due to the parietal cell hyperplasia. The increased parietal cell mass comprises a progressively larger share of the glands, filling their entire length down to their bases. Parietal cells also extend into the neck regions or higher, coming closer to the surface than usual. In some cases, parietal cells completely populate the mucosal glands. Large numbers of parietal cells can also be present in the antrum, an area that usually lacks them. The foveolae appear normal in length or shortened (Fig. 4.110).
FIG. 4.110. Zollinger-Ellison syndrome. 

A: A thick nodular mucosa with expanded glands covers the enlarged folds. 

B: The mucosa contains a hyperplastic glandular compartment and shortened pits. 

C: The parietal cells are hypertrophic, hyperplastic, and located higher than normal in the gastric necks.

Fundic gland polyps also may be present, probably not as the result of the disease itself but due to long-term administration of proton pump inhibitors. Intramucosal cysts of the oxyntic mucosa are found in over 70% of patients with ZES, even in the absence of endoscopically recognizable polyps or nodules (272). These mucosal cysts range in size from 0.3 to 1.1 mm in diameter. The severity of the cystic change correlates with the serum gastrin levels (272a), and the cysts are more common than fundic gland polyps, which likely arise from them. They are typically lined by parietal cells, tall foveolar cells, and/or cuboidal or flattened cells of unrecognizable lineage. The upper parts of the cysts lie near the foveolar epithelium of the gastric pits, but occasionally they have an inverted deep localization.

**Hypertrophic, Hypersecretory Gastropathy**

Hypertrophic, hypersecretory gastropathy combines corpus glandular hyperplasia, normal surface components, and peptic
ulcer disease without hypergastrinemia. The stomach appears as diffusely nodular mucosa with prominent rugal folds, resembling ZES. However, the extensive parietal cell hypertrophy and hyperplasia that characterize ZES is absent.

**Hypertrophic, Hypersecretory Gastropathy with Protein Loss**

Hypertrophic, hypersecretory gastropathy with protein loss, the rarest giant fold disease, exhibits giant gastric folds, hypersecretion, protein loss, and a clinical presentation that resembles a cross between Menetrier disease and ZES. Most patients complain of epigastric pain, asthenia, anorexia, weight loss, edema, and vomiting. By definition, hypoalbuminemia and enteric protein loss exist in most cases. Occasionally, a concomitant gastric ulcer is present. Histologically, foveolar hyperplasia is present with deep cysts, mild glandular atrophy, and increased numbers of lymphocytes and plasma cells. It is not clear if this disorder differs from Menetrier disease or if it represents a stage in the evolution of the disease in which protein loss and edema become excessive and clinically important before the glandular compartment is compromised by loss of parietal cells and hypochlorhydria occurs.

**Helicobacter pylori–Associated Hypertrophic Gastropathy**

Hypertrophic gastropathies with features of Menetrier disease may complicate HP infections, leading to the speculation that the hypertrophic gastropathy is a special form of HP gastritis. Patients exhibit hypertrophic gastric folds and protein-losing enteropathy (273). Antibiotic treatment restores the normal architecture (274). Biopsies demonstrate the presence of a chronic or chronic active gastritis with or without ulceration. The pit-to-gland ratio is normal and the increased mucosal thickness results from the edema and inflammation. The differential diagnosis of enlarged gastric folds is listed in Table 4.22.

<table>
<thead>
<tr>
<th>TABLE 4.22 Differential Diagnosis of Enlarged Gastric Folds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menetrier disease</td>
</tr>
<tr>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>Varioliform gastritis</td>
</tr>
<tr>
<td>Carcinoma (linitis plastica)</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Granulomatous disease</td>
</tr>
<tr>
<td>Allergic gastritis</td>
</tr>
</tbody>
</table>

**Localized Hypertrophic Disorders**

A number of entities cause localized mucosal hyperplasia. Localized polypoid reparative mucosal proliferations occur sporadically, at sites of healed gastric ulcers, or near surgically created stomas.

Focal foveolar hyperplasia is a nonneoplastic regenerative process that compensates for increased epithelial cell turnover and surface cellular exfoliation in situations of mucosal injury, most commonly HP infections or chemical gastropathy. The process creates antral lesions measuring up to 5 mm in diameter (Fig. 4.111) that are frequently multiple (275). Foveolar cells line elongated, but architecturally normal, gastric pits. The cells contain hyperchromatic nuclei and there is an expanded proliferative zone with increased mitotic activity. Foveolar cellular immaturity is present as evidenced by mucin depletion, a cuboidal shape, and a high nuclear:cytoplasmic ratio. There may be up to more than four cross sections of the same pit in a well-oriented gastric biopsy specimen. The major entity in the differential diagnosis is a hyperplastic polyp (see below).

**Gastric Polyps**
Gastric polyps are usually incidental findings. They may be neoplastic or nonneoplastic, with most (80% to 90%) being nonneoplastic. They may be multiple or solitary, and some complicate polyposis syndromes (see Chapter 12). The two main types of nonneoplastic polyps are hyperplastic polyps and fundic gland polyps. Neoplastic polyps are described in Chapter 5.

**Fundic Gland Polyp**

In our experience, FGPs are the most common benign polyps encountered in a surgical pathology practice. They occur sporadically, develop in the setting of familial adenomatous polyposis (FAP), or complicate the use of proton pump inhibitors (see the dug injury section). Sporadic and FAP-associated polyps result from separate and distinct wnt signaling pathway alterations. Sporadic polyps contain activating \( \beta\)-catenin mutations, whereas FAP-associated polyps have biallelic APC mutations (276,277).

**FIG. 4.111.** Localized foveolar hyperplasia. *A:* A microscopic area of foveolar hyperplasia in a patient with gastritis. *B* comes from a patient with a wider area of foveolar hyperplasia that has branching, very irregularly shaped glands.

FGPs are sessile polyps arising in the oxyntic mucosa that can be single or multiple. FGPs developing in the setting of FAP may result in a carpet of several hundred polyps usually measuring <5 mm in diameter with a sessile base and a smooth-domed surface. Some of these polyps may be adenomas and others are FGPs. Unlike adenomas, FGPs are the same color as the surrounding mucosa (278). FGPs can develop and disappear within weeks. Torsion or mechanical traction resulting in autoamputation may cause some polyps to disappear (278).
FGPs are localized hyperplastic expansions of the deep glandular compartment of the oxyntic mucosa (Fig. 4.112). The overlying pits appear shortened or absent. They contain cystically dilated, irregularly deformed oxyntic glands with or without glandular proliferations, increased smooth muscle in the lamina propria, and a lack of hyperplastic foveolar cells. The glands are lined by normal oxytic cells, including a mixture of parietal, chief, and mucous neck cells. The glands appear almost to be tacked onto the surface of a normal or slightly atrophic mucosa. FGPs probably develop from the progressive dilation and infolding of glandular buds to produce irregular tortuous glands and microcysts. These lesions are generally benign. However, in the setting of FAP, they may contain areas of dysplasia.

**Hyperplastic Polyps**

Hyperplastic polyps develop in response to gastric injury such as from *HP* infections or autoimmune gastritis or around gastric remnants, ulcers, or surgically created stomas. They may also develop in the proximal stomach in patients with chronic gastroesophageal reflux. Most hyperplastic polyps develop in the gastric body (Fig. 4.113) and antrum. Hyperplastic polyps
are typically small, smooth, sessile lesions, measuring <2.0 cm in diameter. Rare polyps are large (up to 13 cm) and simulate carcinoma (279). Larger polyps may appear lobulated and/or pedunculated, often with superficial erosions. These may twist on their stalks, leading to superficial ulceration, hemorrhage, pyloric prolapse, or intermittent obstruction.

Most hyperplastic polyps arise on a background of chronic gastritis. Intestinal metaplasia (as part of the surrounding atrophic gastritis) may be present. It is believed that they represent an exuberant regenerative response of gastric foveolar cells. The glands do not normally participate in the formation of the polyps. Two major features categorize hyperplastic polyps. The first is marked elongation, infolding, and branching of the gastric pits leading to a corkscrew or serrated appearance. Tall mucin-secreting foveolar cells line exaggerated, elongated, and distorted pits that extend from the surface deep into the stroma. Hypertrophic foveolar cells resembling goblet cells can be present. The pits also dilate to form variably sized and shaped cysts (Fig. 4.114), which can be quite prominent. Glandular epithelium may be found in the deeper parts of the polyps. The glands are often antral in type, even when the polyps arise in the body or fundus. Occasionally one sees oxyntic glandular mucosa.

FIG. 4.114. Hyperplastic polyp. **A:** Note that the multiple cysts are present in an edematous stroma. **B:** Higher power magnification illustrates cystic glands lined by gastric mucous cells.

The second major change is an excess of an edematous stroma that is infiltrated by plasma cells, lymphocytes, eosinophils, mast cells, macrophages, and variable numbers of neutrophils (Fig. 4.115). Smooth muscle fibers arborize in the lamina propria. These lesions are highly vascularized. Vascular proliferations resembling granulation tissue develop superficially near areas of erosion. The glands may acquire an apparent back-to-back configuration near areas of ulceration, but epithelial atypia is either absent or minimal and often regenerative in nature, especially in areas of surface erosion (Fig. 4.115). Neutrophils are prominent in ulcerated areas. Reparative changes can superficially resemble low-grade dysplasias or adenomas.

The polyps may contain areas of epithelial dysplasia, which may be high grade or low grade (Fig. 4.116). The prevalence of dysplasia ranges from 1% to 20% and is most frequently found in larger polyps (280). Dysplastic changes are generally more extensive than the atypias seen in focally eroded polyps. These areas of dysplasia may give rise to invasive carcinomas. The polyps may contain clonal ras mutations, in the neoplastic as well as the nonneoplastic regions (281). The overall malignant potential is probably <2%. If dysplasia is found in a hyperplastic polyp at the time of biopsy, it is important to determine whether the dysplasia is confined to the hyperplastic polyp or is part of a more diffuse neoplastic process. If the lesion is confined to the polyp and the polyp has been removed by a polypectomy, then the lesion is likely cured.

The differential diagnosis of hyperplastic polyps includes Menetrier disease, juvenile polyposis, and Cronke-Canada syndrome. Menetrier disease is usually a more extensive process and has characteristic clinical features. The distinction from
juvenile polyposis usually relies on the presence of colonic polyps and the clinical features. The distinction from Cronkite-Canada syndrome may be very difficult, although it is a very rare disorder and does have characteristic ectodermal features (see Chapter 12).
FIG. 4.115. Hyperplastic polyp. A: Hyperplastic polyps often contain an edematous stroma widely separating the hyperplastic and irregular glands that are frequently lined by foveolar epithelium. The vessels appear congested. B: In some instances, hyperplasia of the foveolar epithelium causes papillary infoldings. Additionally, severely congested lesions may associate with extravasated red cells in the lamina propria. C: Other lesions have a more cellular lamina propria due to the absence of the edema and an infiltrate of inflammatory cells. D: Hyperplastic polyps become eroded and may contain prominent areas of granulation tissue and acute inflammation.

FIG. 4.116. Hyperplastic polyp containing dysplasia. A: Low magnification showing the presence of benign polypoid fragments (lower). Other parts of the polyp exhibit a more complex architectural pattern. B: Higher magnification of one of the more cellular areas demonstrates the presence of what appears to be adenomatous epithelium. C: In other areas, frank cytologic malignancy is evident and diagnosable as high-grade dysplasia.

Isolated Hamartomatous Polyps
Isolated hamartomatous polyps consist of a prominent submucosal mass of haphazardly arranged oxyntic glands in a framework of smooth muscle tissue and occasional focal accumulations of mature lymphoid tissue. The entire lesion is supported by normal lamina propria. The glands may appear normal or be cystically dilated. One also sees mucous cells resembling foveolar epithelium as well as rare antral or cardiac-type glands containing endocrine cells indigenous to the mucosal site. The lesions differ from those seen in Peutz-Jeghers syndrome, which are usually not submucosal lesions but more mucosally based with possible submucosal extensions (see Chapter 12). Additionally, the arborizing muscle bundles seen in Peutz-Jeghers polyps are typically absent in isolated gastric hamartomas.

Inflammatory Fibroid Polyps
Inflammatory fibroid polyps (IFPs) affect all areas of the GI tract (282). Most lesions develop in adults, although some occur in children (282). The average patient is 63 years old. IFPs may remain asymptomatic or cause abdominal pain due to gastric
outlet obstruction (283). The lesions are reactive in nature. Associated lesions include *HP* gastritis (284), gastric ulcer, adenoma (285), or carcinoma (286). Grossly, IFPs present as sessile, firm, gray-tan polypoid or semi-pedunculated lesions that can be solitary or multiple. Most lesions arise in the antrum, ranging in size from <1 to 12 cm. IFPs originate in the submucosa, are usually covered by normal mucosa (Fig. 4.117), and grossly mimic leiomyomas or GI stromal tumors. The mucosa overlying the polyp is eroded in approximately a quarter of the cases. The lesions extend into the muscularis propria and may reach the serosa.

Histologically, IFPs consist of loosely structured stromal tissue. The predominant cell type consists of spindled fibroblastlike cells intermingled with inflammatory cells and proliferating vessels, arranged in an edematous stroma. Whorls of fibroblasts or myofibroblasts surround thin-walled vessels in a concentric or onion skin–like fashion. Vascularity and cellularity vary (Fig. 4.118) and may be striking. Proliferating cells appear uniform and contain abundant cytoplasm and pale spindle-shaped nuclei. Varying numbers of eosinophils and lymphocytes infiltrate the tissues. The numerous vessels vary in their appearance and some appear thickened with hyalinized walls. Multinucleated giant cells can be present. IFPs gradually merge into the surrounding tissues.

The lesions evolve through several stages. The nodular stage (average size 0.4 cm) contains nodules of immature fibroblasts in a loose myxoid stroma. The fibrovascular stage (average size 1.5 cm) demonstrates concentric aggregations of mature fibroblasts with endothelial proliferation and eosinophilic infiltrates. In larger polyps (average size 4.8 cm), the histologic pattern evolves into the sclerotic or edematous stage by either collagenization or vascular compromise.
The differential diagnosis of this lesion includes eosinophilic gastroenteritis, which typically affects younger patients and is characterized by diffuse eosinophilic infiltrate that may involve long bowel segments as opposed to being relatively restricted lesions. Additionally, there is peripheral eosinophilia, and the lesions of eosinophilic gastroenteritis do not show the marked fibroblastic or vascular proliferation seen in IFPs. Other entities in the differential diagnosis include GI stromal tumors (GISTs) and other mesenchymal lesions. The spindle cells in IFPs are diffusely immunoreactive for vimentin and CD34. They may be focally positive for histiocytic makers. They may show focal immunoreactivity for α smooth muscle actin. Cytokeratin, desmin, S100, factor VIII, and Ki67 are negative in the spindle cells.

**FIG. 4.118.** Inflammatory fibroid polyp. Proliferation of loose fibrovascular tissue and chronic inflammatory cells. Eosinophils are admixed with the chronic inflammatory cells.

**Gastritis Cystica Profunda**

This rare condition primarily affects elderly men and is often encountered in a previously operated on stomach. Cysts develop in the submucosa or muscularis mucosae of the gastric body and antrum (Fig. 4.119). They arise from displaced mucin-producing gastric glands. Sometimes chief and parietal cells lie scattered among the mucin-secreting epithelium. Foveolar cells may also be present. The abnormality results from previous ulceration or gastric surgery that allows the mucosa to gain access to the submucosa (287). A normal-appearing lamina propria usually surrounds the displaced glands providing a clue to the diagnosis. Coexisting hemosiderin deposits and fibrosis support episodes of previous injury. *Heterotopic pyloric glands with an inverted downgrowth pattern*, a lesion consisting of foveolar epithelium and tubular glands with abundant gastrin immunoreactive cells (60), represent a variant of this process.

**Vascular Abnormalities**

Gastric vascular lesions include both neoplastic and nonneoplastic entities (Table 4.23). All typically present with upper GI bleeding. Only the nonneoplastic conditions are discussed here. Vascular neoplasms are discussed in Chapter 19.

<table>
<thead>
<tr>
<th>Nonneoplastic</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varices</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy</td>
<td>Angiomas</td>
</tr>
<tr>
<td>Gastric antral vascular ectasia</td>
<td>Angiosarcomas</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>Glomus tumor</td>
</tr>
<tr>
<td>Persistent caliber artery</td>
<td>Hemangiopericytoma</td>
</tr>
<tr>
<td>Telangiectasias</td>
<td></td>
</tr>
</tbody>
</table>

**Gastric Varices**

Gastric varices are less common than esophageal varices and affect approximately 20% of patients with portal hypertension (288), usually accompanying esophageal varices. Gastric varices typically surround the cardioesophageal junction and they commonly bleed. Their histologic features resemble esophageal varices, which are discussed in detail in Chapter 2.

**Portal Hypertensive Gastropathy (Congestive Gastropathy)**

Portal hypertensive gastropathy (PHG) is a vasculopathy involving the gastric microvasculature in both adults and children with portal hypertension (289). Mild PHG is highly prevalent in cirrhotics, while severe changes are only seen in 10% to 25% of these patients (289). The disorder presents with bleeding in severe cases. A hallmark of the condition is mucosal and submucosal capillary and venous ectasia that in severe PHG imparts a typical mosaic appearance. The mucosa appears “beefy” red with multiple petechial hemorrhages, red spots, ulcers, and erosions. Patients exhibit increased mucosal blood flow. Vascular congestion, rather than erosions, damages the mucosa.
Histologically, mucosal capillary (Figs. 4.120 and 4.121) and venous ectasia and submucosal venous dilation are present. The submucosal vessels may appear thickened and abnormal. These changes occur in the absence of erosions or inflammation. Propranolol and various jugular intrahepatic portosystemic shunts are used to treat PHG (289). The differential diagnosis includes gastric vascular ectasia, another condition that is common in cirrhotic patients.

**Gastric Antral Vascular Ectasia (Watermelon Stomach)**

Gastric antral vascular ectasia (GAVE) differs from PHG in its clinical features, gross appearance, and histologic features. However, both conditions are common to patients with cirrhosis. GAVE presents clinically with bleeding and typically affects elderly females with an average age of 66.5 years (290). GAVE associates with various conditions, including cirrhosis, chronic heart disease, bulimia, bone marrow transplantation, and autoimmune connective tissue disorders. In contrast to the hemodynamic disturbances seen in PHG, motility disturbances may play a role in the pathogenesis of GAVE. It is conceivable that antral mucosal prolapse into the duodenum causes some of the changes that are present.

**FIG. 4.120.** Portal gastropathy. A: Low-power magnification demonstrating the presence of markedly dilated and congested mucosal capillaries. B: Higher magnification of the lesion shown in A demonstrating the presence of markedly dilated spaces lined by endothelial cells and filled with unclotted blood.
FIG. 4.121. Portal gastropathy. A: In some patients, portal gastropathy takes the form of multiple dilated mucosal capillaries that diffusely affect the gastric mucosa. B: Higher magnification.

GAVE is characterized by aggregates of mucosal red spots in the distal stomach. The ectatic red spots may be more diffuse and occasionally involve the proximal stomach. If the red spots are present on a background mosaic pattern, the disorder is more likely to be PHG than GAVE, in which the background mucosa appears normal without the mosaic appearance. Its most distinctive appearance consists of nearly parallel, intensely red, longitudinal stripes situated at the crests of hyperplastic mucosal folds traversing the gastric antrum creating the pattern of a “watermelon stomach” (291). These stripes correspond to markedly dilated, tortuous mucosal capillaries (Figs. 4.122 and 4.123). The ectatic mucosal capillaries often contain fibrin thrombi, and they are surrounded by fibrohyalinosis with fibromuscular hyperplasia of the lamina propria. The fibrohyalinosis appears as a homogeneous light pink substance surrounding ectatic capillaries in the lamina propria and submucosa. The presence of the hyalinosis and the fibrin thrombi are important in differentiating GAVE from severe PHG (Table 4.24) (291). Epithelial damage from gastric acid, intraluminal food, or other factors can disrupt the mucosal barrier in mucosal areas overlying engorged vessels and may explain the presence of the fibrin thrombi. The lesions usually show patchy mild chronic inflammation in the superficial lamina propria. One may also see coexisting atrophic gastritis with intestinal metaplasia. The muscularis mucosae often appears thickened and hyperplastic, perhaps reflective of mucosal prolapse. Submucosal vessels appear dilated and congested, but no vascular malformations are evident.
FIG. 4.122. Gastric antral vascular ectasia. A: A gastric biopsy demonstrating a wider than normal separation of the glands in part of the biopsy. This separation results from sclerosis around the mucosal capillaries and also affects the lamina propria. B: Similar lesions may be encountered in the submucosa. One sees irregular thickening and hyalinosis of the vasculature. Mucosal congestion may also be present.
**FIG. 4.123.** Gastric antral vascular ectasia (GAVE). A: Gastric biopsy showing prominent vascular congestion with thrombosis of the vasculature. The surrounding glands appear regenerative. The vessels in the submucosa are dilated and sclerotic. B: Higher magnification of one of the thrombosed vessels.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Portal Gastropathy</th>
<th>GAVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Fundus and corpus</td>
<td>Antrum</td>
</tr>
<tr>
<td>Degree of ectasia</td>
<td>Mild–moderate</td>
<td>Marked</td>
</tr>
<tr>
<td></td>
<td>ectasia</td>
<td>ectasia</td>
</tr>
<tr>
<td>Presence of cirrhosis</td>
<td>Always</td>
<td>30% of patients</td>
</tr>
<tr>
<td>Presence of fibrohyalinosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence of thrombosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Vascular spindle cell proliferation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Anemia and hemorrhage</td>
<td>Low incidence</td>
<td>High incidence</td>
</tr>
<tr>
<td>Endoscopic lesions</td>
<td>Diffuse erythema</td>
<td>Appear as microvessels</td>
</tr>
<tr>
<td>Sex</td>
<td>More commonly affects men</td>
<td>Predominantly affects women</td>
</tr>
</tbody>
</table>

**TABLE 4.24 A Comparison of Portal Gastropathy and Gastric Antral Portal Ectasia (GAVE)**

**Angiodysplasia**

Patients with angiodysplasia present with overt gastrointestinal bleeding or anemia. Bleeding from the lesions can be massive and recurrent. If the lesions are visible endoscopically, they appear bright red, flat, and well circumscribed, or fernlike. Selective arteriography is the preferred way to establish the diagnosis. Controversy surrounds the etiology of angiodysplasia. Arguments favoring an acquired origin include its association with aortic stenosis, underlying inflammatory gastrointestinal conditions, and von Willebrand disease. Mechanical factors such as vascular destruction may play a role in some cases, with vigorous peristalsis or increased intraluminal pressure causing shunting of blood into the submucosal arteriovenous system. The lesions may also result from progressive dilation of normal vascular structures secondary to vascular degenerative changes present in the elderly.

Most angiodysplasias are mucosal and submucosal lesions that are not always grossly visible. A helpful way to identify the vascular abnormality in resection specimens is to inject an India ink–radiopaque dye combination into the specimen and then to radiograph the specimen and then section it. Angiodysplasia consists of abnormal numbers of dilated, distorted arteries and veins lined by endothelium and rarely by a small amount of smooth muscle between the pre-existing ectatic arteries, veins, venules, and capillaries (Fig. 4.124). The vessels have an abnormal distribution and aberrant morphology and probably represent true arteriovenous malformations.

The earliest abnormality consists of dilated submucosal veins, which may be present in the absence of mucosal disease. As the disease progresses, the mucosal abnormalities become more pronounced with increased numbers of dilated and deformed mucosal and submucosal vessels, eventually leading to distortion of the mucosal architecture and erosions. The vascular channels may be separated from the gastric lumen by a single layer of endothelial cells. The walls of the vessels in the submucosa appear irregularly thickened. The presence of distorted and dysplastic vessels distinguishes this lesion from a hemangioma or telangiectasia.

**Caliber-Persistent Artery (Dieulafoy Lesion)**

The entity variously termed caliber-persistent artery, cirrroid aneurysm, or Dieulafoy lesion tends to affect middle-aged and
elderly men. Median patient age is 52 to 54 years, with patients ranging in age from 16 to 91 (292). The disorder presents as recurrent, massive, and sometimes fatal hematemesis. Massive hemorrhage and rupture occur when a large submucosal artery impinges on the mucosa while pursuing its tortuous course through the submucosa. The lesion is thought to represent a congenital anomaly related to defective arterial involution or elongation and even curling of a deep elongated submucosal vessel (293).

FIG. 4.124. Angiodysplasia affecting the gastric mucosa. Abnormal arteriovenous connections occur.

Because the lesions are flat, they are hard to detect. However, the angiographic appearance is characteristic. The lesion is often not visible endoscopically, although one may see an area of bleeding. When endoscopically identifiable, the lesion presents as a volcanic crater with a central whitish discoloration projecting from an otherwise normal gastric mucosa. An abnormally large submucosal vessel protrudes through a minute mucosal defect (Fig. 4.125). Ulceration is usually not present in the region surrounding the place where the vessel breaks through the mucosa. In most cases, the bleeding site lies within the first 6 cm of the gastroesophageal junction, usually on the lesser curvature (293).

Histologically, an abnormally large oversized tortuous muscular artery measuring about 1.5 mm in diameter runs through the submucosa and approaches the mucosa (Fig. 4.126), often with superficial erosion (Fig. 4.127). Veins often accompany the lesion. The arterial wall may show medial hypertrophy and adventitial fibrosis, but the lesion typically lacks inflammation, aneurysm formation, atherosclerosis, or dystrophic calcification. An elastic tissue stain demonstrates the normal architecture of an arterial wall with only slight intimal hyperplasia and reduplication of the internal elastic lamina. If the wall of the artery is eroded at the base of a mucosal ulcer, hemorrhage ensues. The ulcer is often minute even though the hemorrhage is massive. The overlying ulcer usually lacks the intense inflammation typical of peptic ulcer disease and is superficial with no involvement of the muscularis propria or associated mural fibrosis. The part of the artery at the base of the ulcer usually shows focal necrosis and rupture. A thrombus may be attached to a protruding open artery. The artery forces the mucosa upward and a wide submucosal area characteristically exists between these arteries and the true muscularis propria.

**Hemodialysis-Associated Telangiectasias**

Telangiectasia generally refers to the dilation of pre-existing vessels, whereas angiomatosis refers to new vessel growth. Gastric telangiectasias develop in some patients on long-term hemodialysis (294). The telangiectatic areas appear small, flattened, and reddish with fernlike margins. Several factors may predispose to its development. Chronic sodium and water overload may result in venous hypertension, causing submucosal venous dilation. Additionally, dialysis patients receive aluminum hydroxide on a long-term basis to control hyperphosphatemia. Aluminum compounds are

P.221
known to cause skin telangiectasias (295). Patients on hemodialysis also develop accelerated atherosclerosis (296), which may predispose the gastrointestinal vasculature to develop abnormalities.

FIG. 4.125. Caliber-persistent artery. A: Opened specimen seen from the mucosal side is not very dramatic. The stomach was completely filled with blood and the arrow points to the lesion. B: Higher magnification demonstrates the eroded surface of the prominent vessel. Such lesions must be carefully sought. They characteristically lie in the proximal stomach and are usually very difficult to see.

Gastric Tears, Perforations, Fistulae, Ruptures, and Hematomas

The upper portion of the stomach is subject to the same types of tears, perforations, and linear erosions and fistulae as seen in the lower esophagus (see Chapter 2) (Fig. 4.128). They complicate surgical treatment, foreign bodies, trauma, peptic ulcer disease, severe or persistent vomiting, infections, neoplasms, chemical injury, and lung infections. They can affect adults as well as newborns. They are seen in young women with eating disorders due to the repeated episodes of induced vomiting. The cause of gastric rupture in infants is not always clear, although endotoxins and muscular defects are postulated etiologic factors. Intramural gastric hematomas may develop in patients with coagulopathies, prior surgery, bleeding benign gastric ulcer, or trauma.
**FIG. 4.126.** Caliber-persistent artery. Note the presence of an unusually large vessel underlying the gastric mucosa. In this case, the overlying mucosa remains intact.

**FIG. 4.127.** Histologic section through the vessel illustrated in Figure 4.125. Note the unusually large size. Fresh blood and organizing thrombus are present.
Gastric Siderosis

Approximately 4% of gastric biopsies will demonstrate evidence of gastric siderosis (93). Three patterns of gastric siderosis have been identified: (a) a nonspecific gastric siderosis with predominant iron deposits in the stromal cells including macrophages and focally in the epithelium, (b) an iron pill gastritis (discussed previously in the drug-induced gastritis section of this chapter), and (c) a predominant deposition in antral and fundic glandular epithelium. The first two types of siderosis are focal and patchy and associate with variable inflammation; the third is strong and diffuse and is characteristic of the iron deposition that is seen in hemochromatosis (93).

Hemochromatosis is an iron overload disorder that causes prominent damage to the liver and pancreas. It is diagnosed on the basis of the clinical triad of a micronodular pigmented cirrhosis, diabetes mellitus, and skin pigmentation. The most severe iron overload occurs in a genetic disorder, whereas secondary hemochromatosis results from excessive iron overload. Patients with hemochromatosis have a susceptibility gene located on chromosome 6 closely linked with the HLA locus. The excessive iron accumulates preferentially in the cytoplasm of parenchymal cells (Fig. 4.129). This contrasts with iron deposition in the mononuclear cells in patients with systemic hemosiderosis.

Gastric Involvement in Systemic Diseases

Inflammatory Bowel Disease

The stomach may be abnormal in patients with IBD. The changes associated with Crohn disease were discussed in the section on granulomatous gastritis. Ulcerative colitis patients may also develop gastritis (297). The changes include multiple

FIG. 4.128. Mallory-Weiss tear of the stomach in a patient who had a previous Nissen fundoplication.
tiny ulcers, glandular abscesses, and intraepithelial lymphocytosis. The intensity of the changes reflects the activity of the colonic disease.

**Amyloid**

Gastric amyloid deposits occur in approximately 1% of patients with systemic amyloidosis. Some patients have coexisting small bowel amyloidosis (298). GI involvement may lead to vascular compromise, tumoral deposits, intramural thickening, prolonged nausea and vomiting, weight loss, gastroparesis, and gastric outlet obstruction (298). Other patients remain completely asymptomatic only to have the amyloid demonstrable on gastric biopsies performed for other reasons. In its earliest stages, amyloid tends to accumulate in the intima and media of small submucosal and serosal blood vessels (Fig. 4.130). The lamina propria and muscularis propria are variably involved, and the epithelium appears normal. Amyloid deposition is more massive in primary than in secondary types of amyloidosis. Parenchymal deposits primarily affect the muscularis mucosae and muscularis propria (298), causing thickened gastric folds. Amyloid also surrounds gastric glands. In tumoral amyloidosis, the entire gastric wall becomes replaced by large acellular eosinophilic masses that completely destroy the underlying histology (Fig. 4.131). The amyloid aggregates may be surrounded by macrophages.

**Diabetes**

By far the most common gastric complication of diabetes is diabetic gastroparesis, a condition that results from a peripheral autonomic neuropathy. It is discussed further in Chapter 10.

**Mastocytosis**

Accumulations of mast cells in the skin and parenchymal organs characterize systemic mastocytosis (299). Gastrointestinal symptoms include nausea, vomiting, abdominal pain, and diarrhea. Parietal cell mass increases due to increased histamine levels from the mast cells and results in hyperchlorhydria and peptic ulceration (299). Endoscopic features include the presence of erosions and gastroduodenal ulcers with a bleeding tendency, thickening of the gastric folds, mucosal edema, urticarialike lesions, and, occasionally, varices due to portal hypertension. Because the gastric folds appear hypertrophic, mastocytosis is included in the differential diagnosis of giant fold diseases. Histologically the gastric wall is infiltrated by increased numbers of mast cells. These can be highlighted using an immunohistochemical reaction for tryptase.
FIG. 4.129. Hemochromatosis. A: Patients with hemochromatosis often exhibit marked iron deposition within the epithelium of the gastrointestinal tract. In the stomach, iron deposits in the glandular component of the mucosa, as is demonstrated by this Prussian blue stain. B: Hematoxylin and eosin section showing the presence of pigmented glandular epithelium.

Sjögren Syndrome
Gastric involvement in primary Sjögren syndrome is present in approximately 50% of patients (300). Some individuals show moderate chronic atrophic gastritis, whereas most show superficial gastritis. Antibodies to gastric parietal cells are detectable in approximately 10% of cases.

**Hypercalcemia**

Patients with hypercalcemia often demonstrate dystrophic calcification in various sites. In the stomach, this takes the form of deposits within the mucosa often surrounding individual gastric glands or occasionally lying free in the lamina propria. Slender areas of calcification are visible histologically (Fig. 4.132). Their true nature can be confirmed with the use of a Von Kossa stain.

**Tumorlike Lesions (Pseudotumors)**

A number of lesions may present as pseudotumors. Some of the more common ones are discussed below.

**Gastric Xanthelasma (Xanthoma)**

Xanthelasmas appear to the endoscopist as single or multiple, well-demarcated, circular-oval, whitish yellow lesions measuring 1 to 2 mm and rarely exceeding 5 mm. They may develop in the setting of cholestasis and hypercholesterolemia. Histologically, the lesions consist of collections of lipid-containing macrophages (xanthoma cells) arranged in pavementlike
patterns in the upper lamina propria immediately beneath the surface epithelium (Figs. 4.133 and 4.134). Lymphocytes, plasma cells, and macrophages associate with the foam cells. The macrophages contain a foamy, finely vacuolated cytoplasm and the cells are PAS negative. The etiology of the lipid islands is unknown, but they never occur in a normal stomach. Patients often have evidence of duodenal reflux, varying degrees of gastritis, gastric surgery, or even associated cancer. These lipid islands stain with the macrophage marker KP1 and the foam cells contain low-density lipoproteins (LDLs) and oxidized LDLs.

**FIG. 4.131.** Tumoral amyloidosis of the stomach. Eosinophilic acellular material concentrically surrounds blood vessels.

**Regenerative Lesions with Pseudosarcomatous Stroma**

Regenerative lesions, whether they appear polypoid or surround an area of ulceration, may contain a stroma that appears pseudosarcomatous due to prominent reactive endothelial cells and/or myofibroblasts. In the stomach, the lesions usually affect middle-aged or elderly individuals. The reactive cells contain large nuclei and prominent nucleoli. Often, inflammatory cells associate with the reactive cells. The reactive cells are cytokeratin negative, allowing one to distinguish the lesion from an undifferentiated carcinoma. The overall reactive appearance of the lesion distinguishes it from a mesenchymal tumor in that the cells are typically large and lack mitoses. Vimentin immunostains are usually strongly positive.

**Bezoars and Foreign Bodies**

Multiple factors predispose to bezoar development. Motility disturbances or obstructions predispose to their formation. As a result, bezoars complicate diabetes mellitus, myotonic muscular dystrophy, sclerotherapy, and medications that impair GI motility, such as opioids or neuromuscular blockers. Most foreign objects are swallowed accidentally by children, intentionally by psychiatric patients, or as contraband by smugglers. Patients with bezoars complain of anorexia, epigastric fullness, nausea, or vomiting. Ulceration, bleeding, and peritonitis complicate ingestion of pointed objects such as needles or toothpicks. Bezoars consist of accumulated ingested material that forms a gastric intraluminal mass. Most result from consumption of indigestible organic substances such as hair (trichobezoars), vegetables (phytobezoars), drugs, or a combination thereof (trichophytobezoars). Trichobezoars typically develop in emotionally disturbed young girls chewing and swallowing long hair with the ultimate formation of a hair ball that leads to pyloric outlet obstruction.
FIG. 4.132. Mucosal calcification in hypercalcemia. A: Low magnification shows several glands that appear to stand out due to prominent basophilic staining. One such gland is outlined in the box. This area is shown at higher magnification in B: Dystrophic calcification lies in the lamina propria as well as in a periglandular distribution. The patient had hypercalcemia from parathyroid hyperplasia.

Consequences of Gastrointestinal Surgery

A number of histologic changes complicate the postsurgical stomach. **Marginal, anastomotic, stomal, and surgical ulcer** are terms that refer to the ulcers developing at surgically created gastric outlets. They usually follow duodenal ulcer operations. Today stomal ulcers are uncommon and have largely disappeared with the abandonment of simple gastroenterostomy as the primary ulcer operation.

**Chronic gastritis** is common, particularly if the stomach is connected to the jejunum in a Billroth II operation. The gastritis is often severe with atrophy, pyloric and intestinal metaplasia, and sometimes dysplasia. Proximal to the anastomosis, there is pit hyperplasia, superficial edema, a muscular lamina propria, minimal inflammation, and glandular atrophy secondary to gastrin loss from the antrectomy. Numerous factors contribute to the genesis of these lesions, including chronic bile reflux, stomal ischemia secondary to mucosal prolapse, or mucosal deformities that occur when the anastomosis is constructed. Increased G-cell proliferation after the procedure perhaps explains the increased risk of cancer development in the gastric remnant. These lesions may start as foveolar hyperplasia in response to pancreatic or duodenal secretions.
FIG. 4.133. Gastric xanthelasma. A prominent lamina propria collection of xanthoma cells distorts the architecture of the mucosa, filling it up and widening the interglandular regions.

FIG. 4.134. High magnification of gastric xanthoma showing the collection of foam cells in the lamina propria. These cells are distinguishable from signet ring cell carcinomas by virtue of the small nucleus and large amount of cytoplasm. Additionally, the nuclei are often centrally placed. In cases of doubt, they can be stained with the antibody KP1 to confirm their true nature.

Repetitive injury may lead to release of proinflammatory agents, which may stimulate smooth muscle and later fibroblastic proliferations. The first macroscopically visible lesion is polypoid foveolar hyperplasia, which then evolves into larger masses of hyperplastic polyps found at the gastrectomy site. Grossly, the lesions present as a solitary sessile polyp or as a linear arrangement of polyps encircling the gastric side of the stoma. The gastric pits have an increased depth or diameter with saccular dilations, and the increased stroma appears edematous and/or inflamed, widely separating the gastric glands. The base of the lesion contains fibrous connective tissue replacing or extending through the muscularis mucosae. Histologically, these proliferative lesions resemble hyperplastic polyps in that they contain proliferating nondysplastic foveolar cells. The hypertrophic muscularis mucosae appears irregularly frayed, with penetration of cystic glands into the submucosa, producing gastritis cystica profunda. The lesion microscopically represents a localized rugal hypertrophy, often resembling Menetrier disease. The natural history of these lesions is controversial, and it remains unclear as to whether they represent an
intermediate stage between chronic stromal gastritis and stomal cancer.

**TABLE 4.25 Gastric Remnant Changes**

| Chronic alkaline reflux gastritis |
| Cystic glandular dilatation (similar to fundic gland polyps) |
| Surface (foveolar) hyperplasia |
| Atrophic gastritis |
| Intestinal metaplasia |
| Hyperplastic polyps |
| Gastric cystica profunda |
| Gastric xanthelasma |
| Dysplasia |
| Carcinoma |
| Stomal ulcers |

**References**

Clin Invest 1991;87:1716.
P.227


72. Laine L, Weinstein WM: Histology of alcoholic hemorrhagic “gastritis”: a prospective evaluation. *Gastroenterology*
1988;94:1254.

P.228


P.229


Chapter 4


antibodies: histological and clinical findings. Diabetes Care 2003;26:82.


P.231


The Neoplastic Stomach

Gastric neoplasms constitute a heterogeneous group of tumors; most are adenocarcinomas. Less common gastric cancers, such as lymphomas, neuroendocrine tumors, and stromal tumors, are discussed in Chapters 17, 18, and 19.

Adenocarcinoma Distal to the Cardia and its Anatomic Precursors

The stomach is divided into three subsites: The cardia, the corpus, and the pyloric antrum. Cancers of the cardia and Barrett-associated adenocarcinomas of the esophagus share similar backgrounds, temporal trends, molecular profiles, and behavioral patterns. These two cancers constitute gastroesophageal junction (GEJ) cancer and are discussed in Chapter 3. The epidemiologic backgrounds and temporal trends of cancers arising distal to the cardia are distinctly different from those arising in the cardia. Noncardia stomach cancer was once the most common human cancer worldwide, but it has shown a steep decline in frequency in the United States and Western Europe, where it is now less common than cancer of the GEJ in white males (1). Distal stomach cancer is still very common in developing countries and among migrants from them.

Epidemiology

Gastric carcinoma shows striking temporal and geographic variations in frequency (2), with a more than 10-fold difference in incidence between countries with high and low rates (Table 5.1). England and Wales offer a good example of the temporal decline in noncardia gastric cancer incidence, with male rates falling from 8.5 to 4.1 between 1971 and 1998, and female rates falling from 3.8 to 1.7 over the same time period (3). First-generation migrants from high-risk countries to low-risk countries continue to experience the high rates of their motherland, whereas their children and grandchildren show rates that approach those of the host country (4). This supports the concept that environmental exposures in early life generate cancer precursors that persist into adulthood and are not reversed by a more favorable environment.

The age-specific gastric cancer incidence rates rise steeply after 50 years of age in all populations, peaking at 673 per 100,000 at age 80 in Miyagi, Japan, compared to 103 per 100,000 for 80-year-old white males in low-risk Los Angeles (2). The wide incidence differences in high- and low-risk populations is already apparent at age 25 when the Miyagi and Korean male rates stand at 2.1 and 4.1, respectively, compared to the Los Angeles white male rate of 0.3 per 100,000. This supports the concept that exposure to environmental hazards begins early in life among people in high-risk populations. Gastric cancer incidence rates for men are approximately twice those of women in all populations for persons over 50 years of age, but the male:female incidence ratio is 1 or less at younger ages. The age-related variation in the male:female incidence ratio suggests that host factors may influence the level of risk of acquiring this cancer.

The rapid decline in the frequency of gastric cancer in the United States since World War II is best appreciated by following the age-adjusted mortality rates for this tumor in white males: 16.34 per 100,000 for the years 1950–1969 and 7.33 per 100,000 for the years 1970–1994 (5). A decrease in gastric cancer incidence since 1973 has occurred in both high- and low-risk countries as is shown in Table 5.2 (2). The earlier decrease in stomach cancer in Western countries was unplanned, resulting from modern refrigeration of foods, year-round access to fresh fruits and vegetables, and, more recently, the treatment of Helicobacter pylori infections.

Gastric cancer arising distal to the cardia does not behave as a single disease, but as several diseases that affect different parts of the stomach and vary in their histologic presentations. Lauren (6) first recognized that distal stomach cancers occur in two forms that differ in their structure and behavior: An intestinal type that consists of intestinal-type glands and a diffuse type that consists of discohesive cells supported by a desmoplastic stroma. The intestinal type is more likely to show vascular spread and hepatic metastases. The diffuse form has a less favorable prognosis, is less likely to have hepatic metastases, and is prone to transperitoneal spread. Both types have decreased in frequency in developed countries and share similar environmental exposures. Age, sex, and blood type, as well as inherited predispositions, determine whether a patient will develop an intestinal or diffuse cancer. The distinction between intestinal and diffuse types of gastric cancer has proven to be valuable in epidemiologic studies and in assessing tumor prognosis. Mixed forms of these cancers occur, as well as distinctive subtypes of these tumors, but the practical advantages of this simple classification have held up over time.

| TABLE 5.1 Geographic Variation, Male, Age-standardized Gastric Cancer Incidence Rates per 100,000 |
|---------------------------------------------|---------------------------------------------|
| High incidence: | China, Changle 145.0 |
| | Japan, Yamagata 91.6 |
| | Korea, Busan 72.5 |
| Intermediate incidence: | Costa Rica 40.1 |
| | Belarus 40.5 |
| | Italy, Romagna 32.3 |
| | Portugal 38.3 |
| | Colombia, Cali 30.5 |
| Low incidence: | United States, Utah 4.6 |
| | United States, New Mexico 4.4 |
| | Switzerland, Geneva 7.8 |

Both types of gastric cancer occur in high-risk populations, but the proportion of diffuse tumors is increased in low-risk groups. A retrospective analysis of gastric cancer in the SEER (Surveillance, Epidemiology, and End...
Results) registries of the United States found that diffuse cancers have increased in frequency between the years 1973 and 2000, while intestinal-type cancers have decreased over the same time period (7). A similar trend may account for a recent decrease in antral carcinomas relative to those in the middle third of the stomach in Japan (8), since the proportion of diffuse cancers is higher in the more proximal stomach. The typical differences in intestinal and diffuse gastric cancers are summarized in Table 5.3.

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil (Sao Paulo)</td>
<td>45.7</td>
</tr>
<tr>
<td>Colombia (Cali)</td>
<td>46.3</td>
</tr>
<tr>
<td>United States (Iowa)</td>
<td>7.5</td>
</tr>
<tr>
<td>Japan (Miyagi)</td>
<td>88.0</td>
</tr>
<tr>
<td>Finland</td>
<td>29.7</td>
</tr>
<tr>
<td>Poland (Warsaw)</td>
<td>31.4</td>
</tr>
<tr>
<td>Italy (Varese)</td>
<td>38.5</td>
</tr>
<tr>
<td>Spain (Navarre)</td>
<td>34.8</td>
</tr>
<tr>
<td>United Kingdom (Oxford)</td>
<td>20.0</td>
</tr>
</tbody>
</table>


**Predisposing Factors and Conditions**

The persons at highest risk of acquiring gastric cancer are concentrated in the lower economic strata of developing countries. The initial steps in cancer induction occur in childhood with infection by *H. pylori* (9). The youngest children of large families living in crowded, unsanitary conditions are at highest risk (10). Familial clusters of stomach cancer result from a shared exposure to environmental hazards (11) and to inherited factors (12).

**Genetic Factors**

There are a number of types of genetic and epigenetic changes that play a role in the predisposition to or the development of gastric carcinoma (Table 5.4). These include activation of oncogenes, growth factors and growth factor receptors, inactivation of tumor suppressor genes, DNA repair genes, and cell adhesion molecules, as well as alterations in cell cycle regulatory genes. Inherited factors interact with environmental hazards to increase gastric cancer risk in two ways: (a) germline mutations account for well-defined, but infrequent, familial cancer syndromes; and (b) polymorphisms in genes that govern cell cycling or enzymes that catalyze carcinogen detoxification may also influence gastric cancer risk. Other types of changes occur in sporadic tumors.

Inherited gastric cancer predisposition syndromes account for approximately 10% of gastric cancers. The genetic events are known for some but not all of the predispositions. The *hereditary nonpolyposis colon cancer syndrome* (HNPCC) is an example of the interaction of environmental hazards with germline mutations. Persons with this autosomal dominant condition are at increased risk of developing cancer at sites other than the colon, including the stomach. HNPCC is due to a germline mutation in mismatch repair genes. The risk of gastric cancer in Korean patients who carry these mutations is 3.2-fold greater than the general population of Korea, where gastric cancer accounts for 25% of all male cancers (12). In occidental countries HNPCC-associated gastric cancer has decreased in frequency in parallel with the decline in sporadic cancer (13), as might be expected if a DNA repair defect is not challenged by genotoxic hazards. The Finnish HNPCC registry has identified 45 patients with gastric cancer in 51 HNPCC families (14), and gastric cancer was the only cancer found in 22 of these. The mean age of gastric cancer development was 6 years older than colon cancer in these HNPCC families. Like sporadic stomach cancer, but unlike most Finnish familial stomach cancers, the HNPCC cancers were intestinal in type and arose in the distal stomach.

<table>
<thead>
<tr>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.3</td>
</tr>
<tr>
<td>3.1</td>
</tr>
<tr>
<td>2.1</td>
</tr>
<tr>
<td>8.4</td>
</tr>
<tr>
<td>11.2</td>
</tr>
<tr>
<td>6.4</td>
</tr>
<tr>
<td>4.0</td>
</tr>
</tbody>
</table>

**TABLE 5.3 Intestinal Versus Diffuse Gastric Cancers**

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil (Sao Paulo)</td>
<td>45.7</td>
</tr>
<tr>
<td>Colombia (Cali)</td>
<td>46.3</td>
</tr>
<tr>
<td>United States (Iowa)</td>
<td>7.5</td>
</tr>
<tr>
<td>Japan (Miyagi)</td>
<td>88.0</td>
</tr>
<tr>
<td>Finland</td>
<td>29.7</td>
</tr>
<tr>
<td>Poland (Warsaw)</td>
<td>31.4</td>
</tr>
<tr>
<td>Italy (Varese)</td>
<td>38.5</td>
</tr>
<tr>
<td>Spain (Navarre)</td>
<td>34.8</td>
</tr>
<tr>
<td>United Kingdom (Oxford)</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Chapter 5

Intestinal Epidemic Type
Type seen in high-risk populations
Characteristic subsite Antrum
Gross appearance Polypoid, fungating
Histology Cohesive, gland-forming cells
Distant disease Discrete hepatic metastases
Precursor lesions Multifocal atrophic gastritis
Age, gender Males >60 years of age
Prognosis Better survival

Diffuse Endemic Type
Incidence similar in most countries
Corpus
Linitis plastica
Discohesive, signet ring cells
Diffuse, transperitoneal spread
Superficial gastritis
Females, younger men
Poor

**Familial adenomatous polyposis (FAP)** may involve the stomach as well as the large bowel. As in the colon, gastric cancers are preceded by the development of dysplasia. The dysplasia may be flat or in polypoid lesions including adenomas, hyperplastic polyps, and fundic gland polyps. An environmental influence is suggested by the observation that Japanese patients with FAP have more frequent gastric adenomas and cancers than westerners with FAP (15,16). This may reflect the higher Japanese exposure to gastric cancer risk factors.

Germline mutations in the E-cadherin/CDH1 gene were first recognized as a source of familial stomach cancer in a New Zealand Maori family (17), and have since been shown to have a worldwide distribution (18,19). This form of familial cancer is now termed *hereditary diffuse gastric cancer* (HDGC). E-cadherin is a cell adhesion protein. The loss of its function (and loss of its normal expression on the cell membrane; Fig. 5.1) due to gene mutations results in the discohesive cells that characterize sporadic diffuse gastric cancers and lobular breast cancers. It is not surprising, therefore, that familial gastric cancers associated with germline mutations in this gene are diffuse in type and that HDGC kindreds also show an increased frequency of lobular breast cancer (20). Asymptomatic patients who carry the HDGC mutation are treated with prophylactic gastrectomy since the early lesions are undetectable at the time of endoscopy (21). Multiple superficial mucosal cancers may be found at the time of gastrectomy (Fig. 5.1). The chance discovery of similar lesions in an endoscopic biopsy should alert the pathologist to a possible HDGC mutation (22). Lynch et al (13) suggest that these superficial neoplastic foci represent a widespread field effect due to promoter hypermethylation and that dysregulation of genes required for invasion and metastases are much less common.

**TABLE 5.4 Types of Genetic Alterations in Gastric Carcinogenesis**

<table>
<thead>
<tr>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal losses</td>
</tr>
<tr>
<td>Amplification and/or overexpression</td>
</tr>
<tr>
<td>CpG island methylation</td>
</tr>
<tr>
<td>Microsatellite instability</td>
</tr>
<tr>
<td>Genetic polymorphisms</td>
</tr>
<tr>
<td>Telomerase activation</td>
</tr>
</tbody>
</table>

Carriers of *BRCA1/2* mutations have a substantial increase in the lifetime risk of breast and ovarian cancer. These mutations have been related to a variety of other sites as well, including the stomach. The Swedish Family Cancer Database assessed the cancer incidence in classified family members (n = 944,723) and compared their cancer experience with that of the general population of Sweden and found a twofold increase in the risk of acquiring stomach cancer before age 70 among male members of families with breast and ovarian cancer (23).

Germline *p53* mutations are inherited among families diagnosed with the Li-Fraumeni syndrome. Cancers arise at diverse sites in these families (24). Interaction with environmental factors is suggested by the more common prevalence of stomach cancer in Japanese families with this syndrome than among affected American families (25). Patients with the Peutz-Jeghers syndrome are at very high relative and absolute risk for gastrointestinal and other cancers. The relative risk of stomach cancer risk with this syndrome is 213 (95% confidence interval [CI] = 96 to 368) (26).

A mucoid gastric adenocarcinoma associated with germline mutation in the STK11 gene has been identified in a Japanese Peutz-Jeghers family (27).
**FIG. 5.1.** Hereditary diffuse gastric cancer in a young male with a strong family history of diffuse gastric cancer. *A:* At a low-power cursory glance the mucosa appears to be more or less normal. *B:* Higher magnification discloses multiple foci of intramucosal diffuse (signet ring cell) gastric carcinoma. *C:* E-cadherin immunostain showing staining of the nonneoplastic gastric glands and absence of staining in the tumor cells in the lamina propria and a few isolated tumor cells in the glands (lower right). *D:* Ki-6 immunostain showing the low proliferative index of the tumor cells. A portion of a nonneoplastic gland shows some proliferation (lower right).

**Interaction between the Environment and Inherited Polymorphisms**

By 1966 a large number of studies had found a consistent relationship between the diffuse type of stomach cancer and blood type A (28). It seems unlikely that blood type A has a direct role in the carcinogenic process, but it may serve as a marker for an as yet unidentified mutation, or a genetic polymorphism that increases the cancer risk by modulating the host reaction to environmental hazards. For example, the *interleukin-1* (IL-1) B gene that encodes a proinflammatory cytokine is highly polymorphic (29). Gastric cancer patients are more likely to have the IL-1B-31T/IL-1RN* phenotype. Such persons mount an especially strong inflammatory response to *H. pylori* infection through IL-1 overexpression. The level of gastric cancer risk varies greatly depending on the association of specific genotypes of the infecting organism with different IL-B phenotypes, with an odds ratio (OR) of 87 (CI = 11 to 697) when the vacAs1 strain associates with IL-B-511*T (30). In contrast, when *H. pylori* strain vacAm1 associates with this phenotype, the OR is substantial but falls to 7.4 (CI = 3.2 to 17). Tumor necrosis factor-α (TNF-α), another proinflammatory protein, is increased in the gastric mucosa of persons infected with *H. pylori*. The TNF-α-308* allele increases TNF-α production. The risk of acquiring multifocal atrophic gastritis and gastric cancer increases in persons with the high-risk IL-1B and TNF-α genotypes (31).

Variations in glutathione-S-transferase (GST-1), an enzyme that catalyzes the conjugation of numerous carcinogens, may modify the stomach cancer risk from smoking or ingested carcinogens. The null variant of the µ form of GST-1 constitutes 40% of the Japanese population and associates with a modest increased risk of gastric carcinoma (32). A similar association has been identified between gastric cancer and a variation in the *N-acetyl transferase* gene (*NAT-1*) (33). Aromatic and heterocyclic amine carcinogens are acetylated by NAT-1, but persons with a variant form of this enzyme lack this function. Cytochrome 450 2E1 (CYP2E1) is involved in the metabolism of environmental carcinogens. Two reports suggest that polymorphisms in this gene interact with smoking to increase the risk of gastric cancer (34). Finally, the lining of the stomach is protected from environmental insults by mucin. The *MUC1* gene is polymorphic and individuals with small *MUC1* genotypes have an increased risk of gastric cancer (35).

A recent Korean study has shown that polymorphisms in the DNA repair gene *XRCC1* may either enhance or reduce the risk of gastric cancer in this high-risk population (36). Carriers of one haplotype (194/Trp, 280/Arg, 399Arg) are at decreased risk of gastric cancer, while those with another haplotype (194/Arg, 280/Arg, 399Arg) are at increased risk of antral cancer. The polymorphism in *XRCC1* interacts with a polymorphism in *adenosine diphosphate ribosyl transferase (ADPRT)* in such a way that ADPRT and XRCC1 polymorphisms confer host susceptibility to gastric carcinoma possibly from reduced ADPRT–XRCC1 interactions and attenuated base excision repair, particularly in smokers (36a).
Other Genetic Factors

In addition to the genetic factors listed above, there are a number of somatic alterations that play a role in gastric cancer development. These include sporadic alterations in oncogenes, tumor suppressor genes, and mismatch repair genes. These genetic alterations include many that are altered in other cancers. Genetic instability, CpG island methylation, telomerase activation, and p53 mutations tend to occur early in the development of gastric cancer. Some of the more common alterations are listed in Table 5.5.

Epigenetic alterations, the most common of which is CpG island methylation of the promoter regions of cancer-related genes, are also common in gastric carcinoma. There is global DNA methylation and subsequent gene silencing in gastric cancers and its precursors and tumors showing these changes fall into the CpG island methylator (CIMP) phenotype. When the CIMP phenotype occurs, there is frequently an absence of mutation in genes that are commonly mutated in gastric cancer, such as p53 (36b). Genes that are frequently hypermethylated in the setting of Ebstein-Barr virus (EBV) include p16 and hMLH1 (36c). Promoter methylation of E-cadherin is common in the setting of H. pylori infection (36d). Sonic hedgehog, a gene important in foregut development, is also frequently hypermethylated (36e).

Environmental Factors

Environmental factors may affect gastric cancer risk directly or inversely. Several environmental hazards combine to induce distal stomach cancer; other environmental factors protect the stomach from exposure to these hazards. The risk of acquiring stomach cancer ultimately depends on which prevails.

<table>
<thead>
<tr>
<th>TABLE 5.5 Selected Genetic Alterations in Sporadic Gastric Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Suppressor Genes</strong></td>
</tr>
<tr>
<td>p53</td>
</tr>
<tr>
<td>p16</td>
</tr>
<tr>
<td>FHIT</td>
</tr>
<tr>
<td>APC</td>
</tr>
<tr>
<td>Rb</td>
</tr>
<tr>
<td>DCC</td>
</tr>
<tr>
<td><strong>Mismatch Repair Genes (Altered by Mutation or Hypermethylation)</strong></td>
</tr>
<tr>
<td>hMLH1</td>
</tr>
<tr>
<td>hMLH2</td>
</tr>
<tr>
<td>hMSH2</td>
</tr>
<tr>
<td>hMSH3</td>
</tr>
<tr>
<td>hMSH6</td>
</tr>
<tr>
<td><strong>Oncogenes</strong></td>
</tr>
<tr>
<td>Cyclin D1</td>
</tr>
<tr>
<td><strong>Growth Factors and Their Receptors</strong></td>
</tr>
<tr>
<td>EGFR</td>
</tr>
<tr>
<td>TGF-α</td>
</tr>
<tr>
<td>c-erbB2</td>
</tr>
<tr>
<td>c-met</td>
</tr>
<tr>
<td>K-sam</td>
</tr>
<tr>
<td><strong>Cell Adhesion Molecules</strong></td>
</tr>
<tr>
<td>E-cadherin</td>
</tr>
<tr>
<td>α-catennin</td>
</tr>
<tr>
<td>β-catennin</td>
</tr>
</tbody>
</table>

Helicobacter pylori Infection

*H. pylori* infection is usually the step leading to the development of gastric cancer. The infection is acquired in childhood (37). Infected children carry the infection and its anatomic consequences into middle and old age (9). *H. pylori* gastritis may affect 75% of persons in high-risk populations, but no more than 5% of infected individuals develop stomach cancer.
cancer (38), indicating that infection does not act alone. Prospective studies have shown a consistent association between the presence of distal gastric cancer and high antibody levels against *H. pylori* (39).

Asymptomatic persons with the highest *H. pylori* antibody levels are the most likely to develop gastric cancer in these studies. When compared to other *H. pylori* strains, the cagA strain is associated with heightened antibody levels, a more robust inflammatory response, and a higher risk of gastric cancer (39). One mechanism by which *H. pylori* infection may increase stomach cancer risk is through exposure of replicating cells to reactive oxygen species derived from the inflammatory cells that are part of *H. pylori* gastritis (Fig. 5.2).

**FIG. 5.2.** Mechanisms by which *Helicobacter pylori* increases gastric cancer risk.

The initial manifestation of *H. pylori* infection is severe superficial gastritis, followed by the development of multifocal atrophic gastritis and intestinal metaplasia (see Chapter 4). The process begins at the antral–corpus junction and along the lesser curvature of the antrum. Over time the atrophic foci expand and fuse so that in old age much of the oxyntic mucosa is replaced by intestinalized tissue. Cancer risk is highest in *H. pylori*-infected persons at the nadir of acid production (40). The achlorhydria favors a bacterial flora that may generate carcinogens through the nitrosation of dietary amines (41).

**Diet**

The pattern of food consumption may increase or reduce the risk of acquiring stomach cancer. The addition of nitroso compounds to the diet of experimental animals produces gastric cancer and its precursor, intestinal metaplasia (42). Epidemiologic studies show a direct association between the development of intestinal metaplasia and nitrate/nitrite consumption in humans (43). Salt intake also directly relates to stomach cancer risk in humans (44). The consumption of dried, salted fish in Japan and the consumption of salted, nitrosated foods through the winter months in northern countries are examples of dietary practices that increase the stomach cancer risk. In contrast, fresh fruits and vegetables provide antioxidating effects that protect the stomach from both exogenous and endogenous mutagenic nitroso compounds. Fresh fruits and vegetables function as antioxidants and contain substantial amounts of folate, ascorbic acid, carotene, and tocopherol. Epidemiologic studies of Japanese and European populations suggest that raw green and yellow vegetables protect against the development of gastric cancer (45), and a Japanese cohort study showed that increased fresh produce consumption and reduced consumption of pickled food reduced the gastric cancer risk, even in the presence of atrophic gastritis (46). The year-round availability of fresh produce eliminates the need to use salt to preserve vegetables. Smoking and salting of meat is no longer a necessity with the advent of universal household refrigeration. These two factors have contributed to the dramatic decrease in stomach cancer rates in Western countries after World War II.

**Smoking**

A meta-analysis of 37 case control studies on the relationship of smoking to gastric cancer yielded inconsistent results (47). This inconsistency is surprising and contrasts with the strong association of smoking with gastric ulcer (48), a disease that is closely related to intestinal metaplasia, *H. pylori* gastritis, and gastric cancer. The same analysis, however, found that each of ten prospective cohort studies showed a significantly increased risk of gastric cancer in the order of 1.5 to 2.5, four of the studies showing a dose response. Thus, the magnitude of smoking-related risk is low, but may account for 11% of stomach cancers worldwide (47).

**Radiation**

A dose-dependent increase in gastric cancer frequency has occurred among Japanese atomic bomb survivors, suggesting that ionizing radiation may play a role in gastric carcinogenesis (49). Additionally, radiotherapy in young patients increases their risk of gastric cancer when lymph nodes of the upper abdomen are included in the radiation field, as may occur in the treatment of lymphoma and testicular cancer (50).

**Previous Gastric Surgery**

The creation of a gastroenterostomy after subtotal gastrectomy for peptic ulcer is a well-established risk factor for the development of cancer in the gastric stump (Fig. 5.3) (51). The cancer may not be apparent until 17 to 20 years after the creation of the anastomosis. It is preceded by the appearance of gastritis and hyperplastic polyps at the anastomotic line (52). The cause of the increased risk is attributed to the reflux of bile and pancreatic juice into the gastric remnant, a hypothesis that is supported by rodent experiments that show the sequential development of gastritis, hyperplasia, metaplasia, and adenocarcinoma after duodenal contents were diverted into the stomach (53). Since subtotal gastrectomy is no longer commonly employed to treat peptic ulcer, this risk factor will disappear in the near future. Its place may be taken by subtotal gastrectomy for early antral cancer, a procedure that has become quite common in Asian high-risk countries with active screening programs of asymptomatic subjects (54). The interval between surgery for early cancer and the
development of stump cancer may be shorter than after peptic ulcer surgery. Another potential source of postenterostomy stomach cancer is the Roux-en-Y gastrojejunostomy used to treat morbid obesity. Gastric cancer has been reported in four women at 5, 5, 13, and 22 years after surgery (55). Since bariatric surgery has become a very common procedure, we may expect increasing numbers of such cancers. The defunctionalized gastric segment is subject to the reflux of bile and alkaline secretions and the subsequent development of gastritis (56).

![FIG. 5.3. Large polypoid gastric cancer originating in the gastric stump. The small bowel mucosa is seen on the left.](image)

**Predisposing Gastric Lesions**

Gastric cancer does not arise de novo from a normal mucosa. Gastritis is usually the first step in cancer induction, whatever the underlying cause. In persons with polymorphisms that render them especially vulnerable to exogenous or endogenous carcinogens, an intense superficial gastritis may be the only anatomic precursor to cancer induction.

**Multifocal Atrophic Gastritis and Intestinal Metaplasia**

The intestinal-type cancer so characteristic of high-risk populations is preceded by a sequence of changes that begins with inflammation and passes through atrophy and intestinal metaplasia (IM) to dysplasia and ultimately to invasive cancer (57) (Figs. 5.4 and 5.5). These changes are initiated in childhood by *H. pylori* infection. The dense leukocytic response that affects the superficial lamina propria and the epithelium of the mucous neck region of the gastric glands, as discussed in Chapter 4, is followed by the appearance of foci of atrophic, intestinalized mucosa at the antral–corpus junction. These changes become apparent in adolescents and young adults. The metaplastic glands and the mucosa adjacent to them show increased cell proliferation. The foci of multifocal atrophic gastritis (MAG) enlarge, fuse, and expand proximally and distally so that, by the 6th or 7th decade of life, all but a small portion of the proximal greater curvature of the corpus may be lined by intestinalized mucosa. Two forms of IM are recognized: The “complete” form faithfully reproduces small intestinal-type cells. There are subsite-dependent variations that diverge from this pattern. Some intestinalized glands lack Paneth cells, lose the ability to make some glycopolyneuronal enzymes, or may produce mucus similar to those of the colon, the so-called “incomplete” form of IM (58). There is a widely held view that incomplete IM carries a higher risk of carcinoma than the complete form, but the most common site for early cancer is the antral–corpus junction, where the complete form predominates. The incomplete form is best seen on the distal greater curvature of the antrum, an area that is involved in the later stages of intestinalization. Cancer risk increases with the extent of the IM; the presence of incomplete IM is synonymous with extensive IM.
FIG. 5.4. Neoplastic progression in the stomach. A prominent area of follicular gastritis is present on the right side of the photograph. There is a transition to intestinal metaplasia as one moves toward the center of the figure. Dysplasia develops in the areas of intestinal metaplasia, until finally an invasive carcinoma of the intestinal type develops as seen on the far left side of the photograph. Note the tumor within the lymphatics under the muscularis mucosae.

The mechanisms that underlie the development of IM in MAG are complex. The development and maintenance of specific organ structures and functions in the gastrointestinal tract are regulated by CDX, a homolog of the Drosophila caudal gene, during intestinal development (59). CDX1 and CDX2 are not expressed in the normal stomach, but their mRNAs are expressed in metaplastic glands. CDX2 precedes CDX1 expression and appears to trigger IM. Transgenic mice that express CDX2 in gastric parietal cells have complete replacement of gastric mucosal glands by the full array of intestinal cells, including goblet cells and absorptive cells (60). A mechanism for the activation of this gene has been suggested by Houghton and Wang (61). They found that, in the presence of H. pylori–generated gastritis, circulating bone marrow stem cells are recruited and engrafted into the replicating zone of the gastric mucosa. The presence of these stem cells in the gastric mucosa in patients with H. pylori gastritis may account for the extreme heterogeneity of gastric cancer and the presence of cells with a hybrid intestinal/gastric phenotype (62,63).

FIG. 5.5. Diagram of the pathways of gastric cancer induction. LOH, loss of heterozygosity.

Serum pepsinogen levels reflect the extent of gastric mucosal intestinalization. Pepsinogen is a proenzyme activated by gastric acid to produce pepsin. It is produced in two forms: Pepsinogen group I (PGI) is only produced in the oxyntic mucosa, while pepsinogen group II (PGII) is made throughout the stomach and in Brunner glands. Replacement of oxyntic mucosa by IM results in decreasing PGI serum levels (64). A PGI level <30 ng/mL or a PGI:PGII ratio <2 are established cut-points used in screening programs to identify patients with extensive IM and who are at especially high risk of gastric cancer (65). The predictive value of the PGI level is improved when it is combined with the H. pylori serum antibody levels, as shown in Table 5.6, adapted from a case control study (66). Similar trends are observed with the PGI:PGII ratio.
Autoimmune Gastritis

Autoimmune gastritis, as discussed in Chapter 4, is a well-recognized, but less common, gastric cancer precursor than MAG. Autoimmune gastritis and *H. pylori* gastritis may coexist in most patients with pernicious anemia and the titers of both antibodies inversely relate to disease duration (67). It may be distinguished from late-stage MAG by the absence of antral inflammation and atrophy. The cancers associated with this form of gastritis arise in the antrum or the atrophic corpus, with a relative risk ranging from 2.2 to 5.6 (68). The increased risk stems from several factors: (a) Loss of gastric acidity favors the growth of bacteria that may generate endogenous nitroso compounds from dietary amines. (b) Gastrin production is greatly increased in response to prolonged achlorhydria. The trophic effects of hypergastrinemia result in accelerated cell turnover in a replicating compartment already expanded due to the loss of parietal and chief cells. (c) These replicating cells are exposed to reactive oxygen species from inflammatory cells.

Gastric Ulcer

A stage is reached in the early phases of the expansion of MAG when the proximal antral intestinalized mucosa is exposed to the acid produced by the still intact oxyntic mucosa. The intestinalized mucosa lacks the protective mucous barrier of the normal antrum, so that it is vulnerable to peptic ulceration. Patients with gastric ulcer are at greatly increased risk of gastric cancer. This is not surprising since gastric ulcer and gastric cancer share the same risk factors: *H. pylori* gastritis, a diet rich in salt, smoking (48), and a declining frequency in Western countries (69). As may be expected among patients who have retained the ability to make acid, the mean age of gastric ulcer patients is 10 years younger than the mean age of patients with cancer. Re-epithelialization of the ulcer associates with expansion of the replication zone of the glands bordering the ulcer, exposing a larger number of vulnerable proliferating cells to genotoxic hazards. In contrast, the regenerating epithelial cells that migrate over the ulcer base are arrested in the postmitotic phase of the cell cycle, accounting for the observation that the gastric mucosa bordering the ulcer, rather than the ulcer base, is a common site of early cancer.

<table>
<thead>
<tr>
<th></th>
<th>All Cancers</th>
<th>Intestinal</th>
<th>Diffuse</th>
<th>Distal to Cardia</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>HP/CagA</em> negative, PGI normal</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td><em>HP/CagA</em> negative, PGI low</td>
<td>5.4 (2.61–11.2)</td>
<td>5.06 (2.43–10.97)</td>
<td>8.92 (1.48–53.6)</td>
<td></td>
</tr>
<tr>
<td><em>HP/CagA</em> positive, PGI normal</td>
<td>4.86 (2.9–8.13)</td>
<td>3.64 (2.05–6.45)</td>
<td>14.84 (9.51–54.4)</td>
<td></td>
</tr>
<tr>
<td><em>HP/CagA</em> positive, PGI low</td>
<td>9.21 (4.95–17.13)</td>
<td>6.91 (3.53–13.53)</td>
<td>40.74 (9.51–174.6)</td>
<td></td>
</tr>
</tbody>
</table>
The term *ulcer cancer* defines a gastric carcinoma that arises in a pre-existing peptic ulcer (Figs. 5.6 and 5.7). Tumors arising in this setting account for <1% of all gastric carcinomas. In order to be accepted as an ulcer cancer, the case must show definite evidence of pre-existing chronic peptic ulcer and evidence of coexisting malignancy. About 5% of endoscopically benign ulcers eventually prove to be malignant, but some lesions may require more than one biopsy to detect the underlying malignancy (70). Underestimation of the depth of invasion may occur when the tumor develops from the epithelium of a healed ulcer in which the submucosa and muscularis propria are no longer recognizable because of scarring.

**FIG. 5.6.** Ulcer cancer. *A:* Large, centrally located gastric ulcer. *B:* Closer view. *C:* Ulcer base. Malignant glands are within and below the muscularis mucosae.

**FIG. 5.7.** Invasive carcinoma in healed gastric peptic ulcer. Well-differentiated adenocarcinoma infiltrates the muscularis propria, which is fused with the muscularis mucosae.

### Hyperplastic Polyps

Hyperplastic polyps used to constitute from 75% to 90% of all gastric polyps (71). They arise from the foveolar hyperplasia that frequently accompanies atrophic gastritis, whether of the multifocal or autoimmune type. They may also appear on the gastric side of gastroenterostomy stomas. Patients with hyperplastic polyps are at increased risk of gastric cancer, but the cancers very rarely arise in them. Rather, they are byproducts of
the chronic gastritis that is the underlying cause of cancer induction. In the unusual event that a cancer does arise in a hyperplastic polyp, it is preceded by the development of dysplasia (Fig. 5.8).

**FIG. 5.8.** Dysplasia arising in a hyperplastic polyp. *A:* Low-grade dysplasia spreads from the surface to the deeper portions of gland, replacing the normal foveolar epithelium. *B:* Higher power view of another area of high-grade dysplasia. The cells are hyperchromatic, pleomorphic, and disorganized. The glands are beginning to develop a back-to-back arrangement suggestive of intramucosal carcinoma.

**Dysplasia**
Dysplasia is the first microscopically detectable anatomic change in the neoplastic process. The dysplastic changes may represent cytologic alterations or disorganized architecture. Gastric dysplasia shows two major growth patterns: A flat, grossly inconspicuous dysplasia or polypoid lesions recognizable as adenomas. The dysplastic cells may be gastric or intestinal in type, or they may be hybrid forms from each lineage.

**Nonpolypoid Dysplasia**
Areas of mucosal dysplasia are characterized by histologic and cytologic abnormalities that must be distinguished from regenerative (reactive) atypia. Atypical regenerative changes are usually accompanied by active inflammation without significant architectural or differentiation abnormalities (Fig. 5.9). In contrast, dysplastic cells show one or more nuclear abnormalities (increased size, hyperchromasia, irregular shape, abnormal mitoses) and form abnormal glands with branching and occasional back-to-back configuration (Figs. 5.10 and 5.11) (71). The identification of dysplasia is critical to the management of patients in high-risk populations, but the assignment of grades is subjective, with wide inter- and intravariations in grade selection. A workshop convened to resolve international differences in the definitions of different grades of gastric epithelial dysplasia resulted in the Padova classification (72), as summarized in Table 5.7.
FIG. 5.9. Regenerative hyperplasia. An increased nuclear-to-cytoplasmic ratio and mitotic rate, along with large nucleoli and stromal inflammatory cells, are all present.

### Table 5.7 The Padova Classification of Gastric Dysplasia and Related Lesions

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for dysplasia</td>
<td>Reactive foveolar hyperplasia</td>
</tr>
<tr>
<td>Intestinal metaplasia (IM)</td>
<td>IM, complete type</td>
</tr>
<tr>
<td>IM, incomplete type</td>
<td>Indefinite for dysplasia</td>
</tr>
<tr>
<td>Foveolar hyperproliferation</td>
<td>Hyperproliferative IM</td>
</tr>
<tr>
<td>Noninvasive neoplasia (flat or elevated [synonym, adenoma])</td>
<td>Low grade</td>
</tr>
<tr>
<td>High grade</td>
<td>Including suspicious for carcinoma without invasion (intraglandular)</td>
</tr>
<tr>
<td>Including carcinoma without invasion (intraglandular)</td>
<td>Suspicious for invasive carcinoma</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>Pathologists achieve fairly high levels of agreement in the diagnosis of high-grade dysplasia, but the agreement is only “fair” for low-grade dysplasia and “poor” for indefinite for dysplasia (73). We believe that it is sufficient to identify dysplasia and to classify it as high or low grade. In low-grade dysplasia, the gastric mucosal architecture is generally preserved, although abnormalities sometimes occur, including pseudovilli, irregular branching papillary infoldings, crypt lengthening with serration, and cystic changes (Fig. 5.10). Dystrophic goblet cells may also be seen. The pyloric glands branch at the crypt base and range from normal in appearance to frankly dysplastic. We have also seen cases in which dysplasia occurred in gastric foveolar cells (Fig. 5.12). The term high-grade dysplasia replaces “carcinoma in situ.” Severe gastric dysplasia shows nuclear stratification, increased abnormal mitoses, disordered polarity, and glandular crowding. Problems associated with diagnosing gastric epithelial dysplasia are threefold: (a) one must be able to separate dysplasia from atypical regenerative changes, (b) one should be able to characterize high-grade from low-grade dysplasia, and (c) the dysplasia should be separable from invasive carcinoma. Immunohistochemical detection of p53 overexpression and Ki-67 (Fig. 5.13) stains to detect expansion of cell proliferation to the mucosal surface and abnormal tumor suppressor gene function may help to distinguish dysplastic from atypical regenerative changes.</td>
</tr>
</tbody>
</table>
FIG. 5.10. Gastric dysplasia. A: The gastric gland is partially replaced by neoplastic epithelium. B: Mild dysplasia as illustrated here is characterized by cellular crowding and elongation, generally basally located nuclei, few mitoses, little cellular stratification, and nuclear pleomorphism.

**Gastric Adenomas**

Gastric adenomas are less common than hyperplastic polyps and, unlike colonic adenomas, they are uncommon in the absence of FAP. They may be flat (Fig. 5.14) or pedunculated (Fig. 5.15). An endoscopic study in high-risk Korean patients found that 74.5% of these lesions arose in the distal third of the stomach. Focal areas of malignancy were found in 6.7% of adenomas, all but one arising in the distal stomach (74).

FIG. 5.11. Severe dysplasia. A: Gastric dysplasia with distorted architecture and severely dysplastic epithelium. There are numerous mitoses. B: The cells are so stratified that the nuclei reach the luminal surface.
FIG. 5.12. Foveolar dysplasia. The foveolar epithelium is disorganized with some loss of polarity and the nuclei are pseudostratified. No inflammation is present.

FIG. 5.13. High-grade dysplasia replacing the gastric pits. A: Hematoxylin and eosin–stained section. B: p53 immunostain shows nuclear labeling in virtually all of the neoplastic cells.

FIG. 5.14. Flat villous adenoma.

Gastric and colon polyps share some features. Grossly they have a lobulated or mamilated surface and are often covered by a reddened, velvety mucosa (Fig. 5.15). Abnormal epithelium occupies the surface and the
luminal portions of the pit. With increasing degrees of dysplasia there is cellular stratification, progressive loss of nuclear polarity, and increased cellular crowding. The nuclei appear close to the lumina of the tubules and eventually secondary lumina form. A villous configuration may predominate in larger lesions (Fig. 5.14). When traumatized, adenomas may acquire surface changes resembling those seen in hyperplastic polyps. Gastric adenomas contain many dysplastic cell types, including enterocytes, goblet cells, endocrine cells, and Paneth cells. The World Health Organization (WHO) classification subdivides gastric adenomas into three subtypes: Tubular, papillary, and papillary–tubular. In contrast, Japanese authors recognize two types of adenoma: Protruding and depressed (75). Depressed adenomas (Fig. 5.16) are significantly larger than protruding adenomas and are more likely to contain high-grade dysplasia than protruded adenomas. We have also seen serrated adenomas arising in the stomach (Fig. 5.17). These lesions are far too rare to know whether this morphology reflects the underlying genetic alterations as it does in the colon (see Chapter 14).

**FIG. 5.15.** Gastric adenoma. *A:* The pedunculated adenoma is covered by a reddened mucosa. *B:* Whole mount section of the adenoma depicted in *A* showing the proliferation of the neoplastic cells.

**FIG. 5.16.** Depressed adenoma. The adenoma appears as the central mucosal depression.

**Histogenesis of Gastric Cancer**

Areas of dysplasia may remain stable, regress (76), or take several years to progress to invasive intestinal-type cancer (77). In contrast, invasive diffuse cancers in young persons may arise in a mucosa that does not appear overtly dysplastic (Fig. 5.1), although in situ carcinoma may be present as discussed below. The factors that determine the cancer phenotype and the speed of its progression from normal gastric epithelium are complex. An invasive cancer might arise directly from the replicating compartment in the neck region of gastric glands, from the crypts of intestinalized glands, or from replicating surface cells in areas of dysplasia. The cells of origin may determine the phenotype of an early cancer, but postinduction mutations may introduce so much heterogeneity that the mother cells of advanced cancers cannot be determined. The types and numbers of genetic and epigenetic changes in the cancer influence the speed of its progression from an early superficial lesion to a widely disseminated one.
Early Gastric Cancer

Early gastric cancer is defined as a cancer that is limited to the mucosa or submucosa, regardless of the presence of lymph node metastases (Fig. 5.18). This concept evolved in Japan, where community screening programs discovered many early cancers in asymptomatic patients. In recent years early cancers have come to constitute the majority of gastric cancers among Japanese (78). In the period 1965–1970, early cancers constituted <20% of gastric cancers, but by 1988 the proportion reached 57%. Between 1962 and 1991 there was a marked decrease in the size of early cancers in these screening programs (78).
There is a considerable variation in the configuration of early cancers. The macroscopic classification of the different forms of early cancer, as proposed by the Japanese Endoscopic Society (79), is now accepted worldwide. This classification divides early cancers into three main types, one having three subtypes, as shown in Figure 5.19. The gross appearance of two such tumors is shown in Figure 5.20. Superficial-spreading cancer is a subtype of early cancer and is defined as a tumor >4 cm in diameter that is confined to the mucosa or with minimal invasion of the submucosa (80).

Endoscopic biopsies often permit a straightforward diagnosis of early gastric cancer, but occasional problems arise. The most common of these include the following: (a) a small number of signet ring cells in the lamina propria may be easily missed (Fig. 5.21), and (b) the distinction of high-grade dysplasia from intestinal-type carcinoma and from atypical glandular regeneration may be difficult. Multiple biopsies, particularly from the edges of the lesion and cytologic brush sampling, are usually adequate for diagnosis, even of minute (<5 mm in diameter) carcinomas. Truly malignant cells are most reliably recognized by their pleomorphic and hyperchromatic nuclei, combined with a large hypertrophic nucleolus. Mitoses are uncommon. Histiocytes containing phagocytosed mucin or lipid (Fig. 5.22) may mimic intramucosal malignant signet ring cells. Granulation tissue may simulate malignancy in gastric biopsies when large, bizarre endothelial cells are present. Special stains for intracytoplasmic mucin or cytokeratin immunostains sometimes help resolve these problems.
FIG. 5.20. Early gastric cancer. A: Type IIa cancer. The neoplasm is a slightly elevated, plaquelike lesion in the center of the specimen. B: Type IIc cancer. The lesion is slightly depressed below the level of the surrounding mucosa. (Photographs courtesy of Dr. Onja Kim, ANSA Medical Center, Seoul, Korea.)

One must identify penetration of the muscularis mucosae, with invasion of the submucosa, to make a diagnosis of invasive cancer. The depth of invasion cannot be ascertained with endoscopic biopsies. Lesions detected as early cancers may be tumors with an indolent behavior or may be aggressive lesions that happen to be detected at an early stage. In one series of 56 patients with early cancer, 16 showed no progression during a mean follow-up of 29 months, indicating an unexpectedly slow evolution (81). This is supported by the observation of two men who had gastrectomies 6 and 8 years after the diagnosis of mucosal cancer without deeper penetration occurring in the interval (82).
Chapter 5

FIG. 5.21. Diffuse carcinoma. A: Scattered minimally atypical cells lie deep in the lamina propria. These cells could easily be mistaken for chronic inflammatory cells. B: Cytokeratin stain confirms the presence of an infiltrating carcinoma.

FIG. 5.22. Comparison of lamina propria macrophages and diffuse cancer. A: The lamina propria macrophages contain abundant foamy cytoplasm and small peripherally located nuclei. B: Diffuse carcinoma. Infiltrating signet ring cells are present in the lamina propria. These cells have foamy eosinophilic cytoplasm and peripherally placed nuclei. There is more nuclear atypia in these cells than in those shown in A. In cases where there is doubt, immunohistochemistry using histiocytic markers and cytokeratin allows characterization of the cell type present.

Nodal metastases may accompany early gastric cancers (78), and, as may be expected, their frequency correlates with the depth of tumor penetration into the submucosa (83). Nodal metastases also directly relate to tumor size and the presence of ulceration (79). The frequency of nodal metastases varies from 15% to 30% in Japan (79), but may be from two to three times greater than this if immunohistochemical stains for cytokeratin are used to detect occult micrometastases (84). Although the biologic significance of occult metastases is unclear at the present time, the presence of overt metastases is unfavorable in all studies. Other factors that increase the risk of recurrence of early gastric cancer include vascular invasion (85) and poor differentiation (86). In Japan, the 10-year postoperative survival of patients with early cancer is 99% for patients with mucosal cancer and 91% for those with submucosal cancer (78). The 7-year survival rates for a French study of early gastric cancer were 93% for mucosal cancers and 83% for submucosal cancers, indicating that the value of early diagnosis is not an exclusively Asian phenomenon (87).

The ability to diagnose early gastric cancer allows clinicians to devise function-preserving treatment methods that give the patient a better quality of life than would be seen following gastric resection and eliminates the risk of cancer developing in the proximal stomach after a subtotal gastrectomy. These treatment options include endoscopic mucosal resection (EMR) (88) and wedge resection, with or without lymphadenectomy (89). Selection of either approach depends on the probability that the tumor will recur. The currently acceptable indications for EMR include well-differentiated carcinoma without ulceration, measuring <2 cm if elevated (type Ila) or <1 cm if flat (types IIb and Iic). In examining an EMR specimen, the pathologist must ascertain the tumor-free status of the lateral and deep margins. Patients treated with EMR require periodic surveillance for recurrences of residual tumor or for the development of metachronous cancer, since it must be assumed that the anatomic precursors of the original tumor will be present in the residual stomach.

Following EMR, follow-up biopsies are performed to ensure that there is no residual neoplasia. Mitsuhashi et al performed a retrospective analysis of post-EMR biopsies. The histologic changes included inflammation, stromal edema, foveolar hyperplasia, vascular ectasia, epithelial atypia, increased mitotic activity, clear cell changes, and signet ring–like changes. Many of the alterations were secondary to ischemia following the EMR. Among the most worrisome were areas of clear cell–like changes and signet ring–like changes, since these were the most difficult to distinguish from neoplasia. However, these reactive features were often embedded in a nondesmoplastic stroma (89a).

Advanced Gastric Cancer

Gross Features

The first classification of gastric cancer, the Borrmann classification, is based on the gross appearance of the tumor (90). Four growth patterns are recognized: Polypoid, fungating, ulcerated, and infiltrating (Figs. 5.23, 5.24, and 5.26). Any of the four types may coexist. Polypoid cancers protrude into the lumen without major areas of ulceration. Fungating tumors are irregularly shaped exophytic growths showing areas of ulceration. Ulcerated tumors are irregular in outline and have raised edges. The ulcer margins appear hard and stiff, the ulcer base necrotic. Infiltrating tumors are flat, plaquelike lesions with or without shallow areas of ulceration. Transmural infiltration associates with a characteristic desmoplastic reaction.
giving the stomach wall a marked rigidity. In one large gastric cancer series the percentage for each subtype was as follows: Polypoid, 7%; ulcerated, 25%; fungating, 36%; and infiltrating, 26% (91).

![Image of Borrmann type I polypoid carcinoma](image1)

**FIG. 5.23.** Borrmann type I. Polypoid carcinoma of the stomach. A large vegetating mass without much hemorrhage or necrosis is present. Ularated gastric cancers can be differentiated from benign peptic ulcers in several ways: They have irregular margins with raised edges. The surrounding tissues are firm, thick, and uneven. The ulcer base is necrotic, shaggy, and often nodular. The mucosal folds surrounding the ulcer have a more irregular shape and distribution than is seen adjacent to benign ulcers (see Chapter 4). Additionally, benign ulcers usually penetrate through and replace the muscularis propria, whereas cancers infiltrate between the muscle bundles, so that the muscularis propria is thickened. Malignant ulcers are usually larger than their benign counterparts. Unfortunately, some malignant ulcers are indistinguishable from benign ulcers based solely on their gross appearance, and it is important that all endoscopically detected ulcers be systematically biopsied, even if they are healing.

![Image of Borrmann type II fungating carcinoma](image2)

**FIG. 5.24.** Borrmann type II. Fungating carcinoma with extensive surface ulceration and hemorrhage.
FIG. 5.25. Borrmann type III. Ulcerated gastric carcinoma with heaped-up margins, but without significant intraluminal growth.

Diffuse (infiltrating) tumors spread superficially in the mucosa and submucosa, tending to flatten the mucosal folds. As they extend into the stomach wall they associate with a dense connective tissue reaction that fixes the mucosa to the muscularis propria. Frequently the infiltrating cells involve the entire stomach, producing the picture of linitis plastica, or "leather bottle" stomach. Linitis plastica often involves the pylorus (Fig. 5.26). The gastric rigidity induced by neoplastic infiltration combined with marked desmoplasia accounts for the early satiety that commonly occurs with this tumor.

An analysis of the subsite location of resected gastric cancers among 171,721 Japanese patients between 1975 and 1985 found the distal third to be the most frequent site of cancer development, followed by the middle third, the upper third, and the entire stomach (92). Women are more likely to have tumors involving the entire stomach, as might be expected since the diffuse cancer that produces this growth pattern is most common in women. The subsite distribution is what may be expected in any high-risk population, but there was an increase in the proportion of middle and upper third cancers at the expense of the distal third in later years. The basis of this temporal trend is unclear. It could result from finding more proximal lesions at an operable stage as a result of screening programs, or technical improvements that allowed more aggressive selection of advanced proximal cancer for surgery. The increase in the number of operated cases in each 5-year period is compatible with either explanation.
FIG. 5.26. **Borrmann type IV.** 

A: The gastric wall is thickened with irregularly ulcerated mucosa. 

B: Cancer involving the antrum showing a uniform thickening of the gastric wall.

The extensive surface area of the stomach affected by late-stage multifocal gastritis lends itself to the development of multiple primary cancers. This is a special concern in patients selected for EMR treatment. Multicentric tumors affect from 3.5% to 15% of gastric cancer patients. Two, three, and four or more early cancers may be found in the same stomach (78). Multiple gastric cancers are most frequently seen in men over 65 years of age in high-risk populations. Chromoendoscopy may help identify unsuspected synchronous multicentric tumors; continuing posttreatment surveillance is necessary to discover metachronous cancers.

**Clinical Features**

Gastric cancers that elicit symptoms are usually late-stage tumors and are more likely to precede the diagnosis of cancer in Western, unscreened populations than in Asia or other high-risk areas. The early cancers that may accompany chronic gastric ulcers are exceptions to this rule. A review of 18,265 stomach cancers by the American College of Surgeons (93) found the following frequently overlapping symptoms to be the most common: Weight loss (61.6%), abdominal pain (51.6%), nausea (34.3%), dysphagia (26.1%), and melena (20.2%). Weight loss is an ominous presenting symptom and associates with poor survival. Early satiety may result from either pyloric obstruction or the ability of the stomach to expand. Blood loss from an ulcerated tumor may induce anemia and fatigue. Infection of necrotic, fungating tumors may cause fever. Spread of gastric cancer to a distant site is the presenting symptom in some cases. This may take the form of an enlarged supraclavicular lymph node. Ascites or vaginal bleeding due to endometrial metastases may be the presenting symptom in premenopausal women with diffuse cancer (94).

**Endoscopy, Biopsy, and Cytology**

Upper gastrointestinal endoscopy provides the initial method of evaluating a gastric cancer. Winawer et al studied 63 patients with gastric adenocarcinoma (95) and found that the correct diagnosis was made endoscopically in 90% of patients. Combined brush cytology and biopsy studies were histologically accurate in 92% of exophytic cancers, contrasting with only 50% accuracy in infiltrating lesions. The cardia and the antrum distal to the incisura are more difficult to sample than other parts of the stomach. The diagnostic yield from endoscopy in a population at moderate risk of gastric cancer was assessed in an Asian population, and 10 gastric cancers among 905 (1.1%) symptomatic patients were found (96). The biopsy diagnostic accuracy increases with the number of samples taken. When there is uncertainty as to the distinction between benign or malignant ulcer, quadrant biopsies of the ulcer margin are indicated. Once a diagnosis of gastric carcinoma has been made, endoscopic ultrasonography (EUS) may be employed to estimate tumor stage prior to definitive therapy. This procedure yields 82% accuracy as to the depth of tumor invasion (97), but is less accurate in detecting lymph node metastases (98).

Brushing cytology plays a key role in the diagnosis of gastric malignancy. The cytologic sampling is often supplemented by multiple biopsies in order to increase the diagnostic sensitivity. However, the role of cytology has been questioned because of the possible occasional false-positive results of biopsies (99). Overt gastric adenocarcinoma, regardless of its subtype, has distinctive cytopathologic features (Fig. 5.27). Malignant epithelial cells usually appear larger than normal cells and reveal anisocytosis, anisokaryosis, pronounced nuclear atypia including marked irregular indentations of the nuclear outline, hyperchromasia, irregularly distributed heterochromatin, multinucleation, nucleolar hypertrophy, occasionally abnormal mitotic figures, signet ring features (Fig. 5.27), and microvacuolized cytoplasm. The chromatin often appears very coarse or sharply granular (100) in contrast to abnormal benign cells in gastritis. Nuclear molding also represents a valuable malignant feature that may be appreciated in cell groups. The cell-in-cell (cannibalism) phenomenon might be prominent as might the finding of naked nuclei. Occasionally, features of squamous metaplasia are displayed (Fig. 5.28).
FIG. 5.27. Gastric adenocarcinoma. A: Group of cancer cells with variably sized nuclei. A large cell with vacuolated cytoplasm and smaller cells with granular cytoplasm is visible. B: Extreme variation in nuclear size is seen in these single cancer cells. Note the large nucleoli. C: Intracytoplasmic secretory vacuoles are present as well as overlapping nuclear borders. D: May-Grünwald-Giemsa stain of intestinal-type gastric cancer. The cells are retaining their columnar appearance. The nucleoli are large and basophilic. E: Signet ring cancer cells with prominent nucleoli. F: Scattered signet ring cells are visualized.

The background is often studded with debris and damaged red blood cells. The tumor cells may be predominantly single when derived from poorly differentiated carcinomas or may be present in sheets of more cohesive cells when derived from papillary or well-differentiated adenocarcinomas.

P. 252
Chapter 5

Microscopic Features

Gastric cancers exhibit considerable heterogeneity from tumor to tumor, and also within a given tumor. This heterogeneity results from the complex cellular composition of the gastric and intestinalized glands from which the cancers arise (108,109). Additionally, postinduction mutations in gastric cancers produce diverging clones of cell types that increase in number as tumors evolve from early (86) to advanced stages. Intestinal characteristics may be evident if goblet cells or Paneth cells are identified in hematoxylin and eosin (H&E)-stained sections or neuroendocrine cells specific to the intestine are found. An intestinal origin may also become apparent when the tumor cells are examined for their secretion products, biologic markers, or ultrastructural features. In some cases the tumor cells are gastric in type (Fig. 5.29), or may revert to a gastric phenotype from intestinalized precursors (110). Thus, although many histologic classifications have been proposed, none satisfactorily accounts for the cellular variability that may be encountered in an individual tumor. They are most useful for making rough estimates of the expected behavior of broad classes of tumor types.

Gastric Cancer Classifications

The Lauren classification divides gastric cancers into two major histologic types: Intestinal (Fig. 5.30) and diffuse (Fig. 5.31) (6). From 85% to 90% of gastric cancers fit into these categories. The remainder consist of carcinomas with mixed intestinal–diffuse features and uncommon subtypes (e.g., germ cell carcinomas, squamous cell carcinomas). Cohesive tumor cells that form recognizable glands, regardless of their degree of cytologic differentiation or cell of origin, fall into the intestinal category. They constitute approximately 60% of gastric cancers in high-risk populations, are most common in the antrum, and usually arise in an intestinalized mucosa. They associate with discrete distant metastases since they are likely to show lymphatic channel and/or vascular invasion. Diffuse carcinomas consist of discohesive cells that penetrate through the stomach wall as individual cells embedded in a desmoplastic stroma. They appear as layered signet ring cells in the superficial portions of the wall, where more pleomorphic cells predominate. Cell cycle markers may fail to label superficial signet ring calls, in contrast to the diffusely involved carcinomas. The Lauren classification provides a convenient approach to the histologic classification of gastric cancer. The Lauren classification has been criticized because it does not account for the cellular variability that may be encountered in an individual tumor. They are most useful for making rough estimates of the expected behavior of broad classes of tumor types.

Cytologic subtyping of gastric cancer is not essential (101). If one equates papillary, tubular, and some mucinous carcinomas with Lauren's intestinal-type and signet ring cell carcinoma with the diffuse type, then a specificity rate for cytologic typing of >90% for the former and of 85% for the latter may be obtained (102,103). However, vacuolized cells should be evaluated with special care because signet ring cells are easily simulated by goblet cells. The size of the nucleus and the nuclear outline are helpful diagnostic features. Unless fine needle aspiration is combined with the endoscopic examination, early gastric carcinoma cannot be identified cytologically because no features exist that allow one to distinguish between early and advanced gastric cancer (104). Advanced carcinomas with extensive necrosis and stenosis may not yield sufficient diagnostic material.

Fine needle aspiration during endoscopy providing a somewhat higher sensitivity than that of brush cytology of gastric and esophageal cancer is reported for biopsy touch smear cytology (105,106). With this method, gastric endoscopic biopsies are gently pressed several times on clean glass slides and the imprints processed routinely. Cell features are different from those of brush preparations, so that cytopathologists should be familiar with the difference in the two approaches. In addition to cytologic abnormalities, the percentage of single cells is taken into consideration because malignant tumors yield more than 20% single cells in touch smears (107). The same imprint technique can be used to stage gastric cancer during resections since bisected lymph nodes may be evaluated in this way for the presence of malignant cells.

Gastric adenoacanthoma. A keratinizing cell-in-cell arrangement is seen as well as single glandular cells with foamy cytoplasm.

FIG. 5.28.
and glands. In addition, the glands and foveolae may demonstrate pagetoid spread that is characterized by the presence of a two-layer structure, an inner layer consisting of benign mucous cells under which is a continuous or discontinuous layer of signet ring cells (Fig. 5.35). Furthermore, the tumors arising in this setting lose their membrane staining of E-cadherin (Fig. 5.1), unlike many diffuse carcinomas that are not hereditary in nature and retain their E-cadherin immunoreactivity (Fig. 5.36).

**FIG. 5.29.** Foveolar differentiation in gastric cancer. *A:* The cytoplasm of the neoplastic cells appears eosinophilic. The nuclei are peripherally placed. *B:* Ultrastructurally the cells resemble foveolar cells with prominent apical mucin globules and lateral cytoplasmic extensions.

**FIG. 5.30.** Intestinal-type adenocarcinoma. *A:* Intestinal carcinoma invading the submucosa and infiltrating the muscularis propria. Note that the tumor is composed of well-formed glands similar to carcinomas arising in the small or large intestine. *B:* Higher power view showing well-formed glands and cohesive clusters of neoplastic cells.
FIG. 5.31. Diffuse-type adenocarcinoma. A: The lamina propria contains individual infiltrating, discohesive cells. A few regenerating residual gastric glands are present in the bottom of the photograph. B: A digested periodic acid–Schiff (PAS) stain demonstrates diastase-resistant PAS staining in the cytoplasm of the neoplastic cells.

The simplicity of the Lauren classification that makes it useful for large epidemiologic studies makes it less useful for predicting the outcomes of histologic subsets of gastric cancers. The WHO International Reference Histologic Classification of Gastric Cancer (110), as listed in Table 5.8, has evolved to meet this need. In this classification adenocarcinomas are graded as well, moderately well, and poorly differentiated. Well-differentiated carcinomas produce recognizable, well-formed glands. Poorly differentiated tumors have poorly formed glands composed of very pleomorphic cells arranged in small clusters or solid sheets. Moderately well-differentiated tumors are intermediate between these extremes. WHO subtyping takes into account traditional histopathologic features, with most tumors falling into four types: Papillary, tubular, mucinous, and signet ring forms.


Tubular carcinomas (Fig. 5.37) contain dilated or branching tubules. Acinar structures may be present. Individual tumor cells may be columnar, cuboidal, or flattened by intraluminal mucin. Clear cells may be present. The degree of cytologic atypia varies from low grade (111) to high grade (112). A poorly differentiated variant is sometimes called solid carcinoma. Papillary carcinomas (Fig. 5.38) are well-differentiated exophytic tumors with fingerlike processes, lined by cylindric or cuboidal cells supported by slender vascular cores. The cells tend to maintain their polarity. The degree of cellular atypia varies and may be severe. The invading tumor margin is usually sharply defined from the surrounding structures. The tumor may be infiltrated with acute and chronic inflammatory cells.
Mucinous carcinomas (Fig. 5.39) are sometimes referred to as colloid carcinomas. By definition, >50% of the tumor contains extracellular pools of mucin. They may present in one of two forms: (a) glands lined by mucus-secreting epithelium surrounding collections of extracellular mucin, and (b) irregular clusters of cells floating freely in mucinous lakes. Signet ring cells, if present, do not dominate the histologic pattern. Sometimes the tumors consist of large acellular pools of mucin (Fig. 5.40).

Signet ring carcinomas are tumors in which >50% of the mass consists of cells containing mucin that compresses the nucleus to the periphery of the cell walls. The classic signet ring cells are most numerous in the superficial portions of the tumor where they are stacked in a layered fashion. Signet ring cancers usually exhibit the infiltrating growth pattern and desmoplasia that is called diffuse cancer in the Lauren classification. Infiltrating Borrmann type IV carcinomas are usually signet ring tumors. The tumor cells in the deeper portions of the stomach wall have less cytoplasmic mucin and more centralized nuclei. They may be so widely dispersed through the stroma that they may be difficult to detect in routine H&E-stained preparations. Some form of mucin stain (periodic acid–Schiff [PAS], Alcian blue, mucicarmine) or immunohistochemical staining is needed for diagnosis.

**FIG. 5.33.** Signet ring cell carcinoma. *A:* The neoplastic cells are highlighted with a mucicarmine stain. *B:* Immunohistochemical staining for cytokeratin demonstrates numerous infiltrating signet ring cells.

**FIG. 3.34.** Single cancer cells infiltrating the mesentery stained with an antibody to cytokeratin.
with cytokeratin antibodies may be used to detect these cells. We prefer the latter method since it detects a greater percentage of the neoplastic cells.

**Less Common Types of Stomach Cancer**

**Medullary Carcinoma.**

Medullary carcinomas of the stomach with lymphocytic infiltration associate with two conditions: EBV infection (113) and microsatellite instability (MSI) (114). It is now well recognized that from 5% to 15% of gastric cancers contain EBV DNA and that these cancers have distinct clinicopathologic features (Fig. 5.41). They are most frequent in men, arising in the corpus, but may occur in any part of the stomach. Grossly, many of these cancers present as ulcerated plaquelike lesions, although papillary forms also occur. An EBV association with gastric cancer may be suspected in H&E-stained sections if one of two growth patterns are present, but the diagnosis must be confirmed by in situ hybridization, which demonstrates the virus in the nuclei of the cancer cells (Fig. 5.42). A conspicuous lymphocytic infiltration is present in both types, and in approximately half of the cases this infiltrate may be so dense that the neoplastic epithelial cells are best recognized by cytokeratin stains (Fig. 5.41). EBV-associated tumors of this type probably account for 90% of medullary cancers. The other growth pattern seen with these cancers consists of slender, interlacing glands supported by a delicate stroma, the so-called lacelike pattern (115). If both patterns are present in the same cancer, the lacelike pattern is best seen in the superficial portions of the tumor, a distribution that could be explained by the lacelike pattern being a feature of the early stages of this cancer (116). Patients have been observed with synchronous, multicentric cancers in which EBV DNA sequences were found in only one cancer (113), suggesting that the association is limited to a specific cancer phenotype. The survival of patients with EBV-associated cancers is similar to that of other stomach cancers when assessed on a stage-by-stage basis. EBV-containing gastric cancers, however, are diagnosed at a lower stage than other cancers because they show fewer lymph node metastases than EBV-negative tumors ($p = 0.0018$) (117). It is not unusual for EBV-associated cancers to exceed 10 cm in diameter without acquiring nodal metastases (Fig. 5.41).

**FIG. 5.35.** Hereditary diffuse gastric carcinoma. *A:* This photograph shows the presence of an early infiltrating diffuse gastric cancer along with areas of pagetoid spread in the gastric glands. *B:* Higher magnification of the pagetoid spread. Signet ring cells are seen infiltrating beneath the nuclei of the intact gastric glands.

**FIG. 5.36.** Diffuse gastric cancer stained for E-cadherin. Note that the tumor cells are positive, contrasting with the tumor shown in Figure 5.1.

Abundant T-cell lymphocytic infiltration is a feature of sporadic, poorly differentiated gastric cancers that display MSI (118). These tumors are most common in the antrum among elderly patients and carry a relatively
The survival advantage of patients with this type of cancer has been attributed to an enhanced immune response generated by abnormal tumor-specific peptides that recruit lymphocytes to the tumor (114).

**TABLE 5.8 World Health Organization Histologic Classification of Gastric Epithelial Tumors**

<table>
<thead>
<tr>
<th>Intraepithelial neoplasia-adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
</tr>
<tr>
<td>- Adenocarcinoma</td>
</tr>
<tr>
<td>- Intestinal type</td>
</tr>
<tr>
<td>- Diffuse type</td>
</tr>
<tr>
<td>- Papillary adenocarcinoma</td>
</tr>
<tr>
<td>- Tubular adenocarcinoma</td>
</tr>
<tr>
<td>- Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>- Signet ring adenocarcinoma</td>
</tr>
<tr>
<td>- Adenosquamous carcinoma</td>
</tr>
<tr>
<td>- Squamous cell carcinoma</td>
</tr>
<tr>
<td>- Undifferentiated carcinoma</td>
</tr>
<tr>
<td>- Others</td>
</tr>
<tr>
<td>Carcinoid (well-differentiated endocrine neoplasm)</td>
</tr>
</tbody>
</table>

Paneth Cell Carcinoma.
Paneth cell carcinomas arise from areas of complete intestinal metaplasia (119) and associate with a conspicuous desmoplastic reaction. The tumor cells contain bright red cytoplasmic granules that are highlighted by antilysozyme antibodies (Fig. 5.43). These cancers are too uncommon to assess their impact on survival. The patient with the illustrated cancer showed no nodal metastases, but died with peritoneal metastases 7 years after a subtotal gastrectomy.

Pylorocardiac Carcinoma.
The pylorocardiac gland–type carcinoma may represent a distinct microscopic variant. This type of carcinoma is typically well demarcated and fungating, ulcerated, or fibrotic, and tends to arise either in the antrum or at the cardia. Microscopically, the cells appear predominantly clear (Fig. 5.44) because of the presence of cytoplasmic vacuoles containing PAS-positive diastase-resistant neutral mucin. Papillary infoldings of the glandular lining cells may be a prominent feature.

Gastric Parietal Cell and Parietal Cell-like Carcinoma (Oncocytic Adenocarcinomas).
Gastric cancers that contain cells resembling parietal cells are very uncommon. The tumors tend to be large with lymph node metastases. Histologically, the tumor has a solid, or medullary, appearance with occasional tubular differentiation. The tumor cells contain abundant granular cytoplasm that lacks mucin and neuroendocrine granules (Fig. 5.45). The cell stains with antibodies directed toward the H⁺,K⁺-ATPase pump and human milk fat globulin-2. The tumor cells also contain prominent intracytoplasmic canaliculi that can be identified ultrastructurally (120). As with Paneth cell cancers, clinical observations of these cancers are too few to assess their expected behavior. A favorable prognosis has been observed in some reports (121), but aggressive dissemination occurs in others (120). Well-differentiated adenocarcinomas that are rich in mitochondria have been termed oncocytic adenocarcinoma and are distinguished from parietal cell cancers by the absence of antiparietal cell antibodies (122).
Chapter 5


Adenosquamous and Squamous Cell Carcinoma.

Adenosquamous carcinoma is a rare tumor in which adenocarcinomatous and squamous components coexist (Fig. 5.46). Transitions exist between the two components. Adenosquamous carcinomas differ from tumors that contain discrete foci of benign-appearing squamous metaplasia. The latter are referred to as adenoacanthomas with squamous metaplasia. The prognosis of adenosquamous carcinoma is less favorable than adenocarcinoma, probably because these cancers are usually diagnosed at an advanced stage and show evidence of vascular invasion (123). A pure squamous cell carcinoma at the gastric cardia is likely to represent extension of an esophageal primary lesion into the stomach. The remaining squamous cell carcinomas are either tumors that arise in areas of squamous metaplasia in the gastric mucosa or adenosquamous carcinomas in which the squamous component has become the predominate histologic feature. Pure squamous cell cancers develop in association with tertiary syphilis, after cyclophosphamide therapy (124), and in stump cancers (125). All forms of gastric cancer that express a squamous phenotype probably amount to <0.5% of gastric carcinomas.

FIG. 5.40. Colloid carcinoma. This tumor contains large paucicellular mucin pools infiltrating the gastric wall.
Gastric Adenocarcinomas with Features of Germ Cell Tumors.

Most tumors with features of choriocarcinoma are combinations of variably differentiated adenocarcinoma and choriocarcinoma (Fig. 5.47). Slightly <30% of these tumors are pure choriocarcinomas, otherwise indistinguishable.

From gestational and gonadal cancers. Rarely, the glandular component may be an early carcinoma. Histologically, transitions occur from the trophoblastic areas to the more classic glandular phenotype. The tumors arise in both sexes (male-to-female ratio = 2.1), affecting individuals between the ages of 25 to older than 80 years, with a mean age of 55 to 58 years (126). High circulating human chorionic gonadotropin (hCG) levels may cause gynecomastia and Leydig cell hyperplasia in men or secretory mammary changes and abnormal uterine bleeding in women. The nonneoplastic antral mucosa contains hCG-producing cells (127), and cells that contain hCG may be seen in as many as 8.2% of advanced cancers and 6% of early cancers (128). The adenocarcinomatous component of this tumor is usually negative for hCG (Fig. 5.47), but positive for cytokeratin, carcinoembryonic antigen (CEA), and α-fetoprotein (AFP). It is known that many human malignancies can produce hCG or its subunits, so that the presence of hCG immunoreactivity is insufficient to diagnose a choriocarcinoma. Gastric carcinomas that express hCG have a poor prognosis (128).

FIG. 5.41. Medullary carcinoma. A: Gastrectomy specimen containing a large, fungating mass with surface ulceration and hemorrhage. B: An intense lymphocytic infiltrate surrounds cords of neoplastic cells. C: The neoplastic cells are easily seen in cytokeratin-stained sections.
FIG. 5.42. Epstein-Barr virus (EBV) in gastric carcinoma. A: In situ hybridization for EBV in a medullary carcinoma. B: EBV DNA is present in a small proportion of gastric cancers without lymphoid stroma.
**FIG. 5.43.** Paneth cell carcinoma. *A:* Low magnification showing an infiltrating carcinoma. *B:* The mucosa shows adjacent areas of intestinal metaplasia. *C:* Higher magnification showing the eosinophilic granules of the Paneth cells. *D:* The tumor cells stain with an antibody to lysozyme.

**FIG. 5.44.** Pylorocardiac subtype. *A:* The glands are lined by large cells with clear cytoplasm. *B:* The cytoplasm is diffusely vacuolated.
FIG. 5.45. Parietal cell differentiation in gastric cancer. A: An infiltrating carcinoma is seen extending into the submucosa. B: These glands are lined by cells with brightly eosinophilic, granular cytoplasm resembling that of the nonneoplastic parietal cells in the overlying mucosa.

FIG. 5.46. Adenosquamous cell carcinoma. A: Area of adenocarcinoma. B: Area of squamous differentiation. C: Another area showing both glandular and squamous carcinoma. D: The nodal metastases were poorly differentiated, simulating a mantle zone lymphoma.
FIG. 5.47. Carcinoma with choriocarcinoma. A: Poorly differentiated adenocarcinoma admixed with choriocarcinoma. B: A large trophoblasticlike cell is seen on the right. C: These cells are human chorionic gonadotropin positive.

Rare gastric cancers contain components resembling endodermal sinus tumors (129) and embryonal carcinoma. They may occur in males or females. Like choriocarcinomas, they may be associated with adenocarcinoma. Transitions occur between the germ cell and epithelial components of the cancer. The presence of Schiller-Duval bodies and hyaline droplets allows the recognition of the endodermal sinus component.

Hepatoid Carcinoma and α-Fetoprotein-producing Gastric Cancer.

Hepatoid carcinomas have the histologic and immunohistochemical features of hepatocellular carcinomas. They arise from various organs, including the stomach (130,131). Since the fetal liver is a principal source of AFP, and because hepatocellular carcinomas are characteristically associated with AFP production, this protein has been widely accepted as a marker for hepatic differentiation at other sites (131). Albumin (ALB) mRNA also indicates hepatocellular differentiation (132). Not all primary gastric hepatoid carcinomas produce AFP (133), however, and not all AFP-producing gastric cancers show hepatoid differentiation (133). Most hepatoid carcinomas contain distinctive areas of tubular carcinoma that produce intestinal-type mucins (131). The tubular and hepatoid components of these cancers share common p53 mutations and common patterns of chromosome X inactivation (131). Similarly, hepatoid carcinomas that produce ALB mRNA may or may not produce AFP (132), indicating that the diagnosis of hepatoid adenocarcinoma should be made on the basis of its morphology, irrespective of its AFP production. When compared to AFP-negative cancers, AFP-producing cancers show higher Ki-67 labeling indices and lower apoptosis indices, reflecting the aggressive behavior and poor prognosis of these tumors (133).

Carcinosarcoma and Osseous Stromal Metaplasia.

Carcinosarcomas are very uncommon and are usually encountered among elderly men (134). As in the esophagus, they usually present as large polypoid or fungating masses containing areas of carcinoma and sarcoma. The sarcomatous component usually has spindle cell morphology and, when differentiated, most often shows smooth muscle features. Chondrosarcoma and rhabdomyosarcomas have been reported on several occasions. Recent reports of gastric carcinosarcomas that show neuroendocrine differentiation highlight the heterogeneity of these tumors (135). The sarcomatous components sometimes stain with epithelial markers. The presence of osteoid and mature bone in the desmoplastic stroma of a gastric cancer must be distinguished from carcinosarcoma (136). Stromal ossification occurs in gastrointestinal cancers from the stomach to the rectum and appears to result from tumor production of bone morphogenetic protein (137).

Gastric Carcinomas with Unusual Host Reactions.

Gastric cancers, like those at other primary sites, may associate with intense eosinophilia. Tumor-associated tissue eosinophilia has been observed frequently in cancer tissues, but its cause is unknown (138). A study of
25 early gastric cancers found that eosinophils were more numerous in the stroma of these tumors than in the adjacent normal-appearing mucosa (139). The intensity of the infiltrate does not relate to the size of the tumor, its histologic type, or the presence of necrosis in the tumor. Tumor cells in intimate contact with activated eosinophils exhibited cytopathic changes. This might explain the observation that stage-adjusted gastric cancers with numerous stromal eosinophils carry a lower risk of death than those with none (140).

**FIG. 5.48.** Intramural spread of gastric cancer. *A, B:* Intact overlying epithelium is seen in both of the illustrated cases. The presence of gastric cancer within lymphatics (arrows) at these resection margins was not appreciated grossly.

Sarcoid-like granulomas have been observed in the stroma adjacent to many cancers and in the regional nodes that drain them, including gastric carcinoma (141,142). A recent study found four gastric adenocarcinomas among 14 cancers (28.5%) that associated with this sarcoid-like reaction (142). The carcinoma-associated granulomas resemble those seen in sarcoidosis with respect to their morphology and angiotensin I–converting enzyme expression, but show some differences. CD4+ helper T lymphocytes generally outnumber CD8+ T lymphocytes in sarcoidosis, while the sarcoid reaction to tumors associates with a greater proportion of CD8+ T cells, to the extent that they may even outnumber CD4+ cells. Although the sarcoid reaction may represent a T cell–mediated immune response to the tumors, too few gastric cancers have been observed with this reaction to assess its impact on survival.

### Spread of Gastric Cancer

Most patients in unscreened populations, and a significant minority of patients in screened populations, are diagnosed when their cancer is already advanced. There may be direct extension to adjacent organs, including the pancreas, transverse colon, hilum of the liver, abdominal wall, or esophagus (143). Intramural spread beneath the intact mucosa is common (Fig. 5.48), as is lymphatic invasion (Fig. 5.48).

Lymphatic spread occurs early, and as noted above, may even be observed with small submucosal cancers. Lymphatic and vascular invasion carries a poor prognosis (144) and is frequently seen in advanced cases (145). Surgical resection margins should be monitored by frozen section because gross assessment is inaccurate and margin involvement occurs in 15% of cases. The failure rate of adjuvant postoperative treatment of gastric cancer has prompted investigators to better define the surgical potential of influencing patient prognosis. Intense interest centers on assessment of the extent of mural invasion, because this correlates with the presence of tumor at the resection margins. Infiltration of the proximal margin of the resection is significantly more frequent when the tumor penetrates the serosa than when the lesion is confined to the mucosa, submucosa, or muscularis propria. Proximal or distal infiltration >3 cm does not occur with lesions confined to mucosa, submucosa, or muscularis propria. The pathologist should take pains to identify the proximity of the cancer to the radial margin, which is defined as the surgically dissected surface adjacent to the deepest point of tumor invasion. A deeply penetrating cancer that centers on the lesser or greater curvature may have a radial margin that lies in the connective tissue of the lesser or greater omentum, rather than the serosal surface. Microscopic involvement of a resection margin is almost synonymous with early recurrence or death.

The extent of lymphadenectomy is another area of interest. Lymphatic spread occurs early. The purpose of nodal dissection is to detect and remove metastases, so as to improve the chances of survival and to accurately stage the disease. The Japanese Research Society for Gastric Cancer divides the regional nodes of the stomach into four groups (143), as shown in Table 5.9. Some of the decline in gastric cancer mortality
in Japan has been attributed to the widespread practice of extended lymph node resections to include all N1 and N2 node groups (R-2 resections). These node groupings roughly overlap with those defined in the current American Joint Committee on Cancer (AJCC) staging manual (146), although the number of involved nodes, rather than the node subsite, is the basis for assigning an N level in the AJCC system. It is therefore important that the pathologist search for as many nodes as possible within a resection specimen and that the location of these nodes be accurately documented. Sentinel node technology has the potential of predicting the extent of lymph node involvement (147). One sentinel node mapping study, using both radioisotope and dye labeling, found the sentinel node to be positive in 40 of 41 (98%) of cases with regional node involvement (148). These promising results need to be confirmed by much larger studies.

### TABLE 5.9 Regional Lymph Groups, Cancers at All Gastric Subsites

<table>
<thead>
<tr>
<th>Group 1 (N1): Right and left cardinal nodes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodes along lesser curvature</td>
<td></td>
</tr>
<tr>
<td>Nodes along greater curvature</td>
<td></td>
</tr>
<tr>
<td>Suprapyloric nodes</td>
<td></td>
</tr>
<tr>
<td>Infrapyloric nodes</td>
<td></td>
</tr>
<tr>
<td><strong>Group 2 (N2): Nodes along left gastric artery</strong></td>
<td></td>
</tr>
<tr>
<td>Nodes along common hepatic artery</td>
<td></td>
</tr>
<tr>
<td>Nodes around celiac artery</td>
<td></td>
</tr>
<tr>
<td>Nodes at splenic hilum</td>
<td></td>
</tr>
<tr>
<td><strong>Group 3 (N3): Nodes in hepatoduodenal ligament</strong></td>
<td></td>
</tr>
<tr>
<td>Nodes behind pancreas head</td>
<td></td>
</tr>
<tr>
<td>Nodes at root of mesentery</td>
<td></td>
</tr>
<tr>
<td><strong>Group 4 (N4): Nodes along middle colic artery</strong></td>
<td></td>
</tr>
<tr>
<td>Para-aortic nodes</td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 5.49.** Micrometastases of a diffuse gastric carcinoma in a regional lymph node highlighted by a cytokeratin immunostain.

Micrometastases, unsuspected by standard H&E stains, can be identified with immunochemical (Fig. 5.49) (148) and molecular markers (149), but their clinical significance is uncertain. One study suggests that identification of micrometastases in lymph nodes may predict prognosis (148). In another study immunohistochemical stains discovered micrometastases to the bone marrow in 44 of 50 (88%) patients undergoing resection for GEJ cancer (150). This is far more frequent than the clinical frequency of bone metastases from this site. Large, prospective studies will be required to determine the prognostic value of detecting nodal and bone marrow micrometastases.

Age, gender, and histologic type strongly influence the patterns of spread to distant sites. The intestinal-type cancers that typically arise in the distal third of the stomach in older men frequently metastasize to the liver, where they form discrete masses (151). The diffuse cancers that predominate in premenopausal women show a predilection for transperitoneal spread. Ovarian metastases from gastric cancer (Krukenberg tumors) are acquired by this route (Fig. 5.50). While Krukenberg tumors classically result from the spread of diffuse gastric carcinomas, ovarian metastases of intestinal-type tumors also occur, usually in older women with widespread disease (151a). Transperitoneal spread also accounts for metastases to the endometrium and uterine cervix in the same age group (152). Peritoneal involvement, combined with lymphatic obstruction, may result in the development of ascites, a presenting symptom in some cases. Blood-borne metastases occur even in the absence of lymphatic involvement with seeding to the liver, lungs, bone, and skin. Direct extension to the pancreas, the colon, and other neighboring organs is common. When the cancer penetrates the serosal surface, peritoneal implants may flourish in the greater
The prognosis of gastric carcinoma is best estimated by assessing its stage at the time of diagnosis. The TNM system (T, extent of primary tumor; N, extent of lymph node metastases; M, presence of distant metastases), as published by the WHO (110), is now the standard stage classification worldwide and is summarized in Table 5.10. The age-adjusted 5-year survival of patients with stage I cancer approximates 95% (78), but only 7% of patients with stage IV cancers are 5-year survivors (153). The presence and number of nodal metastases are important determinants of survival (154), and the correct assignment of an N stage clearly depends on the number of nodes removed by the surgeon (155). More extensive lymph node dissection probably accounts for much of the difference in the 5-year survival of patients with stage I cancer in Japan (95%) versus in the United States (78%) (153).

The standard of care in the treatment of gastric cancer in the United States is reflected by an analysis of 50,169 patients treated by gastrectomy during the years 1985–1996. Less than half of these patients could be staged by the WHO system (153). This study found that only 33,806 (67%) cases had sufficient node data for TNM staging, and of those with
counted nodes, 25% had less than seven nodes examined. None of these patients could be assigned to stage IIIB, since this stage is defined by having metastases in seven or more nodes. The conclusion of the report was that undertreatment of patients with gastric cancer is a problem in the United States. It should be emphasized, however, that perfunctory pathology reporting may have made significant contributions to staging errors as well. Lymph node harvesting is noticeably better in American hospitals that specialize in cancer treatment than in the country as a whole, but a direct comparison between one of them and two Japanese institutions found that more accurate staging contributed to the more favorable outcome of gastric cancer patients in Japan (155). The depth of invasion is the most important TNM variable for gastric cancer staging (144), and this is fortunately less subject to error than nodal appraisal.

**TABLE 5.10 World Health Organization TNM Classification of Gastric Tumors**

<table>
<thead>
<tr>
<th>T—Primary Tumor</th>
<th>Stage</th>
<th>Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX—Primary tumor cannot be assessed</td>
<td>Stage 0</td>
<td>TisN0M0</td>
</tr>
<tr>
<td>T0—No evidence of primary tumor</td>
<td>Stage IA</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Tis—Carcinoma in situ</td>
<td>Stage IB</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>Intraepithelial tumor without invasion of lamina propria</td>
<td></td>
<td>T1N1M0</td>
</tr>
<tr>
<td>T1—Tumor invades lamina propria or submucosa</td>
<td>Stage II</td>
<td>T1N2M0</td>
</tr>
<tr>
<td>T2—Tumor invades muscularis propria or subserosa</td>
<td></td>
<td>T2N1M0</td>
</tr>
<tr>
<td>T3—Tumor penetrates serosa (visceral peritoneum)</td>
<td>Stage III</td>
<td>T3N0M0</td>
</tr>
<tr>
<td>T4—Tumor invades adjacent structure*</td>
<td>Stage IIIA</td>
<td>T2N2M0</td>
</tr>
<tr>
<td>*Spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, retroperitoneum</td>
<td></td>
<td>T3N1M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4N0M0</td>
</tr>
<tr>
<td></td>
<td>Stage IIIB</td>
<td>T3N2M0</td>
</tr>
<tr>
<td></td>
<td>Stage IV</td>
<td>Any T Any N M1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4N1–3M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1–3N3M0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N—Regional Lymph Nodes</th>
<th>Stage</th>
<th>Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX—Regional nodes cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0—No lymph node metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1—Metastases in one to six lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2—Metastases to 7 to 15 lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3—Metastases to more than 15 lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M—Distant Metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MX—Distant metastases cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0—No distant metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1—Distant metastases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pathology variables not included in the TNM system also influence survival with stomach cancer, including tumor size, location, and histologic type. A Japanese retrospective, multivariate analysis of survival after curative resection found that, in addition to the depth of invasion, the size of the cancer and location in the proximal third of the stomach were independent predictors of the time interval between treatment and recurrence (156).

**Immunohistochemical Markers**

It is now common practice to use immunohistochemical stains to assess the phenotypic heterogeneity of gastric cancers, to identify tumor characteristics that might influence prognosis, and to determine whether these characteristics might make them more, or less, responsive to chemotherapeutic agents.

**Phenotypic Markers**

Markers are available that identify the different gastric and intestinal cells from which cancers may arise, but loss of specific traits through dedifferentiation and the accumulation of other traits through postinduction alterations complicate attempts to identify the progenitor cells of specific cancers. Analysis of large numbers of cancers, however, provides levels of probability that a cancer in the proximal stomach derives from the cardia, the distal esophagus, or the corpus, or that a distal gastric cancer derives from metaplastic intestinal cells or residual antral glands. Cytokeratin 20 (CK20) is a marker for antral epithelium, while CK7 generally...
As noted above, metabolic abnormalities independently associate with gastric cancer progression, especially when coexpressed with AMFr and urokinase-type plasminogen activator receptor. Androgen receptor (AR)

Several other biomarkers have been associated with aggressive growth and poor prognosis with gastric cancer, including thioredoxin, a putative oncogene (176); microsatellite stability; and the non-CIMP phenotype 

Expression of two members of the VEGF family, VEGF-C and VEGF-D, in gastric cancer correlates with lymphatic invasion and increased mortality (174,175).

Expression of two motility factors, fascin (171,172) and autocrine motility factor (AMFr) (173), also associates with poor survival. A cancer enhances its chances of dissemination by stimulating angiogenesis with vascular endothelial growth factor (VEGF). Expression of two members of the VEGF family, VEGF-C and VEGF-D, in gastric cancer correlates with lymphatic invasion and increased mortality (174,175).

Prognostic and Therapeutic Markers

Amplification of growth factors, such as epithelial growth factor (EGF) and its receptor (EGFR), associate with higher proliferative indices, an effect that is enhanced when coexpressed with other growth factors, such as TGF-α and p185c-erb-2 (163). EGFR overexpression associates with more frequent metastases and less favorable prognosis (164). The influence of growth factors on tumor progression is augmented by abnormalities in cell cycling. Thus, adenocarcinomas dependent on the TGF-α–EGFR autocrine loop exhibit increased aggressiveness in the presence of aberrant p53 expression (165). Clonal heterogeneity of EGFR and other tumor markers in advanced cancer is especially ominous, with the amplified components showing a selective advantage in vascular invasion (Fig. 5.51).

The met oncogene is a tyrosine kinase that encodes the hepatocyte growth factor receptor and stimulates mitogenesis, motogenesis, vasculogenesis, and morphogenesis in a wide range of cellular targets. Abnormalities in this gene are implicated in gastric carcinoma (165a). Importantly, like other tyrosine kinases that become abnormal in cancer, it represents an attractive therapeutic target (165a).

The Wnt signaling pathway is also commonly abnormal in gastric cancer. TC1, a novel regulator of the Wnt signaling pathway, is up-regulated in gastric cancers. It plays a role in poor differentiation and aggressive biologic behavior in gastric cancer (165b). Cyclin D1, a Wnt signaling target, regulates cell cycle progression from the G1 to S phase (166). It is not expressed in normal gastric mucosa, but is expressed in 40% of gastric cancers (167). Patients whose tumors show cyclin D amplification, but not overexpression, have a less favorable 5-year survival than those who do not, although there is no correlation between cyclin D1 amplification and either nodal metastases or histologic grade (unpublished observations).

One would predict that loss of tumor suppressor factors also spurs abnormal cell growth, but the results of numerous studies on p53 are conflicting in this regard (168). p53 expression does not exactly correlate with mutational status since it does not detect deletions or nonsense mutations in this gene. Observed differences respecting the influence of p53 immunohistochemical expression on prognosis (168) are less consistent than growth or cell cycle factors. A higher cancer stage is more likely, however, when p53 expression accompanies an amplified growth factor than with the growth factor alone.

As may be expected, factors that mark the transition from preinvasive to invasive cancer are also associated with less favorable prognosis. Immunohistochemical expression of MMP7 associates with lymphatic invasion and poor survival (169,170). Expression of two motility factors, fascin (171,172) and autocrine motility factor (AMFr) (173), also associates with poor survival. A cancer enhances its chances of dissemination by stimulating angiogenesis with vascular endothelial growth factor (VEGF). Expression of two members of the VEGF family, VEGF-C and VEGF-D, in gastric cancer correlates with lymphatic invasion and increased mortality (174,175).

Several other biomarkers have been associated with aggressive growth and poor prognosis with gastric cancer, including thioredoxin, a putative oncogene (176); microsatellite stability; and the non-CIMP phenotype (36b). As noted above, met abnormalities independently associate with gastric cancer progression, especially when coexpressed with AMFr and urokinase-type plasminogen activator receptor. Androgen receptor (AR)
activation enhances VEGF gene transcription and may have antiapoptotic activity as well. Approximately 17% of gastric cancers express AR, with no gender difference in frequency. AR-expressing gastric cancers are more likely to have nodal metastases and less favorable prognosis than those that do not (177). Overexpression of cyclooxygenase-2 (COX-2) associates with deep invasion and nodal metastases (178). COX-2 frequently associates with HER-2 or tumors with reduced expression of Smad4 (an intracellular transducer), suggesting that signal transduction through the HER-2 and SMAD system may regulate COX-2 expression. There are polymorphisms in this gene, some of which associate with reduced gene expression. There is a greater than twofold higher risk for progressing to gastric cancer among patients with chronic gastritis who have the homozygous variant 1195AA COX2 genotype than heterozygotes and those who are homozygous wild type (178a).

**Treatment**

The almost limitless heterogeneity of most advanced gastric cancers creates a barrier to the development of customized chemotherapeutic approaches. Surgery remains the mainstay of treatment of advanced gastric cancers. Palliation, rather than cure, is the primary goal of adjuvant therapy (177). Most patients who have had a resection for gastric cancer with extensive lymph node metastases will have a disease relapse. No randomized trial has shown a benefit for this subset of patients and no single agent has proved effective for postoperative chemotherapy (179). This is not unexpected since successful response to treatment with drugs that target specific oncogenes allows subsets of other cells to survive and serve as the seedbeds for recurrent tumors.

**Metastases to the Stomach**

The stomach may be the recipient of cancers from other sites, the most common primary sources being melanoma, lung cancer, and breast cancer. If the tumor produces multiple, discrete, ulcerated nodules such as may occur with disseminated melanoma (Fig. 5.52), the diagnosis is fairly obvious. In contrast, metastases from breast cancer may mimic liminitis plastica, both clinically and anatomically (180), and a gastric metastasis may be the presenting symptom of a primary breast cancer (180,181). In one recent study of 51 breast cancers metastatic to the stomach, this was the metastatic site in 14 cases (180). Lobular cancer is a frequent type of breast cancer that metastasizes to the stomach (Fig. 5.53). Endoscopic biopsies may be negative in up to a quarter of these cases, because the metastases may be localized to the deep layers. The desmoplasia associated with lobular carcinoma and its discohesive growth pattern may so closely resemble diffuse gastric cancer that distinction between the two tumors may be difficult. The fact that gastric cancers, irrespective of gender, may be estrogen receptor (ER) positive (182) and that diffuse gastric cancer may metastasize to the breast (183) does not make the problem any easier. A study that compared primary gastric cancers with positive gastric biopsies from patients with a history of breast cancer found that the tumors in 14 of 28 (50%) patients with breast cancer were ER positive, compared to only 1 of 46 (2%) gastric cancers (184). Stains for E-cadherin expression are more likely to be negative with breast than gastric cancer, even when the comparison is limited to diffuse gastric cancer and lobular breast cancer ($p = 0.01$). These findings indicate that a gastric biopsy that yields an ER-positive, E-cadherin-negative cancer is diagnostic of a metastatic breast cancer rather than a primary stomach cancer.

**FIG. 5.52.** Metastatic melanoma in the stomach. The mucosal surface contains numerous ulcerated and hemorrhagic tumor nodules.
Handling of Gastric Resection Specimens

The gastrectomy specimen should be sent to the pathology department as soon as possible after its removal from the patient. The stomach should be opened along the greater curvature and pinned to a cork board or paraffin plate and floated upside down in 10% neutral buffered formalin for at least 12 hours. The gross limits of the tumor are more easily assessed if the specimen is well fixed, and small, unsuspected multicentric tumors may be more easily identified. However, if alkaline phosphatase staining is performed, the specimen should be fixed in formalin prechilled to 4°C because this enzyme is thermolabile. This procedure is usually reserved for investigational purposes and need not be performed in routine cases.

The gross description of the fixed specimen should include the type of resection (proximal subtotal, distal subtotal, or total), the lengths of the greater and lesser curvatures, the length of attached esophagus and/or duodenum, the axial and transverse diameters of the tumor, and the location of the tumor within the stomach. The gross configuration of the tumor should also be noted (i.e., fungating, ulcerated, diffuse, etc.). All lesions should be described and sampled, including areas of ulceration and polypoid or elevated lesions. The location of such lesions should be accurately described in relation to the main tumor mass. In many cases, an explanatory diagram or photograph is useful for documenting the distance of the tumor from resection margins and its relationship to other lesions present in the stomach.

The cut edges of the specimen should be marked with India ink before sectioning. Circumferential blocks are obtained from the margins of resection to rule out grossly inapparent intramural spread to the surgical margin. Two to four sections should be taken from the tumor, depending on its size. At least one of these sections should include the full thickness of the gastric wall so that the maximum depth of penetration can be determined.

A generous sample of the intact nonneoplastic mucosa on the proximal and distal sides of the tumor should be included with the neoplasm in order to identify precursor lesions, including intestinal metaplasia, atrophic gastritis, and areas of dysplasia. The pathologist should harvest as many nodes as possible from the lesser curvature and the distal and proximal greater curvature, separately identifying those <3 cm or >3 cm from the tumor.

Histologic examination should include the following: (a) the TNM status of the tumor; (b) the histologic type of the cancer using the Lauren or WHO classification, and its degree of differentiation; (c) the presence and extent of vascular and perineural invasion; (d) the histologic findings in the nonneoplastic gastric mucosa; and (e) the presence or absence of lymph node metastasis. Each report should contain, as a minimum, the information needed to assign an accurate TNM stage, the gastric subsite location of the tumor, a histologic classification of the tumor, and an estimate of its degree of differentiation. EMR specimens should be handled as discussed in Chapter 3.

References


P.270


P.271


Acquired Anatomic Variations

Duodenal Diverticula

Duodenal diverticula are found in 1% to 6% of radiologic examinations and in an average of 8.6% of autopsies (147). They complicate peptic ulcer disease, choledocholithiasis (148), duodenal obstruction, and genetic or systemic disorders such as Marfan syndrome. Most duodenal diverticula develop as a result of chronic peptic ulcer disease (149). The ulcerating process causes fibrosis of the muscularis propria and abnormal contractility. Their frequency increases with age; they rarely develop before age 40. The diverticula usually involve the second portion of the duodenum in a juxtapapillary location and are usually solitary and medial in location. Diverticula arise in weakened areas of the bowel wall that gradually balloon out, causing the diverticula to enlarge over time. The diverticular wall consists of variably inflamed mucosa and submucosa with only scattered muscle cells.

![Image](FIG. 6.71. Congenital duodenal diverticulum. A large duodenal diverticulum extends into the underlying pancreas (P). The overlying duodenal mucosa appears ulcerated and flattened at the edges of the ulcer.)

Jejunal and Ileal Diverticulosis

Jejunal diverticulosis is a heterogeneous disorder affecting 1.3% to 4.6% of the population (150). It consists of single or multiple diverticula predominantly involving the jejunum (Fig. 6.72). However, both the duodenum and the ileum may be involved (150). Jejunal diverticula develop seven times more commonly than ileal diverticula (151); men are affected twice as frequently as women. Most affected individuals are over age 40 (150); 82% of patients remain asymptomatic. The diverticula become evident as an incidental finding at the time of surgery, autopsy, or radiographic examination. Neuromuscular disorders typically coexist with jejunal diverticulosis, including Fabry disease, visceral myopathies or neuropathies, scleroderma, and neuronal inclusion disease (150). As a result, patients often suffer from pseudo-obstruction or malabsorption secondary to bacterial overgrowth. Diverticular resection cures the malabsorption. Small intestinal diverticula perforate, bleed, become inflamed, and undergo other complications. These complications lead to morbidity and mortality rates as high as 40%.

Small intestinal diverticula begin as a pair of small outpouchings along the mesenteric border. The mucosa herniates through the muscle layer along the path of the penetrating vessels. Alternatively, localized areas of muscular fibrosis and atrophy may weaken the bowel wall, creating localized mural sacculations. Uncoordinated muscular contractions from an underlying motility disorder lead to focal areas of increased intraluminal pressure and mucosal herniation through the weakened areas. The pair of outpouchings then enlarges until the outpouchings meet and they may fuse in the line of the mesentery, thereby forming a...
Acquired Anatomic Variations

single thin-walled diverticulum. The diverticula usually measure <1 cm in size, although they may be larger. Jejunal diverticula tend to be larger in the proximal jejunum and become smaller and fewer as one progresses distally in the GI tract. As many as 400 diverticula ranging in size from 1 to 22 cm in diameter can exist in a single patient (150).

Histologically, diverticula are lined by mucosa, muscularis mucosae, and submucosa, but they usually lack a muscularis propria. The mucosa usually shows some degree of crypt hyperplasia, villous atrophy, and chronic inflammation, probably resulting from intestinal stasis and bacterial overgrowth. Lipid-containing histiocytes often lie in the mucosa, in the submucosa, and along lymphatics close to the collar of muscularis propria surrounding the diverticular neck (152). The histology of the bowel wall sometimes shows an underlying myopathy or neuropathy (see Chapter 10) or only fibrosis of the muscularis propria (150).

![Jejunal diverticulosis. A: Multiple outpouchings along mesenteric border of jejunum characteristic of jejunal diverticulosis. B: Cut section demonstrating thin-walled diverticular outpouchings.](image)

**FIG. 6.72.** Jejunal diverticulosis. A: Multiple outpouchings along mesenteric border of jejunum characteristic of jejunal diverticulosis. B: Cut section demonstrating thin-walled diverticular outpouchings.

**FIG. 6.73.** Diagram of an intussusception showing the relationship of the intussusceptum with the intussuscipiens and the overall intussusception.
Intussusception

An intussusception results from invagination of an intestinal segment (the intussusceptum) into the next part of the intestine that forms a sheath around it (the intussuscipiens) (Figs. 6.73, 6.74, 6.75, and 6.76). Intussusceptions are classified as primary (without an identifiable cause) or secondary (due to a pre-existing lesion). They are one of the most common abdominal emergencies in early childhood. Two thirds of cases occur in infancy, with a peak incidence between 3 and 5 months of age (153,154). Intussusception is the most common cause of intestinal obstruction in children (155,156), affecting 1.5 to 3.8 cases per 1,000 live births a year. The incidence varies considerably in different parts of the world (157). Some patients have strong family histories of intussusception (158). Paradoxically, there appears to be a high incidence of intussusception in doctors’ families (159). In the United States, there is a male predominance of 2:1 and a seasonal prevalence with two peaks, one in the winter and one in the summer (160). Patients are typically well nourished, without a history of gastrointestinal disease.


Lead points are common in children 6 years of age or older. Predisposing factors include masses, bezoars, Meckel diverticula, motility disorders, inflammatory fibroid polyps, or localized lymphoid hyperplasia secondary to adenovirus or other infections (Figs. 6.76 and 6.77). It also develops in some patients following rotavirus vaccination (161) and AIDS infections (162). The intussusception constricts the mesentery between the inner intussusceptum and the ensheathing intussuscipiens blocking both venous outflow and the arterial supply, leading to secondary ischemia. As a result, the intussusception continues to swell, causing bowel obstruction and possibly gangrene and perforation. Some intussusceptions reduce spontaneously. The intussuscepted bowel may show the features of the intussusception, the pathology of the predisposing cause, and secondary ischemia.

The histology differs depending on whether the intussusception is acute, chronic, or acute superimposed on chronic intussusception. In patients with chronic or recurrent intussusceptions, the muscularis mucosa sometimes buckles upward, indicating the lead point of the intussusception, and the subserosal or even intramural vessels may show evidence of a “pulling artifact” with tethering in the same direction as the muscularis mucosae. One can imagine similar traction forces acting on the mucosa, muscularis propria, and subserosal vessels. Recurrent intussusceptions can produce florid submucosal vascular proliferations that may be so pronounced as to raise the possibility of a primary vascular neoplasm (163). Characteristically, there is also prominent muscular hypertrophy and neural hyperplasia. Most intussusceptions show variable degrees of ischemia. The histologic features of the ischemia resemble gastrointestinal ischemia due to other causes. They reflect the length of time that the injury lasted and the degree of vascular compromise that occurred. In children with adenovirus infections, the lymphoid tissue appears markedly hyperplastic and the
epithelium overlying the lymphoid hyperplasia at the lead point appears damaged or even necrotic. Intranuclear viral inclusions appear as reddish globules surrounded by halos or as poorly demarcated purple nuclear smudges.

FIG. 6.75. Intussusception. The intussuscipiens exhibits early ischemic changes as demonstrated by the presence of the mottled speckling on the serosal surface and the dusky color in comparison to the paler intussusceptum.

**Volvulus**

Volvulus accounts for 5% to 10% of all cases of intestinal obstruction. It develops when any portion of the intestine loops around itself (Fig. 6.78). Intestinal volvulus is divided into primary and secondary forms. Primary volvulus develops in patients lacking a predisposing cause. Secondary volvulus affects patients with an acquired or congenital structural abnormality that predisposes the bowel to rotate on itself (Fig. 6.79). Underlying abnormalities include a congenitally long mesentery with a narrow base, the presence of congenital bands, an elongated small intestine, Meckel diverticulum, or inflammatory diseases.
Small bowel volvulus is a rare but life-threatening surgical emergency. Volvulus occurs acutely, causing complete obstruction, or intermittently, producing partial or complete obstruction with compromise of the blood supply, ischemia, gangrene, perforation, and peritonitis. The intestinal obstruction presents with severe abdominal pain, nausea, bilious vomiting, abdominal distension, and rectal bleeding. Often the patient collapses due to occlusion of the venous return by the mesenteric twist while arterial perfusion continues. As much as 50% of the blood volume may accumulate within the volvulus. Obstruction, tachycardia, and fever occur less commonly (164). A history of recurrent minor attacks of similar problems is present in approximately 50% of patients (165). Approximately 37% of patients present with a frankly gangrenous small bowel at the time of resection. Histologically, the tissues manifest variable degrees of ischemia.

**Fistulae**

Fistulae develop between the small intestine and adjacent organs or skin as a result of underlying diseases or previous surgery. *Enteroenteric fistulae* represent communications between two portions of the GI tract. *Bouveret syndrome* consists of a cholecystoduodenal or choledochoduodenal fistula due to the passage of a gallstone into the duodenal bulb and subsequent gastric outlet obstruction. Most patients spontaneously pass the eroding gallstone(s) without any complications. However, if the stone measures >2.5 cm in greatest diameter, it may lodge in the bowel, producing symptoms of obstruction, perforation, or “gallstone ileus.” Peptic ulcers or duodenal carcinomas may also erode into the gallbladder or bile duct, forming a fistula. Primary fistulae between the abdominal aorta and the gut are rare and fatal. *Aortoenteric fistulae* usually result from disorders involving either the aorta (usually atherosclerosis or following the insertion of an aortic bypass graft) or the GI tract (cancer, peptic disease, infections, or trauma). Fistulae may also develop in an ulcerating disease, regardless of the etiology.
Perforations

Intestinal perforations occur spontaneously or following trauma. The basis of the perforations differs from country to country. In countries with poor hygiene, underlying infectious diseases, including typhoid ulcers, intestinal tuberculosis, and parasitic diseases, result in perforation. In Western countries, foreign bodies, ischemia, Crohn disease, tumors, diverticula, trauma, and radiation therapy represent the most common causes of perforation.
Adhesions

Any time the peritoneal or serosal surfaces of the bowel become inflamed, fibrous or fibrinous bands can form causing loops of bowel to become adherent to one another (Fig. 6.80) or to become adherent to any peritoneal surface. Adhesions commonly complicate previous transmural small intestinal inflammation as seen in ischemia, perforation, Crohn disease, previous surgery, or radiation therapy. Intestinal obstruction, volvulus, and ischemia all complicate adhesions. The adhesions appear as strands of variably fibrotic or inflamed tissue on the serosal aspect of the bowel wall. These changes may associate with variable degrees of mesothelial hyperplasia.

Stenosis of the Ampulla of Vater (Papillary Stenosis)

Papillary stenosis complicates impacted gallstones, biliary tract infections, inflammation of the ampulla, previous endoscopic retrograde cholangiopancreatography, endoscopic sphincterotomy, and heterotopic pancreas. Traumatizing the papillae by repeated attempts at cannulation leads to edema and sphincter spasm and temporarily occludes the outflow of pancreatic juice, thereby increasing the intrapancreatic pressure and the risk of complications. Most patients are middle-aged women.
FIG. 6.78. Volvulus. A: The intestines rotated around an intestinal band, causing infarction of both the large and small intestine. B: Acute coagulative necrosis. The tissues lack an inflammatory response.

The histologic features of papillary stenosis include edema with acute and/or chronic inflammation, glandular hyperplasia, granulation tissue, granulomatous inflammation, and submucosal fibrosis (Fig. 6.81). One often sees a hyperplastic, regenerative mucosa with marked atypia. One must be careful to avoid making a diagnosis of malignancy in this setting unless all of the histologic features of unequivocal malignancy are present. The presence of a desmoplastic response suggests that cancer is present. However, as a note of caution, healed diverticulitis may associate with a fibrotic response. One should be especially wary of establishing a diagnosis of malignancy if one sees evidence of acute and chronic inflammation, marked hyperplasia, and/or stromal edema (Fig. 6.81).
**FIG. 6.79.** Volvulus around intestinal band. *A:* This adult died from gangrenous necrosis of the small bowel. The cause of the necrosis was a torsion and volvulus around a congenital band demonstrated by the linear structure lying next to the thumb (*arrow*). *B:* The tissues are spread apart to show the bands and adhesions between various intra-abdominal structures.

**FIG. 6.80.** Adhesions. *A:* Opened abdomen in a child with necrotizing enterocolitis. The bowel is dusky and appears hemorrhagic and infarcted. Additionally, fibrinous adhesions attach the bowel loops to one another. The bubbly areas are patches of pneumatosis intestinalis. *B:* Well-formed fibrous adhesions in a patient with previous surgeries.

**Other Stenoses**

Small intestinal stenosis complicates a number of conditions, including heterotopic pancreas; ischemia; peptic injury; radiation; drug injury, especially nonsteroidal anti-inflammatory drugs (NSAIDs); Crohn disease; infections; and trauma.
Autoimmune Enteropathy

Autoimmune enteropathy is a life-threatening disorder of infancy that almost exclusively affects males. It is characterized by intractable diarrhea and a constellation of associated autoimmune diseases, including membranous glomerulonephritis, insulin-dependent diabetes, hemolytic or sideroblastic anemia, autoimmune hepatitis, sclerosing cholangitis, and hypothyroidism (553). Infants present with unexplained episodes of protracted diarrhea and no response to dietary therapy. The disease can also occur in adults (553).

Infants with autoimmune enteropathy demonstrate circulating antienterocyte antibodies (554). The autoantigen is a 75-kD protein encoded on chromosome 19p13, with homology to the tumor suppressor gene MCC. It has therefore been named MCC2 (555). A subset of patients suffers from the systemic familial syndrome of autoimmunity: IPEX (immune dysregulation, polyendocrinopathy, and X-linkage) syndrome. This syndrome is also referred to as XLAD (X-linked autoimmunity and allergic dysregulation) (556). All patients with this syndrome develop autoimmune enteropathy. The IPEX syndrome results from germline mutations in the FOXP3 gene on the X chromosome (557). FOXP3 controls the development of regulatory CD4+ CD25+ T cells that are essential for maintenance of tolerance to self-tissues. The small intestinal lamina propria normally contains a CD25+ FOXP3+ CD4+ cells (558).

Small bowel biopsies show partial or complete villous atrophy, crypt hypertrophy, mononuclear cell infiltrates in the lamina propria, and increased expression of MHC class II antigens (559). Only a subset of patients has an immunodeficiency, even though the etiology is thought to be related to abnormal T-cell or B-cell regulation. Some patients demonstrate associated IgA deficiencies and T-cell abnormalities. There is a recently described patient with a severe FOXP3+ and CD4+ and CD8+ naïve T-cell lymphopenia who developed a non-IPEX form of autoimmune enteropathy combined with immunodeficiencies and recurrent infections (560).

The histologic features may be surprisingly subtle or they may be severe and involve both the large and small intestines (Fig. 6.201). The changes may be patchy in their distribution. Often, the most consistent feature is a nonspecific increase in lymphocytes involving both the epithelium and the lamina propria (Fig. 6.201). The IELs differ from those present in celiac disease in that they lack γδT-cell receptors and they tend to infiltrate the deep crypts rather than the surface epithelium. There may also be mild villous atrophy and crypt hyperplasia or crypt disorganization and increased apoptoses (561), producing a pattern reminiscent of graft versus host disease. Pyloric metaplasia may be present. Autoimmune enteropathy is often refractory to treatment, and is potentially fatal. Tacrolimus treatment may lead to a partial remission of the disease (562).
FIG. 6.201. Autoimmune enterocolitis. A: Duodenal biopsy demonstrating the presence of mild villous atrophy and a very minimal infiltrate of lymphocytes within the epithelium. B: Colonic biopsy in the same patient showing a mild increase in cells in the lamina propria and mild regenerative features with a barely noticeable increase in intraepithelial lymphocytes.
Benign Lesions Presenting Clinically as Masses

Various polyp types occur in the small intestine including lesions normally thought of as polyps, such as adenomas or Peutz-Jeghers polyps, as well as other lesions presenting as polypoid masses (Table 6.57). Most polypoid lesions remain asymptomatic and are detected either endoscopically or radiographically. Symptomatic lesions cause bleeding, obstruction, or intussusception. Uncommonly, the whole GI tract, including the small intestine, is affected by a polyposis syndrome, including juvenile polyposis and Peutz-Jeghers syndrome (see Chapter 12).

FIG. 6.237. Histology of pneumatosis. Figure shows variably sized, air-filled cysts in a mucosal biopsy.

Inflammatory polyps assume two major forms: Those associated with inflammatory bowel disease (see Chapter 11) and inflammatory fibroid polyps (IFPs). IFPs develop in all age groups and usually arise in the stomach. The small intestine represents the second most common site of origin. Lesions in the small bowel present with intussusception (648), chronic diarrhea, or obstruction. These lesions are inflammatory reactive proliferations of CD34+ perivascular cells (649). The pathologic features (Fig. 6.239) of this lesion are extensively discussed in Chapter 4.
**FIG. 6.238.** Pneumatosis intestinalis. Typical macrophage and giant cell lining of a cyst.

**TABLE 6.57 Lesions Presenting as Small Intestinal Polyps**

<table>
<thead>
<tr>
<th>Lesions Presenting as Small Intestinal Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory polyps</td>
</tr>
<tr>
<td>Inflammatory fibroid polyps</td>
</tr>
<tr>
<td>Peutz-Jeghers polyps</td>
</tr>
<tr>
<td>Juvenile polyps</td>
</tr>
<tr>
<td>Lymphoid polyps</td>
</tr>
<tr>
<td>Adenomas</td>
</tr>
<tr>
<td>Heterotopic tissues</td>
</tr>
<tr>
<td>Gastric</td>
</tr>
<tr>
<td>Pancreatic</td>
</tr>
<tr>
<td>Neoplasms</td>
</tr>
<tr>
<td>Lipomas</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors</td>
</tr>
<tr>
<td>Lymphangiomas</td>
</tr>
<tr>
<td>Hemangiomas</td>
</tr>
</tbody>
</table>
Benign Lesions Presenting Clinically as Masses

Reactive fibromuscular proliferative lesions consisting of exuberant smooth muscle cell and neural proliferations arise in the small intestinal wall. The smooth muscle fascicles are haphazardly arranged with clusters of ganglion cells, ectatic lymphatic and vascular channels, and fibrous tissues. The smooth muscle bundles merge imperceptibly with the muscularis mucosae. These lesions complicate other disorders, such as inflammatory bowel disease. They produce polypoid lesions covered by smooth, normal-appearing mucosa. They vary in size from several millimeters in diameter to 3 or 4 cm. The lesions arise from a damaged muscularis mucosae to represent an exuberant reparative response. Evidence supporting a reparative process is twofold: (a) the lesion often complicates other diseases and (b) the proliferation involves multiple cell types, including inflammatory cells.

Patients with motility disorders, especially those who have had recurrent intussusceptions, sometimes develop what appear to be polypoid lesions, which, when examined, simulate a papillary adenoma. However, histologic examination discloses the presence of accordionlike folds consisting of the normal mucosal layers. The central core of the fold contains submucosa herniated upward. Often one sees evidence of previous intussusception by examining the muscularis propria or the vessels in the subserosal area.

Inflammatory pseudotumors develop on the serosal surfaces of intestinal sites of transmural inflammation, particularly in Crohn disease, *Yersinia* infections, and tuberculous infections as well as volvulus and intussusception. The presence of a marked inflammatory response protects the bowel from perforation. The reactive proliferations consist of fibroblasts, blood vessels, and variable numbers of inflammatory cells. The overall cellu

**FIG. 6.239.** Inflammatory fibroid polyp. *A:* α₁-Antitrypsin immunostain showing the presence of numerous cells with a mesenchymal histiocytic phenotype. *B:* CD34 immunostain showing the presence of numerous vessels.
larity of the lesion, its myxoid appearance, its vascularity, and the nature of the inflammatory cells vary depending on the age of the lesion and distinguish the inflammatory process from a neoplasm. Fat necrosis is also often present (Fig. 6.240).

**FIG. 6.240.** Fat necrosis in the small intestinal serosal fat. *A:* Low magnification showing the presence of lobulated structures demonstrating fat necrosis. *B:* Higher magnification showing the presence of fat cells surrounded by histiocytes and giant cells.
Blood Supply

The duodenum is supplied by the celiac and superior mesenteric arteries (Fig. 6.11). The celiac trunk branches into the gastroduodenal artery. The superior mesenteric artery supplies the jejunum, cecum, and appendix, traveling through the mesentery in several major branches (Fig. 6.12). Ten to fifteen jejunoileal arteries arise from the left side of the superior mesenteric artery, which originates 1 to 2 cm below the celiac artery. Each divides into two branches, which join adjacent branches to form a series of arcades. These in turn branch and form a second series of arcades before the vasa recta penetrate the intestinal wall (33). The ileocolic artery, which arises from the lower superior mesenteric artery, supplies the terminal ileum, cecum, appendix, and proximal ascending colon. It anastomoses with the right colic artery. This and subsequent branches form complex arcades.

**FIG. 6.10.** Normal small intestine. A: The surface of the small intestine is covered by numerous regular folds (plicae circulares) with a submucosal core. B: Convolutions of mucosa and submucosa are the histologic equivalent of the folds of Kerckring.

**FIG. 6.11.** Diagram of duodenal arterial supply.
Intramural arteries enter the intestinal serosa and pierce the muscularis propria to form an extensive submucosal vascular plexus (Fig. 6.13). The submucosal arterial plexus gives rise to arterioles, which supply the mucosa, submucosa, and muscular layers. However, the mucosal capillary bed is isolated from that of the muscularis propria. The capillary bed in the muscularis mucosae has two layers (34). These two groups of arteries make their way into the mucosa. Some ramify on the luminal side of the muscularis mucosae and give rise to a capillary network that surrounds the crypts. Others continue into the villus, entering it at its base before arborizing into a dense capillary network. A rich network of blood capillaries ramifies through the lamina propria and is closely apposed to the epithelial basement membranes (Figs. 6.14 and 6.15). Villi are more highly vascularized than are the crypts (35). The mucosa receives approximately 75% of the blood flow. The bowel can autoregulate its blood flow, which means that it maintains a constant blood flow in the face of fluctuating arterial pressures. Following eating, small intestinal blood flow increases by over 100%, with the majority of the blood flow being diverted to the mucosa.

![FIG. 6.12. Distribution of superior mesenteric artery.](image)

Villous capillaries drain into a single venule that starts high in the villus. One or two veins form in each villus. These course downward, eventually joining veins at the crypt bases and merging with veins draining into the submucosal plexus. These vessels continue on through the muscularis propria and serosa, merging with other veins draining into the portal vein via the superior mesenteric vein. The superior mesenteric vein receives its drainage from the distal duodenum, jejunum, ileum, appendix, and cecum, as well as the ascending and transverse colon. Venous drainage of the duodenum parallels its arterial supply. Inferior pancreaticoduodenal veins drain to the right gastroepiploic vein. The major veins draining the GI tract form the portal system (Fig. 6.16). The portal vein forms by the junction of the splenic vein and the superior mesenteric vein. The portal
Blood Supply

vein receives direct input from the right and left gastric veins, superior pancreaticoduodenal vein, accessory pancreatic vein, and pyloric vein. Blood in the portal vein is carried to the liver, where nutrients are absorbed and processed.

FIG. 6.13. Diagram of the submucosal vascular plexus.
FIG. 6.14. Diagram of distribution of arteries (red), veins (blue), lymphatics (yellow), and nerves (green) in the small intestine.
FIG. 6.15. Dilated capillaries in a small intestinal villus showing the prominent capillary structure.
FIG. 6.16. Diagram of the portal system.
Celiac Disease

Celiac disease (CD), also known as gluten-sensitive enteropathy and celiac sprue, is a malabsorptive disease in which the intestinal mucosa is injured as a result of ingestion of gluten-containing foods in genetically predisposed individuals. Withdrawal of dietary gluten causes prompt improvement of nutrient absorption and improvement of the characteristic mucosal lesions unless refractory sprue has developed.

Epidemiology

Celiac disease is the most common cause of malabsorption in Western populations. The prevalence of CD in Europe and North America is 0.5% to 1% (489,490,491). Celiac disease is rare in Japanese, Chinese, and African patients. The disorder is more common in women than men. It is now recognized that there is a substantial number of undiagnosed cases in the general population possibly ten times as many as actually have been diagnosed (492).

Celiac disease appears to have a strong genetic component, demonstrating a higher incidence in siblings than in the general population (493). There is 70% concordance for CD in identical twins (494). About 10% of first-degree relatives of celiac patients also have the disease (495), although a significant proportion (about 50%) remain asymptomatic and are said to have latent CD.

The incidence of CD increases 10- to 30-fold in patients with other autoimmune disorders when compared with the normal population (496).

Pathogenesis

Celiac disease has a complex etiology that results from the interaction of environmental agents, genetic predispositions, and immunologic factors (497).

Gluten and Other Prolamines

Celiac disease is an autoimmune enteropathy triggered by ingestion of wheat gluten (gliadins), barley (hordeins), rye (secalins), and possibly oats (avenins). Gluten is found in grains such as wheat and buckwheat. Gluten is also found in many processed foods such as gravies, sausage, beer, ale, bread, and bread products. It can be separated electrophoretically into four major fractions: α-, β-, γ-, and v-gliadins. Gliadins are prolamines with a high proline and glutamic acid content. All four types appear to be toxic, although α-gliadin is the most pathogenic (498). Toxic gliadins contain pro-ser-gln-gln and gln-gln-gln-pro sequences. These sequences are absent from nontoxic peptides (499). A 33-mer peptide generated by digestion of α-gliadin by intestinal enzymes is highly stimulatory for CD4+ T cells (500). This peptide is resistant to further digestion by intestinal brush border enzymes and is a highly specific substrate for deamidation by tissue trans-glutaminase. This 33-mer peptide is not present in cereal proteins that do not cause CD.

CD may be triggered in genetically susceptible individuals by activation of the immune system by a virus, usually an adenovirus. Later the mucosal system mistakenly reacts against gliadins bound to the intestine. α-Gliadin contains an amino acid region that is homologous to the 54-kDa E1b protein coat of adenoviruses. In addition, CD patients have a significantly higher prevalence of past adenovirus 12 infections than control subjects (501).

CD has the strongest association of any illness with a specific class II HLA molecule. The disorder is triggered by an environmental insult (gluten consumption), and the HLA haplotype acts as a classic immune response gene that operates at either the T-cell or antigen-presenting cell level to favor gliadin-specific responses. The primary HLA association in most CD patients is with DQ2. Fewer patients are of haplotype DQ8. An increased risk for CD also exists among individuals who are DR3-DQ2 homozygous and DR3-DQ2/DR7-DQ2 heterozygous (497).

In addition to the HLA linkage, CD has also been linked to several other chromosomal regions. Linkage to 2q33, an area of regulation for T-lymphocyte activation, has been seen in a Finnish family (502). Linkage to other regions on other chromosomes has also been reported, but linkage to 5p31-33 is the most consistently identified (497).

Gluten-reactive T cells can be isolated from small intestinal biopsies of celiac patients but not from nonceliac controls. These T cells are CD4+ and express the α/β TCR. A number of distinct T-cell epitopes within gluten exist. Lamina propria antigen-presenting cells that express HLA-DQ2 or -DQ8 present gliadin peptides bound to their α/β heterodimer antigen, presenting grooves to sensitized T lymphocytes that express the α/β TCR. These lymphocytes then activate B lymphocytes to produce immunoglobulins and stimulate other T cells to produce cytokines including interferon (IFN)-γ, IL-4, IL-5, IL-6, IL-10, IL-15, tumor necrosis factor (TNF)-α and TGF-β.

Tissue Transglutaminase and Other Autoantigens

Tissue transglutaminase (tTG) is expressed in many different tissues and is found both extra- and intracellularly. tTG is expressed just beneath the epithelium in the gut wall. Calcium-dependent tTG catalyzes selective cross-linking or deamidation of protein-bound glutamine residues. Deamidation of the glutamine residues of gliadin by tTG prepares the gliadin molecule to bind with HLA-DQ molecules (504). In addition, tTG can also cross-link glutamine residues of peptides to lysine residues in other proteins, including tTG itself. This may result in the formation of gluten--tTG complexes. These complexes may permit gluten-reactive T cells to stimulate tTG-specific B cells, thereby explaining the occurrence of gluten-dependent tTG autoantibodies that are a characteristic feature of active CD.

Furthermore, tTG-catalyzed cross-linking and consequent haptenization of gluten with extracellular matrix proteins allows for storage and extended availability of gluten in the mucosa. tTG is necessary for activation of TGF-β, which is involved in differentiation of intestinal epithelium, regulates IgA expression, and modulates immune responses (505). Antibodies to tTG in CD patients interfere with fibroblast-induced differentiation of epithelial cells, possibly by inhibiting the cross-linking activity of tTG.
Celiac Disease

**Cell-mediated and Antibody-mediated Immune Responses**

Gluten ingestion in untreated CD induces nonproliferative activation of CD4⁺ TCR-a/b- positive cells in the lamina propria accompanied by proliferative activation of intraepithelial lymphocytes (a/b- and g/b-positive T cells) in the epithelial compartment. CD patients harbor a population of DQ2⁺ (or DQ8⁺) antigen-presenting dendritic cells that efficiently capture and present deamidated gluten peptides leading to the activation of gluten-reactive T cells (506). Activated CD4⁺ T cells activate B lymphocytes and plasma cells that produce autoantibodies and T lymphocytes to secrete cytokines. These cytokines not only damage the enterocytes, but also induce expression of aberrant HLA class II cell surface antigens on the luminal surface of enterocytes, facilitating additional direct antigen presentation by these cells to the sensitized lymphocytes. Cytokines produced by DQ2- restricted T cells are of the Th1 type and are dominated by the secretion of IFN-γ. Cytokines produced by DQ8-restricted T cells have a Th0 profile. Increased γ/δ- cells in the epithelium and lamina propria of the small intestine have also been observed in CD patients, and these cells persist even after gluten withdrawal. These cells may play a protective role through activation of a nonspecific immune response that helps to lessen the antigen-specific immune response (497).

Celiac disease characteristically results in accumulation of IgA-, IgM-, and IgG-producing plasma cells within the mucosa. The antibodies produced by them are directed against gliadin, transglutaminase, endomysium, reticulin, and enterocyte actin. The exact physiologic role of these antibodies is still unclear. Recent evidence also suggests that gliadin or its metabolites may directly injure the intestinal mucosa. Up-regulation of mucosal HLA-DR and intercellular adhesion molecule within 2 hours of in vitro exposure to gliadin suggests an early effect that may not be immune mediated (507). This early effect is followed by activation of CD4⁺ CD25⁺ T cells, producing the immunologic injury. There may also be a role for intraepithelial lymphocytes in the pathogenesis of CD (508). In fact, these cells may play a key role in the development of refractory sprue and the development of enteropathy-associated T-cell lymphomas (509).

**Clinical Features**

Celiac disease is well known to be associated with gastrointestinal manifestations and malabsorption. However, over the years there has been increasing awareness of nongastrointestinal manifestations of the disease such as osteoporosis, cancer, and infertility. The clinical spectrum of CD is diverse and includes the following forms:

- **Typical CD**: This is fully expressed gluten-sensitive enteropathy associated with classic features of malabsorption. The full expression includes positive serology for endomysial and tTG antibodies and a diagnostic biopsy. This form of the disease usually affects younger patients.

- **Atypical CD**: This is fully expressed gluten-sensitive enteropathy found in association with atypical manifestations including short stature, anemia, infertility, etc.

- **Latent CD**: Patients have normal small bowel villous architecture on biopsy, but villous atrophy develops later on. Two variants have been described. The first includes patients in whom CD was diagnosed in childhood and who recovered completely with a gluten-free diet. The disease then remains latent in these individuals even after a normal diet is adopted. In the second variant, a normal mucosa is present in early biopsies while the patient is consuming gluten, but more typical features of CD develop later. The conversion of the latent state to active disease is often precipitated by nutritional deficiencies, by the effects or complications of a tumor, or by other environmental triggers, especially intracellular infections, changes in the environment, or physiologically imposed stresses such as surgery, trauma, or pregnancy. Such patients exhibit abnormal jejunal permeability and high levels of antiendomysial antibodies. Such patients may have increased numbers of IELs in their biopsies (510) in the absence of villous changes.

- **Potential CD**: This includes patients who never had biopsy changes but have characteristic serologic abnormalities. HLA-DQ2 is more frequent in these patients and they frequently have a first-degree relative affected by CD.

- **Silent CD**: This includes asymptomatic patients with positive serologic autoantibodies and diagnostic biopsy.

- **Refractory CD**: These patients have severe, symptomatic, intestinal atrophy not responding to at least 6 months of a strict gluten-free diet. The clinical presentation of any given patient with CD depends on the severity of the damage and patient age at presentation. The classic presentation of CD is that of steatorrhea with abdominal cramps and vomiting. In infants, the symptoms begin after weaning, when cereals are first introduced into the diet. Signs of nutritional deficiency, such as anemia, are the next most common presenting findings affecting children. Other manifestations include growth retardation, failure to thrive, short stature, muscle wasting, hypotonia, abdominal distension, and watery diarrhea. Celiac disease should be suspected in children with mild GI symptoms who have signs of nutritional deficiencies or a first-degree relative with celiac disease. It should also be suspected in children with IgA deficiency, dental enamel hypoplasia, or dermatitis herpetiformis or in children who have other diseases known to be associated with celiac disease (Table 6.35).

**TABLE 6.35 Diseases Commonly Associated with Gluten-sensitive Enteropathy**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated with Gluten-sensitive Enteropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory CD</td>
<td>These patients have severe, symptomatic, intestinal atrophy not responding to at least 6 months of a strict gluten-free diet.</td>
</tr>
<tr>
<td>Latent CD</td>
<td>Patients have normal small bowel villous architecture on biopsy, but villous atrophy develops later on. Two variants have been described. The first includes patients in whom CD was diagnosed in childhood and who recovered completely with a gluten-free diet. The disease then remains latent in these individuals even after a normal diet is adopted. In the second variant, a normal mucosa is present in early biopsies while the patient is consuming gluten, but more typical features of CD develop later. The conversion of the latent state to active disease is often precipitated by nutritional deficiencies, by the effects or complications of a tumor, or by other environmental triggers, especially intracellular infections, changes in the environment, or physiologically imposed stresses such as surgery, trauma, or pregnancy. Such patients exhibit abnormal jejunal permeability and high levels of antiendomysial antibodies. Such patients may have increased numbers of IELs in their biopsies (510) in the absence of villous changes.</td>
</tr>
<tr>
<td>Potential CD</td>
<td>This includes patients who never had biopsy changes but have characteristic serologic abnormalities. HLA-DQ2 is more frequent in these patients and they frequently have a first-degree relative affected by CD.</td>
</tr>
<tr>
<td>Typical CD</td>
<td>This is fully expressed gluten-sensitive enteropathy associated with classic features of malabsorption. The full expression includes positive serology for endomysial and tTG antibodies and a diagnostic biopsy. This form of the disease usually affects younger patients.</td>
</tr>
<tr>
<td>Atypical CD</td>
<td>This is fully expressed gluten-sensitive enteropathy found in association with atypical manifestations including short stature, anemia, infertility, etc.</td>
</tr>
<tr>
<td>Latent CD</td>
<td>Patients have normal small bowel villous architecture on biopsy, but villous atrophy develops later on. Two variants have been described. The first includes patients in whom CD was diagnosed in childhood and who recovered completely with a gluten-free diet. The disease then remains latent in these individuals even after a normal diet is adopted. In the second variant, a normal mucosa is present in early biopsies while the patient is consuming gluten, but more typical features of CD develop later. The conversion of the latent state to active disease is often precipitated by nutritional deficiencies, by the effects or complications of a tumor, or by other environmental triggers, especially intracellular infections, changes in the environment, or physiologically imposed stresses such as surgery, trauma, or pregnancy. Such patients exhibit abnormal jejunal permeability and high levels of antiendomysial antibodies. Such patients may have increased numbers of IELs in their biopsies (510) in the absence of villous changes.</td>
</tr>
<tr>
<td>Potential CD</td>
<td>This includes patients who never had biopsy changes but have characteristic serologic abnormalities. HLA-DQ2 is more frequent in these patients and they frequently have a first-degree relative affected by CD.</td>
</tr>
<tr>
<td>Silent CD</td>
<td>This includes asymptomatic patients with positive serologic autoantibodies and diagnostic biopsy.</td>
</tr>
<tr>
<td>Refractory CD</td>
<td>These patients have severe, symptomatic, intestinal atrophy not responding to at least 6 months of a strict gluten-free diet. The clinical presentation of any given patient with CD depends on the severity of the damage and patient age at presentation. The classic presentation of CD is that of steatorrhea with abdominal cramps and vomiting. In infants, the symptoms begin after weaning, when cereals are first introduced into the diet. Signs of nutritional deficiency, such as anemia, are the next most common presenting findings affecting children. Other manifestations include growth retardation, failure to thrive, short stature, muscle wasting, hypotonia, abdominal distension, and watery diarrhea. Celiac disease should be suspected in children with mild GI symptoms who have signs of nutritional deficiencies or a first-degree relative with celiac disease. It should also be suspected in children with IgA deficiency, dental enamel hypoplasia, or dermatitis herpetiformis or in children who have other diseases known to be associated with celiac disease (Table 6.35).</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
</tr>
<tr>
<td>Sarcoid</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td></td>
</tr>
<tr>
<td>Autoimmune chronic active hepatitis</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Dental enamel defects</td>
<td></td>
</tr>
<tr>
<td>Pseudohypoaldosteronemia</td>
<td></td>
</tr>
<tr>
<td>Selective Ig deficiency</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td></td>
</tr>
<tr>
<td>Splenic atrophy</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral calcifications</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td>Floating harbor syndrome</td>
<td></td>
</tr>
<tr>
<td>Speech impediment</td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td></td>
</tr>
<tr>
<td>Short stature</td>
<td></td>
</tr>
<tr>
<td>Facial anomalies</td>
<td></td>
</tr>
<tr>
<td>Polyglandular autoimmune syndrome III</td>
<td></td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td></td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td></td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Sarcoid</td>
<td></td>
</tr>
<tr>
<td>Autoimmune eye lesions</td>
<td></td>
</tr>
<tr>
<td>Choroiditis</td>
<td></td>
</tr>
<tr>
<td>Papillitis</td>
<td></td>
</tr>
<tr>
<td>Lung lesions</td>
<td></td>
</tr>
<tr>
<td>Cavitary lung lesions</td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td></td>
</tr>
<tr>
<td>Interstitial pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td>Alopecia areata</td>
<td></td>
</tr>
<tr>
<td>α₁-Antitrypsin deficiency</td>
<td></td>
</tr>
<tr>
<td>Cavitary lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Tumors</td>
<td></td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>Small intestinal carcinoma</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td></td>
</tr>
</tbody>
</table>
Celiac disease in adults is most often diagnosed in the 3rd and 4th decades of life, but it may develop at any age. Approximately 20% of cases are diagnosed in individuals over the age of 60. Women are more frequently affected than men and are generally diagnosed at a younger age. Many adults with CD present with diarrhea, but as many as 50% do not. The classic presentation includes prolonged diarrhea, flatulence, weight loss, and fatigue. The degree of weight loss reflects the severity of the steatorrhea and an individual's ability to compensate for the nutritional deficit by increasing caloric intake. Patients with celiac disease may only have subtle signs of chronic malnutrition or nonspecific GI complaints. Patients may also present with anemia, short stature, nutritional deficiencies, or motility disturbances in the absence of diarrhea. Since the introduction of highly sensitive autoantibody tests, the number of patients presenting with classic features of CD has decreased. In fact, iron deficiency anemia, formerly regarded as an atypical presenting sign, is now the most common presentation of adult patients with CD.

Iron deficiency is primarily due to iron malabsorption. Changes attributable to malabsorption and mineral, vitamin, and other essential nutrient deficiencies are listed in Table 6.36. The clinical presentation often reflects the degree of malabsorption present. Atypical presentations include neurologic manifestations, osteopenia, and dermatitis herpetiformis without gastrointestinal manifestations. The most common neurologic finding is ataxia followed by epilepsy, cerebral calcification, cerebral white matter lesions on magnetic resonance imaging (MRI), myelopathy, peripheral neuropathy, seizures, and myopathy. CD also associates with an adverse fetal outcome in women with undiagnosed CD. Gastrointestinal bleeding occurs occasionally, and may represent an indicator of complications such as ulcerative jejunoileitis or malignancy.

Other extraintestinal features of the disease include vague abdominal pain, bone disease, abnormal peripheral blood smear findings, infertility (both male and female), amenorrhea, recurrent abortion or low-birth-weight babies, and hypoglycemia. Up to 8% of patients are detected due to mucosal changes on duodenal endoscopy performed for other conditions. From 7% to 15% of patients are detected through serum antibody tests performed because of a family history of CD.

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Hemorrhage, hemolysis</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>Anemia</td>
</tr>
<tr>
<td>Calcium</td>
<td>Osteomalacia, bone pain, compression fractures</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Night blindness</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Follicular hyperkeratosis of the skin</td>
</tr>
<tr>
<td>Vitamin B</td>
<td>Neuropathies</td>
</tr>
<tr>
<td>Pituitary, adrenal, parathyroid</td>
<td>Endocrine gland hypofunction</td>
</tr>
</tbody>
</table>

Symptoms and histologic features improve while the patient follows a gluten-free diet. Gluten rechallenge causes symptom recurrence in many patients with uncertain diagnoses, especially those patients who lack typical GI symptoms.

Associated Diseases

Table 6.35 shows the wide variety of systemic diseases that are associated with celiac disease. Dermatitis herpetiformis and CD both associate with IgA-mediated epithelial injury. Initially, dermatitis herpetiformis was considered a skin disease occurring often concomitantly with CD, but currently it is believed that dermatitis herpetiformis is a cutaneous manifestation of celiac disease, affecting approximately 25% of patients. tTG also represents the autoantigen in dermatitis herpetiformis. Dietary restriction is essential in the treatment of both conditions.
Another IgA-mediated autoimmune disease associated with CD is IgA nephropathy. Patients with IgA nephropathy carry a risk of contracting CD. However, there is no increase in CD-type HLA-DQ in IgA nephropathy patients. It has been hypothesized that the increased intestinal permeability in IgA nephropathy may predispose genetically susceptible patients to celiac disease. A wide spectrum of hepatobiliary diseases occurs in association with CD, including asymptomatic elevations of liver enzymes, nonspecific hepatitis, nonalcoholic fatty liver disease, and autoimmune and cholestatic liver disease (516). Increased alanine aminotransferase, aspartate aminotransferase, and/or alkaline phosphatase are seen in up to 47% of celiacs (516). Two main mechanisms underlying the development of the liver damage have been proposed. First, CD may result in increased intestinal permeability to toxins and antigens injurious to the liver. Second, chronic intestinal mucosal inflammation may represent a primary trigger. Prompt diagnosis and dietary treatment may prevent the progression to hepatic failure in patients with severe liver disease (517).

Associated autoimmune disorders include insulin-dependent diabetes, autoimmune thyroid disease, Addison disease, Sjögren syndrome, alopecia areata, and rheumatoid arthritis. Approximately 5% of insulin-dependent diabetics have associated CD, and one third of insulin-dependent diabetics with DQ2 have CD (518). The prevalence of the autoimmune disorders is related to the duration of the exposure to gluten (519). It is possible that chronic autoimmune stimulation of lymphocytes in the intestine predisposes to increased formation of other autoantibodies. Another important association is with trisomy 21 (Down syndrome). The prevalence of CD is 20 times that of the general population in patients with Down syndrome. Some patients with CD develop lymphocytic colitis and/or lymphocytic gastritis (see Chapters 4 and 13). Patients with CD and microscopic colitis share certain predisposing HLA-DQ genes. However, these are not exactly related conditions. The intraepithelial lymphocytes in lymphocytic colitis are predominantly CD8+, unlike the IELs of CD. In addition, epithelial abnormalities and increased mononuclear inflammation are more prevalent in lymphocytic colitis than in CD patients. Furthermore, the watery diarrhea that is characteristic of lymphocytic colitis often does not respond to a gluten-free diet.

Patients with CD have an increased risk of cancer including lymphomas, oropharyngeal carcinomas, esophageal carcinoma, and small intestinal adenocarcinoma (520). There is also a small increased risk of colorectal carcinoma and liver cancer (520). Indeed, the primary cause of mortality in CD is malignancy (521). Abnormal lymphoid proliferations and lymphomas represent the most common malignant complication of celiac disease, affecting 5% to 10% of patients (522). An average of 8 years of celiac disease precedes the discovery of the malignant lymphoma, but both diseases may be discovered simultaneously or a diagnosis of celiac disease may follow the lymphoma diagnosis (522). Most celiac disease–associated lymphomas derive from mucosal T cells (521) and celiac disease is the most common setting in which enteropathy-associated T-cell lymphoma (EATL) is likely to occur. There is good evidence that uncontrolled IL-15 overexpression promotes the emergence of clonal T-cell proliferations (523). A strict gluten-free diet may lead to decreased cancer incidence and increased survival (521). An example of a duodenal somatostatinomas has also been reported in the setting of CD (524).

Diagnosis of Celiac Disease

The single most important step in diagnosing CD is to consider the disorder by recognizing its myriad clinical features. There is no one test that can definitively diagnose or exclude celiac disease in every individual. Just as there is a clinical spectrum of CD, there is also a continuum of laboratory and histopathologic results. IgA endomysial antibody and IgA tissue transglutaminase antibody are based on the target antigen tTG. Antibodies bind to connective tissue surrounding smooth muscle cells (525). In the laboratory, IgA endomysial antibody (EMA) is most often detected by indirect immunofluorescence examination of sections of human umbilical cord. The test is reported as either positive or negative. The IgA endomysial antibody test has a sensitivity of 85% to 90% and a specificity of 97% to 100% (525). Antibody levels decrease when the patient is placed on a gluten-free diet, and may become undetectable in treated patients (526). The sensitivity of this test is lower in children younger than 2 years of age than in older patients.

*IgA tTG antibodies* are detected by an automated enzyme-linked immunosorbent test. This test is less expensive and easier to perform than the test used to detect IgA endomysial antibodies. IgA tTG has a sensitivity of 95% to 98% and a specificity of 94% to 95% (512). Like endomysial antibody tests, sensitivity is lower in children younger than 2 to 3 years of age.

The IgA antigliadin assay has a sensitivity of 75% to 90% and a specificity of 82% to 95%. The IgG antigliadin assay has a sensitivity of 69% to 85% and a specificity of 73% to 90% (512). Most reports suggest that tests for antigliadin antibodies are more sensitive than EMA studies in infants and children younger than 2 to 3 years of age. High antigliadin antibody levels, however, have been reported in some normal individuals (527).

IgA endomysial antibodies and IgA tTG are used interchangeably as first-line tests for the diagnosis of celiac disease. In patients with IgA deficiency, IgG tTG testing is recommended as the first-line serologic test. Antibody levels decrease during treatment with a gluten-free diet and are useful in assessing dietary compliance. An IgA antigliadin antibody test is the most commonly used marker to monitor response to a gluten-free diet. A normal baseline value is reached within 3 to 6 months of dietary restriction. Currently, experience with IgA tTG in assessing dietary response is limited.

In a patient with suggestive symptoms and a negative serology test, three scenarios are possible: (a) the patient does not have CD, (b) the patient may have a selective IgA deficiency, and (c) the test is a “false negative” and should be repeated.
Other Laboratory Tests

Biochemical tests to be performed in the evaluation of CD patients include serum iron, folate, albumin, calcium, and potassium. Liver function studies should also be performed since serum transaminases are elevated in up to 40% of patients with untreated CD (516). Peripheral blood smears show features of iron deficiency anemia in the form of hypochromic microcytic anemia with low mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Many target cells, siderocytes, Heinz bodies, and Howell-Jolly bodies are seen in patients with splenic atrophy. Patients with folic acid or vitamin B₁₂ (unusual) deficiency will show macrocytosis and ovalocytosis with hypersegmented neutrophils on peripheral blood smears.

Microscopic stool examination to detect steatorrhea as a screening test for malabsorption is useful in the early stages of patient evaluation. Quantitative estimation of stool fat content is necessary to document steatorrhea. However, this and the D-xylose absorption test do not provide a specific diagnosis and are not routinely performed in the workup of celiac patients.

<table>
<thead>
<tr>
<th>Marsh Type</th>
<th>IEL/100 Surface Epithelial Cells</th>
<th>Crypts</th>
<th>Villi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0 (normal)</td>
<td>&lt;30–40</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Type I (infiltrative)</td>
<td>&gt;40</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Type II (hyperplastic)</td>
<td>&gt;40</td>
<td>Hyperplastic</td>
<td>Normal</td>
</tr>
<tr>
<td>Type IIIA (partial villous atrophy)</td>
<td>&gt;40</td>
<td>Hyperplastic</td>
<td>Mild atrophy</td>
</tr>
<tr>
<td>Type IIIB (subtotal villous atrophy)</td>
<td>&gt;40</td>
<td>Hyperplastic</td>
<td>Marked atrophy</td>
</tr>
<tr>
<td>Type IIIC (total villous atrophy)</td>
<td>&gt;40</td>
<td>Hyperplastic</td>
<td>Absent</td>
</tr>
<tr>
<td>Type IV (hypoplastic)</td>
<td>&gt;40</td>
<td>Hypoplastic</td>
<td>Absent</td>
</tr>
</tbody>
</table>

IEL, intraepithelial lymphocyte.

Endoscopic Findings

Endoscopic examination with biopsy is considered the "gold standard" for the diagnosis of celiac disease. Celiac disease can be patchy in its early stages and targeted biopsy of affected areas is necessary. Endoscopic findings include loss of villi, a mosaic mucosal pattern, scalloping of the duodenal folds, micronodularity, and visible vascularity. The endoscopic findings are not specific for CD, as similar changes may be seen in patients with eosinophilic gastroenteritis, giardiasis, tropical sprue, and other diseases (528). A biopsy is necessary to define the presence and extent of injury.

Histologic Features while on a Gluten-containing Diet

Small intestinal biopsies are used to diagnose or exclude celiac disease, to assess the severity of the damage, and to identify life-threatening complications of the disease. The presence of an abnormal biopsy while the patient is on his or her usual diet and improvement in the histologic features while he or she is on a gluten-free diet are diagnostic. Subsequent gluten challenge damages the mucosa. Since the histologic changes of CD are often patchy in their distribution, multiple biopsies from endoscopically normal and abnormal areas should be examined in order to establish the diagnosis. The histologic changes are most pronounced in the second and third parts of the duodenum. The microscopic features become less severe and patchier in the distal small bowel, particularly in the ileum.

Major histologic features of celiac disease include villous flattening, blunting, or absence; crypt hyperplasia; enterocyte degeneration; an intraepithelial lymphocytosis; and increased mononuclear cells and eosinophils in the lamina propria. However, the changes of celiac disease are not specific because similar lesions occur in patients with infections, allergies, and other immunologic conditions. Therefore, the pathology report should specify the degree of crypt hyperplasia and villous atrophy as well as assess the number of intraepithelial lymphocytes.

Standardization using the modified Marsh criteria (Table 6.37) facilitates communication with clinicians.

The histologic features vary depending on the presence or absence of gluten in the diet (Table 6.38). Two extremes of lesions occur in celiacs: A flat lesion with marked mucosal atrophy (Figs.
6.190 and Fig 6.191) and a relatively normal architecture with an intraepithelial lymphocytosis in the surface epithelium, with or without crypt hyperplasia and villous atrophy (Figs. 6.192 and 6.193). The histologic changes are highly characteristic, and when full-blown always suggest the diagnosis of celiac disease to the pathologist. However, this diagnosis should not be made purely on histologic findings because other diseases mimic CD (Table 6.39).

<table>
<thead>
<tr>
<th>TABLE 6.38 Histopathologic Features in Relation to Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On a normal diet</strong></td>
</tr>
<tr>
<td>● Malabsorption syndrome</td>
</tr>
<tr>
<td>● Flat jejunal biopsy (absent or severely blunted villi) with:</td>
</tr>
<tr>
<td>Damaged surface epithelium</td>
</tr>
<tr>
<td>Numerous intraepithelial lymphocytes</td>
</tr>
<tr>
<td>Chronic inflammation in lamina propria</td>
</tr>
<tr>
<td>Increased crypt mitoses</td>
</tr>
<tr>
<td>Crypts elongated (hyperplastic pattern)</td>
</tr>
<tr>
<td><strong>Short-term gluten-free diet</strong></td>
</tr>
<tr>
<td>● Early onset of clinical improvement</td>
</tr>
<tr>
<td>● Within days, evidence of diminished surface epithelial damage</td>
</tr>
<tr>
<td>● Reduced number of intraepithelial lymphocytes</td>
</tr>
<tr>
<td>● Reduced chronic inflammation</td>
</tr>
<tr>
<td>● Mild to moderate villous atrophy</td>
</tr>
<tr>
<td><strong>Gluten-free diet &gt;3 months</strong></td>
</tr>
</tbody>
</table>

Celiac Disease

- Villi gradually become normal
- No crypt hyperplasia
- Decreased mitoses
- Chronic inflammation diminished

Gluten challenge

- Early increase in intraepithelial lymphocytes and epithelium
- Eventual return of all lesions
- Malabsorption returns

**FIG. 6.191.** Celiac disease. *A:* Mild disease with blunted shortened villi and increased inflammatory cells. *B:* Blunted villi in celiac disease demonstrating more severe villous change than seen in A. Crypt hyperplasia is evident. *C:* Severe villous atrophy. A small portion of duodenum is seen.

The severity of the histologic changes does not correlate well with the clinical signs and symptoms. However, the extent of the small intestinal disease does correlate with the clinical severity of the disease. Celiac patients with severe villous atrophy can be asymptomatic provided that the length of small bowel involvement is short. On the other hand, minimal histologic changes involving a longer segment of intestine can be associated with clinical symptoms.
# TABLE 6.39 Conditions Associated with a Flat Mucosa That Mimic Celiac Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious gastroenteritis</td>
<td>Giardiasis</td>
</tr>
<tr>
<td>Cow's milk intolerance</td>
<td>Radiation enteropathy</td>
</tr>
<tr>
<td>Soy or soy protein sensitivity</td>
<td>AIDS enteropathy</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Crohn disease</td>
</tr>
<tr>
<td>Tropical sprue</td>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Kwashiorkor</td>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>Microvillous inclusion disease</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Familial enteropathy</td>
<td>Viral enteritis</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Bacterial overgrowth syndromes</td>
<td>Ischemic enteritis</td>
</tr>
<tr>
<td>Graft vs. host disease</td>
<td>Drug effects</td>
</tr>
<tr>
<td>Common variable hypogammaglobulinemia</td>
<td>Autoimmune enteritis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A hallmark of CD is intraepithelial lymphocytosis (Fig. 6.192) and may be seen in celiacs in the absence of villous atrophy. It is a sensitive marker of CD, particularly when the IELs lie evenly within the villi (529), but it has relatively low specificity, thereby limiting its usefulness. Disorders associated with elevated IEL counts are listed in Table 6.40. IEL counts should be performed on 3 to 4 micron, well-oriented sections. Normal small bowel epithelium contains up to 20 lymphocytes per 100 enterocytes on H&E-stained sections (530). Slightly greater numbers of lymphocytes may be observed in immunostained sections. Higher numbers of lymphocytes are also seen overlying lymphoid follicles and lymphoid aggregates. As a result, counts of intraepithelial lymphocytes should not be performed in these areas. According to the modified Marsh classification for the diagnosis of celiac disease (Table 6.37), a significant increase in intraepithelial lymphocytes is defined as more than 40 lymphocytes per 100 surface or upper crypt enterocytes. Some authors suggest that clustering of lymphocytes (>12) in the epithelium at the tips of the villi also strongly indicates the disease (529). Others have observed a significant increase in villous tip lymphocytes in early celiac disease compared to controls, but did not find any difference in distribution of intraepithelial lymphocytes between controls and patients with early celiac disease (531).

# TABLE 6.40 Disorders Associated with Increased Intraepithelial Lymphocytes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td><em>Helicobacter pylori</em> infection</td>
</tr>
<tr>
<td>Giardiasis</td>
<td>Collagen vascular diseases</td>
</tr>
<tr>
<td>HIV enteropathy</td>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>Lymphocytic enteritis</td>
</tr>
<tr>
<td>Blind loop syndrome</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Tropical sprue</td>
<td></td>
</tr>
<tr>
<td>Cow's milk protein intolerance</td>
<td>Viral infections</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>Luminal stasis</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Celiac Disease

FIG. 6.192. Celiac disease. The biopsy is hypercellular due to epithelial crowding and infiltration of the epithelium by T lymphocytes. The lamina propria contains a dense infiltrate of mononuclear cells and plasma cells.

Small bowel IELs consist of a heterogeneous population of T lymphocytes. In normal individuals, most IELs are CD3+ CD8+ T-cells, mostly TCR-αβ+, while CD4+ IELs are only a small component. In contrast, patients with untreated CD have an increase in CD3+ CD8- cells expressing TCRγδ. Since an intraepithelial lymphocytosis is not specifically diagnostic for CD, there may be a role for immunophenotyping of the IELs to show a preponderance of CD3+ CD8- cells (532).

Enterocytes show nonspecific changes in CD including attenuation of the brush border, a cuboidal appearance, supranuclear cytoplasmic vacuolation, cytoplasmic basophilia, loss of polarity, and loss of basal nuclear orientation. They may also become pseudostratified as the cells become more crowded together (Figs. 6.194 and 6.195). Surface erosion is uncommon, but can be seen in severe cases of CD. Goblet cells are normal or occasionally increased in number. The subepithelial basement membrane may appear normal or thickened. Early histologic changes include a slight shortening of the villous height with an apparent increase in the villous width. Enterocyte destruction, associated with a marked increase in enterocyte proliferation and turnover, causes the villous changes. A mucosal hyperkinetic state with increased crypt mitoses (sometimes abnormal ones) compensates for the surface damage, maintaining the total mucosal thickness early in the disease. The proliferative zone of the crypt is expanded and there is an increase in enterocyte mitotic activity. The enterocytes at the bases of the crypts appear regenerative and goblet cells are decreased in number. The accepted normal ratio of villous length:crypt depth is 1:3 or greater, usually being even 1:4 or 1:5. Ratios less than this are considered to represent villous atrophy. Endocrine cells and Paneth cells are often increased in number and irregularly distributed within the crypt (Fig. 6.196). These changes progress with increased mucosal flattening and expansion of the crypt cells. It has been postulated that the increase in endocrine cells is a selective process to meet the demands of a small intestinal mucosa with a decreased absorptive area. The endocrine cell hyperplasia may contribute to the diarrhea present in celiacs. Pyloric metaplasia may develop. Gastric metaplasia as evidenced by the presence of gastric markers in the goblet cells may occur in untreated pediatric celiacs (533).

Edema, vascular congestion, and variable degrees of lamina propria inflammation are present (Fig. 6.187). The inflammatory infiltrate consists predominantly of lymphocytes and plasma cells,
although eosinophils, mast cells, basophils, and, sometimes, neutrophils may also be seen. The presence of cryptitis and crypt abscesses are unusual in CD, and may point to another etiology such as infection or Crohn disease. IgA-, IgG-, and IgM-producing cells are increased two- to sixfold, with IgA-producing cells predominating. Patients with IgA deficiency and CD show a lower intensity of chronic inflammatory infiltration in the lamina propria. Lamina propria nerves may increase.

**Histologic Features on a Gluten-free Diet**

Morphologic recovery of the small intestine following consumption of a gluten-free diet and subsequent relapse upon gluten challenge represents the ultimate diagnostic criterion adopted by many. Repeat biopsies following gluten withdrawal usually demonstrate features of healing enteritis without evidence of active disease. If biopsies fail to return to normal, two alternatives should be considered: The patient is noncompliant with the dietary restriction or some other disease is present. Adults usually experience a prompt clinical improvement.

in their symptoms with gluten withdrawal and therefore fail to have a repeat biopsy following dietary modification. In contrast, children often have a more confusing diagnostic picture, and therefore biopsies are more regularly employed to evaluate the response to gluten withdrawal from the diet.

The most immediate effect of dietary gluten restriction is a change in the enterocytes lining the villi. As the mucosa heals, the inflammatory infiltrate decreases and the epithelial cells reassume their columnar shape and surface microvilli reappear. The cells become taller and one sees a progressive reduction in the number of intraepithelial lymphocytes. Patients clinically improve during this period of time. It takes villi several months to recover. If biopsies are obtained during the recovery period, the enterocytes may lack some of the classic features, including the intraepithelial lymphocytosis and subtle epithelial damage, but the crypts may appear somewhat hyperplastic and the villi somewhat atrophic. Several years may be required for lesions located at the duodenal–jejunal junction to return to normal on strict gluten-free diets.
FIG. 6.194. Comparison of the normal mucosa (A) with celiac disease (B). The hypercellularity of both the lamina propria and the lining epithelium is evident. The cells in celiac disease are palisaded, and there is an increase in lymphocytes.

Table 6.38 shows the chronology of the clinical and histologic responses to a gluten-free diet.

FIG. 6.195. Celiac disease (A) versus normal (B). Both specimens have been stained with periodic acid–Schiff stain to accentuate the brush border, the site of the digestive enzymes. Note the absence of prominent brush border in the celiac specimen.

**Treatment and Prognosis**

Removal of gluten from the diet is essential for treatment of patients with CD, and generally is required lifelong. Symptomatic response to the institution of a gluten-free diet is often rapid, with many patients responding within 48 hours (534). In others, weeks or even months may be required before clinical remission is achieved. In addition to a gluten-free diet, patients with severe celiac disease may require supplemental therapy to correct nutritional deficiencies related to malabsorption.

P.424
The prognosis is excellent for patients who are diagnosed early and adhere strictly to the gluten-free diet. Late diagnosis or noncompliance with dietary restrictions may result in malnutrition and debilitation. In general, both treated adult and pediatric patients have life expectancies similar to those of the general population (535).

**Refractory Sprue**

Refractory sprue is defined as symptomatic severe villous atrophy that does not respond to a strict gluten-free diet for at least 6 months. Refractory sprue strongly associates with partial trisomy at 1q22-q44 (536). Since refractory sprue is a diagnosis of exclusion, the possibilities of inadvertent gluten ingestion and other causes of villous atrophy including disaccharidase deficiency, protein enteropathy, autoimmune enteropathy, and bacterial overgrowth should be ruled out. Refractory sprue in some patients suggests that the patient has developed ulcerative ileojejunitis or a neoplasm. Recent evidence suggests that refractory sprue may represent a manifestation of an aberrant clonal IEL-mediated neoplastic process. Cellier et al demonstrated that intraepithelial lymphocytes in patients with refractory sprue are a monoclonal population that lacks CD8, a marker found in normal intraepithelial lymphocytes (506). These histologically undetected monoclonal T cells may be designated *cryptic intestinal T-cell lymphoma*. Others suggest that CD30 expression by the IELs in refractory sprue may indicate a poor prognosis including the occurrence of overt lymphoma (537). The lymphocyte-induced injury leads to intestinal ulceration and lymph node cavitation in some patients. In some but not all cases, the condition progresses to full-blown lymphoma.
Collagenous Sprue

Collagenous sprue is diagnosed histologically and is characterized by the development of a subepithelial collagen band thicker than 10 microns. Collagenous sprue typically affects patients with a long history of CD, but has been regarded by some as a distinct entity. The disorder most commonly affects adults with a long history of celiac disease and may be barely perceptible or be quite prominent. The typical clinical history is of a patient with celiac disease who initially responded to a gluten-free diet but subsequently becomes refractory to treatment. The small bowel biopsy shows variable villous atrophy and other features typical of celiac disease. In addition, a prominent subepithelial collagen band is present, a change highlighted by trichrome stains (Fig. 6.197). When marked, the mucosa shows variable crypt hypoplasia with Paneth cell deficiencies. Although patients with collagenous sprue should be given a trial of a gluten-free diet, the prognosis is poor and many patients develop other complications such as ulcerative jejunoileitis and lymphoma (509).

Ulcerative Jejunoileitis

Ulcerative jejunoileitis is an uncommon but serious complication of celiac disease, characterized by multiple chronic small intestinal ulcers. Although this entity has been regarded by many as synonymous with lymphoma, ulcerative jejunoileitis without any evidence of lymphoma has been documented in a few cases (538). The ulcers affect adults, generally after many years of malabsorption. Patients typically present with worsening of their malabsorption symptoms, abdominal pain, and complications including obstruction, perforation, and hemorrhage. Patients are often diagnosed late in the course of the disease. Intestinal perforation and peritonitis may develop. The linear and shallow ulcers demonstrate a transverse orientation and little surrounding fibrosis but are morphologically nonspecific, usually multiple, and predominantly jejunal in location (Fig. 6.124). Histologically, the bases of the ulcers consist of purulent exudate overlying granulation tissue and fibrosis. The inflammation extends into the submucosa or even the muscle. The serosa may appear edematous and inflamed. Surgical excision is the most effective therapy. Some patients respond to glucocorticoids and azathioprine.
Changes Occurring in Intestinal Transplants

Total intestinal transplantation is used to correct the short gut syndrome. Pediatric candidates for intestinal transplantation are those who undergo extensive intestinal resections for gastroschisis, volvulus, and necrotizing enterocolitis, as well as those with functional disorders such as intestinal pseudo-obstruction, microvillous inclusion disease, and juvenile polyposis (652). The optimum treatment depends on buying time and hoping for maximal intestinal growth and adaptation.

Intestinal transplantation inevitably involves transection of the intestinal wall causing intrinsic and extrinsic denervation, interruption of lymphatic drainage, and preservation-induced injury. Immunologic reactions and immunosuppressive agents may further compromise normal intestinal function. Rejection of the transplant increases intestinal permeability, resulting in bacterial translocation and leading to sepsis. The large amount of transplanted lymphoid tissue present in the Peyer patches, lamina propria, and mesenteric lymph nodes is responsible for the highly immunogenic character of intestinal allografts. Table 6.58 lists some of the major complications of intestinal transplantation.

<table>
<thead>
<tr>
<th>TABLE 6.58 Complications of Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preservation injury</td>
</tr>
<tr>
<td>Graft failure</td>
</tr>
<tr>
<td>Ischemic damage</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Graft rejection</td>
</tr>
<tr>
<td>Graft vs. host disease</td>
</tr>
<tr>
<td>Posttransplant lymphoproliferative disorders</td>
</tr>
</tbody>
</table>

Lymphatic regeneration needs to occur following the graft to establish the lymphatic drainage so critical to the nutritional functions of the small bowel, including the absorption of chylomicrons. If this does not occur, lymphedema will develop. Lymphedema reduces absorption of nonlymphatic-dependent proteins and carbohydrates. Impaired gut barrier function may eventually lead to sepsis and multiorgan failure.

Part of the ability of the graft to function normally involves regeneration of the neural components. When failed grafts are evaluated, they demonstrate a lack of extrinsic adrenergic and perivascular fibers in all layers of the bowel wall, but intrinsic neural endocrine transmitters are preserved. Both peptidergic nerves and their receptors are retained following transplantation (653). Patients on cyclosporin therapy may have atypical changes in the bowel wall that do not allow one to detect GVHD or rejection.

A rejected graft demonstrates edema, cellular infiltration of the mucosa and submucosa, and epithelial damage. The number of infiltrating T cells correlates with the extent of tissue damage (654). Lymph nodes in the transplant become totally necrotic by the time of full-thickness intestinal necrosis, perhaps due to host versus graft reaction or therapy.
Early acute rejection usually occurs within 12 days, although it can occur later. Acute allograft rejection exhibits varying combinations of crypt injury, mucosal infiltration primarily by mononuclear cells, intraepithelial lymphocytes including blastic-appearing lymphocytes, and increased crypt cell apoptoses (>2/10 crypts). The lamina propria appears edematous. CD3+, CD4+, CD8+, and CD25+ T cells are seen along with increased HLA-DR expression by the crypt enterocytes. Rejection presents as a patchy, often ileal-centered process that progresses to mucosal ulceration and eventual fibrosis of the wall (655). Endothelial and crypt damage occurs within 3 days. Cellular infiltrates can be present in the muscle and submucosa in the absence of mucosal changes. In mild rejection, the inflammatory infiltrate surrounds small venules and capillaries in the deep mucosa at the crypt bases (Fig. 6.241). These appear as early as 2 weeks and as late as 12 months. Other features of rejection include large numbers of lymphocytes between the muscularis mucosae and crypts adjacent to the crypt epithelium. Vessels between the crypts frequently appear activated with enlarged endothelial cells, sometimes with lymphocytes in the lumen. Other inflammatory cells are occasionally present, including plasma cells, eosinophils, and neutrophils. With more substantial involvement, the inflammatory infiltrate becomes more widely dispersed in a patchy or coalescent distribution along with varying degrees of mucosal edema and lymphatic dilation. Markedly enlarged Peyer patches expanded by prominent accumulations of blastic lymphocytes are found in the first month following transplant. This infiltrate consists predominantly of mononuclear cells admixed with lesser numbers of eosinophils and neutrophils. Pronounced mucosal eosinophilia may develop. When patients exhibit extensive mucosal ulceration, they often have coexisting CMV infections. The patient who survives the episodes of acute graft rejection becomes susceptible to the posttransplantation complications seen in other transplant patients. Chronic graft rejection histologically causes villous atrophy and T-cell infiltration associated with vascular lesions and muscular fibrosis. The lamina propria is infiltrated by CD3+ CD25+ lymphocytes and CD25+ macrophages, abrasion of the cell surface epithelium, and ultimately mucosal sloughing (656). An obliterative arteriopathy is usually present. This occurs in allografts removed up to 660 days posttransplant. The large arteries of the serosa and mesentery are primarily affected, and show patchy luminal narrowing by myointimal hyperplasia and subendothelial accumulation of foamy macrophages and scattered lymphocytes. The mucosa becomes focally necrotic with ulceration and associated granulation tissue and inflammatory exudates. Intact areas show patchy mononuclear infiltrates and distorted mucosal architecture with villous blunting, crypt atrophy and irregularity, and focal lamina propria fibrosis. Biopsies following treated resolving rejection often demonstrate fibrosis with focal glandular loss, regenerative glands with reparative atypia, and atrophy with a thin mucosa and blunted villi. These changes occur more commonly following severe or persistent rejection, although they are not always present. Patients may develop moderate to severe eosinophilia. A high incidence of infection complicates small bowel transplantation. These result from both excessive immunosuppression and a compromised barrier function of the native or engrafted small bowel. Small bowel transplant patients who develop rejection or GVHD may have shifts in the intestinal microflora toward potentially pathogenic organisms and bacterial translocation into recipient tissues. Bacterial colony counts are higher in grafts than in the native intestine, and one may see massive bacterial overgrowth in the native intestine in patients developing GVHD. At least two apoptotic figures in a gland or several single apoptotic cells in the presence of a lymphoid infiltrate with activated lymphoid follicles and prominent endothelium correlate best with clinical rejection. The patients may develop
Changes Occurring in Intestinal Transplants

posttransplant lymphoproliferative disorders, discussed in Chapter 18.
FIG. 6.241. Mild rejection in a patient who underwent a small bowel–pancreatic transplant for diabetes. The transplant failed and the sections come from the duodenal portion of the resected, failed allograft. A: The specimen showed evidence of ischemic necrosis presumably as the result of vascular compromise. The specimen demonstrates marked vascular congestion and loss of the epithelial cells on the surface that lies to the left. B: Mild regenerative features and an almost inconspicuous infiltrate at the base of the mucosa overlying the muscularis mucosae. C: Mild perivascular inflammation. D: The muscle shows evidence of denervation injury, presumably the result of the previous surgery.
Chronic Duodenitis Associated with *Helicobacter Pylori* Infection

Gastric *Helicobacter pylori* infections associate with various changes in the duodenal bulb. These include intraepithelial lymphocytosis (166), chronic duodenitis, chronic active duodenitis, gastric metaplasia-associated duodenitis (167), and duodenal ulcer (discussed in a later section). Endoscopically, the duodenum may appear normal or there may be mucosal edema, erythema, petechial hemorrhages, or erosions. These changes may be especially prominent in areas adjacent to peptic ulcers.
FIG. 6.81. Sclerosing papillitis. A: Low magnification of tissue removed endoscopically as a polyp. It came from the area around the ampulla of Vater. In the upper portion of the photograph, one sees more or less normal duodenal mucosa. The three lower fragments are abnormal. The largest piece (arrow) consists of edematous tissue covered by small intestinal epithelium. In some places, glandular crowding is evident. B: Higher magnification of the edematous, inflamed tissue. C, D: Higher magnifications of the epithelium from these tissue pieces that, if examined in isolation, might be interpreted as representing an area of dysplasia. One might be worried about severe dysplasia in C due to the tangential cutting of the specimen. Features that suggest dysplasia are the glandular crowding, the nuclear palisading, and the high nuclear:cytoplasmic ratio. The intensity of the associated inflammatory changes and the gradual transition to more mature epithelium indicate that this is a reactive process, not a neoplastic one. D: Glands superficially resembling adenomatous epithelium lining the upper portion of the gland gradually merge with more normal-appearing epithelium.
The diagnosis of chronic duodenitis is fairly subjective since the criteria for the diagnosis are not well established and the architecture of duodenal villi is normally quite variable. However, one has the sense that the overall cellularity of the lamina propria is increased. The diagnosis is more certain if acute inflammation is present, if there is an intraepithelial lymphocytosis, or if there is foveolar metaplasia. Since the acute inflammation is usually patchy in nature, one may need to examine multiple sections or levels to detect its presence. The surface epithelium may appear degenerated and the crypts regenerative secondary to the inflammation. The number of duodenal IELs ranges from 3 to 42 per 100 enterocytes with a mean of 18.5. This contrasts with a mean of 6.6 in a control population (166). The IELs are T cells and their increase is patchy in nature. This level of intraepithelial lymphocytosis resembles that seen in celiac disease but the villous architecture is normal. The increased duodenal IELs occur even when the *H. pylori* is restricted to the stomach (166). Treatment of the gastric infection leads to a decrease in IELs (168).
**FIG. 6.83.** Erosive duodenitis due to alcohol. *A:* A congested duodenal mucosa shows artifactual denudation of the superficial epithelium. Red cells have extravasated into the lamina propria. There is also focal glandular dropout. *B:* A more severe form of the disease in which amorphous eosinophilic material fills the area of the lamina propria, and the tissues are diffusely congested and infiltrated with red cells. The superficial epithelium is destroyed.
Numerous diseases cause small intestinal ulcers (Table 6.9). The rare disorder, chronic ulcerative jejunitis, also known as nongranulomatous chronic idiopathic enterocolitis and chronic ulcerative nongranulomatous jejunoileitis (251), is usually rapidly fatal and has a controversial etiology. Patients are typically middle-aged individuals who present with abdominal pain, anorexia, weight loss, fever, diarrhea, malabsorption, steatorrhea, hypoalbuminemia, protein-losing enteropathy, celiac disease, lymphoma, hypogammaglobulinemia, pulmonary fibrosis, and polymyositis. Features shared with celiac disease include generalized severe malabsorption, profuse diarrhea, villous atrophy, and an intense mucosal mononuclear infiltrate, but dietary gluten exclusion does not ensure clinical improvement because the changes typically occur in refractory sprue. The clinical features mimic those of Crohn disease due to the presence of granulomas in some biopsies and a clinical response to anti-inflammatory drugs in some patients.

**TABLE 6.9 Causes of Small Intestinal Ulcers**

| Infections: Bacterial, fungal, viral parasitic |
| Crohn disease |
| Acute jejunoileitis |
| Celiac disease |
| Tumors: Carcinomas, lymphomas, sarcomas, metastases |
| Ischemia |
| Uremia |
| Hyperacidity syndromes |
| Drugs |
| Arsenic |
| Gold |
| Mercury |
| Nonsteroidal anti-inflammatory drugs |
| Potassium chloride |
| Corticosteroids |
| Radiation |
| Behçet syndrome |
| Peptic ulcer |
| Idiopathic mucosal enteropathy |
| Graft vs. host disease |

The patients develop well-demarcated but nonspecific ulcers in the duodenum and proximal jejunum (Fig. 6.124). They resemble those seen in ischemia or other ulcerating diseases. Polymorphonuclear and chronic inflammatory cells infiltrate the lamina propria, and the mucosa demonstrates varying degrees of villous atrophy (Fig. 6.124). Enterocytes lack significant cellular abnormalities. Gastric metaplasia may develop (252). Rarely, patients exhibit colonic lesions resembling those seen in the small bowel. These patients have a T-cell lymphoma as discussed further in Chapter 18.
FIG. 6.124. Ulcerative jejunitis. A well-demarcated superficial ulcer extending into the upper portion of the submucosa is identified.
Intestinal malpositions include disorders of malrotation, malfixation, reversed rotation, incomplete rotations, fixation abnormalities, and situs inversus. Intestinal malrotations or nonrotations (Fig. 6.44) result from disordered or interrupted embryonic intestinal counterclockwise rotations around the superior mesenteric artery. The normal rotations and fixations are either incomplete or occur out of order. Nonrotations result from an interruption early in the rotation, so that the duodenal–jejunal loop remains on the right side of the abdomen. The cecal position varies, but it usually lies in the upper abdomen on the left side (Fig. 6.44). Incomplete rotations reflect interruptions occurring after the duodenal–jejunal loop has partially rotated around the superior mesenteric artery. Variants of classic rotation also occur. These include reversed duodenal and colonic rotation and reversed duodenal rotation and normal colonic rotation. In reversed rotation, the dorsal and ventral loops rotate to the left rather than to the right. The cecum lies in the right iliac fossa but the small bowel lies superficial to the transverse colon (Fig. 6.44), often herniating into the right colonic mesentery (104). The small bowel may also fail to rotate fully. As the intestine returns to the abdominal cavity, the small intestine rotates 180 degrees but fails to continue rotating to the normal point of fixation at the ligament of Treitz. Considerable variations exist in the degree of rotation beyond 180 degrees. A short small intestinal and mesenteric segment often becomes fixed to the retroperitoneum along a line generally confined to the right upper quadrant. This line of fixation, rather than anchoring the small bowel securely, becomes a new point of rotation, substituting for the superior mesenteric artery as a rotation point. Fibrous bands or adhesions form between the bowel and other abdominal structures in an attempt to secure the mobile bowel (Fig. 6.45). These commonly cross and compress the duodenum, obstructing it. Rotational abnormalities also complicate developmental defects when the intestine occupies an extra-abdominal position, as occurs in congenital diaphragmatic hemias or in abdominal wall defects (105).

Intestinal malrotations affect approximately 1 in 6,000 live births (106). Three percent of patients have associated abnormalities (Table 6.1). Patients present with signs and symptoms of duodenal obstruction, intermittent volvulus, or acute life-threatening midgut volvulus characterized by bilious vomiting, abdominal distention, rectal bleeding, or intussusception. Infants may also develop malabsorption with steatorrhea and protein-losing enteropathy resulting from mesenteric lymphatic obstruction. Adults with malrotations often have a lifetime history of nonspecific abdominal complaints, including acute symptoms when they were children (107).
Malrotations exhibit obvious intestinal misplacement within the abdominal cavity. The intestines often lie to one side, appearing as a large mass of nonrotated bowel (Fig. 6.44). The entire bowel, from the duodenum to splenic flexure, remains unanchored and supported by a single mesentery with a very narrow base, predisposing the intestines to torsion and volvulus.

**Situs Inversus**

In *situs inversus*, the organs lie in mirror image locations of their normal positions. When *complete*, it affects both thoracic and abdominal organs. When *incomplete*, it affects only the abdominal organs. *Limited situs inversus* affects only the stomach and duodenum. Situs inversus affects 1 in 1,400 live births and it forms part of Kartagener syndrome.

Many children with situs inversus and a neural tube defect have mothers with insulin-dependent diabetes mellitus. Partial situs inversus usually associates with other malformations, including asplenia, duodenal stenosis, and cardiac defects. Major associated gastrointestinal anomalies include annular pancreas, midgut volvulus, duodenal atresia, and mucosal duodenal diaphragms. Situs inversus does not change organ function or histology. One group of patients that may have a somewhat worse prognosis than others are those with *Kartagener syndrome*. These patients have abnormal cilia and as a result they produce thick, tenacious bronchial and sinus secretions that lead to chronic sinusitis and bronchiectasis.

**TABLE 6.1 Abnormalities Associated with Small Intestinal Malrotation**

<table>
<thead>
<tr>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia or stenosis</td>
</tr>
<tr>
<td>Duodenal atresia or stenosis</td>
</tr>
<tr>
<td>Prune belly syndrome</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
</tr>
<tr>
<td>Annular pancreas</td>
</tr>
<tr>
<td>Internal hernias</td>
</tr>
<tr>
<td>Paraduodenal hernia</td>
</tr>
<tr>
<td>Midgut volvulus and facial anomalies</td>
</tr>
<tr>
<td>Omphalocele and gastroschisis</td>
</tr>
<tr>
<td>Intestinal atresia</td>
</tr>
<tr>
<td>Craniofacial anomalies (especially in infants with intrauterine opiate or heroin exposure)</td>
</tr>
<tr>
<td>Trisomy 13, 18, and 21</td>
</tr>
</tbody>
</table>
**Omphaloceles**

Omphaloceles consist of an external mass of abdominal contents covered by a variably translucent peritoneal and/or amniotic membrane. They result from the failure of the anterior abdominal wall to form completely during fetal development combined with the failure of the abdominal viscera to return to the abdomen at the end of the 10th fetal week. Omphaloceles affect 2.52 per 60,000 to 2 per 3,000 live births. Significant heterogeneity exists in the prevalence rates among different geographic regions, with especially high prevalence rates occurring throughout the British Isles. In the United Kingdom and Ireland, there is a tendency for omphaloceles to associate with anencephaly and spina bifida. The male-to-female incidence is 3:1; however, a significant female excess exists among the cases of omphalocele associated with neural tube defects. Up to 54% of infants with omphaloceles have associated anomalies (Table 6.2) compared with only 5% of those with gastroschisis (108,109). Many fetuses with an omphalocele have an abnormal karyotype. Chromosomal anomalies are particularly common in omphaloceles that do not contain the liver (110).
FIG. 6.45. Intestinal bands. Several views of the same intestinal band and its consequences. A: The mesenteries have herniated through a mesenteric defect underlying the band (probe). The surrounding bowel loops appear ischemic and erythematous secondary to a volvulus that occurred around the band. B: Further dissection shows the band elevated by the probe. A loop of dusky bowel is twisted around it (arrows).

The rare OEIS (omphalocele, cloacal extrophy, imperforate anus, spinal defects) complex affects 1 per 200,000 to 400,000 pregnancies. OEIS occurs sporadically or it affects twins or siblings from separate pregnancies, suggesting that some cases have a genetic basis. Some patients with omphalocele and the Miller-Dieker syndrome have a deletion at 17p13.3, suggesting that a gene in this region plays a major role in lateral fold closure or the return of the midgut from the body stalk to the abdomen. Trisomy 18 affects some patients. OEIS associates with a history of maternal diabetes mellitus or hydantoin or diazepam administration (111,112).

<table>
<thead>
<tr>
<th>TABLE 6.2 Defects Associated with Omphaloceles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart anomalies</td>
</tr>
<tr>
<td>Intestinal atresia</td>
</tr>
<tr>
<td>Chromosomal defects</td>
</tr>
<tr>
<td>Genitourinary anomalies (cloacal or bladder extrophy)</td>
</tr>
<tr>
<td>Craniofacial defects</td>
</tr>
<tr>
<td>Diaphragmatic abnormalities</td>
</tr>
<tr>
<td>Liver and bile duct abnormalities</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
</tr>
<tr>
<td>Macroglossia</td>
</tr>
<tr>
<td>Gigantism</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>
Congenital Abnormalities

- Umbilical abnormalities
- Cantrell pentalogy
- Ectopia cordis
- Sternal cleft
- Diaphragmatic defect
- Cardiac disease
- Omphalocele
- OEIS complex
- Omphalocoele
- Cloacal extrophy
- Imperforate anus
- Spinal defects

The OEIS complex arises from a single localized mesodermal defect early in development that contributes to infraumbilical mesenchymal, cloacal septum, and caudal vertebral abnormalities. Four somatic folds (a cephalic fold, two lateral folds, and a caudal fold) define the anterior thoracic and abdominal walls during the third fetal week. These folds migrate centrally to fuse at the umbilical ring, usually by the 18th gestational week. Arrested fold migration or development results in anterior wall defects and a widening of the umbilical ring. The average birth weight and gestational age of infants with omphalocele is low. The amniotic membrane and peritoneum protect the developing intestinal loops from the damaging effects of exposure to amniotic fluid seen in gastroschisis. Omphaloceles range in size from only a few centimeters to lesions involving almost the entire anterior abdominal wall (Fig. 6.46). Abdominal viscera are present within a sac that initially is moist and transparent but with time becomes dry, fibrotic, opaque, friable, and prone to rupture with secondary evisceration. One often can see its contents through the glistening membrane. Abdominal skin may cover the sac base and the umbilical cord is usually attached to its apex or slightly to the side. Large omphaloceles, measuring 5 cm or more in greatest dimension, may contain the stomach, liver, spleen, pancreas, and intestines. They may also contain segments of duplicated bowel. Smaller omphaloceles usually only contain intestines.

The function and histology of the displaced organs tends to be normal unless there is a coexisting congenital abnormality. The lining of the sac that covers the eviscerated organs consists of peritoneum internally and amnion externally.

P.302
Gastroschisis

Gastroschisis is the persistent herniation of abdominal viscera through an abdominal wall defect at the base of the umbilicus. The abdominal organs remain outside the abdominal cavity. No peritoneal sac or amniotic remnant covers the eviscerated abdominal contents. The incidence of gastroschisis has risen, increasing from 0.48 per 10,000 births in 1980 to 3.16 per 10,000 in 1993 (113,114). Young, socially disadvantaged women have the highest risk of having a child with gastroschisis (115). An increased risk of gastroschisis also associates with intrapartum use of recreational drugs or smoking (113), exposure to salicylates, and radiation (116). Gastroschisis predominates among male infants. It is often an isolated lesion (109). Sixteen to twenty percent of infants have associated congenital malformations, including total intestinal atresia (113,117,118).

Gastroschisis probably results from vascular injury and ischemia of the abdominal wall during the 5th to 11th fetal weeks, leading to defective somatopleural mesenchymal differentiation (118). The ischemia results from intrauterine disruption of the right omphalomesenteric artery. Exposure of the bowel to inflamed amniotic fluid (119) leads to perivisceritis and premature birth. The damaged bowel frequently develops secondary motility problems and malabsorption, which may present even following surgical repair. Other complications include obstruction due to coexisting malrotation, diverticulitis, ischemia, and perforation. Patients with ectopic gastric mucosa in the eviscerated bowel may develop a GI hemorrhage.

Gastroschisis may involve only the intestines or it may affect many other organs. Parts of the stomach, small intestine, and colon herniate through an abdominal wall defect, usually to the right of the umbilical cord (Fig. 6.47). All infants with gastroschisis have coexisting nonrotation and abnormal intestinal fixations. The small intestines typically appear thickened and shortened.
Congenital Abnormalities

Omphalocele and gastroschisis are both associated with increased maternal serum and amniotic fluid α-fetoprotein (AFP) levels. Acetyl cholinesterase is also nearly always detectable in the amniotic fluid, albeit at much lower concentrations than in open neural tube defects (120). Antenatal ultrasound often allows an accurate diagnosis of gastroschisis. The histology of the various organs may be normal (rarely) or changes may be present reflecting the presence of associated congenital abnormalities, heterotopias, atresia, meconium peritonitis, or perivisceritis. The last two entities lead to gastrointestinal wall thickening, serosal edema, and fibrinous exudates and fibrosis. The intestinal muscularis propria may also become hypertrophic. Acute inflammation consisting predominantly of neutrophils and mononuclear cells may be present in gastroschisis and may lead to postnatal bowel dysfunction. Functionally, there is often malabsorption and hypomotility as the result of the inflammation.

FIG. 6.47. Gastroschisis. This infant shows external herniation of most of the abdominal contents, including the liver, spleen, and intestinal tract.

Long-term outcome in the absence of major chromosomal and structural abnormalities is excellent (121). Patient prognosis depends in part on whether the gastroschisis is an isolated lesion or whether there are associated abnormalities. The goal of the surgeon in both gastroschisis and omphalocele is to accomplish abdominal wall closure in a single stage. An alternate approach is to perform a staged closure using prosthetic materials while maintaining adequate nutritional support.
Bands

Peritoneal bands, known as Ladd bands, extend from the cecum, ascending colon, or posterior wall transduodenally to the subhepatic region, compressing the duodenum and causing partial obstruction, vascular compression, and intestinal ischemia. The bands represent incomplete absorption of the cecal and ascending colonic mesentery. Limb–body wall malformations, also known as amniotic band syndrome (Fig. 6.48), cause body wall, limb, and intestinal malformations.

Atresia and Stenosis

Intestinal atresia and stenosis cause intestinal obstruction. Atresia occurs more often than stenosis. Their incidence varies from 1 per 2,000 to 6,000 live births (122). Atresia results from an occluding mucosal diaphragm, whereas stenosis represents either a narrowed intestinal segment or a luminal diaphragm with a small central opening. Duodenal atresia is the most common small intestinal atresia, followed by jejunal and ileal lesions. Duodenal atresia is less common than duodenal stenosis. Jejunoileal atresias affect 1 per 500 to 2,000 live births. Some patients have multiple atresias (123).

Intestinal atresia occurs on both a sporadic and a familial basis. Most intestinal atresias follow some form of ischemic injury (124) or intrapartum asphyxia (125) occurring after the intestine has developed and produce segmental intestinal necrosis with subsequent fibrosis or tissue loss (125). The presence of meconium, bile, squames, and lanugo hair in the atretic areas (Fig. 6.49) supports an intrauterine injury. Small intestinal atresia may complicate midtrimester amniocentesis (126), intrauterine intussusception due to Meckel diverticulum, or fetal infections (varicella and syphilis). Fetal exposure to cocaine in the mother may predispose to intestinal atresia due to vascular disruptions (127). Twins have a higher rate of small intestinal atresia than single-birth infants, possibly due to vascular disruption in monozygotic twins. Associated congenital abnormalities affect fewer than 10% of patients with jejunoileal atresia, contrasting with a 35% incidence of associated congenital anomalies in patients with small intestinal atresia (Table 6.3) (128,129). Familial jejunal atresia may associate with renal dysplasia. Apple-peel atresia probably results from a narrow mesenteric attachment, volvulus, and occlusion of the superior mesenteric artery distal to its proximal branches (130). Of all types of jejunoileal atresias, the apple-peel variety has the highest rate of associated anomalies (130). There is an increased frequency of cystic fibrosis among infants with small intestinal atresia (131). Ileal atresia may coexist with colonic aganglionosis (132).
Congenital Abnormalities

FIG. 6.49. Intestinal atresia. A: Blind-ending atresia is shown on the right. B: Fibrosis in atretic wall. C: Blind area of atresia on the right with stenotic area on the left. The atretic area is filled with meconium. D: Granulomatous reaction surrounding stenotic area.

Most duodenal atresias lie in a postampullary location or at the ampulla of Vater. Duodenal atresia can be diagnosed ultrasonographically at 15 weeks' gestation by finding polyhydramnios, a lack of amniotic fluid, intestinal dilation proximal to the atretic intestine, meconium peritonitis, and ascites. Elevated maternal serum AFP levels and polyhydramnios occur in the second trimester of pregnancy in 50% of cases (133). Signs of distress or ischemia are frequent. Approximately 50% of infants with intestinal atresia are premature. Small intestinal atresias present in the neonatal period. Bilious vomiting (unless a coexisting esophageal atresia is also present) usually occurs during the first few hours of birth. Partial obstruction causes intermittent symptoms. The vomitus lacks bile staining when the obstruction lies proximal to the ampulla of Vater. Duodenal atresia is also suggested radiographically by the presence of a double bubble on a plain abdominal x-ray, particularly when gas is present in a distended stomach and proximal duodenum. In contrast, because stenoses allow passage of some enteric contents, they present later in life. Some patients with duodenal stenosis remain asymptomatic, whereas others present with an intermittent or delayed history of duodenal ulcer, symptoms associated with hiatal hernia, gastritis, duodenogastric reflux, a motility disturbance, duodenal diverticula, and bezoars (134).

Atresia results from a complete occlusion, whereas stenosis represents either a narrowed intestinal segment or a luminal diaphragm with a small central aperture. In atresia, a bowel segment is entirely missing, leaving a proximal segment with a blind end separated some distance from the distal segment. Alternately, the proximal and distal segments are united by a solid fibrous cord, or there is an occluding mucosal diaphragm. Some patients have multiple atresias (135). Intestinal atresia falls into four major types (Figs. 6.50 and 6.51). Two main types of stenosis exist. In type 1, a septum identical to that seen in type 1 atresia is present, but instead of being complete it has a central hole within it. In type 2 lesions, the GI lumen appears uniformly narrowed over a variable length of intestine (Fig. 6.52). All bowel layers form...
TABLE 6.3 Lesions Associated with Small Intestinal Atresia and Stenosis

<table>
<thead>
<tr>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malrotation of the gut</td>
</tr>
<tr>
<td>Meckel diverticulum</td>
</tr>
<tr>
<td>Volvulus</td>
</tr>
<tr>
<td>Esophageal atresia</td>
</tr>
<tr>
<td>VACTERL associations</td>
</tr>
<tr>
<td>Other small intestinal atresias</td>
</tr>
<tr>
<td>Imperforate anus</td>
</tr>
<tr>
<td>Biliary atresia</td>
</tr>
<tr>
<td>Annular pancreas</td>
</tr>
<tr>
<td>Perforation</td>
</tr>
<tr>
<td>Pancreatic lipomatosis</td>
</tr>
<tr>
<td>Ocular abnormalities</td>
</tr>
<tr>
<td>Microcephaly</td>
</tr>
<tr>
<td>Spina bifida</td>
</tr>
<tr>
<td>Gastrourinary abnormalities</td>
</tr>
<tr>
<td>Immunodeficiency states</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Cytogenetic changes</td>
</tr>
<tr>
<td>Internal deletion on chromosome 13</td>
</tr>
<tr>
<td>Ring chromosome 4</td>
</tr>
<tr>
<td>Trisomy 21 (Down syndrome)</td>
</tr>
<tr>
<td>Maternal lesions</td>
</tr>
<tr>
<td>Polyhydramnios</td>
</tr>
<tr>
<td>Intrapartum hemorrhage</td>
</tr>
</tbody>
</table>

Normal small intestinal mucosa lines both sides of the atretic or stenotic intestinal segment. The height of the circular folds declines and the muscularis mucosa thickens as one approaches the blind segment. In complex atresia, the proximal bowel appears dilated and gangrenous. The circular folds widen due to stromal edema. The villi may appear shortened or only simple tubular glands may be present. The villi and crypts also often appear necrotic or ulcerated, with only a few residual intestinal glands. As a result, the mucosa contains granulation tissue, granulomas, foreign body giant cells, fibroblasts, and hemosiderin-laden macrophages. Dystrophic calcification and inflammation at or near the atretic site suggest previous injury. The blind segment may contain dense fibrosis, meconium, keratinizing squamous cells, lanugo hair, bile pigment, and mucin. The intervening mucosa between atretic areas is histologically normal. The muscularis propria eventually becomes markedly hypertrophic and the myenteric plexus may show inflammatory or degenerative changes.

**Annular Pancreas**

Annular pancreas, a congenital disorder of failed duodenal development, consists of a ring of pancreatic tissue surrounding the second part of the duodenum (Fig. 6.53) that presents in the neonatal period or in the 4th and 5th decades of life (136). The incidence of annular pancreas is 1 in 20,000 persons. Annular pancreas may be part of a more generalized embryogenic disorder associated with trisomy 21, tracheoesophageal fistulae, or cardiorenal abnormalities (136), or it occurs alone. Eighty percent of infants with annular pancreas...
Congenital Abnormalities

have associated anomalies, in contrast to 20% of adults. Neonates present with duodenal obstruction. Adults present with duodenal stenosis, peptic ulcers, upper abdominal pain, and chronic pancreatitis, or the lesion is found incidentally. Peptic symptoms result from gastric stasis and antral overdistention due to partial duodenal obstruction and secondary hypergastrinemia, hyperchlorhydria, and peptic ulceration. Although the pancreatic location is abnormal, the pancreatic histology is completely normal. Secondary inflammatory changes occur if the patient develops duodenal stenosis or peptic ulceration.
FIG. 6.50. Different types of atresia. A: In type 1, an imperforate septum, covered on each side by mucosa, stretches across an otherwise continuous bowel. B: In type 2, a thin fibromuscular cord with or without an associated mesenteric defect replaces the bowel. C: In type 3, a complete gap and a corresponding mesenteric defect separate the two blind intestinal ends. D: Type 4 atresia is characterized by the presence of atretic areas. The different forms of atresia may coexist and may be single or multiple.

FIG. 6.51. Intestinal atresia. A: Resected portion of small intestine showing intestinal dilation proximal to the atretic area. B: Close-up of atretic portion of small bowel showing a marked narrowing of a segment partially encircled by a fibrous band. C: Type 2 atresia with thin fibromuscular core. D: Type 2 atresia in situ> No mesenteric defect is present.

Enterogenous Cysts, Congenital Diverticula, and Duplications

Congenital diverticula, duplications, and enterogenous cysts are related lesions that contain all three bowel layers (Fig. 6.54). A **duplication** is a complete or partial doubling of a variable length of bowel. **Duplication cysts** are localized duplications that become incorporated into the bowel wall or embedded within its serosa. They often coexist with rotational disorders or vertebral body defects. These congenital malformations involve the mesenteric side of the intestine and they share a common blood supply with the native bowel. They may possess their own mesentery, but more commonly they are included in the mesentery of the normal bowel. The major distinction that separates this group of lesions is their gross appearance (Figs. 6.54 and 6.55). Duplications tend to be longer in their axial length than cysts or diverticula and they appear as tubular intestinal reduplications that may or may not communicate with the native intestinal lumen. They have thick walls and are filled with mucus. Initial manifestations include obstruction, intussusception, and volvulus. Duplication cysts may be single or multiple and vary widely in size. Spherical duplications do not communicate with the intestine and are usually filled with clear secretions. Fistulae may result from the inflammation and necrosis.
Duplications

Thirty-nine percent of duplications involve the foregut; 61% originate in the midgut or hindgut. Approximately 50% of cases affect the ileocecal valve. Small bowel duplications are occasionally multiple. Most patients are boys. Duplications may communicate with the intestinal lumen by opening proximally, distally, or both (Figs. 6.54 and 6.56). In other cases, the duplicated segment fails to communicate with the intestinal lumen (Fig. 6.56). The clinical manifestations depend on the form the duplication takes. Patients present with an abdominal mass, bouts of abdominal pain, vomiting, distention, chronic rectal bleeding, intussusception, perforation, and obstruction. Bleeding is especially likely if the anomaly contains ectopic gastric epithelium. Ileocecal duplications act as lead points for chronic or recurrent intussusception. Grossly, two intestinal lumens are present. Triplications also occur.

**FIG. 6.52.** Type 2 intestinal atresia that has been opened.
FIG. 6.53. Annular pancreas. The annular pancreas wraps around the first portion of the duodenum. Note the lobulated appearance of the pancreatic tissue.
FIG. 6.54. Comparison of duplications, enterogenous cysts, and congenital diverticula. Panels A through D represent true duplications in which a significant portion of the intestinal length is duplicated. The arrows indicate the flow of intestinal contents. 

A: Both the proximal and distal ends of the duplicated segment communicate with the native intestinal lumen. This results in a free flow of intestinal contents through both lumens. 

B: The proximal portion of the duplication communicates with the native intestine. The distal portion of the duplication ends blindly. As a result, the intestinal contents pass into the duplication but then accumulate, causing dilation and inflammation. 

C: The duplicated segment fails to communicate with the native intestine, and as a result no intestinal contents flow into the duplicated lumen. If the lining of the duplicated segment produces significant secretions, these may accumulate and form a cystic dilation. 

D: Intestinal duplication in which the proximal end fails to communicate with the native intestinal lumen but the distal portion of the duplication does communicate with it. Intestinal contents do not enter the duplication and secretions produced by the duplicated segment are free to exit the duplicated segment and enter the main lumen. 

E: Enterogenous cyst. In this setting, the duplicated bowel represents a localized segment of duplicated bowel embedded within the intestinal wall. It fails to communicate with the native intestine. The enterogenous cyst may enlarge as the result of accumulated secretions. 

F: Congenital diverticulum. The duplication in this situation is relatively localized but it communicates freely with the intestinal lumen. The wall of the diverticulum contains all of the usual layers of the intestinal wall, distinguishing it from an acquired diverticulum.
FIG. 6.55. Enterogenous cyst. A: A large, cystically dilated mass extends from the mesenteric portion of the bowel. It fails to communicate with the intestinal lumen. It was filled with mucinous secretions. B: Same specimen opened to show its internal structure.

Hypotheses to explain duplications include persistence of embryonic diverticula, fusion of embryologic longitudinal folds (the most popular theory) (137), abortive twinning (138), intrauterine intestinal ischemia (139), endodermal–neurodermal adhesions, and sequestration of embryonic tissues during embryonic movements. Small diverticula and epithelial islands in the mesentery of the developing small intestine may explain the presence of isolated intestinal duplications. Extensive intestinal duplications associated with multiple anomalies including the urinary bladder presumably result from teratogenic insults affecting several developing organs.

FIG. 6.56. Intestinal duplication. A: Unopened specimen. The native intestinal lumen that communicates with the rest of the gastrointestinal (GI) tract lies to the left of the smaller lumen. B: Both structures are opened, showing the wide dilated native GI lumen and a smaller lumen at the periphery and edge of the C-shaped structure. Several atretic areas are present in the duplicated bowel (arrows).

Duplications can be complete or incomplete, long or short segment, communicating or noncommunicating. Communicating duplications open proximally, distally, or at both ends. Grossly, duplications appear as hollow, cylindric, oval, or spheric cystic masses ranging in size from a few millimeters to up to 15 cm (140).
Congenital Abnormalities

FIG. 6.57. Intestinal duplication. A: Cross section through duplicated segments shows two complete intestinal walls lying side by side. They share a common muscularis propria. B: Higher magnification showing strands of muscularis propria extending into the septum between the duplicated segments. The lumen of each segment is illustrated by the star and the attenuated muscularis propria (MP) separates the two submucosae (SM).

The three criteria for the diagnosis of a duplication are the presence of an intimate attachment to the GI tract, a smooth muscle coat, and an alimentary mucosal lining. Of these criteria, only the presence of a smooth muscle coat is absolutely necessary to define the lesion. Pressure within a cyst may lead to atrophy of the muscle component, causing it to appear incomplete. Generally, intestinal epithelium lines a duplicated segment (Fig. 6.57), but it may also contain heterotopic tissues, including thyroid stroma, pancreas, gastric mucosa (Fig. 6.58), lymphoid aggregates resembling Peyer patches, ciliated bronchial epithelium, lung tissue, and cartilage. A normal submucosa and inner circular muscle layer and myenteric plexus are present.

**Congenital Diverticula**

Duplication cysts that widely communicate with the lumen are termed *congenital diverticula*. Of the three related lesions, duplications, enterogenous cysts, and congenital diverticula, the latter are the rarest, affecting 1% to 2% of all individuals. Patients with congenital diverticula present with one of the following: Abdominal pain, distension, pressure, pain, and possibly perforation due to diverticulitis; ulceration and bleeding, usually from the presence of acid-secreting heterotopic gastric mucosa; or intussusception leading to sudden pain and bleeding. Duodenal diverticula may become large, causing obstructive jaundice, pancreatitis, duodenal obstruction, fistulas, hemorrhage, and perforation (141). Congenital diverticula may also remain asymptomatic, only to be discovered incidentally in adults.
Congenital Abnormalities

**FIG. 6.58.** Small intestinal duplication. Aberrantly formed crypts are present. The glands superficially resemble those seen in the gastric foveolae. Histochemical stains showed that the mucin was small intestinal mucin. Gastric glands are present.

Congenital diverticula present as localized outpouchings (Fig. 6.59), sometimes being multiple. Some congenital duodenal diverticula pass upward behind the stomach through a separate opening in the diaphragm to enter the right thoracic cavity, where they attach to defective thoracic vertebrae.

P.310

Congenital diverticula consist of all three bowel layers (Fig. 6.60). The lining epithelium is usually that of the site of origin. Some diverticula contain heterotopic tissues, similar to those found in duplications and enterogenous cysts. Diverticula containing oxyntic mucosa may develop peptic ulcers within them. If the diverticular orifice becomes blocked, diverticulitis develops.

**FIG. 6.59.** Congenital duodenal diverticulum proximal to an intestinal band (*arrow*).

**Meckel Diverticulum**

[Image of histological section and congenital duodenal diverticulum]
Meckel diverticulum, which represents a persistent omphalomesenteric or vitellointestinal duct, affects 1% to 4% of the population. Complete failure of the duct to atrophy produces a patent vitellointestinal duct with free communication between the ileal lumen and the umbilicus. Meckel diverticulum affects males and females equally, but males are more likely to become symptomatic. Overall, only 5% of Meckel diverticula produce symptoms. A Meckel diverticulum has no clinical consequences unless complications develop (Figs. 6.61 and 6.62). Hemorrhage occurs if the diverticulum contains acid-secreting epithelium causing peptic ulceration. Diverticulitis develops secondary to peptic ulcerations or obstruction of the diverticular orifice. Intestinal obstruction, without diverticulitis, affects 25% of symptomatic patients. The obstruction results from intussusception, volvulus, adhesions, compression by a mesodiverticular band, or the presence of a tumor or heterotopic tissue, enteroliths, or bezoars.

**FIG. 6.60.** Comparison of an acquired diverticulum versus a congenital diverticulum. *A:* An acquired diverticulum in which the mucosa and submucosa, and variable amounts of the muscularis propria and serosa (*not shown*), herniate through the bowel wall at areas of weakness. *B:* Congenital diverticulum. It is lined by all three layers of the bowel wall.

Meckel diverticulum always lies on the antimesenteric ileal border (Fig. 6.63). In the infant, it usually lies about 30 cm proximal to the ileocecal valve; in the adult, it usually lies within 100 cm of the ileocecal valve. An apical fibrous band may connect the diverticulum to the umbilicus or to other abdominal structures. Meckel diverticulum may also be connected to other intestinal loops or mesenteries by a congenital band or by adhesions resulting from previous episodes of diverticulitis. Meckel diverticulum varies in length from 2 to 15 cm (Fig. 6.63), but it usually measures <2 cm in width and has a narrow lumen. Variations in size, location, and shape are common. Meckel diverticulum may coexist with a duplication. Sometimes, a giant Meckel diverticulum develops. These appear as rounded, fusiform dilations resembling duplications rather than as sac-like diverticula, and they are sometimes referred to as omphalomesenteric cysts. Normal small intestinal epithelium lines the diverticulum, and heterotopic pancreatic tissue is common (Fig. 6.64). The latter usually appears as a nodular mass close to the diverticular tip. The pancreatic tissue sometimes acts as the lead point of an intussusception or it may cause obstruction. Heterotopic gastric mucosa (Fig. 6.65) leads to peptic ulceration, bleeding, or perforation, especially if oxyntic mucosa is present. Other heterotopic tissues include duodenal, jejunal, colonic, or biliary epithelium. Tumors may also form in the diverticulum.

**Umbilical Fistula**

Umbilical fistula represents a persistent vitelline duct. The fistula tract communicates from the umbilicus to the small bowel. It represents 2% of vitelline duct anomalies. The umbilical cord represents the fusion of the yolk sac containing the vitelline duct and the body stalk with its paired umbilical arteries, the umbilical vein, and the allantois. It contains primitive mesenchymal tissue (Wharton jelly) and is covered by an outer layer of amnion. Normally, the vitelline duct obliterates between the fifth and ninth weeks of intrauterine life. When it fails to obliterate, an umbilical fistula results. Umbilical fistula presents with persistent umbilical drainage. The diagnosis is confirmed when the dye is visualized in the lumen of the small bowel.
CONGENITAL ABNORMALITIES

FIG. 6.62. Complications of Meckel diverticulum. A: Complications that lead to obstructions and diverticulitis and/or bleeding. B: Some of the tumors that may develop in the diverticula.

FIG. 6.63. Meckel diverticulum. A: Typical Meckel diverticulum arising from antimesenteric border of distal ileum. B: Cross section through an opened Meckel diverticulum. The diverticulum lies in a plane perpendicular to the long axis of the intestine. The mouth of the diverticulum is illustrated by the arrow. The lining of the diverticulum resembles that of the native intestine.

CONGENITAL HETEROTOPIC GASTRIC MUCOSA
Heterotopic gastric epithelium occurs in the small intestine as the result of a congenital abnormality or a metaplasia. Acquired gastric mucosa (foveolar or pyloric metaplasia) usually associates with peptic duodenitis or chronic inflammatory disorders. Congenital heterotopic gastric mucosa exists alone (Fig. 6.66) or it complicates other congenital anomalies such as Meckel diverticulum (Fig. 6.65), duplications, and heterotopic pancreas.

Congenital heterotopic gastric epithelium often remains asymptomatic only to be discovered incidentally. Most cases of heterotopic gastric mucosa present as duodenal polyps at the time of upper endoscopy. However, an exceptional example of extensive gastric heterotopia that presented as multiple, carpetlike, nonpolypoid lesions that involved a large part of the small intestine in a child was recently reported (142). Typically, the duodenal bulb appears nodular, often with small sessile polyps measuring <1.5 cm in maximum diameter. They are usually surrounded by normal-appearing mucosa. Symptomatic lesions present with intestinal obstruction, peptic ulceration, or intussusception. The ectopic tissue may appear solid or cystic. Larger lesions with central depressions may mimic a superficial ulcerating duodenal cancer (143).

**FIG. 6.64.** Ectopic pancreas in Meckel diverticulum. *A:* Ectopic pancreatic tissue subjacent to mucosal lining. *B:* Pancreatic acini and ducts in ectopic pancreatic tissue.

Duodenal biopsies typically demonstrate intact duodenal villi and Brunner glands interrupted by discrete masses of gastric glands covered by foveolar epithelium. Congenital gastric mucosa usually consists of oxyntic mucosa. It appears well organized, consisting of superficial foveolar epithelium and glands. The latter contains chief and parietal cells. Antral glands may also be present. The glandular elements display their normal topographic relationships (Fig. 6.66). Rarely, the ectopic tissue develops diseases resembling those of the native stomach. These include areas of foveolar hyperplasia, hyperplastic polyps (Fig. 6.67), and oxyntic glandular mucosal cysts. Figure 6.68 compares the appearance of heterotopic gastric mucosa and gastric metaplasia.
FIG. 6.65. Ectopic gastric mucosa within a Meckel diverticulum. A: Low magnification showing the lining of the Meckel diverticulum. The majority consisted of small intestinal epithelium. The arrow indicates the junction of the intestinal epithelium with gastric epithelium. B: Higher magnification of the gastric epithelium showing the foveolar epithelium lining the surface (star), a well-developed mucous neck region (double star), and well-formed glands containing parietal cells and chief cells. C: Portion of another Meckel diverticulum with a peptic ulcer in the mucosa adjacent to an area with oxyntic gastric epithelium.

Heterotopic Pancreas

Heterotopic pancreatic tissue affects 0.55% to 13.7% of duodenal or jejunal strictures, duplications, and Meckel diverticulum. It is particularly common in autosomal trisomy, especially involving chromosomes 13 and 18. Most cases remain asymptomatic. Grossly and endoscopically, the lesion usually appears well demarcated. Heterotopic pancreas presents as a mass lesion that, on cut surface, has a solid, tan or cystic, lobular appearance, depending on whether or not the pancreatic ducts are dilated. The presence of a central mucosal dimple usually corresponds to the entrance of pancreatic ducts into the intestinal lumen. The lesion lies in the mucosa, in the submucosa, transmurally, or on the serosa (Figs. 6.69 and 6.70), and may coexist with heterotopic Brunner glands and/or gastric tissue (144).
Congenital Abnormalities

FIG. 6.68. Comparison of congenital gastric ectopia versus gastric metaplasia. Congenital gastric epithelium usually shows an orderly arrangement of the foveolar epithelium usually covering oxyntic glands. In contrast, gastric metaplasia lacks the three components of surface epithelium, gastric pits, and glands. It comes in two forms: The foveolar metaplasia commonly associated with peptic duodenitis and pyloric metaplasia commonly complicating chronic inflammatory diseases such as Crohn disease. In foveolar metaplasia, a mucous neck region and glands are completely absent. In pyloric metaplasia, foveolar cells and the mucous neck region are absent.

Pancreatic acini, ducts, or islets occur alone or in combination with one another. When the lesion contains only ducts surrounded by the circular and longitudinal muscle of pancreatic ducts (Fig. 6.70), they are sometimes erroneously referred to as adenomyomas. However, the orderly arrangement of the two muscle layers around the ducts distinguishes the two lesions. Heterotopic pancreas can become inflamed or develop malignancies, often leading to variably sized and shaped duodenal wall cysts. In the setting of chronic pancreatitis, the cysts are surrounded by smooth muscle and myofibroblastic proliferations and may result in duodenal stenosis (145).

Brunner Gland Hamartomas

Brunner gland hamartomas are very unusual polypoid or nodular lesions that occur in the 4th to 6th decades of life. It is difficult to ascertain their true incidence because the lesions are confused with Brunner gland hyperplasia. They contain an admixture of muscular, glandular, and fatty elements including heterotopic pancreatic acini and ducts. Rarely, they cause massive upper GI bleeding. These lesions usually lie entirely beneath the muscularis mucosae. Dilation of the glandular acini or ducts gives them a cystic appearance.
**FIG. 6.69.** Heterotopic pancreas. *A:* Cross section of a duodenal “polyp” produced by heterotopic pancreatic tissue in the submucosa. Prominent pancreatic ducts can be seen within the lesion. *B:* Histologic features. *BG* indicates surrounding Brunner glands.

**Peritoneal Encapsulation**

Peritoneal encapsulation is intestinal encasement by a peritoneal membrane. It probably results from the formation of an accessory peritoneal membrane from the mesocolon during the return of the intestinal loop to the abdomen following its herniation into the umbilical cord at the 10th fetal week. The dorsal mesentery covers most of the small intestine. It eventrates and moves counterclockwise, fusing with the posterior abdominal wall. Alternatively, the accessory membrane forms from part of the yolk sac peritoneum as it is drawn back into the abdominal cavity with the intestine (146).

**FIG. 6.70.** Heterotopic pancreas. This lesion, originally diagnosed as an adenomyoma, represents heterotopic pancreas. It consists of pancreatic ducts surrounded by smaller ductules and a prominent proliferation of muscle fibers. No acini or islets are present. The lesion usually remains asymptomatic and is detected incidentally. However, patients may present with cramps, obstruction, abdominal pain, vomiting, and constipation alternating with diarrhea (146). Peritoneal encapsulation may mimic a left mesocolic hernia. Peritoneal encapsulations can measure up to 20 cm. A thin, peritoneumlike sac encases the entire
small bowel. The sac lies freely and does not adhere to the mesentery, the parietal peritoneum, or other abdominal organs. The encased intestinal loops often have their own mesenteries. The histology of the encapsulated organs is normal. The histology of the membrane is that of a fibrous band. The differential diagnosis includes *sclerosing encapsulated peritonitis*, usually a complication of peritoneal dialysis or other abdominal interventions. Sclerosing encapsulating peritonitis is characterized by a thick, grayish white fibrous membrane covering the small intestinal wall. It must also be differentiated from the *abdominal cocoon*, in which the small bowel is found totally or partially curled up in a concertinalike fashion encased in a dense white membrane.
Adverse reactions to cow's milk affect approximately 0.1% to 7.5% of children. Infants generally present at 1 week to 3 months of age with protracted vomiting, malabsorption, diarrhea, and dehydration (539). Cow's milk sensitivity is the most frequent cause of this syndrome, but it also occurs with soy, egg, and wheat.

Reactions to cow's milk proteins may be classified clinically as quick onset (symptoms develop within 1 hour of food ingestion) or slow onset (symptoms develop after >1 hour from food ingestion). Quick-onset allergic reactions are IgE mediated and do not result in structural gastrointestinal damage (540). Slow-onset reactions may also be IgE mediated, or they may be the result of T-cell–mediated immune reactions. Such reactions may result in a macrophage influx associated with cytokine release and direct damage to gastrointestinal tissues (540).

Patients develop fever; leukocytosis; cyanosis; vomiting; massive blood-tinged, mucoid diarrhea; dehydration; and metabolic acidosis. Infants with a more insidious onset have diarrhea, protein-losing enteropathy, iron deficiency anemia due to chronic intestinal blood loss, weight loss, and failure to thrive (541). The abnormalities resolve on cow's milk–free diets and recur on cow's milk challenge. Important predisposing factors are age younger than 3, transient IgA immunodeficiency, atopy, and early bottle feeding.

The stool contains occult blood, PMNs, and eosinophils. Typically, the intestinal mucosa appears thin with patchy areas of villous atrophy producing a pattern resembling celiac disease (542). Biopsy specimens reveal flattened villi, edema, a prominent mononuclear cell infiltrate of the epithelium and lamina propria, and an accompanying small number of eosinophils. IELs are usually fewer than seen in celiac disease (542). There is often a large number of IgE-containing plasma cells. The histology becomes normal when milk, soy, or other offending antigens are removed from the diet.
Cystic Fibrosis

Cystic Fibrosis (CF) is an autosomal recessive disorder that affects 1 in 100,000 to 200,000 live births. CF results from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). More than 350 different point mutations in the gene are described (638). These different mutations produce a disease spectrum ranging from malnutrition, chronic bronchitis, asthma, and infertility to fatal pulmonary disease. CFTR is the receptor for *S. typhi* and it is conceivable that heterozygosity of the CFTR allele is selected for in certain populations because it protects against the development of typhoid (639).

CF patients develop a well-defined epithelial abnormality because the mutant protein fails to perform its normal function. The CFTR mutation results in a chloride transport defect with relative chloride impermeability in ductal epithelium and inhibited sodium chloride reabsorption resulting in hypertonic secretions. When secretion falls below a critical minimum, thick mucus develops, blocking the ducts and leading to glandular swelling, cystic degeneration, and atrophy (640). The small intestinal mucosa shows a relatively high expression level of CFTR mRNA with a decreasing gradient of expression along the crypt-to-tip axis. Cells in Brunner glands also express high CFTR levels.

CF has traditionally been diagnosed in the presence of chronic pulmonary disease, pancreatic exocrine insufficiency, and an abnormal sweat test. The clinical features are dominated by respiratory tract involvement. GI involvement affects most patients. The earliest symptom is intrauterine intestinal obstruction due to meconium ileus, which leads to perforation, meconium pseudocysts, meconium peritonitis, intestinal atresia, volvulus, and intussusception. These complications affect 50% of infants with meconium ileus (641). Meconium ileus is seldom seen in the absence of CF. The ileus results from inspissated, protein-rich meconium in the terminal ileum. Uncomplicated meconium ileus demonstrates a narrow terminal ileum with a beaded appearance. The ileal wall appears hypertrophic and becomes distended with extremely sticky, dark green pellets of protein-rich meconium and mucus (Fig. 6.226). Older patients experience severe anorexia, fecal impaction, rectal prolapse, pneumatosis, bleeding, watery stools, and intussusception (641). Intussusception, usually involving the ileocecal region, results from intestinal obstruction with a tenacious fecal bolus that acts as the lead point. Coexisting GI conditions are listed in Table 6.54. Many patients undergo pancreatic enzyme replacement, which causes colonic complications (see Chapter 13). The histologic appearance of the mucosa is similar in CF whether or not ileus is present. The villi appear taller than normal (Fig. 6.227). Increased mucus production results in enlarged goblet cells and an abundant layer of mucus attached to the luminal surface (Fig. 6.228). Although the goblet mucous cells are often larger than those seen in normal individuals, considerable overlap exists between normal individuals and patients with CF, so that distinguishing among them reliably is difficult at best. Small numbers of inflammatory cells infiltrate the lamina propria.
FIG. 6.226. Gross appearance of the bowel in cystic fibrosis.
Diseases Associated with Abnormal Deposits in the Tissues

Hemochromatosis

Hereditary hemochromatosis (HH), an autosomal recessive disease, causes 1 in 7,000 hospital deaths and 1 in 20,000 annual hospital admissions (628). When the disease presents in adults, the patients are usually homozygous for a missense mutation (C282Y) in the \textit{HFE} gene (629). Rare patients with mutations in the gene encoding the \textit{transferrin receptor 2} (TfR2) also present with a clinical phenotype that is similar to that seen in patients with \textit{HFE} mutations. The disease in adults tends to be milder than that seen in children. Most juvenile cases have been mapped to chromosome 1q where the gene \textit{hemojuvelin} (HJV), previously called \textit{HFE2}, is located. Some children with HH may have mutations in the HAMP gene, which encodes hepcidin, a peptide that plays a key role in iron absorption (630).

Because there is no efficient pathway for iron excretion from the body, it is generally accepted that the main underlying pathophysiology of hereditary hemochromatosis is the excessive absorption of dietary iron in the face of adequate raised body iron stores. However, the mechanism underlying the enhanced iron uptake in HH remains poorly defined and complex, with many biochemical defects being present as summarized in reference 630.

Iron deposits in many organs including the gut (Fig. 6.222), resulting in structural and functional abnormalities. Histologically, one sees mucosal iron deposits throughout the lamina propria in the macrophages, in the epithelium (Fig. 6.222), and in a perivascular distribution.

Hemosiderosis

Hemosiderosis usually follows oral or parenteral iron administration or multiple transfusions. The lamina propria of the villi contains macrophages filled with hemosiderin (Fig. 6.223). The epithelial cells lack iron, contrasting with primary hemochromatosis.

Pseudomelanosis

The presence of spotty brownish or blackish pigmentation in the duodenal mucosa seen at the time of endoscopy is termed \textit{duodenal melanosis} or \textit{pseudomelanosis} (631). Pigmentation is usually maximal in the second part of the duodenum and the duodenal bulb is affected to a lesser extent. The lesion affects AIDS patients and individuals on maintenance hemodialysis. Most patients receive oral iron supplementation. Patients may present with upper abdominal discomfort and anemia, which is the usual reason for the endoscopy. Mucosal pigmentation probably does not cause the symptoms. The macrophages acquire melanin, pseudomelanin, and iron. It is postulated that duodenal pseudomelanosis begins with mucosal iron deposition (631). However, sulfur becomes incorporated into the granules, altering their staining characteristics so that they react positively with both iron stains and the Fontana-Masson stain. These pigments include iron, sulfur, and other metallic substances.
**FIG. 6.222.** Small bowel in a patient with hemochromatosis (autopsy). An iron stain has been performed and demonstrates the presence of iron within the epithelium. It appears as bluish staining.
**FIG. 6.223.** Intestinal hemosiderosis. Iron stain shows the presence of numerous iron-filled intestinal lamina propria macrophages.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma and other monoclonal B-cell and plasma cell proliferations</td>
<td>Immunoglobulin light chain (AL)</td>
</tr>
<tr>
<td>Secondary amyloidosis associated with chronic disease</td>
<td>Serum amyloid-associated protein (AA)</td>
</tr>
<tr>
<td>Hereditary amyloidosis</td>
<td>Mutated transthyretin, prealbumin (AF)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>$\beta_2$-microglobulin</td>
</tr>
<tr>
<td>“Senile” amyloidosis</td>
<td>Normal transthyretin</td>
</tr>
</tbody>
</table>
Diseases Associated with Abnormal Deposits in the Tissues

Amyloidosis

The gastrointestinal tract is a frequent site of amyloid deposition in patients with systemic or isolated amyloidosis. The term *amyloidosis* includes heterogeneous disorders characterized by extracellular acellular hyaline deposits, known as amyloid. Amyloid consists of $\beta$-pleated polypeptides, the components of which vary (Table 6.52). The disease may be localized or systemic, affecting any organ or tissue. All types of amyloidosis (Table 6.53) affect the GI tract (632,633,634). If one is investigating a patient for amyloidosis, the best places to biopsy are the stomach and the rectum, since these are more likely to be involved than the small intestine.

GI amyloidosis remains asymptomatic or it may present with malabsorption, severe diarrhea, weight loss, abdominal pain, protein-losing enteropathy, ischemia, perforation, or a spectrum of motility disorders (634). Intestinal involvement, in the absence of a chronic inflammatory disease and in the absence of a family history, is most consistent with primary (AL) amyloidosis (Table 6.52). Patients with amyloidosis often have multiple myeloma, plasmacytomas, or Waldenstrom macroglobulinemia.

FIG. 6.224. Amyloidosis. A: Gross appearance of the bowel demonstrates a loss of the usual folds. The bowel is rigid and has lost its distensibility and motility. B: Histologic section of small bowel with amyloid as evidenced by the smudgy material in the area surrounding the submucosal blood vessels, as well as in the muscularis mucosae.

**TABLE 6.53 Forms of Amyloidosis**

<table>
<thead>
<tr>
<th>Form</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary amyloidosis</td>
<td>Systemic disease associated with plasma cell dyscrasia (deposits in heart, kidney, gut, liver, and spleen), especially around blood vessels and sometimes between muscle fibers (AL amyloid)</td>
</tr>
</tbody>
</table>


Secondary amyloidosis:
Systemic chronic disease; amyloid deposits in blood vessels and in the mucosa (AA amyloid)

Hereditary familial amyloidosis:
Perireticular deposition throughout muscle fibers and in neural plexuses; single organ amyloid deposition (AF amyloid)

Amyloid A (AA) produces a coarse mucosal pattern with innumerable fine granular elevations that reflect expansion of the lamina propria by amyloid deposits. Polypoid protrusions and fold thickening occur only in light chain protein, correlating with the presence of massive amyloid deposits in the muscularis mucosae and submucosa. α2-Microglobulin produces marked delays in transit time and dilation of large and small intestines due to extensive amyloid deposits in the muscularis propria (635).

Macroscopically, amyloidosis is not visible in its early stages, but in advanced disease the small bowel becomes thickened and waxy in appearance. It slowly converts to a rigid tube with walls measuring up to 1 cm in thickness (Fig. 6.224). Rarely, large amyloid deposits, often referred to as tumoral amyloid, cause masses and intestinal obstruction. Regardless of the specific type of amyloidosis, almost all patients have the so-called linear pattern of distribution in which the amyloid deposits heavily in the submucosal vessels, muscle fibers (Fig. 6.225), and nerve trunks. A much rarer type of amyloid deposition pattern is the so-called globular form of amyloid that complicates AA and AL amyloidosis (636,637). This form can result in the presence of multiple duodenal and jejunal polyps. Any unusual eosinophilic deposits with a homogenic quality potentially obliterating underlying structural features within the vasculature, muscularis mucosae, or lamina propria should raise the possibility of the diagnosis of amyloid. This would then prompt the use of specialized stains, such as Congo red, coupled with examination with polarizing microscopy to look for its presence. Perivascular deposits (Fig. 6.225) may cause patchy ischemia, infarction, perforation, or bleeding. Because amyloid is usually first detected in submucosal blood vessels, superficial small intestinal biopsies will fail to detect its presence. Lamina propria or submucosal deposits cause malabsorption. The mucosa only becomes infiltrated in cases with massive amyloid deposits, and patients may exhibit partial villous atrophy.
Drug Effects

Drugs affect small intestinal structure and function in many ways. They may act as direct mucosal toxins, inhibit mucosal enzymes, interfere with micelle formation, alter the physiochemical state of dietary ions or other drugs, cause ischemia, alter bowel motility by interfering with neural transmission or blocking receptor sites, and produce structural alterations. Drug injuries result from the drugs themselves or from byproducts of food–drug interactions.

Drugs that Inhibit Intestinal Transport or Cause Malabsorption

Drugs associated with malabsorption include arsenic, biguanides, methotrexate, methyldopa, azathioprine, and neomycin (253,254). Neomycin induces villous clubbing, brush border fragmentation, microvillus loss, lamina propria inflammation, and ballooning degeneration. Micelle disruption and decreased pancreatic lipase leads to malabsorption. Some progestational agents cause crypt atrophy of the hypoplastic type, resulting in an immaturity of the intestinal epithelium and giving rise to secondary malabsorption. Alcohol causes both mucosal and microvascular injury (255). It directly damages the crypts and villi, leading to malabsorption. Cyclamates cause reversible malabsorption. Histologically, the bowel is inflamed and shows crypt hypoplasia and slight villous atrophy and goblet cell depletion. Erythromycin produces diarrhea, increases GI motor activity, and inhibits intestinal absorption. Colchicine given regularly causes steatorrhea, megaloblastic anemia, and abnormal xylose absorption (256). Chemotherapeutic agents may induce lactose intolerance (257).

The eosinophilia-myalgia syndrome (EMS) usually follows ingestion of L-tryptophan. Patients present with profound eosinophilia, an abnormal hepatic profile, and myalgia. Some patients develop a connective tissue disease that resembles scleroderma (258) with dysmotility and diarrhea. GI involvement leads to significant malabsorption with steatorrhea, hypoalbuminemia, and weight loss. Diffuse eosinophilic infiltrates occur in the small bowel, stomach, and colon (259). The differential diagnosis of the GI eosinophilia usually includes parasitic infection, lymphomas, polyarteritis nodosa, allergic gastroenteritis, eosinophilic gastroenteritis, systemic mastocytosis, and Crohn disease.

Drugs Causing Vasculitis or Inhibiting Intestinal Blood Flow

Cyclosporine therapy following renal transplantation causes generalized microvascular small intestinal disease (260). High concentrations of potassium salts and hydrochlorothiazide cause venous smooth muscle spasm, producing ischemic ulcers, fibrosis, and strictures. Ingestion of oral contraceptives predisposes to superior mesenteric vein thrombosis. Ergotamine-induced vasoconstriction leads to small intestinal ulceration. Cocaine abuse results in bowel ischemia by blocking the reuptake of released norepinephrine and causing vasoconstriction and decreased blood flow. Patients experience sudden crampy abdominal pain and bloody diarrhea. Severe and prolonged ischemic episodes eventually result in bowel necrosis, perforation, peritonitis, or abscess formation. A different form of cocaine damage occurs in the so-called cocaine body packer syndrome. Body packers, or “mules,” ingest multiple small drug packets, which may rupture and cause death. Cocaine can also leak out from semipermeable wrappings to be absorbed through the mucosa (261).

Antineoplastic Agents and Antiproliferative Agents

Antineoplastic drugs often induce anorexia, diarrhea, and small intestinal morphologic changes secondary to massive cell death in the proliferative compartment. Cell death becomes apparent as apoptoses within an hour; the number of dead cells peaks within the first 8 hours (262). The dead cells or dead cell fragments are phagocytosed by neighboring healthy enterocytes and mucosal macrophages (263). Antineoplastic drugs also decrease crypt mitotic rate, villous height, and villous width. The morphologic changes superficially resemble those present in celiac disease.
Drug Effects

The epithelium becomes mucin depleted. Surface epithelial cells become foamy, brush borders are lost, and the enlarged pleomorphic nuclei contain prominent nucleoli. After a few days, lymphocytes and eosinophils infiltrate the lamina propria. In cases of severe damage, all crypts are affected and frank erosions or ulcers develop. Regeneration, recognizable by a burst in mitotic activity and marked variation in nuclear size, follows therapy cessation. Mitoses are present at all levels of the mucosa, even on the villous surface. These changes usually occur within 2 weeks, but inflammation and telangiectasia persist for up to a month. Megaloblastic nuclei develop in patients with vitamin B₁₂ or folate deficiency, particularly in patients on extended chemotherapeutic protocols (Fig. 6.125). Patients treated with adjuvant CTLA-4 monoclonal antibodies develop an autoimmune panarteritis that is characterized by aphthous ulcers, larger ulcers, intraepithelial lymphocytosis in the crypt bases, increased apoptoses, and a mononuclear cell infiltrate in the lamina propria (264).

Duodenal lesions may complicate the hepatic artery infusion therapy typically used to treat primary or metastatic liver tumors. The lesions consist of large solitary ulcers or polypoid inflammatory areas that cause a characteristic striking structural distortion and cellular pleomorphism. The changes affect the epithelium, stroma, and endothelial cells.

FIG. 6.125. Megaloblastic changes in a patient with cancer who received long-term chemotherapy.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs cause various small intestinal lesions (Table 6.10) (265). Sixty to seventy percent of patients develop an enteropathy associated with bleeding and protein loss. Patients most at risk for the development of intestinal disease are the elderly and those who have had prior GI abnormalities while on NSAIDs (266). Even in control populations, endoscopic abnormalities develop within 2 weeks of the start of NSAID therapy (267). The development of NSAID enteropathy is a multistep process involving biochemical and subcellular organelle damage, followed by a relatively nonspecific tissue reaction. There is increased intestinal permeability in most patients. It also likely involves decreased mucosal blood flow and prostaglandin levels and diminished neutrophil function (265), all of which can interfere with mucosal barrier integrity. NSAIDs also induce dose-dependent drug–enterocyte adducts (268). These relationships are modified in each patient by specific host responses, drug dose, route of administration, choice of
drug, and concomitant consumption of aspirin, alcohol, and other drugs. The nonselective cyclooxygenase (COX) inhibitors such as indomethacin or naproxen are more likely to cause intestinal damage than the more recently introduced selective COX-2 inhibitors (269).

### TABLE 6.10 NSAID-induced Small Intestinal Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravates duodenal peptic ulcer disease</td>
</tr>
<tr>
<td>Diaphragm (strictures)</td>
</tr>
<tr>
<td>Ulcers</td>
</tr>
<tr>
<td>Perforation</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>NSAID enteropathy</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
</tr>
<tr>
<td>Bile acid malabsorption</td>
</tr>
<tr>
<td>Enhanced intestinal permeability</td>
</tr>
<tr>
<td>NSAID, nonsteroidal anti-inflammatory drug</td>
</tr>
</tbody>
</table>

In the duodenum, the drugs cause erosions, ulcers, and nonspecific inflammation. If *H. pylori* is present, the effects may be additive. Distal erosions, ulcers, and strictures may be seen at the time of endoscopy (270). Multiple mucosal diaphragmatic strictures, also known as *mucosal diaphragm disease*, are now thought to be pathognomonic for NSAID injury. Circumferential linear ulcers may be the precursors to the diaphragms. Smaller ulcers often surround larger ones. Three patterns of diaphragm-like strictures exist: (a) extreme exaggeration of the normal plica circularis in which delicate, elongated folds composed of minimally eroded mucosa, muscularis mucosae, and submucosa containing dense collagen bundles obstruct the lumen; (b) broad-based rigid strictures consisting of dome-shaped accumulations of hyalinized collagen occupying the submucosa and interdigitating with the muscularis mucosae; and (c) conventional flat strictures. The mucosa may show nonspecific inflammation, mucosal eosinophilia, increased numbers of intraepithelial lymphocytes, and increased numbers of apoptoses in the crypt bases. In patients who have had ulcers, there may be areas of pyloric metaplasia underlying a distorted and chronically damaged mucosa.

### Immunosuppressive Agents

Patients on immunosuppressive therapies experience various GI complications, some of which have an ischemic basis. Ulceration and hemorrhage, with superimposed infection and perforation, also occur. *Indomethacin* inhibits mucosal bicarbonate production and causes localized ulcers, intestinal perforations, and tissue eosinophilia. Villous necrosis, hemorrhage, and neutrophilic infiltration also develop. This predisposes the duodenal mucosa to peptic ulceration and to enhanced bacterial translocation. *Corticosteroids* deplete lymphoid tissues, including gut-associated lymphoid tissues. Lymphoid follicles and domes decrease in size. The dome epithelium develops focal small erosions with M-cell necrosis (271). The follicular regions of Peyer patches become severely B-cell depleted. These histologic effects have a profound impact on the mucosal immune response and host resistance to microbial infections because of the important role played by M cells in mucosal defense.

### Heavy Metals

Clinical features of heavy metal toxicity include nausea, vomiting, abdominal cramps, and severe, watery, bloody diarrhea. *Iron* damages the intestinal tract after prolonged contact and may cause intestinal perforation. Other heavy
metals, including cadmium, mercury, and zirconium, cause degenerative changes. **Gold** produces enterocolitis, deep ulcers, and tissue eosinophilia (see Chapter 13). **Lead** causes small bowel toxicity by modifying the biochemical properties of the enterocyte surface coat, which then leads to microvillus damage (272). **Aluminum** toxicity occurs at low levels of ingestion. Patients develop enteropathy, encephalopathy, bone disease, and anemia (273). **Cadmium** toxicity results in a decrease in the number of Paneth cells; those that remain appear vacuolated (274).

**Other Drug- and Chemical-Induced Injuries**

Enterocolitis may complicate the use of levetiracetam in patients with refractory epilepsy (275). The use of povidone iodine for peritoneal lavage may result in sclerosing encapsulating peritonitis (276). Intestinal hematomas may complicate the use of anticoagulants (277). **Clofazimine** used to treat leprosy may cause a crystal-storing histiocytosis that may mimic hematologic malignancies. The crystals appear red on frozen sections and they show a bright red birefringence (278).
Peptic duodenitis and peptic duodenal ulcers represent different phases in the response to increased acid secretion often as the result of antral predominant H. pylori gastritis. The incidence of duodenal ulcers also increases in cigarette smokers, patients with chronic renal disease, and alcoholics. Disturbed motility also predisposes to active duodenal ulceration due to prolonged mucosal contact with the acid. Factors associated with refractory ulcers are listed in Table 6.4. Severe peptic duodenitis also occurs in patients with Zollinger-Ellison syndrome.

Peptic duodenitis is typically confined to the duodenal bulb. Endoscopic appearances vary from simple erythema to mucosal friability and nodularity. The erythema results from shunting of blood to the villous tips, a change induced by the hydrochloric acid (169). Severe cases exhibit erosions and ulcers. Alternatively, mucosal atrophy, thickening, or irregularity is present.

**TABLE 6.4 Factors Associated with Refractory Ulcers**

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>Intestinal wall penetration by the ulcer</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Use of nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Gastric outlet obstruction or duodenal stenosis</td>
</tr>
<tr>
<td>Postsurgical bypassed antrum without vagotomy</td>
</tr>
</tbody>
</table>

The principal findings of peptic duodenitis include any or all of the following: (a) inflammatory cells in the epithelium or lamina propria; (b) altered enterocyte morphology due to degeneration, regeneration, or the presence of foveolar metaplasia; (c) mucosal hemorrhage and edema; and (d) Brunner gland hyperplasia (Fig. 6.86) and foveolar metaplasia. The foveolar metaplasia may be extensive or patchy in its distribution. The inflammation may include neutrophils, lymphocytes, plasma cells, and eosinophils. Patients may also develop lymphoid hyperplasia (Fig. 6.87). Whitehead et al proposed dividing duodenitis into three grades based on the severity of the inflammation and the villous architecture (170). In the severest form of duodenitis, the villi appear flat (Fig. 6.87). The superficial epithelium and the brush border become progressively less distinct, with nuclear pseudostratification, mucosal erosions, and foveolar metaplasia. Neutrophils extend into the crypts and Brunner gland ducts. Lymphoid aggregates and hyperplasia, vascular dilation, and edema may all be present.
FIG. 6.84. Duodenitis. The epithelium appears very reactive and inflamed. There is syncytial formation.

FIG. 6.85. Crypt abscess in a patient with active duodenitis and associated active regeneration.

The presence of foveolar cell metaplasia (gastric surface epithelial metaplasia) provides a helpful clue to the diagnosis of peptic duodenitis (Fig. 6.87). Foveolar metaplasia probably represents an adaptive response to either duodenal hyperacidity or H. pylori infection (171) and may protect against ulceration because this epithelium has the ability to transport hydrogen ions.
out of the mucosa back into the GI lumen (see Chapter 4). If *H. pylori* bacteria are present in the stomach, some may colonize areas of foveolar cell metaplasia in the duodenum via the same specific adherence mechanisms used in the stomach (see Chapter 4). The metaplastic cells are histologically identical to foveolar cells in the stomach, and not surprisingly, they express a gastric mucinous phenotype rather than an intestinal one (171). *H. pylori* attached to the foveolar cells then contribute to an acute or chronic active duodenitis and the development of duodenal peptic ulcer disease (172). A high density of cagA-positive strains of the bacteria in the patients with severe duodenitis is an important determinant of duodenal ulcer disease (173). The most persuasive argument supporting the dominant role of *H. pylori* in duodenal ulcer disease is the dramatic decrease in relapse rates after successful cure of the infection, with subsequent healing of the mucosa (174).

Brunner gland hyperplasia is common in patients with *H. pylori* infections and peptic duodenitis. It is characterized by a nodular proliferation of normal-appearing Brunner glands that have a lobular architecture accompanied by ducts and stromal elements. Voluminous Brunner glands may extend high into the overlying mucosa. Histologically, the glands appear identical to normal Brunner glands except that they are increased in number and size. They retain their lobular architecture, but the lobules vary in size and fibromuscular strands course through the lesion. Larger polypoid lesions may become superficially eroded or they may bleed or cause obstruction, requiring endoscopic or surgical removal (175). Exceptionally, areas of dysplasia may develop in the hyperplastic Brunner glands (176). When the latter occurs in patients with areas of foveolar metaplasia and Brunner gland hyperplasia, both the metaplastic and hyperplastic glands may show cytologic atypia, leading some to suggest that these lesions may be precursors of Brunner gland carcinoma (176).
Duodenal Peptic Diseases

**FIG. 6.86.** Peptic duodenitis. *A:* Low magnification showing Brunner gland hyperplasia, erosion and distortion of the overlying epithelium, and a lymphoid aggregate (*arrows*). *B:* Higher magnification of the lining epithelium demonstrates eroded foveolar metaplasia. No goblet cells or enterocytes are identified. *C:* Almost complete replacement of the duodenal villi by gastric surface (foveolar) epithelium. *D:* Higher magnification of the foveolar epithelium showing various degrees of metaplastic change. *Helicobacter pylori* is present in the overlying exudate (*arrow*).

It should be noted that many of the histologic features of peptic duodenitis are nonspecific, except for the foveolar metaplasia. Similar findings occur in patients with Crohn disease, stress-induced duodenitis, celiac disease, NSAID-induced injury, and certain infections.

**Peptic Ulcer Disease**

A major insight in the last decade or so is that gastric peptic ulcers primarily result from altered mucosal defenses, whereas duodenal ulcers (DUs) result from hyperchlorhydria. *H. pylori* plays a vital role in peptic ulcer development in both sites. A complicated relationship exists between host defense mechanisms and the presence of elevated acid, pepsin levels, and *H. pylori* (Fig. 6.88). Indeed, *H. pylori* is found significantly more often in patients with peptic ulcer disease and duodenitis than in patients with normal endoscopic findings. *dupA* is a novel *H. pylori*-encoded gene that associates with an increased risk for the development of duodenal ulcer disease (177). The decline in duodenal ulcer disease in recent decades is likely the result of two factors, the decline in the incidence of *H. pylori* infections as discussed in Chapter 4 and the widespread use of acid-suppressive therapies.

Peptic duodenitis progresses from erosive peptic duodenitis with superficial mucosal loss to frank peptic DUs. The sequence of events leading to DU formation includes mucosal inflammation, weakening of the mucous bicarbonate barrier, superficial epithelial cell damage, increased serum gastrin levels with defective feedback control, a possible increase in parietal cell mass, and the development of gastric metaplasia in the duodenal cap. Colonization by *H. pylori* further weakens mucosal defenses and plays a major role in the genesis of the peptic ulcer disease (178).
Patients with DUs experience dyspepsia and intermittent abdominal pain. DUs are more prone to perforate (Fig. 6.89), hemorrhage, or cause obstruction than are gastric ulcers. Bleeding causes massive upper GI hemorrhage in a significant number of cases. Rebleeding, sometimes massive, affects 13.6% to 32% of patients, tends to affect older patients (especially those on NSAIDs), and occurs more commonly in patients with a visible vessel (Fig. 6.89) (179). DUs in children may present in atypical ways. Only about 50% of children experience dyspepsia, approximately 61% have nocturnal pain, abdominal pain occurs in 70%, and bleeding affects about 33% of patients. Children with cystic fibrosis are particularly prone to develop DUs due to decreased duodenal bicarbonate secretion. Most duodenal ulcers develop in the first part of the duodenum, usually immediately distal to the pylorus.

Multiple DUs have different clinical features and pathophysiologies, and represent a more aggressive side of the ulcer spectrum (180). Peptic ulcers in the second and third portions of the duodenum or jejunum, repeated penetrating or perforating ulcers in the third portion of the duodenum or first portion of the jejunum, or the presence of multiple ulcers (Fig. 6.89) should arouse suspicion of Zollinger-Ellison syndrome.

Refractory ulcers heal slowly, recur rapidly after initial healing, or follow a prolonged course of exacerbation and short or absent remissions. Scarring leads to deformation of the duodenal bulb and stricture formation. Larger ulcers take longer to heal and recur more often once they have healed.

Grossly, DUs appear circular or oval, usually measuring <3.0 cm in maximum diameter (Fig. 6.90). Ulcers located posteriorly in the bulb are more likely to bleed than those situated elsewhere (181) because two sizable arteries (i.e., the pancreaticoduodenal and the gastroduodenal) lie in the vicinity. Penetration of the duodenal wall by an ulcer results in erosion...
of one or both vessels (Fig. 6.91), producing massive hemorrhage. Perforation gives rise to generalized peritonitis. Ulcer scarring may lead to the formation of a prestenotic diverticulum. The histologic features of DUs resemble those of gastric ulcers (see Chapter 4). The surrounding mucosa usually shows evidence of peptic duodenitis. Antral gastritis is also usually present, as is *H. pylori*. These may be restricted to the stomach but they may also colonize areas of foveolar metaplasia.
Embryology and Development

Gastrulation occurs 2 weeks after fertilization, inducing a massive rearrangement of the embryo. It transforms a relatively uniform cell ball into a multilayered organism with recognizable body plans. Some cells divide faster than others, resulting in a change in embryonic shape. Cells converge on the embryonic midline. As they crowd together, they push each other toward the future head and tail, and the embryo lengthens.

There are two major steps in gastrointestinal (GI) development: The formation of the gut tube and the formation of individual organs each with their own specialized cell types (1). These events are regulated by homeobox or Hox genes (2), particularly Cdx1 and Cdx2, which are only expressed in the intestine. These two genes are important in the anterior to posterior patterning of the intestines and in defining patterns of proliferation and differentiation along the crypt–villus axis (3). Their importance in intestinal differentiation is important not only in normal intestinal development, but also in the development of intestinal metaplasia in the stomach and in Barrett esophagus as discussed in Chapters 2, 3, 4. Other signaling cascades also play a major role in gut development. These include the Hedgehog, Hh, Bmp, FGF, and Wnt signaling pathways (4,5,6,7,8). They are used at multiple steps of the developmental process. Congenital abnormalities, including malrotations, associate with germline mutations/deletions of genes encoding hedgehog signaling components as reviewed in reference 8.

The endoderm is the precursor to the gastrointestinal epithelial lining, and endodermal development requires the expression of the homeotic genes MIXER, SOX17α and SOX17β (9). Multiple interactions occur between the endoderm, mesoderm, and ectoderm during development. The endoderm induces the mesoderm, conferring on it a dorsal–ventral pattern. Endoderm and ectoderm contact one another in the 2- to 4-week embryo, with the endoderm forming the yolk sac roof. This contact results in up-regulation of growth factors, including transforming growth factor (TGF)-α, TGF-β, epidermal growth factor (EGF), and hepatocyte growth factor (HGF), all of which stimulate cell proliferation. A primitive gut forms in the third to eighth weeks secondary to cephalocaudal and lateral foldings that incorporates the dorsal endodermally lined yolk sac cavity. The amnion and yolk sac communicate through the neuroenteric canal (Fig. 6.1). The neuroenteric canal closes and the notochord grows forward, becoming intercalated within the endoderm. The neural tube then separates from the ectoderm. Mesoderm surrounds the notochord, separating the ectoderm and endoderm (10). (Gastrointestinal duplications associate with a defective spinal cord and/or vertebra if mesodermal ingrowth does not occur and neural and gastrointestinal elements fail to separate.)

Splanchnic mesoderm surrounding the primitive gut forms the muscular and connective tissue layers. The former yolk sac elongates under the developing nervous system to form the primitive foregut anteriorly and the primitive hindgut posteriorly. The central portion develops into the midgut, which has a free communication with the yolk sac (the vitellointestinal duct). The anterior abdominal wall develops by simultaneous cranial, caudal, and lateral infoldings, which attenuate the yolk sac, causing it to become intracoelomic in location (Fig. 6.1). The foregut is short at first, lying closely apposed to the developing vertebrae, and it becomes suspended by a short mesentery. The foregut gives rise to the esophagus, stomach, duodenum as far as the ampulla of Vater, liver, pancreas, and respiratory system, and it has its own arterial blood supply deriving from the celiac axis (11).

The duodenum distal to the bile duct, and the jejunum, ileum, cecum, ascending colon, and proximal one half to two thirds of the transverse colon derive from the midgut and are supplied by the superior mesenteric artery. At about the 5- to 12-mm stage, the midgut lengthens, becoming tubular and growing away from the vertebral axis. It then coils, inducing dorsal mesenteric development. During the fifth fetal week the midgut is U-shaped and suspended by a dorsal mesentery distributed around the superior mesenteric artery. The apex of the intestinal loop communicates with the vitelline duct, which rapidly decreases in size. During the fifth to sixth fetal weeks, increases in intestinal length, along with the disproportionate amount of abdominal space occupied by the fetal liver, cause the intestines to herniate into a mesothelial-lined sac within the umbilical cord (11). The cecum develops on the caudal limb and the vitellointestinal duct lies at the apex. A small portion of the caudal limb, between the attachment of the vitellointestinal duct and cecum, forms the terminal ileum. The midgut starts sliding back into the abdomen between the 10th and 12th fetal weeks, a process accomplished in three phases (Fig. 6.2). The first is a 90-degree counterclockwise rotation around the superior mesenteric...
artery. The second occurs at about the 10th week, when there is enough room for the bowel to return to the abdominal cavity. The cranial loop of the small bowel re-enters the abdomen, first passing to the right of the superior mesenteric artery and rotating a further 180 degrees, thereby making the total rotation 270 degrees. Small intestinal loops fill the central abdomen. Although an anatomically distinguishable intestinal tract develops early in embryonic life, functional absorptive cells do not appear until later in gestation. Intestinal differentiation occurs along a proximal-to-distal gradient. The epithelium develops from simple endodermal tubules early in embryogenesis (12) appearing as a multilayered sheet of undifferentiated endodermal cells with short microvilli. Deeper cells do not demonstrate any polarity; mitoses occur throughout the epithelium. Villous formation with mesenchymal infiltration into the villous core begins at the ninth gestational week. Between 9 and 10 weeks, the stratified epithelium converts to a simple columnar epithelium (13). The progenitor cell region, which gives rise to the crypts, localizes to the intervillous area (14). Villi are long and tapering by 20 weeks and the muscle coats are obvious at this time. Enterocyte proliferation occurs along the entire villous length until several days before birth.

The diverse small intestinal functions require multiple cell types arranged in specific locations. Enterocyte differentiation depends on the cell's location along both a vertical and a horizontal axis. It parallels the pattern of cellular migration from the base of the crypts to the tips of the villi. The horizontal axis refers to a cell's position in the intestine as one progresses from the duodenum distally to the ileum (Fig. 6.3). Functional differences along both the vertical and the horizontal axes (15) reflect
both different patterns of gene expression and different epithelial cell types. Fully differentiated cells of a given lineage may express a different spectrum of gene products depending on their location along the gut (15). The pattern of brush border enzyme gene expression in the distal small intestine resembles that in the proximal gut, but it is delayed by several days. This establishes a proximal-to-distal gradient of gene expression (9). The basis for regional differences in gene expression results from differences in the transcription factors that interact with the promoter and enhancer region of these genes. Homeobox genes participate in establishing differentiation gradients during development and then maintaining these patterns in adult tissues. The epithelium finishes its morphologic differentiation into enterocytes, goblet cells, endocrine cells, and Paneth cells in the 4 to 5 days prior to birth (16).

This differentiation process appears to rely on *Math1* and *Cdx2* expression (17,18).

---

Primordial intestinal lymphoid structures appear approximately halfway through gestation. At the time of birth, Peyer patches have the greatest density of any proliferating lymphoid tissue in the body. T- and B-cell aggregates form early Peyer patches by 16 weeks’ gestation, and by 19 weeks organized Peyer patches are present. T cells populate the lamina propria and epithelium from 11 weeks’ gestation and increase in number thereafter. Following birth, there is a marked increase in the number of Peyer patches, reflecting the initial response of the host immune system to environmental antigens passing through the intestinal tract.
Eosinophilic Diseases

Food Allergies

Up to 45% of the population report adverse reactions to food (572). Various enteric antigens play a role in the pathogenesis of conditions loosely termed food allergic diseases; many conditions associate with food allergies (Table 6.42). Milk and other dairy products are more commonly allergenic among children than among adults. Other common offending agents include nuts, eggs, and soy products (573). The increased susceptibility of young infants to food allergies results from their general immunologic immaturity and the overall immaturity of the GI tract (244). There is also a variant of the IPEX syndrome that results in autoimmune enteropathy, hyper-IgE, and severe food allergies that become manifest after weaning. It results from a deletion in the FOXP3 gene (574).

Food allergies affect up to 8% of children. Tissue damage results from either the primary pathologic event or from unavoidable side effects of protective immune responses. A definitive diagnosis of a food allergy requires (a) the demonstration of an unequivocal clinical reaction after a controlled food challenge and (b) elimination of the symptom complex subsequent to removal of the offending food. Thus, one can accept the diagnosis of milk allergy only if (a) symptoms subside with elimination of milk from the diet, (b) symptoms occur within 48 hours after refeeding, (c) three sequential challenges are positive, and (d) symptoms abate after each challenge.

**TABLE 6.42 Diseases Associated with Food Allergies**

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic anaphylaxis</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Allergic alveolitis</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Cow's milk protein enteropathy</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Angioedema</td>
</tr>
<tr>
<td>Atopic eczema</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
</tbody>
</table>

The clinical features of food allergy are extensive and vary in location, severity, and time of onset (575). Clinical findings correlate with the site and extent of mast cell degranulation. The principal organs affected by allergic food reactions are the intestinal tract, skin, and lungs. In some patients, the signs and symptoms of an immediate reaction remain limited to the GI tract, with cramping, bloating, nausea, vomiting, diarrhea, growth failure in children, and weight loss in the adult. Any disease that disrupts mucosal integrity promotes the development of a food allergy by allowing allergens into the lamina propria, facilitating their interaction with immune cells.

Histologically, biopsies show partial villous atrophy with vacuolated cytoplasm, particularly at the surface, and mucosal eosinophilic infiltrates. The eosinophils may aggregate in the lamina propria or extend into the epithelium (Fig. 6.205). Since these infiltrates are usually focal, multiple biopsies are often required to make the diagnosis (576). Also, lymphonodular hyperplasia of the duodenal bulb is present in more than 50% of cases.

**Eosinophilic Gastroenteritis**

Eosinophilic gastroenteritis is a diagnosis applied to a diverse group of patients who share the following: (a) GI symptoms, (b)
gastrointestinal eosinophilic infiltrates, and (c) no demonstrable cause of the eosinophilia such as parasitic infection or a specific allergic response. Nonetheless, many patients have allergic histories, including hay fever, allergic rhinitis, eczema, asthma, drug sensitivities, or elevated IgE levels. Peripheral eosinophilia affects 72% to 90% of patients. Some patients have associated connective tissue diseases, including scleroderma, scleroderma variants, polymyositis, and dermatomyositis. Food intolerance has been postulated as an etiologic factor in eosinophilic gastroenteritis. However, most cases lack a specific allergen that triggers the disease and some patients demonstrate few or no allergic features. The most likely explanation for these discrepancies is that multiple unidentified antigens cause the disease (577).

**FIG. 6.205.** Allergic enteritis. The lamina propria contains an eosinophilic infiltrate. The infiltrate causes subtle epithelial changes including increased mitotic activity (arrow), eosinophilic degranulation within the epithelium (double arrow), and a lamina propria infiltrate.

The clinical presentations vary widely. GI symptoms may include nausea, vomiting, diarrhea, abdominal pain, growth retardation, malabsorption, steatorrhea, protein-losing enteropathy, secondary iron deficiency anemia, hypoalbuminemia, and intestinal obstruction. Patients may also present with an acute abdominal emergency such as acute appendicitis or intestinal perforation. Rare fatalities have been described. The clinical presentation depends on both the site and extent of the intestinal involvement. Any part of the gut may be involved, but the stomach and small intestines are the most common sites of involvement. Mucosal disease generally presents with diarrhea, bleeding, malabsorption, and protein-losing enteropathy. Submucosal disease manifests as intestinal obstruction and abdominal pain. Ascites develops when eosinophils infiltrate the serosa or muscularis propria. If the patient
develops ascites, the fluid contains eosinophils. Most patients with eosinophilic enteritis show at least partial spontaneous improvement. Patients respond dramatically to a short course of corticosteroid therapy.

**FIG. 6.206.** Eosinophilic gastroenteritis. *A:* Resection specimen showing adherent loops of small bowel with fistulae between them. The origin of the fistulae is seen as dark geographic areas. The bowel was resected due to a perforation (arrow). Light from the background shows through the perforated site. *B:* Histologic section through an area of the specimen showing the intense eosinophilic infiltrate. (Case courtesy of the Department of Pathology, Tygerberg University, Republic of South Africa.)

The lesions of eosinophilic gastroenteritis tend to be patchy and multiple (Fig. 6.206), and they may be localized or diffuse. Involvement of GI segments measuring up to 50 cm long produces diffuse bowel thickening. The bowel becomes markedly rigid and edematous and contains prominent eosinophilic infiltrates. Increased numbers of eosinophils populate the lamina propria and the epithelium shows variable degrees of damage. The number of eosinophils varies; they often range up to 50 eosinophils per high-powered field (hpf) (Fig. 6.207). However, it should be kept in mind that the presence of eosinophils is nonspecific because they are also seen in other diseases (Table 6.33). Because tissue eosinophils may be increased in other diseases, it is helpful to find the eosinophils extending into the underlying submucosa or to find associated edema (Fig. 6.208). It is also helpful to find eosinophils within the epithelium of the crypts or villi. The localized eosinophilic infiltrates may cause crypt hyperplasia, epithelial cell necrosis, and villous atrophy. In a minority of cases (approximately 10%), a diffuse enteritis develops with complete villous atrophy producing an appearance identical to that seen in celiac disease. Variable degrees of fibrosis, necrosis, atrophy, and mast cell infiltrates also develop. Often the lesions occupy the submucosa. Submucosal edema is common, and destruction of the wall and fibrosis may also occur. Unexpectedly, large numbers of degranulating mast cells may be present. Contiguous smooth muscle fibers in the muscularis mucosae appear hyperchromatic, enlarged, and irregular.
with reactive nuclei separated by inflammatory cells. The muscularis propria usually shows some degree of eosinophilic infiltration. Sometimes the mesenteric lymph nodes become hyperplastic and infiltrated with eosinophils. Establishing the diagnosis by endoscopic biopsy can be problematic. In about 10% of cases, mucosal biopsies are nondiagnostic, either because of the sampling error inherent in diagnosing a patchy process or due to mucosal sparing. In these instances, the diagnosis is established by multiple biopsies, full-thickness biopsy, or surgical resection.

**FIG. 6.207.** Eosinophilic gastroenteritis. *A:* Medium-power micrograph illustrating the marked eosinophilic infiltrate within the muscularis propria and deep submucosa. The individual fibers of the muscularis propria are separated by the edema. *B:* In some places the infiltrate centers around small vessels and associates with prominent edema.
Hypertrophic Eosinophilic Gastroenteropathy

Patients with hypertrophic eosinophilic gastroenteropathy are typically children who present with recurrent bowel obstruction and protein-losing enteropathy. Grossly, ileal and/or jejunal mucosa appears thickened with apparent pseudopolyps. The patients develop massive elongation of the small intestinal villi. This results in a crypt:villus ratio that is two to four times that seen in the normal small bowel. This elongation appears to result from decreased apoptosis. The mucosa may be ulcerated and the inflammatory infiltrate overlying the ulcers as well as the lamina propria is heavily infiltrated by eosinophils. Eosinophils may also be present in the submucosa and muscularis propria (486).
Food-Associated Illnesses

Patients with food-related complaints pose a diagnostic challenge to their physicians because it is often difficult to document the underlying nature of the offending agent(s). Patients tend to report vague symptoms that are often chronic and delayed in onset. The patients generally fall into several distinct clinical groups: (a) patients with IgE-dependent mediated hypersensitivity allergic reactions, (b) patients who consume infected foods, (c) patients who consume food containing metals or toxins, and (d) infants on certain formulas.

Infants who receive hydrolysate formulas may develop necrotizing enterocolitis. This formula activates intestinal mast cells, thereby stimulating local immune mechanisms and inflammatory cells and increasing epithelial permeability (279). The mucosa becomes infiltrated with chronic inflammatory cells. Certain food additives induce GI disease via allergic reactions. Yellow dye No. 6, an artificial coloring found in candy, foods, and many drugs, serves as a GI allergen and results in allergic gastroenteritis with mucosal infiltration by large numbers of eosinophils (280,281). Heavy metal intoxication may occur when foods are stored or cooked in tin, antimony, or copper containers. Patients develop GI symptoms, including diarrhea. Patients who consume poisonous mushrooms develop GI symptoms 1 to 8 hours following their consumption. Rapid-acting toxins usually affect a patient within 1 hour, and patients develop diarrhea and abdominal pain. Patients often remember consuming food with a metallic taste.

Seafood Neurotoxins

There are three similar syndromes produced by neurotoxins ingested in seafood: Paralytic shellfish disease, ciguatera, and puffer-fish intoxication. The neurotoxins are produced by dinoflagellates, the marine algae responsible for red tides (282). The toxins block voltage-gated sodium channels in myelinated and nonmyelinated nerves. These disorders are often misdiagnosed and attributed to fish allergies, gastroenteritis, or nonspecific neurologic disorders. Paralytic shellfish poisoning results from ingestion of bivalve mollusks (mussels, clams, oysters, and scallops) that contain toxins produced by the Gonyaulax species of dinoflagellates. GI symptoms include nausea, vomiting, abdominal pain, and diarrhea. Ciguatera is the most common fish-borne illness worldwide and is the most common type of nonbacterial food poisoning reported in the United States. Ciguatera follows consumption of fish, oysters, or clams. GI symptoms occur within the first 3 to 6 hours and include nausea, watery diarrhea, vomiting, and abdominal pain. It results from toxin or toxins produced by the dinoflagellate Gambierdiscus toxicus. Puffer-fish intoxication occurs within 4 to 10 hours of ingesting toxin-contaminated seafood. The toxins in these related disorders cause severe congestion of the villous and submucosal vessels with red cell extravasation into the lamina propria. Degeneration of microvilli also develops followed by localized desquamation of cells from the villous tips.

Scombroid Poisoning

The highest morbidity worldwide from fish poisoning results from ingestion of spoiled scombroid fish such as tuna, mackerel, and jacks. The syndrome is produced by Gram-negative enteric bacteria usually of the Proteus or Klebsiella species with decarboxylate histidine-producing saurine, a histaminelike substance (283). The scombroid toxins represent metabolic byproducts of bacterial degradation of fish flesh (284). GI symptoms include nausea, diarrhea, and, less commonly, vomiting. The diagnosis is made clinically, and there are no specific laboratory tests to diagnose the disorder. Affected patients invariably report a metallic, sharp, or peppery taste of the consumed fish.

Bacterial Food-Borne Diseases

Many food-related disorders result from the consumption of infected foods as discussed in a later section.
Graft Versus Host Disease

GVHD is an immunologic disorder that results in severe gastrointestinal damage. It represents the response of immunocompetent donor cells to the histocompatibility antigens of the recipient. GVHD follows bone marrow or organ transplantation. Less commonly, it complicates maternal–fetal cell transfer in immunodeficient children (615) or transfusion of nonirradiated cells and blood products (616). GVHD also associates with malignant thymoma.

Basic requirements for GVHD reactions to occur include the following: (a) the graft must contain immunocompetent cells, (b) the host must be sufficiently genetically different from the graft to be perceived as antigenically foreign, and (c) the host must be unable to reject the graft (617). These conditions allow engrafted cells to react to the host through immunologically mediated processes. The incidence of GVHD ranges from <10% to >80%, depending on the degree of incompatibility, the number of T cells in the graft, patient age, and the nature of the immunosuppressive regimen (617). It should be remembered that GVHD may occur even in fully matched MHC donors and recipients due to incompatibilities in minor histocompatibility antigens. The incidence of GVHD is possibly higher in blacks than in other individuals.

CD8+, CD3+, and TiA1+ cytotoxic T cells mediate epithelial cell death in GVHD (619). CD8 cells recognize class II MHC-restricted antigens, producing the lymphokines that lead to the development of the enteropathy associated with P.444

GVHD (620). Apoptosis may occur through the Fas/Fas ligand pathway (621).

Acute GVHD occurs within days (7 to 100) in recipients who are not HLA matched or in patients without any prophylaxis. Rarely, acute GVHD occurs later than 100 days posttransplant (618). It is characterized by epithelial cell death mainly in the gastrointestinal tract, liver, and skin, whereas chronic GVHD associates with fibrosis of these and other organs. Clinical features range from mild to intractable diarrhea, malabsorption, abdominal pain, protein-losing enteropathy, and severe malnutrition.

Chronic GVHD is less common than acute GVHD and occurs more than 100 days following transplantation either as an extension of acute GVHD or following a quiescent disease-free interval. It develops up to 400 days following transplantation (615). Fifteen to forty percent of long-term survivors suffer from chronic GVHD. It may result from long-living lymphocytes of donor origin that have become sensitized to unknown antigens, probably minor histocompatibility antigens of the host (622).

The principal target organs of GVHD include skin, GI tract, biliary tree, bone marrow, and lymphoid tissues. These organs have high cell turnover rates and may continually express differentiation antigens, resulting in increased immune surveillance. Alternatively, cells in these organs may harbor latent viruses that could act as targets for donor immune surveillance.

The typical clinical presentation of acute GVHD includes skin rashes, nausea, anorexia, profuse watery diarrhea, intestinal hemorrhage, ileus, cramped abdominal pain, abdominal tenderness, paralytic ileus, malabsorption, and jaundice. The intestine is involved in 70% of cases (623). Intestinal infections account for 13% and acute GVHD for 48% of diarrheal processes in bone marrow transplant patients. The most common infections are astrovirus, C. difficile, adenovirus, and CMV. The degree of diarrhea does not always correspond to the severity of the intestinal inflammation. The severity of intestinal disease varies from grade I to grade IV (Table 6.49). The mortality of moderate to severe acute GVHD is as high as 50%.
FIG. 6.219. Graft versus host disease. A through C show increasing degrees of severity. A: Areas of intestinal ulceration are present in a moderately affected patient. B: More diffuse ulceration and marked erythema. C: The bowel has been converted to a fibrotic, rigid tube with little residual intervening mucosa.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stage I to stage II skin rash; no gut involvement; no liver involvement; no decrease in clinical performance</td>
</tr>
<tr>
<td>II</td>
<td>Stage II to stage III skin rash; stage I gut involvement or stage I liver involvement or both; mild decrease in clinical performance</td>
</tr>
<tr>
<td>III</td>
<td>Stage II to stage III skin rash; stage II to stage III gut involvement or stage II to stage IV liver involvement or both; marked decrease in clinical performance</td>
</tr>
<tr>
<td>IV</td>
<td>Similar to grade III with stage II to stage IV organ involvement and extreme decrease in clinical performance</td>
</tr>
</tbody>
</table>

Mucosal biopsy provides a sensitive test for detecting GVHD in the intestine. However, the biopsy should not be taken during the first 3 weeks of immunosuppressive therapy because all patients will show some degree of inflammation in the immediate posttransplant period. The lesions of acute GVHD range from necrosis of individual crypt cells to total mucosal loss, with the most severe disease affecting the ileum (Fig. 6.219; Table 6.50). Apoptotic bodies are the sine qua non of the diagnosis (Fig. 6.220). However, it is important to remember that increased apoptoses or apoptoses located at the crypt bases occur in other settings as well (Table 6.51). These collect at the crypt bases. The necrotic foci in cellular lacunae are sometimes referred to as “popcorn lesions.” As the lesions evolve, an entire crypt can drop out of the mucosa, creating single crypt loss. The mucosal architecture is progressively lost with ulceration, mucosal denudation, and submucosal edema. Ulcer healing leads to fibrosis and stricture formation. Ulcers
Graft Versus Host Disease may become infected, particularly by fungi. In chronic GVHD, one sees segmental lamina propria fibrosis and submucosal fibrosis extending to the serosa. These lesions occur throughout the entire length of the GI tract extending from the esophagus to the colon. Occasional patients pass ropy, tan material resembling strands of sloughed mucosal tissue, known as mucosal casts, per rectum (Fig. 6.221). The composition of the material is rarely clear-cut. It usually contains fibrin, PMNs, cellular debris, bacteria, or fungi, and very little identifiable tissue. One confirms the presence of free intestinal epithelium by immunostaining with cytokeratins (624).

### TABLE 6.50 Histologic Lesions of Graft Versus Host Disease

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild necrosis of individual crypts</td>
</tr>
<tr>
<td>2</td>
<td>Crypt abscesses and crypt cell flattening</td>
</tr>
<tr>
<td>3</td>
<td>Dropout of many crypts</td>
</tr>
<tr>
<td>4</td>
<td>Flat mucosa</td>
</tr>
</tbody>
</table>
Granulomatous and Histiocytic Inflammatory Conditions

Small intestinal granulomas form in many disorders (Table 6.15). The nature of the granulomas varies significantly from small macrophage collections that may or may not contain foreign material to classic granulomas. Small crypt-associated mucin granulomas complicate mucosal injury. Histiocytes may lie under the free surface or occupy the lamina propria and may contain microorganisms. Vessel-associated histiocytic collections complicate infections, especially CMV (Fig. 6.119). Histiocytic cells also surround the air spaces, characteristic of pneumatosis intestinalis (Fig. 6.208), or they form small mucosal collections in transplant patients without evidence of infection. They also aggregate in the lamina propria (Fig. 6.209) or submucosa in patients with xanthomas. The etiology of granulomas or histiocytic collections differs depending on whether they are compact or loose, are diffuse or localized, contain giant cells or not, and associate with areas of necrosis or not. Peritoneal rosetting microgranulomas may also be encountered in incarcerated small intestinal loops. The rosetted cells are CD68+, distinguishing them from areas of reactive mesothelial hyperplasia (578).

FIG. 6.209. Localized xanthoma. A collection of histiocytes lies beneath the base of the gland (star), widening the distance from the gland base to the muscularis mucosae. Special stains for organisms were negative.

Crohn Disease

The small intestine in Crohn disease often contains granulomas, but the pathology of this disorder is highly variable (see Chapter 11).

Sarcoid

Sarcoid, a systemic granulomatous disease, preferentially affects lymph nodes, but it also involves many other organs, including the gut. Malabsorption, protein-losing enteropathy, and lymphangiectasia may develop secondary to lymphatic obstruction due to the abnormal lymph nodes (579). It is unwise to make a definitive diagnosis of sarcoid in the absence of classic disease in the liver or lungs. The histologic features consist of compact bland granulomas that lack necrosis. These may involve both the bowel wall and the regional lymph nodes. Areas of necrosis suggest the
Granulomatous and Histiocytic Inflammatory Conditions

presence of an infection such as tuberculosis or *Yersinia* infection, especially when the granulomas affect the terminal ileum.

**Granulomas Associated with Foreign Material**

Granulomas develop around foreign material such as talc or sutures. Suture granulomas usually contain a central suture surrounded by palisading histiocytes and foreign body giant cells. Talc granulomas typically contain foreign body–type giant cells and can be distinguished from other granulomas by the use of polarizing lenses, which reveal typical birefringent crystals. Starch-based glove powders also produce granulomas recognizable under polarized light by the presence of a distinctive “Maltese cross.” Accidental entry of barium into the intestinal wall during radiologic examinations may provoke barium granulomas. They exhibit distinctive birefringent granular material with a pale green color in the histiocytic collections.

**Xanthomas**

Small mucosal xanthomas are encountered throughout the GI tract, but they are least common in the small bowel. These represent superficial aggregates of histiocytes in the lamina propria. The lesions are sometimes seen endoscopically as yellowish nodules and may represent vestiges of some prior minor mucosal damage. A more extensive form of xanthomatosis consists of accumulations of lipid-laden macrophages that form mural plaques (Fig. 6.210) or nodules. Generalized or localized xanthomatosis may complicate motility disorders (580). GI xanthomatosis also occurs in patients with hypercholesterolemia and hypertriglyceridemia. An unusual case involved an 85-cm segment of small bowel. The intestinal wall was distorted by regularly spaced nodular accumulations of lipid-laden macrophages expanding the submucosa, muscularis, and serosal surface.

**Malakoplakia**

Malakoplakia is a distinctive form of a granulomatous process that may form tumorlike masses. This entity is discussed in greater detail in Chapter 13.
Gross Features

The human small intestine, which extends from the gastric pylorus to the ileocecal valve, measures about 7 m in length. The C-shaped duodenum encloses the head of the pancreas in its concavity. It measures approximately 20 to 25 cm in length and, except for its first part, lies in the retroperitoneum. The first part of the duodenum measures approximately 5 cm in length, and it ascends posteriorly from the pylorus to the right. It lies above and anterior to the head of the pancreas, below the gallbladder, and anterior to the common bile duct, gastroduodenal artery, and portal vein. The second portion measures approximately 7 cm in length and is covered by the peritoneum of the infracolic compartment of the peritoneal cavity, which separates it from coils of the small bowel. The transverse colon and its mesentery cross it. The hilum of the right kidney and right renal vessels lie behind it, and the bodies of the lumbar vertebrae and inferior vena cava lie medially.

The common bile duct and pancreatic duct enter the second part of the duodenum posteromedially at the ampulla of Vater approximately 9 to 10 cm from the pyloric ring (Fig. 6.7). In most patients, the common bile duct and pancreatic duct join before draining into the ampulla (Fig. 6.8), but in about 10% of cases, the bile duct and pancreatic duct open separately into the intestinal lumen. In about 30% of patients, an accessory, more proximal pancreatic duct drains into the duodenal lumen. Both the bile duct and the pancreatic duct have their own muscular coats. A cross section through this area of the duodenum contains numerous ramifying ducts in all layers of the duodenal wall (Fig. 6.9). The sphincter of Oddi at the ampulla of Vater measures approximately 9.5 mm in length (32).

The third part of the duodenum arches transversely across the vena cava and aorta at the level of the body of the third lumbar vertebra. It is 7 to 9 cm in length. The root of the mesentery obliquely crosses its terminal portion. It is also crossed by the superior mesenteric artery and vein. Superiorly, it relates to the pancreatic uncinate process. The fourth part of the duodenum varies in length and is difficult to distinguish from the third part. It curves up to the left to the duodenojejunal flexure, where it is attached by a
suspensory duodenal ligament, the ligament of Treitz.

**FIG. 6.7.** Normal ampulla of Vater. Opened duodenum with gallbladder posteriorly. The common bile duct is shown by adjacent green and blue probes at ampulla of Vater. The solitary blue probe is an accessory duct of Wirsung.

**FIG. 6.8.** Ampulla of Vater. The pancreatic and bile ducts enter separately and have been opened, showing their entrance into the duodenum.

Although the duodenum has a fairly constant length, the length of the rest of the small intestine is not as clearly established. Measurements taken at autopsy suggest adult lengths between 300 and 900 cm with a mean of approximately 600 cm. Other measurements taken during life give a much shorter length of 280 cm. The mesentery supporting the small intestine fans out from an origin only 15 to 20 cm long. The mesentery runs along an oblique line crossing the posterior abdominal wall from the left to right, from the duodenojejunal flexure to the right iliac fossa.
Gross Features

There is no recognizable line of division between the three parts of the small intestine: Duodenum, jejunum, and ileum. Traditionally, the jejunum represents the proximal 40 cm after the ligament of Treitz and the ileum the distal 60 cm of the small intestine. The lumen of the jejunum is wider than that of the ileum, and its wall is thicker due to prominent circular mucosal folds, known as folds of Kerckring (Fig. 6.10). These folds run parallel to the longitudinal axis of the bowel, are most prominent between the midduodenum and jejunum, and are absent in the distal ileum. They contain both the mucosa and the underlying submucosa.

**FIG. 6.9.** Ramifying ducts in the submucosa are surrounded by a muscular coat. The architecture in this area can normally be very complex.
Histologic Features

General Structure

Small intestinal epithelium is organized into two morphologic and functionally distinct compartments: The crypts of Lieberkühn and the villi. Villi that are unique to the adult small intestine are fingerlike or leaflike mucosal evaginations lined by epithelium overlying a connective tissue core that contains a highly cellular lamina propria, a capillary network, lacteals, and nerves. Simple tubular invaginations (crypts of Lieberkühn) at the base of the villi extend down toward the muscularis mucosae but do not penetrate it (Figs. 6.20 and 6.21). Several crypts open into the intervillous basin. Villi vary in height and form in different regions of the small bowel. The duodenum has the greatest villous variability. Villi in the proximal duodenum are shorter and broader than elsewhere, not infrequently showing increased numbers of stunted and leaf-shaped or branched forms when compared to the jejunum. Jejunal villi vary little in their width from their base to their apex. In the ileum, the villi become broader and shorter than in the jejunum (Fig. 6.21). Villous morphology also varies among different ethnic groups and geographic locales. Villi in persons from Thailand, Africa, India, South Vietnam, and Haiti are shorter and thicker and have an increased portion of leaf-shaped forms with a more intensely cellular lamina propria when compared to biopsies from the English or Northern Americans (40). It is unclear whether this variation represents true racial differences or results from exposure to the infections endemic to the former areas.

The ratio of villous height to crypt length, a feature best appreciated in well-oriented sections, allows one to assess small intestinal absorptive function. In adults, villous height is approximately three or more times the length of the crypts, whereas in children this ratio is lower, more typically being 2:1. Villous height is also lower in the elderly (41). The duodenal crypt:villus ratio is 3:1 to 7:1, whereas the ileal crypt:villus ratio is 4:1. Villi overlying lymphoid areas are often stubby or absent. Each villus contains an arteriole with capillary network veins and a central lymphatic as well as numerous nerve fibers (Fig. 6.22).
FIG. 6.20. Ileal mucosa. *A:* Crypts and villi. The crypts contain numerous goblet cells, allowing one to identify this area as ileal. *B:* Higher magnification of the crypts shows prominent Paneth cell differentiation.
**FIG. 6.21.** A comparison of proximal ileal (A) versus jejunal (B) villi. The more distal villi are more irregular in shape than those of the proximal region.
Each crypt consists of a single clone of cells; several crypts contribute cells to each villus. The epithelial lining harbors a heterogeneous cell population, including Paneth cells, undifferentiated crypt cells, endocrine cells, cup cells, tuft cells, goblet cells, absorptive cells (enterocytes), and M cells. Each cell type possesses distinctive structural features and functions (see below). The epithelium maintains a close association with the underlying stroma.

**Cell Proliferation and Differentiation**

Maintaining the integrity of the gut epithelium as well as ensuring its continuous turnover is essential for mucosal defense. As a result, the gut has one of the most rapid proliferative rates in the body (42). Regular cellular renewal maintains an equilibrium between cell birth and cell death. When the mucosa is damaged, replacement of the injured cells guarantees mucosal integrity. New epithelial cells arise from a fixed proliferating stem cell population located in the lower part of the crypt (Figs. 6.23 and 6.24) (43,44,45). These pluripotential stem cells give rise to descendants that undergo three or four divisions while migrating up the villus or to the top of the lymphoid dome (44).
Histologic Features

FIG. 6.23. Mucosal renewal. The mucosa continuously generates new epithelial cells from a population of anchored stem cells. These give rise to all of the epithelial cell types lining the crypts and villi. Most of the cells migrate upward, undergoing progressive differentiation into enterocytes, goblet cells, and endocrine cells, as well as a minor population of other cells. At the surface, the mature and effete cells either undergo extrusion into the lumen via shedding from the basement membrane or undergo apoptosis and apoptotic bodies are passed into the underlying lamina propria, where macrophages ingest them. In contrast to the upward migration, some cells migrate downward, differentiating into Paneth cells and endocrine cells.

The duration of cellular proliferation and migration is approximately 5 to 6 days in most of the human small intestine and 3 days in the ileum. Differentiated enterocytes live for little more than 2 days (46). Cells at the villous tip undergo Fas-mediated apoptosis (47) and slough off and are extruded into the lumen; sloughing cells can also be seen on the edges of the villi (48). Apoptotic cell death occurs without any apparent disruption of the mucosal barrier integrity (49). Mitotic figures are present in the deep crypt, but they are never normally present on the villi. Stem cells give rise to four major epithelial cell types: Absorptive cells (enterocytes), goblet cells, endocrine cells, and Paneth cells (44). The production and maturation of these cells is under the control of homeobox genes including \textit{MATH1}, \textit{Cdx1}, and \textit{Cdx2} (3,17,18) and the Wnt signaling pathway (45). The MYC-MAD-MAX network is another key regulator of intestinal cell maturation (45).

Newly produced cells migrate out of the crypt, differentiate, and assume the functional characteristics of mature surface cells. Precursors of absorptive enterocytes comprise 90% of the cells in the crypt and mature absorptive cells comprise 95% of the cells located on proximal intestinal villi (43,44). The other three primary epithelial phenotypes constitute a small but important percentage of the total cell number. Cell migration occurs in a linear fashion, with cells moving directly vertically upward or downward from their site of genesis in the crypt bases. The process of proliferation and cellular differentiation are topologically well organized and maintained within this progressively...
differentiating epithelium. As the cells mature, enterocytes gain digestive enzymes. Gene expression profiling studies show that different genes are differentially expressed in the crypt and on the villi. Genes that are up-regulated in the crypt and down-regulated at the villous tip include those related to the cell cycle, RNA processing, and protein translation. In contrast, genes related to cytoskeletal assembly, lipid uptake, and enzyme biosynthesis show the opposite pattern (50).

FIG. 6.24. Mucosal proliferation. The epithelium at the base of the duodenal crypts shows a population of brown-stained nuclei corresponding to the proliferating cells. Additionally, proliferating cells are seen in the lamina propria.

There are also specific specializations of intestinal cells, such as the M cell, which derive from the multipotential stem cell. M cells play a major role in antigen sampling from the GI mucosa and are described in a later section.

**Enterocytes (Absorptive Cells)**

Enterocytes are highly polarized cells with two structurally and functionally distinct plasma membrane domains: The apical microvillous membrane and the basolateral membrane. The apical domain includes the brush border and extends to the tight junction that forms a band around the membrane, creating a relatively impermeable joint between adjacent epithelial cells. The remainder of the cell membrane constitutes the basolateral domain. The basolateral membranes contain abundant Na⁺, K⁺-ATPase and adenylate cyclase and are the site of the receptor for dimeric IgA attachment before its transport to the apical membrane. It is also the transfer site for chylomicrons and other foodstuffs from the enterocyte into the intercellular space and the lamina propria (Fig. 6.25). This activity is restricted from the apical surface by tight junctions that maintain these differences and prevent lateral movement of membrane components (51).
Enterocytes are highly polarized cells with distinct apical, lateral, basolateral, and basal portions, each of which serves special roles. Enterocytes continuously synthesize new components of the cell membrane and surface coat and transport them to the microvillous surface. Microvilli exhibit bidirectional cell trafficking with various metabolites being absorbed and transported inward while the hydrolytic enzymes are synthesized in the endoplasmic reticulum, glycosylated in the Golgi, and transported to the brush border for insertion into the brush border membranes (Fig. 6.25). Some intestinal diseases result from impaired membrane protein trafficking including microvillous inclusion disease, congenital sucrase-isomaltase deficiency, and adult lactase deficiency disease.

The mature brush border, which covers the cell apex, consists of closely packed microvilli and the terminal web (Fig. 6.26). Microvilli vary in length, increasing in height as the cells migrate up the crypt–villus axis. Mature microvilli measure approximately 1.5 to 2 µm in length and 100 nm in diameter. These structures are periodic acid–Schiff (PAS) positive (Fig. 6.27). Each microvillus contains a core bundle of approximately 20 vertically oriented, polarized actin filaments extending from the tip of the microvillus to the base of the terminal web (Fig. 6.28). These are cross-linked by the actin-bundling proteins fimbrin and villin. The other major actin-binding protein of the microvillous core is myosin 1 (52). Myosin 1, coupled with calmodulin, forms a double spiral of bridges cross-linking the actin bundles to the plasma membrane (53). The microvilli house a wide array of brush border enzymes that play critical roles in the digestion and absorption of proteins, fats, and carbohydrates. A complex anastomosing meshwork of filaments called the terminal web surrounds the microvillous rootlets. It consists of a network of actin filaments cross-linked with myosin 2, nonerythroid spectrins, α-actinin, and tropomyosin (52). The filamentous network links with the junctional complex at the edge of the cell.
**FIG. 6.26.** Enterocytes. This photograph is from a thick section showing mature enterocytes and goblet cells at the free surface. The enterocytes are covered by a prominent purple fringe, which corresponds to the brush border.

**FIG. 6.27.** Normal jejunum. The brush border is highlighted by a periodic acid–Schiff stain.
Histologic Features

FIG. 6.28. Normal small intestine. Striated border of absorptive cells is made of large numbers of closely packed parallel microvilli.

The intercellular space is a dynamic area. When the cell is in a resting state, it remains collapsed and represents a potential space. In contrast, the intercellular space dilates in actively transporting cells, particularly at its most basal part (54). The junctional complex, a series of intercellular junctions, is present at the apical end of the intercellular space. The most basal member of this complex is usually the desmosome, a macular structure resembling a spot weld or adhesion point between adjacent epithelial cells (55). The zonula adherens (ZA), or intermediate junction, is a more apically located circumferential adhesive structure. Filaments from the ZA extend into the terminal web to form part of the cytoskeleton. The tight junction or zonula occludens lies at the most apical aspect of the lateral cell surface and it surrounds each epithelial cell, forming a gasketlike seal that restricts the movement of substances through the paracellular pathway by forming semipermeable barriers (56). Signaling via interactions of the cytoskeleton with the tight junctions may regulate paracellular permeability of solutes and water. Diverse microfilament-associated proteins contribute to the cellular morphology, motility, and other cellular specialized functions.

P.290
Histologic Features

**FIG. 6.29.** Pericryptal fibroblasts are flattened fusiform cells closely apposed to the crypt basement membrane (arrows). Notice the Paneth cells in the crypt base identified by their eosinophilic apical granules.

**Goblet Cells**

Goblet cells play an important role in mucosal protection. They secrete mucus, ions, and water into the overlying mucous gel that protects epithelial cell surfaces. Goblet cells also produce trefoil peptides (57), which are important in preventing intestinal injury and promoting wound healing (58). They occur in both the crypts (Fig. 6.29) and among the surface absorptive cells, but they progressively decrease in number as one progresses toward the villous tip (Fig. 6.30). At the tip of the villus the ratio of enterocytes to goblet cells is about 8:1. Goblet cells increase in frequency along the length of the small intestine, being most numerous in the lower ileum. Goblet cells are primarily columnar in shape and mucus droplets accumulate in the supranuclear cytoplasm. This area also contains the Golgi apparatus at its center and rough endoplasmic reticulum at its periphery. As the mucus droplets accumulate, the supranuclear cytoplasm bulges so this part of the cell appears like a barrel or a wine goblet. When the vacuole opens into the intestinal lumen, mucus pours out (Fig. 6.31). The microvilli resemble those on enterocytes, although they are fewer in number. The terminal web of goblet cells is poorly developed, facilitating mucus release from the apical cytoplasm. The nucleus lies in a basal location and its superficial part is flattened by cytoplasmic mucin droplets (Fig. 6.31).
Histologic Features

**FIG. 6.30.** Decreased numbers of goblet cells are present at the luminal surface.

**FIG. 6.31.** Thick section of the superficial mucosa with several prominent goblet cells, two of which are extruding mucus into the overlying lumen.

**Follicle-Associated Epithelium**

Follicle-associated epithelium (FAE), a one-cell-thick layer, forms the interface between intestinal lymphoid aggregates and the intestinal luminal environment (Figs. 6.32 and 6.33). This area has fewer goblet cells, no endocrine cells, and abundant
intraepithelial lymphocytes (IELs) when compared with the epithelium of the crypts and the villi (59,60,61). FAE has a different differentiation program than cells along the crypt–villus axis. The FAE and villous enterocytes are also functionally different since absorptive and digestive functions are down-regulated in the FAE (62). The epithelium of the FAE originates from crypts and differentiates into FAE enterocytes and M cells as they move toward the apex of the dome of the lymphoid follicle. The FAE lacks the subepithelial myofibroblasts seen in the crypts and villi, and the basal lamina underlying the FAE differs from that of the rest of the mucosa (63).

**FIG. 6.32.** Electron micrograph of an M cell (MC) flanked on the left by an absorptive cell (AC). M cells characteristically have microvilli that are shorter and wider (arrowhead) than those of neighboring absorptive cells. Lymphoid cells (L) are often found within the central hollow of M cells. (Courtesy of Dr. James L. Madara, University of Chicago, Chicago, IL. Reprinted with permission from the author.)
**FIG. 6.33.** M cells. *A:* M cells (*arrow*) are present in the epithelium overlying Peyer patches. They are highlighted with a vimentin immunostain. *B:* Cytokeratin staining is positive in absorptive cells, but not M cells in the dome epithelium.

*M (membranous) cells* are a unique epithelial subtype that only exists in the FAE, where they are seen at the periphery of the dome at sites where the epithelial cells exit the crypts (64). Intestinal M cells derive their name from the luminal microfolds or membranous projections formed by lymphocytes invaginating their basolateral surfaces (Fig. 6.32). Their key structural features include the following: Fewer, shorter, and more irregular microvilli, less glycocalyx, and fewer lysosomes than found on adjacent absorptive cells; a close spatial association with immunocompetent cells that reside in pocketlike extensions of the intercellular space between M cells and adjacent epithelium; a thin apical cytoplasmic rim created by intrusive lymphocytes and macrophages (there are no junctions between the M cells and their enclosed lymphocytes and plasma cells; this thin cytoplasmic rim is the only epithelial barrier between the intestinal lumen and the immunocompetent cells); and numerous endocytic vesicles that are especially abundant in the apical cytoplasmic rim. These features allow the approach of microorganisms and other intestinal luminal particles that are normally kept at bay by the closely packed microvilli and thick glycocalyx of enterocytes. Additionally, M-cell apical membranes contain abundant glycoconjugates that serve as binding sites for cationic molecules and possibly for lectinlike microbial surface interactions. As a result, certain pathogenic microorganisms selectively adhere to M cells, such as rotaviruses.

Recent data suggest that the M-cell phenotype is transiently expressed by cells as they migrate to the dome surface (63). M cells increase in number in chronic ileitis or when individuals are exposed to pathogens or antigens (65). Vimentin and cytokeratin 18 expression identifies M cells in tissue sections (Fig. 6.33) (66) since adjacent enterocytes are vimentin negative. M cells facilitate uptake and transport a wide variety of macromolecules and microorganisms (67). The endocytosed material is delivered into apical endosomal tubules and vesicles (68), which then deliver the particles to lymphoid cells nestled in invaginations in their basolateral membranes (69). Antigens transported by the M cells first interact with antigen-presenting cells and lymphocytes in the intraepithelial pocket (70). This transepithelial transport delivers immunogens directly to organized mucosal lymphoid tissues, the inductive sites for mucosal immune responses (71). Thus, M cells form a crucial component of the afferent limb of the intestinal immune system, but they also provide a site through which potential pathogens and other noxious substances can breach the epithelial barrier. M cells may also rupture, releasing lymphocytes into the GI lumen. The bursting of the M cells at the top of the lymphoid follicles interrupts epithelial lining and allows access of the luminal contents to the lymphoid tissues. This mechanism may be responsible for the genesis of aphthous ulcers (72). Also, enterocyte attachment overlying lymphoid follicles is more labile than that of other cells, and this too may be physiologically important during the development of pathologic processes such as the development of aphthous ulcers (73).
Paneth Cells

Paneth cells populate the crypt bases and their number differs along a cranial–caudal gradient, with a greater number of Paneth cells seen caudally. Paneth cells constitute approximately 1% of small intestinal cells (74) and they arise from a common stem cell in the crypt base (74). Intermediate cell types can be encountered during their development. Paneth cells are renewed every 30 days, a rate much slower than that of other crypt cells. These strongly eosinophilic, pyramidal cells have the cytologic characteristics of zymogenic or secretory cells (Fig. 6.34). Irregular microvilli cover their apical ends. The supranuclear Golgi complex contains large, apical, membrane-bound, eosinophilic, refractile granules. The red staining quality of Paneth cells depends on the fixative used. If an acidic fixative such as Bouins is used, the cells may appear less eosinophilic. Paneth cells release granules into the crypt lumen where they participate in mucosal immunity. The granules contain various proteins involved in host defenses including lysozyme, secretory phospholipase A₂, and α-defensins, also known as cryptdins (75).

Endocrine Cells

At least 16 different subpopulations of endocrine cells are present in the small intestines. This cell population is discussed in Chapter 17, along with the proliferative lesions that arise from them.

Undifferentiated Crypt Cells

Undifferentiated crypt cells are the most abundant cells in the lower crypt. They are columnar cells with basally located nuclei and short microvilli that are less numerous than those seen on absorptive cells. The terminal web and glycocalyx are not well developed. Secretory granules may be present in the apical cytoplasm.
Histologic Features

FIG. 6.34. Paneth cells. Cross sections of several crypts demonstrating the presence of Paneth cells with their prominent supranuclear granules.

Pericryptal Myofibroblasts

Intestinal subepithelial myofibroblasts are present immediately subjacent to the basement membrane and close to the basal surface of the epithelium (Fig. 6.29). These cells underlie the epithelium of the crypts and the villi but they are absent from the FAE (63). The subepithelial myofibroblasts replicate and migrate in synchrony with the replicating and migrating epithelium, thereby enhancing mucosal structural integrity and functional efficiency (76). Myofibroblasts play a crucial role in the differentiation of villous epithelium by elaborating the basal lamina (77). They also play a role in the maintenance of the intestinal mucosa via the secretion of proinflammatory cytokines and arachidonic acid metabolites. Their paracrine effects on other mucosal cells are also important in mucosal immunophysiology and the regulation of a number of epithelial functions including epithelial restitution and barrier function (78,79,80).

Lymphoid Tissues

The gut-associated lymphoid tissues are thought to function as secondary lymphoid organs (81), although recent evidence suggests that the small intestinal epithelium is a site of primary extrathymic T-cell differentiation (82). The organized gut-associated lymphoid tissue in the small intestines primarily consists of Peyer patches (PPs) and the mesenteric lymph nodes (81). Other forms of lymphoid aggregations include isolated lymphoid follicles (ILFs), which lie within the mucosa, and submucosal lymphoid aggregations (SLAs), which lie within the muscularis mucosae. Both ILFs and SLAs are thought to represent normal components of the small intestinal mucosa and they are assumed to represent solitary PPs. The numbers of all of these lymphoid structures increases in the distal small intestine. SLAs are submucosal extensions from an overlying ILF (83). The typical ILF resembles the follicular units that comprise PPs. There are variants of ILFs that are either completely confined to the mucosa or extend into the superficial fibers of the muscularis mucosa. In most cases, these mucosal variants do not contain a germinal center, suggesting that they are inactive under normal circumstances. These structures may represent a reserve of mucosal lymphoid tissue that can be activated under conditions of mucosal antigenic stimulation. These lymphoid aggregates and Peyer patches differ from lymph nodes because they lack a capsule, do not have a medulla, and do not have afferent lymphatics or a capsule. The most recently described lymphoid structures are the lymphocyte-filled villi described below.

Peyer Patches and Lymphoid Aggregates

PPs are lymphoid aggregates that are randomly distributed around the circumference of the small intestinal wall (84). They split the muscularis mucosae, being partially mucosal and partially submucosal, often with a central germinal center (Fig. 6.35). The number and size of PPs increases for the first 10 years of life and reaches a maximum at puberty (84). They increase in number as one proceeds distally in the small intestine, becoming confluent in the ileum. The duodenum may also contain well-formed lymphoid nodules that extend from the surface to the base of the mucosa. The most obvious parts of the PPs are their germinal centers and a surrounding corona of B cells. Germinal centers (Figs. 6.36 and 6.37) are much more common in children than in adults.
Histologic Features


Peyer patches contain three major domains: The follicular B-cell area, the parafollicular T-cell area, and the FAE described above (Fig. 6.38). The epithelial basement membranes overlying lymphoid follicles within Peyer patches are very porous. This porosity may facilitate bidirectional passage of lymphocytes during immune responses (85). Lymphocytes and other mononuclear cells are constantly migrating into and out of the spaces in the dome epithelium. The subepithelial tissue immediately beneath the FAE contains IgM+ B cells, CD4+ T cells, Ia+ dendritic cells, and macrophages, allowing for efficient antigen processing and antibody production (86).

PPs are important sites of lymphocyte recirculation (81). Peyer patch–derived lymphocytes give rise to lamina propria plasma cells. There are also circulating small lymphocytes within the Peyer patches. The localization of B cells and T cells to Peyer patches is mediated by interactions between these cells and endothelial cells lining postcapillary HEVs (87). PPs contain at least three different populations of nonlymphoid cells: Scavenger macrophages in the dome areas, dendritic cells just beneath the epithelium in the dome in the T-cell area, and tingible body macrophages in the germinal centers of the B-cell follicles. Macrophages, particularly those near the dome of the lymphoid tissue, may contain bacteria. A mixed cell zone that contains follicular center B cells, numerous helper T cells, and human leukocyte antigen (HLA)-DR+ macrophages lies between the M cells and the small lymphocytes that form the mantle of the follicle. The overlying epithelium contains intraepithelial B cells and suppressor T lymphocytes. The distribution of lymphocytes in the PP epithelium differs from IELs in the villi in that the dome epithelium lymphocytes cluster in groups and frequently occur above the level of the enterocyte nuclei.
**FIG. 6.36.** Lymphoid follicles. *A:* Slightly tangentially cut mucosa with several lymphoid follicles. *B:* The prominent germinal centers containing tingible body macrophages and a prominent lymphocytic rim.

**FIG. 6.37.** Peyer patch. *A:* A flattened epithelium lies over the surface of the Peyer patch (arrows). A prominent lymphocyte mantle is present and the germinal center (GC) is seen at the lower portion of the photograph. *B:* Higher magnification shows the intraepithelial lymphocytes (arrow).
Histologic Features

**FIG. 6.38.** Morphology of Peyer patches.  
*A:* CD20 immunostain shows B cells located primarily in germinal centers.  
*B:* T cells localize to the parafollicular region (UCHL-1 immunostain).  
*C:* Tingible body macrophages are present in the germinal centers, and scavenger macrophages are visible in the dome area overlying the follicle. The macrophages are highlighted with a HAM56 immunostain.  
*D:* Factor VIII immunostain highlights the capillaries and small vessels surrounding the follicle.  
*E:* Small nerve twigs populate the lamina propria surrounding the lymphoid follicles (synaptophysin immunostain).

The sides of the follicles are populated by a diffuse population of small lymphocytes, macrophages, and plasma cells. Variable numbers of eosinophils are also present. Underlying the follicles, there is a T-cell–rich population with a T-helper:T-suppressor ratio of 8:1. The lamina propria and Peyer patch immune cells participate in immunoglobulin synthesis and T-cell functions.
CD4+ and CD8+ cells are both present in the dome of Peyer patches, the site where B cells are preferentially found. The B cells may cluster in aggregates. B cells migrate more rapidly to the center of the Peyer patch follicles than do T cells. In contrast, CD4+ T cells accumulate in the interfollicular zones. The distribution of cells in the dome epithelium differs from non-Peyer patch areas of the mucosa where T cytotoxic/suppressor cells predominate and B cells are few. Lymphocytes are usually absent from the crypts outside Peyer patches.

If migrating lymphocytes do not engage in an immune response, they continue their migration through the PPs and exit via the efferent lymphatics (88). The lymphocytes then move toward the submucosal lymphatics under the Peyer patches. Peyer patches have the potential capacity to store lymphocytes and modulate lymphocyte migration (89). Lymphocytes from PPs follow a migratory pattern from mesenteric lymphatics to the mesenteric lymph nodes, the superior mesenteric duct, and the thoracic duct before draining into the peripheral circulation. This dynamic lymphocyte recirculation facilitates effective surveillance for foreign invaders and alterations within the body's own immune system (89).

**Lymphocyte-filled Villi**

Lymphocyte-filled villi (LFV) are recently described structures that resemble Peyer patches. Morphologic features that distinguish LFV from classical villi are the presence of tightly packed lymphocytes that fill most of the lamina propria and a high concentration of IELs in the overlying epithelium. These IELs are enriched for CD4+ T cells that are often found in clusters, but the majority of the cells do not express surface immunoglobulin, CD3, or the T-cell receptor. Many of the cells are CD25+. They also contain major histocompatibility complex (MHC) class II–positive dendritic cells and a variable B-cell component. The epithelium overlying these structures resembles that of the FAE and includes the presence of M cells. These features suggest that the epithelium of LFV resembles the FAE. However, LFV lack HEVs and obvious lymphoid follicles. These structures are confined to the jejunum (83).

**Intraepithelial Lymphocytes**

IELs constitute a distinct and heterogeneous lymphocyte population nestled among the epithelium (90). They express the T-cell receptor (TCR)-αβ and -γδ with functional and phenotypic features that differ from cells in peripheral lymphoid tissues. There is also an intraepithelial population of functional killer lymphocytes (91). Cellular and molecular cross-talk between epithelial cells and IELs appears to play a key role in the reciprocal growth and activation of these cells and in the maintenance of intestinal homeostasis. IELs contribute to cytokine secretion, expression of MHC and adhesion molecules, and the integrity of mucosal defenses (92,93). They also possess cytotoxic activity, which is important in protecting against the invasion of luminal pathogens and the destruction of transformed epithelium (94,95).

IELs typically lie in the basal portion of the epithelium. They range from 3 to 11 µm in diameter and possess small dense nuclei, contrasting with the paler, more vesicular enterocyte nuclei (Figs. 6.39 and 6.40). IELs have a small nuclear: cytoplasmic ratio. They lack any junctional attachments to the surrounding epithelium, so that they can easily migrate in and out of the epithelium (96). The small intestine contains a large number of IELs, estimated to be approximately one IEL per six to ten epithelial cells (97). Fewer numbers are present in the ileum. In contrast to the IELs in the villi, IELs overlying lymphoid follicles are predominantly of B-cell derivation. There appear to be differences in the IEL populations of the crypt and the villus that facilitate different types of interactions of the IELs with the enterocytes. Specifically, there is an increased frequency of γδ TCR-carrying T cells in the villus as compared to the crypts (98).
Histologic Features

FIG. 6.39. Intraepithelial lymphocytes. The photograph has an artifact in which the epithelium has become separated from the underlying lamina propria. A single intraepithelial lymphocyte is present, as indicated by the arrow, and several lymphocytes are indicated by the double arrows.

Lamina Propria

The lamina propria provides the scaffolding on which the intestinal epithelium rests. It contains the blood vessels that nourish the epithelium and supplies a support structure for the immune cells. The majority of the cells are in the crypt region rather than in the villous region. These cells consist of immunocytes, particularly plasma cells and lymphocytes (Fig. 6.40). The majority are IgA-containing plasma cells, although IgM-, IgD-, IgG-, and IgE-containing cells are also present. IgM-containing cells are the second most numerous (99). The ratio of IgA to IgM cells in the intestinal mucosa is 15 to 20:1. Plasma cells never normally infiltrate the epithelium. The increased number of plasma cells seen in the lamina propria following antigenic challenge results from recruitment of circulating lymphocyte pools and proliferation of newly recruited cells in the lamina propria. The majority of the lamina propria T lymphocytes exhibit a helper-inducer phenotype, whereas only 30% to 40% are suppressor cytotoxic T cells. Numerous macrophages aggregate in the lamina propria at the tips of the villi. They extend pseudopods into the epithelial lining and internalize components of apoptotic aging enterocytes. The basal lamina propria, especially in the small bowel, contains large numbers of dendritic cells. These present antigens to mucosal CD4+ T cells. Polymorphonuclear leukocytes (PMNs) are uncommon. It is estimated that there are between 100 and 200 eosinophils per millimeter of lamina propria in the jejunum (Fig. 6.41) (100). However, this figure varies significantly depending on the geographic locale in which one lives. In those parts of the world associated with a high incidence of environmental allergies, such as to pollens, eosinophils may increase in number, particularly during the height of the allergy seasons. Basophils are not very prominent.
**FIG. 6.40.** Lamina propria immunocytes. *A:* The lamina propria contains a large number of lymphocytes and plasma cells, as well as eosinophils and mast cells. Additionally, intraepithelial lymphocytes are present. *B:* Higher magnification of the area of the lamina propria showing plasma cells and lymphocytes.

In the normal adult jejunum, there are up to 300 mast cells/mm² of mucosa (101) compared with 750 mast cells/mm² of the ileal lamina propria in children (102). Abundant mast cells lie in the superficial aspect of the mucosa. Mast cells may be highlighted by CD25, CD117, or tryptase immunostains. The cells are evenly distributed throughout the bowel wall and some maintain a relationship with neural structures.
Histologic Features

FIG. 6.41. Eosinophils and mast cells within the lamina propria.

Brunner Glands

Brunner glands form a continuous series of branched or coiled tubular glands in the submucosa and basal mucosa of the first part of the duodenum. In the first part of the duodenum, where Brunner glands are relatively large, bands of smooth muscle from the muscularis mucosae occasionally lie between the acinar lobules. Ducts of individual glands open either directly into the duodenal lumen or into the crypts of Lieberkühn. Occasionally, small groups of glands occur within the superficial epithelium, particularly in patients with peptic duodenitis. Their size and number gradually decrease from the proximal to the distal duodenum (Fig. 6.42). In the second portion, at the level of the ampulla of Vater they are scattered. In the third portion, only a few small glands are present (103).

Three morphologically distinctive cell types are present in Brunner glands: Cells with a central nucleus and uniform glassy eosinophilic basal cytoplasm, similar cells with a clear basal cytoplasm, and cells with basal nuclei and small clear perinuclear vacuoles. The glands produce neutral glycoproteins that do not stain with mucicarmine but are PAS positive. Brunner glands produce MUC6, bicarbonate, epidermal growth factor, trefoil peptides, bactericidal factors, proteinase inhibitors, and surface active lipids (104). Brunner glands also contain endocrine cells storing somatostatin, gastrin, cholecystokinin (CCK), and peptide YY.
Histologic Features

FIG. 6.42. Brunner glands. A: The submucosa of the duodenum is almost completely filled with highly branched tubular duodenal glands (Brunner glands). The muscularis mucosae may be disrupted as these glands penetrate into the deep lamina propria of the mucosa. B: Higher magnification showing the clear cytoplasm of the Brunner glands.

Neural Structure
A complex neuronal circuitry regulates GI function. The overall mucosal and submucosal neural organization is described in Chapter 10.

Ampulla of Vater
The ampulla of Vater lies in the second part of the duodenum. The common bile duct and major pancreatic duct pass through this structure. The mucosa overlying this area appears highly variable. A complex collection of glands lies in the submucosa and passes through the muscularis mucosae into the overlying mucosa. They are surrounded by smooth muscle cells and a loose stroma (Fig. 6.43). This area is the weakest part of the duodenum and hence the most common site for diverticula to develop.
Immunodeficiency Diseases

Patients with immunodeficiency syndromes often present with chronic diarrhea, malabsorption, and other intestinal abnormalities, as well as with the effects of the immunodeficiency, particularly infections. The immunodeficiency syndromes fall into primary and secondary (or acquired) forms (Table 6.45). Primary immunodeficiencies fall into several categories: Those primarily associated with failure to produce antibodies (Table 6.46), those associated with lymphocyte abnormalities, or those involving neutrophils.

![Ultrastructural features of brown bowel disease. Numerous intralysosomal inclusions containing cellular membranes and osmiophilic debris are present.](image)

**TABLE 6.45 Classification of Immunodeficiency Diseases**

<table>
<thead>
<tr>
<th>Predominantly antibody defects (see Table 6.46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly defects of cell-mediated immunity</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis</td>
</tr>
<tr>
<td>Nezelof syndrome</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunodeficiency associated with other disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous diseases</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Transcobalamin II deficiency</td>
</tr>
<tr>
<td>Bare lymphocyte syndrome</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency</td>
</tr>
</tbody>
</table>
Immunodeficiency Diseases

AIDS

Antibody Deficiency Disorders

Selective IgA Deficiency

Selective IgA deficiency is the most common immunodeficiency in Caucasians, being present in about 1 of 600 in the general population as assessed by blood donor screening (588). The incidence varies depending on the population being studied. Published figures range from 1 in 400 in Finland to 1 in 1,500 in Japan (589). IgA deficiency is 10 to 15 times more common in patients with celiac disease than in the general population.

TABLE 6.46 Antibody Deficiency States

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked infantile agammaglobulinemia</td>
</tr>
<tr>
<td>X-linked hypogammaglobulinemia with growth hormone deficiency</td>
</tr>
<tr>
<td>Transcobalamin II deficiency and hypogammaglobulinemia</td>
</tr>
<tr>
<td>Immunodeficiency with thymoma</td>
</tr>
<tr>
<td>Immunodeficiency after a hereditary defective response to Epstein-Barr virus</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>Immunoglobulin deficiency with normal or increased levels of IgM and IgD</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
</tr>
<tr>
<td>Selective IgM deficiency</td>
</tr>
<tr>
<td>Selective deficiency of other immunoglobulin isotypes</td>
</tr>
<tr>
<td>Light chain deficiency</td>
</tr>
<tr>
<td>Immunodeficiency caused by hypercatabolism of immunoglobulin molecules</td>
</tr>
<tr>
<td>Immunodeficiency caused by excessive loss of immunoglobulins and lymphocytes</td>
</tr>
</tbody>
</table>

In selective IgA deficiency, IgA, the major mucosal immunoglobulin, is not produced. Patients exhibit an isolated absence or near absence (i.e., <0.10 g/L [<10 mg/dL]) of serum and secretory IgA. In most cases, the cause of the immunodeficiency is unknown. The disease may be congenital or induced by viral infections, leukopenia, and drugs. Unusual cases result from deletion of an IgA gene on chromosome 14 (590). Selective IgA deficiency associates with extended HLA haplotypes that include either a C4A null allele (C4AQ0), 21-hydroxylase gene deletions in the HLA class III region, or rare class IIIC gene haplotypes (591), especially in Caucasians. These haplotypes are rare in Blacks and Asians.

Most patients have defective B-cell maturation with abnormal terminal differentiation of membrane IgA-positive B cells into IgA-secreting plasma cells. A smaller percentage of individuals have a defect in immune regulation of a putative suppressor T cell that selectively inhibits IgA production (592).

Many patients lack clinical abnormalities due to a compensatory increase in IgM. Other patients, especially if deficient in IgG subclasses, present with sinopulmonary disease, diarrhea, malabsorption, autoimmune disease, or bacterial infections, including GI infections (593). Patients with IgA deficiency also frequently have antibodies directed against cow's milk and ruminant serum proteins, immunoglobulins, thyroglobulin, and collagen. Diseases associated with IgA deficiency are listed in Table 6.47.

Biopsies in IgA-deficient patients may appear completely normal with a seemingly full complement of lymphocytes and plasma cells in the lamina propria, especially in adults. Immunohistochemical analysis for immunoglobulins demonstrates that the lamina propria plasma cells produce IgM and IgG but not IgA. Patients may also have evidence of coexisting celiac disease or bacterial infections (Fig. 6.215). Rarely, patients with a selective IgA deficiency will present with a completely flat mucosa (Fig. 6.216) in the absence of bacterial overgrowth or *Giardia*. Such patients may die from severe malabsorption (594).

TABLE 6.47 Conditions Associated with IgA Deficiency

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>.AutoField A</td>
</tr>
</tbody>
</table>
Pernicious anemia
Addison disease
Thyroiditis
Hemolytic anemia
Idiopathic thrombocytopenic purpura
Systemic lupus erythematosus
Rheumatoid arthritis
Primary biliary cirrhosis
Chronic active hepatitis
Celiac disease
Crohn disease
Nodular lymphoid hyperplasia
Disaccharide deficiency
Antibodies to cow's milk protein
Immunodeficiency Diseases

FIG. 6.215. IgA deficiency combined with celiac disease. A: There is an essentially normal architecture with a mild increase in the lamina propria infiltrate. B: Higher magnification showing intraepithelial lymphocytes. Immunostaining demonstrated a complete absence of IgA-producing plasma cells and the intraepithelial lymphocytes suggested a diagnosis of latent sprue. The patient was put on a gluten-free diet and responded dramatically.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVI) is a heterogeneous group of immunoglobulin deficiencies that share the following: (a) low levels of most immunoglobulin isotypes, (b) inability to form antibodies to antigens, (c) absence of a gross defect in cell-mediated immunity, and (d) presence of recurrent bacterial infections. Patients suffer from the effects of their defective antibody production with decreased serum IgG in combination with decreases in serum IgA and IgM (595). Other patients exhibit a different type of CVI that predominantly manifests as a T-cell deficiency and the antibody deficiency is less prominent. The two clinical syndromes tend to be mutually exclusive (595).

CVI is the second most common primary immunodeficiency, following isolated IgA deficiency. It affects 6 to 12 per 1 million live births. The disease is usually sporadic, but familial clustering associated with an autosomal dominant mode of transmission does occur in 20% of patients (596). Haplotype analysis and linkage studies indicate that the HLA-DQ/DR locus is the major site of involvement (597). An association between CVI and homozygosity for genes encoding HLA class II molecules, especially HLA-DQ, has been reported (598). In some patients, there is an association with the TNF-α+488 A allele (599). In one recent study, 4 of 32 patients with adult-onset CVI demonstrated a homozygous deletion of the ICOS gene, an inducible costimulator found on activated T cells (600).

The major defect in CVI is a failure of B-cell differentiation with impaired secretion of immunoglobulins, but it is not clear whether this is due to a primary B-cell defect or abnormalities in T cells. B cells in CVI are immature, and show impaired up-regulation of markers of activation (601). In some patients, a defect in IgV gene somatic hypermutation is present, an abnormality that would result in production of immunoglobulins with reduced or absent antigen affinities (602). In addition to B-cell abnormalities, CVI patients also show abnormalities in T-cell function. CVI patients exhibit decreased T-cell proliferation and activation, defective antigen-driven responses, and reduced production of cytokines (603).

CVI may clinically resemble X-linked agammaglobulinemia (Fig. 6.217). The major difference is that the patients usually have a later age of onset and somewhat less severe infections.
Also, the disorder is almost equally distributed between sexes, contrasting with X-linked agammaglobulinemia, which almost invariably affects boys. Chronic and recurrent sinopulmonary infections are the hallmark of the disease (604). Twenty to thirty percent of patients have mild to moderate malabsorption frequently due to coexisting *Giardia* infections. The enteropathy may also be accompanied by a deficiency in jejunal brush border enzymes (605). Patients with accompanying T-cell abnormalities have fungal or protozoal infections sometimes causing persistent infections, such as with *strongyloides*. Approximately 33% to 50% of patients have achlorhydria due to a coexisting chronic atrophic gastritis. Patients develop a pernicious anemia-like syndrome with intrinsic factor deficiency, gastric atrophy, loss of parietal cells, and low vitamin *B*<sub>12</sub> levels. However, unlike classic pernicious anemia, the disease develops at an earlier age, the gastric mucosa lacks a plasma cell infiltrate, and antibodies to parietal cells or intrinsic factor are absent. Coexisting diseases are listed in Table 6.48 (606). Adults are much more likely to develop complications, including lymphomas and small and large intestinal carcinomas. Lactose and gluten intolerance may result from mucosal inflammation and increased mucosal permeability.
FIG. 6.216. Selective IgA deficiency and celiac disease. A: Small intestinal biopsy taken in a patient at the time of pretreatment. Severe mucosal atrophy is present. There is a marked diminution of the number of glands. B: Another area of the mucosa demonstrates more atrophic glands. C: Nature of the biopsy following therapy. D: IgA staining of the biopsy. Note that no IgA-containing cells are present in the lamina propria. Normally, these are the most common cells found in the lamina propria.

FIG. 6.217. Agammaglobulinemia. The epithelium often becomes flattened and shares features with other causes of villous atrophy.

<table>
<thead>
<tr>
<th>TABLE 6.48 Disorders Associated with Common Variable Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent infections</td>
</tr>
<tr>
<td>Respiratory and sinonasal</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Malabsorption with steatorrhea and villous atrophy</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
</tr>
<tr>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Cholangitis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
</tr>
<tr>
<td><em>Giardia</em> infection</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
</tr>
<tr>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Lymphomas</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
</tbody>
</table>

The mucosal appearance varies from normal to severe villous atrophy resembling celiac disease (607). Crypt distortion and crypt destruction can be present. Plasma cells are absent.
There may also be an intraepithelial lymphocytosis. In contrast to celiac disease, there is only a modest mononuclear cell infiltrate in the lamina propria. Lymphoid aggregates in the lamina propria and between epithelial cells primarily contain T cells rather than immature B cells. Single-cell necrosis (apoptosis) is increased in the crypt bases (608). Biopsies often show an enteritis. Plasma cells are absent. A granulomatous enteropathy is another manifestation of CVI, perhaps due to an underlying infection. Nodular lymphoid hyperplasia consisting of hyperplastic lymphoid follicles with immature B cells may be found throughout the GI tract. Various infections may stimulate the lymphoid hyperplasia.

Cellular and Combined Immunodeficiency Disorders

**Nezelof Syndrome**

Nezelof syndrome is characterized by lymphopenia, diminished lymphoid tissue, an abnormal thymus, and normal or increased serum immunoglobulin levels. Infants present with recurrent or chronic pulmonary infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, and recurrent infections. Other findings include neutropenia and eosinophilia. Selective IgA deficiency and markedly elevated IgE and IgD levels affect some patients. The disease is usually inherited as an autosomal recessive disorder, but some children exhibit an X-linked mode of inheritance (604). Peripheral lymphoid tissues, including those in the GI tract, appear hypoplastic and demonstrate paracortical lymphocyte depletion. Small intestinal biopsies may show villous atrophy with increased numbers of plasma cells and neutrophils in the lamina propria. Peyer patches are absent.

**Severe Combined Immunodeficiency Disease**

The severe combined immunodeficiency disease (SCID) syndromes are characterized by a congenital absence of all adaptive immune functions and by great diversity in the genetic, enzymatic, hematologic, and immunologic features (604). There are multiple variants of SCID, but all of them show a block in T-cell differentiation, which usually requires urgent therapy with allogeneic hematopoietic stem cell transplantation to provide the missing T-cell progenitors. Nine different molecular defects are known to cause SCID as summarized in reference 609. SCID usually is inherited as either an X-linked or an autosomal recessive defect. GI changes include esophageal atresia, imperforate anus, chronic candidiasis, and watery diarrhea. Patients with these disorders have the most severe form of the recognized immune deficiencies.

In one form of SCID, patients lack T cells but have normal numbers of B cells. It associates with a novel defect in the CD 3 gene that results in an early arrest in T-cell development with a nearly complete absence of mature T cells and a complete lack of γδ T cells (610). Patients lack T-cell and B-cell immunity and have an increased incidence of viral, fungal, protozoal, and bacterial infections. As a result, children may exhibit serious GI manifestations, including chronic diarrhea, malabsorption, and infections. GI infections result from *Giardia, Salmonella*, enteropathic *E. coli*, rotavirus, candidiasis, coccidiosis, aspergillosis, and cryptosporidiosis. Histologically, Peyer patches are absent or extremely underdeveloped. Biopsies show a partial reduction in intraepithelial T lymphocytes, partial villous atrophy, and numerous vacuolated PAS-positive macrophages in the lamina propria. The intestinal lamina propria is devoid of lymphocytes and plasma cells.

Patients undergoing bone marrow transplantation lack the ability to reject foreign tissue and are therefore at risk for developing GVHD. Some patients develop lactose intolerance. Today complications are rare because most patients receive bone marrow transplants.

**Chronic Granulomatous Disease**

Chronic granulomatous disease (CGD) is a rare, predominantly male disease with either an X-linked or autosomal recessive inheritance pattern. The neutrophils of patients with X-linked CGD have defective neutrophil cytochrome B, whereas the autosomal recessive form involves abnormalities in the NADPH oxidase system. Leukocytes from these patients fail to show normal oxygen consumption, direct oxidation of glucose, or hydrogen peroxide formation. GI involvement may cause diarrhea, steatorrhea, vitamin B12 malabsorption, or intestinal obstruction due to the presence of granulomas. Neutrophils from patients with CGD are defective in their ability to kill catalase-positive bacteria and some fungi such as *Candida* and *Aspergillus*, despite their normal ability to phagocytose the organisms. As a result, patients are prone to severe infections and multiple abscesses. The intestinal wall may contain granulomas, fistulae, fissures, and abscesses, producing a disease resembling Crohn disease. The lamina propria may contain characteristic darkish brown, lipid-filled histiocytes, giant cells, and granulomas (611). These changes affect both the small and large intestines.
Infectious Diseases

Mechanisms of Bacterial Injury

Numerous factors predispose to microbial intestinal colonization and contribute to diarrhea, malnutrition, sepsis, and extraintestinal infections. Vigorous peristaltic forward propulsion of intestinal contents into the colon discourages bacterial colonization. This peristaltic defense is enhanced by the continuously secreted mucous layer that bathes the mucosal surface and mechanically prevents organisms from contacting enterocyte surfaces and adhering to them. Pancreatic enzymes in the intestinal lumen degrade bacterial toxins. Bacterial enteropathogens possess several distinct virulence properties (Table 6.12). The specific bacterial virulence pattern determines the way it interacts with the intestinal mucosa and influences the clinical syndromes that result.

**FIG. 6.130.** Bacterial interactions with intestinal mucosa. A: Bacteria may directly invade into the epithelial cells or the intercellular junctions to become enclosed within phagocytic vesicles, where they multiply. Eventually, when a critical number of organisms are present, the cell lyses, reinitiating the process. Some bacteria pass directly into the underlying lymphoid follicle, where they are sequestered and multiply. The lysis of the cells attracts an inflammatory infiltrate, usually consisting of neutrophils. B: Bacteria may also attach directly to the epithelium without invading the enterocytes. They do this either by attaching via pili that recognize specific receptors on the enterocyte membranes or they produce attaching and effacing lesions. C: Bacteria also produce some of their effects by producing toxins. The two major groups of toxins either cause increased electrolyte and water secretion (represented by the circles) as exemplified by cholera toxin or inhibit protein synthesis leading to cellular death, as indicated by the triangles.

**TABLE 6.12 Mechanisms of Bacterial Pathogenicity in Small Intestinal Injury**

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingestion of preformed bacterial enzyme or toxin (i.e., <em>Staphylococcus</em>)</td>
</tr>
<tr>
<td>Elaboration of an enterotoxin following gastrointestinal colonization (i.e., <em>Cholera, Shigella, Salmonella, Yersinia</em>)</td>
</tr>
<tr>
<td>Elaboration of a tissue-damaging cytotoxin (i.e., <em>Shigella</em>)</td>
</tr>
<tr>
<td>Mucosal invasion (i.e., <em>Shigella, Salmonella</em>)</td>
</tr>
</tbody>
</table>

Since bacterial adherence to epithelial cells is an important prerequisite for intestinal colonization and virulence (Fig. 6.130), bacteria have developed several mechanisms to attach...
to enterocytes (294). Enterocyte adherence results from specific interactions between a ligand expressed on the bacterial surface (sometimes called an adhesin) and a receptor on the epithelial cell surface (295). Various bacteria produce plasmid-encoded adhesive pili that radiate from the bacterial surface and recognize specific glycoconjugates on mucosal cells (296). Other bacteria attach to epithelial cells in such a way that the outer membrane of the enterocyte appears to wrap around it. This gives the impression that the bacterium is perched on an enterocyte pedestal. Bacterial toxins interact with receptors on the enterocytes surfaces and activate cellular signal transduction mechanisms, causing fluid and electrolyte secretion and toxigenic diarrhea.

*Bacterial translocation* implies the passage of viable bacteria from the gastrointestinal lumen through the mucosa to distant sites, such as mesenteric lymph nodes, spleen, liver, kidney, and blood (296). Mechanisms inducing bacterial translocation include disruption of the normal ecologic microbial balance with overgrowth of Gram-negative enteric bacilli, impaired host defenses, and physical disruption of the mucosal barrier. Some invasive bacteria cross the intestinal barrier via M cells (296). Others enter cells and remain trapped inside phagocytic vacuoles, where they utilize antiphagocytic strategies to continue to multiply and resist cellular defense mechanisms (297). Still others, such as *Shigella*, escape from phagocytic vacuoles to invade the cytoplasmic compartment. The pathogens then pass from cell to cell.

**Epidemiologic Settings in which Infections Occur**

Diarheal diseases are a global problem, particularly affecting populations living in underdeveloped areas. Both children and immunologically naive travelers are susceptible to the enteric pathogens that heavily contaminate the water and food in places with poor sanitation. Food-borne and water-borne illnesses account for significant numbers of diarrheal outbreaks worldwide. The pathogenic bacteria must be ingested in large numbers to cause clinical disease. Food- and water-borne illnesses develop not only in countries with poor sanitation, but also on cruise ships, at picnics, and at fast-food restaurants. Diarrheal illnesses also lead the list of infectious diseases that affect the military. Travelers of all ages from industrialized countries experience high rates of diarrheal illness and other infections when they visit developing tropical areas (298). Regional differences in the consumption of unpasteurized milk or raw or undercooked fish, shellfish, or meat increase the risk of certain bacterial, parasitic, and viral infections. Mass production of eggs also plays a role in bacterial enterocolitis. Globalization of the food supply also increases the opportunity for widespread food contamination. Table 13.11 lists factors that should trigger suspicion of widespread food contamination. Diarrheal illnesses are also increasing in daycare centers, hospitals, and extended-care facilities. Nosocomial diarrhea is particularly prevalent in intensive care units and pediatric wards, and is an increasingly difficult problem for bedridden patients and their caregivers.

The synthesis of large numbers of antibiotics over the past several decades has resulted in increased bacterial antibiotic resistance (299). The emergence of drug-resistant bacterial strains has contributed significantly to the increase in nosocomial infections (300). Increased international travel offers new opportunities for outbreaks and plagues to develop, and offers opportunities for the genesis of new bacterial genetic variations (301). Finally, the increased frequency of immune deficiencies, whether from AIDS, immunosuppressive therapy, aging, or other alterations, places patients at risk for life-threatening infections.

**Patterns of Gastrointestinal Infection**

Most diarrheal illnesses are noninflammatory, usually arising in the upper small bowel from the action of an enterotoxin or other process that specifically alters the absorptive function of the villous tip. Patients with toxigenic bacterial infections present with dysenteric syndromes characterized by fever, abdominal pain, and numerous small-volume stools containing blood, mucus, and neutrophils. In contrast, patients with invasive bacterial infections usually have a colonic infection and diarrhea dominates the clinical picture. Neutrophilic mucosal infiltrates are the hallmark of acute invasive disease. Toxigenic organisms tend to produce less severe morphologic damage than invasive bacteria. Another type of enteric infection results in enteric fever, often with constipation early in its course. The organisms enter Peyer patches and regional lymph nodes and then become systemic infections, returning to the gut later. In order to establish the diagnosis of infectious diarrhea, the organism must be found in, or cultured from, the stool or intestinal tissues. Alternatively, one should be able to demonstrate a rise in specific serum antibodies to the organism. With the advent of recombinant DNA technology, genes for the heat-labile and heat-stable enterotoxins have been cloned, allowing diagnosis of the toxin-producing bacterial strains.

**Bacterial Overgrowth Syndromes (Blind Loop Syndromes)**

Bacterial overgrowth leads to malabsorption. Proposed mechanisms for the abnormal bacterial proliferation include (a) failure to clear bacteria from the upper GI tract, usually due to achlorhydria; (b) continuous seeding of the small bowel with colonic contents as a result of jejunal-colic fistulae or reflux following abnormalities of the ileocecal valve; and (c) motility disturbances. The diagnosis of bacterial overgrowth relies on three criteria: (a) presence of an increased intestinal volume, (b) demonstration of increased bacterial concentrations, and (c) a positive response to antibiotic therapy. Multiple conditions predispose to bacterial overgrowth (Table 6.13).

**TABLE 6.13 Conditions Predisposing to Bacterial Infection and Overgrowths**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strictures (congenital, radiation, tuberculosis, Crohn disease, vascular)</td>
<td>Immunodeficiency states</td>
</tr>
<tr>
<td>Small intestinal stagnation</td>
<td>Entities that destroy mucosal barrier function</td>
</tr>
<tr>
<td>Afferent loop of Billroth II partial gastrectomy</td>
<td>Drugs</td>
</tr>
<tr>
<td>Duodenal diverticula</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Small intestinal diverticulosis</td>
<td>Radiation</td>
</tr>
<tr>
<td>Surgical blind loops (end-to-side anastomoses)</td>
<td>Infections</td>
</tr>
<tr>
<td>Surgical recirculating loops (end-to-end anastomoses)</td>
<td>Ischemia</td>
</tr>
<tr>
<td>Multiple laparotomies resulting in adhesions</td>
<td>Toxemia</td>
</tr>
<tr>
<td>Obstructions</td>
<td>Thermal injury</td>
</tr>
</tbody>
</table>
Most mucosal biopsies appear normal, but careful studies eventually demonstrate patchy mild histologic abnormalities that are easily missed by a single random biopsy or are so mildly abnormal as to be easily overlooked. In severe cases, one sees a spectrum of changes ranging from patchy, villous broadening and flattening to complete villous atrophy with crypt hyperplasia or hypoplasia. Numerous microorganisms, including bacteria and protozoa, adhere to the mucosa and are embedded in the unstirred mucous layer overlying the epithelium (Fig. 6.131). There is often an increase in the number of lamina propria mononuclear cells.

**FIG. 6.131.** Bacterial overgrowth. Note the presence of prominent collections of bacteria in the pyogenic membrane that was overlying an area of devitalized tissue.

The recognition of specific pathogens may result from their localization in specific tissue sites, as in the colon (Table 13.12).

### Specific Bacterial Infections

**Escherichia coli Infections**

*E. coli* bacteria are Gram-negative organisms that constitute part of the normal GI flora. They spread to contiguous structures when the mucosal barrier is damaged. The organisms tend to settle in necrotic tissues. Patients often have decreased host defenses as a result of underlying diseases. Several types of *E. coli* infections exist (Table 6.14) (302). However, they cannot be differentiated from one another on Gram stain or routine culture.

The characterization of a strain of *E. coli* as an enteropathogen requires serotyping, tissue culture, immunochemical methods, or DNA hybridization studies, techniques that are not always routinely available. *Enteropathogenic E. coli* (EPEC) account for outbreaks of severe fatal diarrhea in newborns (303), are a major bacterial cause of dehydrating infant diarrhea in developing areas, and cause traveler's diarrhea. The organism is acquired by ingesting contaminated food or water. Risk factors for death include a young patient age and the virulence of the bacterial strain. Almost all deaths occur before age 2. The organisms are not invasive; nor do they produce toxins. They colonize the proximal small intestine via specific attachment mechanisms, producing characteristic attachment–effacement lesions on the enterocyte plasma membrane. Because EPEC colonizes the duodenum, it can be detected by culturing duodenal aspirates (304).

![Image of bacterial overgrowth](image-url)
### Infectious Diseases

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteropathogenic</td>
<td>Attaches to epithelium; mechanism of injury unknown</td>
</tr>
<tr>
<td>Enterotoxigenic</td>
<td>Produces toxins that activate adenylate cyclase and guanylate cyclase</td>
</tr>
<tr>
<td>Enteroinvasive</td>
<td>Invades colonic epithelium</td>
</tr>
<tr>
<td>Enteroadherent</td>
<td>Adheres to brush borders and destroys microvilli; no invasion; rare villous atrophy</td>
</tr>
<tr>
<td>Enterohemorrhagic</td>
<td>Mechanism of action unknown</td>
</tr>
</tbody>
</table>

*Enterohemorrhagic E. coli* (EHEC) cause hemorrhagic colitis, hemolytic uremia syndrome, and thrombotic thrombocytic purpura; they are discussed in Chapter 13. 

*Enteroadherent E. coli* are nontoxigenic and does not invade the mucosa (302). They avidly adhere to the epithelial brush border via specific receptors (Fig. 6.132). Often the histology of the small intestine in infected individuals is normal. Children with this infection develop chronic prolonged diarrhea (305). Rarely, villous atrophy results. The lesions may resemble celiac disease. 

*Enterotoxigenic E. coli* (ETEC) elaborate an enterotoxin similar to cholera toxin (306). They represent a major cause of traveler's diarrhea and infant diarrhea in underdeveloped countries. The disease is initiated by consumption of contaminated food or water or by contact with infected persons. Once the bacteria are ingested, they pass to the small bowel, where they colonize the surface epithelium. ETEC adhere to enterocyte brush borders without damaging them. The adhesion is specific, and pili and fimbrial colonization factor antigens determine host specificity. Once in the small intestine, the bacteria produce two toxins: A heat-labile toxin resembling cholera toxin and a heat-stable toxin that activates guanylate cyclase and stimulates active fluid secretion without injuring the enterocytes (307). The disease often begins with upper intestinal distress followed by watery diarrhea. The clinical course may be extremely mild or very severe, mimicking cholera and producing severe dehydration and rice water stools. Symptoms consist of the sudden onset of abdominal cramps, nausea, borborygmi, and malaise. Acute watery diarrhea then develops, followed by dehydration with low-grade fever and chills.
Infectious Diseases

**FIG. 6.132.** Enteroadherent *Escherichia coli.* A: Hematoxylin and eosin–stained section showing bacteria adhering to the surface epithelium in an area of mucosal denudation. The area of epithelial loss with adherent organisms is contained within the circle. The underlying lamina propria and crypts appear normal. B: Giemsa-stained section showing the presence of attached bacteria in the denuded area. The area of epithelial loss with adherent organisms is contained within the circle. (This particular picture is from the colon, but similar lesions occur in the terminal ileum.)

The presenting symptoms of *enteroinvasive E. coli* (EIEC) infection include diarrhea, tenesmus, fever, and cramps. The organism penetrates and multiplies within epithelial cells. Clinically, most patients manifest watery, nonbloody diarrhea. This organism is unusual in the United States, although it is relatively common in Thailand (308).

*Enteroaggregative E. coli* (EAEC) have been implicated as an important agents of persistent diarrhea among infants in the developing world and as a cause of traveler's diarrhea. A plasmid encodes the gene for the aggregative adherence properties of EAEC. Ultrastructurally, one can show that the EAEC strains have four morphologically distinct kinds of fimbriae that mediate cellular adhesion and induce mucosal damage (309). The typical illness presents with a watery mucoid secretory diarrhea with low-grade fever and little or no vomiting. The diarrhea may last for several weeks. The disease is diagnosed by isolating the organism from the stool and the demonstration of an aggregative adherent pattern on HEp-2 assay.

**Salmonella Infections**

*Salmonella* organisms are Gram-negative bacilli that produce five clinical syndromes: (a) gastroenteritis (70% of infections); (b) bacteremia with or without GI involvement (10%); (c) typhoid or enteric fever; (d) localized infections in joints, bones, and meninges (5%); and (e) an asymptomatic carrier state. Most *Salmonella* species can produce any of these syndromes, but certain serotypes more commonly associate with specific clinical presentations (310). Usually, *Salmonella* causes a mild self-limited illness, but very young, elderly, and immunocompromised patients develop serious complications, sepsis, and death. The disease pattern reflects the inherent bacterial virulence, the number of organisms ingested, their ability to survive and/or replicate, the presence of a normal flora in the upper intestinal tract, and host status. *Salmonella* species are generally divided into typhoid and nontyphoid species.

Infection with *Salmonella typhi* is almost always transmitted person to person (311). Infections with most other *Salmonella* species, except for *Salmonella paratyphi*, derive from environmental sources, principally poultry and livestock. The current rarity of typhoid fever in the United States reflects good hygiene, lack of crowding, and high public standards for home and industrial sewage.

Typhoid fever is spread by contaminated food or water. Humans are the only known reservoir for *S. typhi*, which is transmitted via a fecal–oral route. Its annual incidence in the United States is 0.2 cases per 100,000 population. Higher incidence rates occur in areas with contaminated water supplies and inadequate waste disposal. The usual victims are children and young adults. However, recently a nosocomial outbreak of fluoroquinolone-resistant *Salmonella enterica* was described among elderly individuals in a nursing home (312). Typhoid fever may also be sexually transmitted among men having sex with men (312a).

Patients usually remain relatively asymptomatic during an incubation period of a week followed by a 2- to 3-week period of illness. Then the patients present with fever, abdominal pain, and headache. Abdominal rash, delirium, hepatosplenomegaly, and ecchymosis are common. Diarrhea begins in the second and third weeks of the infection. It is watery at first but may become bloody, and perforation may occur. Typhoid fever is a chronic systemic illness with a mortality rate of 15% in untreated individuals and 1% in treated individuals. A prolonged convalescent stage of 3 months is usual. GI complications include perforation, massive intestinal hemorrhage (4% to 7%), peritonitis, and paralytic ileus (313). Perforation causes death in 25% to 33% of patients who die of the disease (314). If the patient recovers, intestinal lesions heal with minimal fibrosis so that stricture formation is unusual.

Nontyphoid species (*Salmonella enteritidis, Salmonella typhimurium, Salmonella muenchen, Salmonella anatum, S. paratyphi, and S. give*) result in a milder, more self-limited gastroenteritis with nausea, vomiting, fever, and watery diarrhea.

*Salmonella* organisms are facultative intracellular parasites capable of penetrating, invading, surviving, and multiplying in many cells. Plasmids encode the virulence factors involved in adherence to, invasion of, and growth within the epithelium (315). *Salmonella* organisms adhere to M-cell and enterocyte surfaces, where they induce almost complete destruction (316) as described in Chapter 13. When two or more cells are destroyed, the resulting mucosal defect predisposes to deeper infection (317). If bacteria pass between enterocytes, the tight junctions separate and then reseal following bacterial passage. Internalization of *Salmonella* is receptor mediated, possibly involving the epidermal growth factor receptor> Once inside the cells, the bacteria become enclosed by membrane-bound cytoplasmic vacuoles and they then multiply. Following their release from the vacuoles, they disseminate to the regional lymph nodes, spleen, and liver, sites where the bacteria multiply further (316).

*Salmonella* may infect any part of the gastrointestinal tract, but the ileum, appendix, and right colon are preferentially affected. The bowel wall appears thickened. Swollen, raised, ulcerated Peyer patches produce the typical gross appearance of small, longitudinally oriented (oval) terminal ileal ulcers (Fig. 6.133). Other ulcers appear aphthous, linear, discoid, or full thickness in nature. Ulcers are less prominent in the proximal small bowel. With progressive bowel wall involvement, it becomes paper thin and susceptible to perforation. In some cases, the bowel may appear grossly normal or only mildly erythematous in nature.

Shortened edematous villi contain neutrophilic infiltrates coexisting with crypt hyperplasia. There is marked vascular congestion and lymphoplasmacytic infiltrates along with histiocytes with abundant eosinophilic cytoplasm containing nuclear debris and red blood cells. Peyer patches become hyperplastic (Fig. 6.134) followed by acute inflammation of the follicle-associated epithelium. Edema, fibrinous exudates, and vascular thromboses herald the onset of tissue necrosis and ulceration, causing the lymphoid follicles to appear elevated over the mucosal surface (Fig. 6.135). As the follicle-associated epithelium ulcerates, the lymphoid tissue extends from the submucosa to the mucosal surface, discharging large numbers of bacilli into the intestinal lumen. Eventually the lymphoid follicles become infiltrated and obliterated by macrophages. Architectural distortion severe enough to mimic irritable bowel disease (IBD) may be present.
FIG. 6.133. *Salmonella* enteritis. Note the presence of the prominent longitudinal ulcer overlying the Peyer patches (arrows).

FIG. 6.134. Histologic lesion of the specimen shown in Figure 6.133 showing prominent lymphoid hyperplasia in the Peyer patches surrounded by atrophic small intestine and demonstrating superficial ulceration with surrounding regeneration.

The proliferation of monocytic elements is arranged in both a diffuse and nodular pattern. The nodular areas lie at the periphery of the lesions and the diffuse proliferations are in the center. The nodules are of two types. One contains a germinal center and consists of a mixture of centrocytes, centroblasts, and macrophages surrounded by a ragged compressed mantle zone. The second and predominant type of nodule consists of uniform sheets of monocytes/macrophages, many containing numerous apoptotic bodies and cellular debris rimmed by small lymphocytes. Some of these areas may contain foci of amorphous eosinophilic debris and cells with peripherally displaced nuclei. The interfollicular and diffuse areas are dominated by phagocytic macrophages with a round to irregular (occasionally crescentic) shape and also contain intermingled small, mature-appearing lymphocytes. Occasional plasma cells and immunoblasts are also present. Neutrophils are surprisingly rare, even in the areas of ulceration. This inflammatory reaction extends into the muscularis propria and may even reach the serosa. Small mucosal erosions in areas of nonthickened bowel wall also consist of lymphoid infiltrates with germinal center formation and clusters of monocytes/macrophages, likely representing the early lesions (318).
Infectious Diseases

Biopsies of both the enteritis and the colitis show nonspecific acute and chronic changes resembling other infections. Small intestinal lesions include inflammation and edema of the lamina propria, neutrophilic infiltrates, itself. The ulcers sometimes coincide with the region of Peyer patches.

Inflammatory bowel disease. Grossly, one sees a diffuse, bloody, edematous enterocolitis with multiple, superficial ileal ulcers measuring up to 1 cm in diameter just proximal to the ileocecal valve and involving the valve itself. The ulcers sometimes coincide with the region of Peyer patches.

Endoscopic features of Campylobacter infections include patchy mucosal inflammation, hyperemia, bloody exudates, segmental mucosal edema, loss of a normal vascular pattern, and ulceration. The changes mimic inflammatory bowel disease. Grossly, one sees a diffuse, bloody, edematous enterocolitis with multiple, superficial ileal ulcers measuring up to 1 cm in diameter just proximal to the ileocecal valve and involving the valve itself. The ulcers sometimes coincide with the region of Peyer patches.

Biopsies of both the enteritis and the colitis show nonspecific acute and chronic changes resembling other infections. Small intestinal lesions include inflammation and edema of the lamina propria, neutrophilic infiltrates.
Infectious Diseases

vomiting, diarrhea, and progressive dehydration. The affected bowel becomes dilated, Darmbrand enteritis, or Enteritis necroticans. The lesion starts abruptly in the proximal jejunum and usually extends distally into the ileum. It presents as abdominal pain, necrosis jejunitis.

Enteritidis is a life-threatening infectious disease caused by Clostridium perfringens type C, a β-toxin–producing strain of clostridia causing necrosis and sepsis (340). The disease is characterized by segmental necrosis of the proximal jejunum and is associated with a high mortality rate if not diagnosed and treated early. It was first reported in Northern Germany after World War II among previously starved children and adults who ate large meals of meats and vegetables. The disease rarely occurs in developed countries; when it does it typically affects diabetics (341).

This disorder is also known as Darmbrand enteritis (342), necrosis jejunitis, or jejunitis acta. The lesion starts abruptly in the proximal jejunum and usually extends distally into the ileum. It presents as abdominal pain, vomiting, diarrhea, and progressive dehydration. The affected bowel becomes dilated.
edematous, thickened, rigid, and markedly congested. Valvulae conniventes become very prominent, imparting a washboard appearance to the mucosal surface. When the necrotic mucosa sloughs, extensively ulcerated areas remain. More severe cases have transmural inflammation.

**FIG. 6.136. Aeromonas enteritis.** A: This case shows the presence of prominent lymphoid hyperplasia and a marked inflammatory infiltrate containing large numbers of acute inflammatory cells. These are seen at higher magnification in B.

Histologically, one sees severe mucosal necrosis with hemorrhage, mural thickening due to marked submucosal edema, and fibrinous or fibrous serosal exudate. Pseudomembranes and fibrin thrombi may be present in the inflamed areas. The mucosa between the thickened valvulae may appear normal, whereas the surfaces of the valvulae are more damaged. This pattern suggests a clostridial infection. There is little in the way of a neutrophilic response (342).

**Pig Bel**

A similar disease, pig bel, is endemic in Papua, New Guinea. It results from *Clostridium welchii* and *C. perfringens* infections (343), and it is the most common cause of death in children. Individuals become ill from eating infected pigs during ceremonial occasions. Patients present with symptoms lasting for a few days. These consist of severe, progressive abdominal pain, vomiting, blood-stained feces, and constipation. The small intestine shows segmental necrosis starting at the villous tips and progressing toward the base. The disease affects the duodenum to cecum. Alternatively, multiple segments of small intestine are involved, separated by normal-appearing unaffected segments. Kinking and adhesions between adjacent loops of bowel affect 50% of cases. At the time of surgery, the small intestine appears dilated and the distended bowel has a thickened wall and a red serosal surface. In about 25% of cases one or more yellow patches exist on the serosal surfaces. These represent areas of full-thickness infarction (Fig. 6.111).

Histologically, one sees ischemic changes with necrotic villi. Numerous bacteria are present. A clearly defined junctional zone exists between the necrotic mucosa and the submucosa. The vessels at this junction are thrombosed. Neutrophils accumulate at the edges of infarction. The mucosa becomes infiltrated with neutrophils, mononuclear cells, and eosinophils. Arterial walls appear edematous and infiltrated by inflammatory cells, and they demonstrate a homogeneous or granular eosinophilic appearance classically linked with fibrinoid necrosis.

**Yersinia Infections**

*Yersinia enterocolitica* (YE) and *Yersinia pseudotuberculosis* (YP) are facultative, anaerobic, non–lactose-fermenting, Gram-negative coccoid bacilli. The incidence of infection is highest in the cold months and in cold climates. YE and YP are a common cause of bacterial enteritis in Western and Northern Europe, but increasing numbers of cases have been reported in North America and Australia. Transmission usually follows ingestion of contaminated meats, vegetables, water, and milk (344). Swine constitute an important reservoir for human infections. However, the organism has also been isolated from numerous other animals. Transmission also occurs from dogs and cats and from person-to-person transmission via blood transfusion. Belgium is the country with the highest reported increase of the disease, strongly correlating with the consumption of raw pork. Most infections are self-limited. However, immunocompromised and debilitated patients as well as patients with iron overload are at a risk of serious disease.

The pathogenicity of *Yersinia* species is determined by a number of virulence factors encoded by the bacterial chromosomes or by the virulence plasmid pYV (345,346). Chromosomally encoded proteins facilitate bacterial
intestine attachment, mucosal penetration, survival, and proliferation. Virulence factors include various adhesins, invasin, and attachment-invasion locus. In addition, the pYV proteins make up a type III secretion system similar to that seen in pathogenic E. coli and Salmonella. A “high pathogenicity island” (HPI) is present in only highly pathogenic strains of Yersinia. The Yersinia HPI carries a cluster of genes involved in the biosynthesis, transport, and regulation of the siderophore yersiniabactin. The major function of the island is to acquire the iron molecules essential for bacterial growth and dissemination (347). Luminal bacteria adhere to M cells or absorptive cells in areas of the follicle-associated epithelium. Once inside the cell, the bacteria become enclosed by membranous vesicles (348). YE penetrate into the lamina propria by passing through the enterocyte cytoplasm in a manner similar to that exhibited by Salmonella. Only potentially pathogenic strains invade the lamina propria. YE organisms multiply within lymphoid follicles in Peyer patches, then drain into the mesenteric lymph nodes, eventually giving rise to systemic infections.

Yersinia preferentially involves the ileocecal and appendiceal regions and causes a wide spectrum of clinical and pathologic changes, ranging from self-limited enterocolitis to potentially fatal systemic infections. Diffuse enterocolitis, the most common clinical manifestation, usually affects children younger than 5 years of age (349). Patients present with gastroenteritis, diarrhea, low-grade fever, abdominal pain, ileitis, colitis, diffuse mesenteric lymphadenitis, pseudoappendicitis, sepsis (350,351), intestinal perforation, and the hemolytic uremia syndrome. Older children and adults develop mesenteric adenitis mimicking acute appendicitis. Immunosuppressed hosts often develop severe, fatal, Yersinia bactemia. Patients who are in iron-overloaded states such as those with hemochromatosis or transfusional siderosis develop particularly virulent infections (352). Postinfection manifestations result from bacteremia and include erythema nodosum, bullous skin lesions, and reactive arthritis.

Grossly, Yersinia infections mimic Crohn disease. The bowel wall appears thickened, inflamed, congested, ulcerated, and edematous. Patients develop diffuse, focal, or aphthous mucosal ulcers. Even though numerous ulcers may be present, they are usually not very deep. The intestinal serosa appears dull and hyperemic (Fig. 6.137). The muscularis propria thickens. Massively enlarged lymph nodes may become matted, and they may contain yellowish microabscesses. The enlarged mesenteric lymph nodes may become matted and contain yellowish microabscesses. Both the small and large intestines are involved, with the most severe changes centering on the ileocecal region and appendix.

**FIG. 6.137. Yersinia.** Gross appearance in a patient with culture-proven Yersinia infection. The mucosal folds are unduly prominent due to the presence of the granulomas.

There is considerable overlap in the histologic features of YE and YP. Both infections can produce mucosal ulceration, cryptitis, granulomatous inflammation with prominent lymphoid capping, lymphoid hyperplasia, transmural lymphoid aggregates, and nodal involvement. The affected bowel appears congested, edematous, and ulcerated with massively enlarged lymphoid follicles. Sharply demarcated areas of lymphoid hyperplasia contain prominent germinal centers. The follicular ileitis may persist for months. The mucosa overlying the follicles develops small punctate aphthoid ulcers measuring 1 to 2 mm in diameter (351) resembling similar lesions in Crohn disease. These ulcers are covered by fibrinopurulent exudates and large numbers of Gram-positive coccobacilli. Sharply demarcated lymphoid hyperplasia is present with prominent germinal centers and small aphthous ulcers overlaying the hyperplastic lymphoid follicles. Epithelial granulomas with central necrosis may be seen in the bowel wall and in the lymph nodes. The bowel and lymph nodes contain epithelioid granulomas with central necrosis (Fig. 6.138). Granulomas are located in the mucosa and submucosa, but they can also occur on the serosa. The muscularis propia and serosa become infiltrated by pleomorphic cellular infiltrates including eosinophils. Acute vasculitis or intussusception may cause ischemia (Fig. 6.139). Crypt hyperplasia occurs throughout the small intestine with villous atrophy (351). Strictures are rare. The changes superficially resemble those found in cat-scratch fever.

The most important entity in the differential diagnosis is Crohn disease, which may be very difficult to distinguish from Yersinia infections histologically. Culture, serologic studies, and polymerase chain reaction (PCR) assays may confirm Yersinia as the cause of the disease. Features that favor a diagnosis of Crohn disease include prominent neural hyperplasia and evidence of chronic changes including crypt distortion and hyperplasia of the muscularis mucosae.
Yersinia enterocolitis. A and B show the prominent necrotizing granulomas that characterize Yersinia infections. 

A: Contains two granulomas (arrows). The overlying epithelium appears atrophic and ulcerated. 

B: Higher magnification showing palisading histiocytes without foreign body giant cells. The entire granuloma is surrounded by a prominent cuff of lymphocytes.

**Tuberculosis**

In the 1980s, after decades of steadily declining rates of tuberculosis, ambitious plans were made to eliminate the disease in the United States. However, despite these plans, the control of tuberculosis was neglected, resulting in a resurgence of the disease (353). Between the mid-1980s and the early 1990s, the synergistic combination of a deteriorating public health infrastructure, inadequate institutional control of infection, urban crowding, the HIV epidemic, and immigration resulted in a resurgence of tuberculosis including infections with multidrug-resistant strains.

Tuberculosis is currently uncommon in North America but it remains endemic in Asia, where it constitutes a major health problem. In 2000, 16,377 cases (5.8 cases per 100,000 population) were reported to the Centers for Disease Control and Prevention (CDC), representing a 45% decrease in the incidence rate and the lowest rate in U.S. history (354). In the United States, 50% of all cases of tuberculosis occur in foreign-born individuals (355), who represent only 10% of the total population (356). Tuberculosis in the immigrant population is largely attributed to the importation of latent infection with subsequent reactivation of the disease (357). The rate of tuberculosis among immigrants who have lived in the United States for 5 years or less is three times as high as that among immigrants who have lived here for more than 5 years (358). Recognizing that existing public health practices are inadequate, both the CDC and the Institute of Medicine have called for stronger measures to detect and treat latent infection in immigrants to the United States (359). In addition to immigrants, HIV-
infected persons, minorities, the homeless, incarcerated, alcoholics, and the poor have increased infection rates. Others at risk for the infection may include hospital workers and the military. Blacks are more likely to contract tuberculosis than persons of other races (360). Recent developments in bacterial genotyping are providing a better understanding of the pathogenesis, transmission, drug resistance, and reinfection of tubercular infections (361).

The severity of GI involvement relates to the severity of pulmonary infections and is most common in individuals with cavitary lung lesions and a positive sputum. Swallowed organisms pass through the small bowel mucosa without causing a local lesion, only to arrest in the regional lymph nodes. Ulcerative small intestinal lesions develop as the result of retrograde spread.

Complications of intestinal tuberculosis include severe enterocolitis, hemorrhage, perforation, obstruction, fistula formation, strictures, malabsorption, and severe secretory diarrhea. The latter results from bacterial overgrowth in dilated intestinal loops lying proximal to points of obstruction. It may also result from obstruction of the mesenteric lymphatics by granulomas in the regional lymph nodes. Chronic nonspecific abdominal pain is the most common complaint. Other findings include fever, weight loss, and malaise. The clinical differential diagnosis includes carcinoma, tuberculosis, Crohn disease, and Yersinia infections. AIDS patients may develop generalized tuberculosis, and up to 50% of patients who die are undiagnosed premortem (362). This is due to the fact that generalized tuberculosis in the setting of AIDS often lacks the typical features of the disease. Inflammatory foci show areas of necrosis with numerous neutrophils, numerous acid-fast bacilli, few or no epithelioid histiocytes, and no Langhans giant cells (362). The ileocecal region is affected in 90% of patients (Figs. 6.140 and 6.141); other affected locations in decreasing order of frequency include the ascending colon, appendix, jejunum, duodenum, stomach, sigmoid, and rectum. This distribution follows the distribution of the lymphoid tissues.

The area of the ileocecal valve is frequently obscured by a mass that consists of mesenteric fat, fibrotic tissue, lymph nodes, and other inflammatory changes. The appendix and distal terminal ileum are usually thickened and strictured, with mucosal ulceration and surface fibrin deposits. The wall of the colon may be so extensively destroyed by the inflammatory process that one cannot tell which side of the ileocecal valve one is on.
Infectious Diseases

FIG. 6.141. Tuberculous ileocolitis exhibits extensive lymph node involvement.

FIG. 6.142. Miliary tuberculosis. Gross and microscopic features of miliary tuberculosis. A: Gross resection specimen with numerous whitish mucosal nodules representing tubercles within the Peyer patches. The fat in the surrounding bowel also shows large numbers of 1- to 2-mm whitish nodules, one of which is indicated by an arrow. Fine adhesions are also present. B: Histologic section through several of the serosal tubercles (arrows). Mucosal and submucosal tubercles are not seen in this photograph.

Classically, intestinal tuberculosis assumes one of three forms: (a) the ulcerative form (60% of cases), which exhibits multiple superficial ulcers and has a virulent course with a high mortality; (b) the hypertrophic form (10% of cases), which grossly mimics Crohn disease because of the scarring, fibrosis, and heaped-up mass lesions; and (c) the ulcerohypertrophic form (30% of cases), in which the intestinal wall becomes thickened and ulcerated by an inflammatory mass centering around the ileocecal valve (363). The cut surface of the bowel appears friable, and necrotizing granulomas are easily seen.

Tubercles always begin in Peyer patches or lymphoid follicles and may give the mucosa a cobblestoned appearance. As the disease progresses, tubercles encircle the entire bowel wall (Fig. 6.140). Multiple tubercles may also stud the serosa and mesentery (Fig. 6.142). The ulcerative form of the disease begins as ragged, undermining ulcers. The ulcers may be single or multiple, large or small (Fig. 6.143). In contrast to Crohn disease,
tuberculous ulcers tend to be circumferential with their long axis perpendicular to the lumen without fissuring. The ulcers may contain acid-fast bacilli (AFB), even in the absence of granulomas. The nonulcerated mucosa usually appears markedly edematous and focally hemorrhagic. Hyperplastic lesions cause pronounced intramural thickening with ulceration and obstruction (Fig. 6.140). Fibrosis, strictures, and stenosis result when the ulcers heal. Areas of irregular stenosis may measure several centimeters in length. This leads to the hypertrophic form of the disease. Giant cell granulomas with obvious caseation occur more frequently in ulcerative than hyperplastic lesions. They are distributed throughout the entire thickness of the intestinal wall (Fig. 6.140). Although tuberculosis classically associates with granulomas, it is only one of several causes of ileocecal granulomas (Table 6.15). Regional mesenteric lymph nodes become enlarged, containing areas of caseous necrosis (Fig. 6.144). Isolated organisms can be visualized in the tubercles and lymph nodes with the use of special stains, or they are recoverable from tissue culture.

![Fig. 6.143. Tuberculous enteritis. A: Resection specimen demonstrating the presence of the ulcerative form of tuberculosis. B: The ulceration at higher magnification.](image)

**TABLE 6.15 Intestinal Granulomas**

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoid</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Actinomyces</td>
</tr>
<tr>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Yersinia</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Hyperinfective strongyloidiasis</td>
</tr>
<tr>
<td><em>Mycobacterium avium-intracellulare</em></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td><em>Mycobacterium bovis</em></td>
</tr>
<tr>
<td><em>Salmonella</em></td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
</tr>
</tbody>
</table>
**Brucella**
- Foreign material (talc, sutures, barium)
- Feces due to perforation or fistulae
- Pneumatosis intestinalis
- Histiocytosis
- Malakoplakia
- Cell injury with mucin release

**FIG. 6.144.** Histologic section of the lymph node removed from the resection specimen shown in Figure 6.143. The lymph node is almost completely replaced by a caseating granuloma.

Sometimes it is difficult to detect the bacteria in suspected cases of tuberculosis, even in AFB-stained sections, due to the scarcity of the organisms. In this setting the detection of mycobacterial DNA in formalin-fixed paraffin-embedded tissue by duplex PCR reactions may prove valuable in the management of patients with granulomatous enterocolitis (364).

**Mycobacterium avium-intracellulare Infections**

*Mycobacterium avium-intracellulare* (MAI), a highly prevalent (ubiquitous) AIDS-associated pathogen, affects 15% to 40% of AIDS patients. Persons acquire the organisms through environmental exposure to aerosols, water, food, and soil. Unlike tuberculosis, which appears to result from reactivation of a previously contracted infection, disseminated MAI usually results from a primary infection. A period of asymptomatic colonization of the respiratory or GI tract often precedes disseminated disease, suggesting that the organism is acquired from the environment via the gut and then disseminates. The GI tract is involved twice as frequently as the lungs. Disseminated disease usually follows the primary infection within months.

Healthy people who become colonized by MAI do not normally develop active disease. The major risk factor for the infection is the level of immune dysfunction, as reflected by the CD4+ cell count. Between 76% and 90% of MAI infections develop late in the course of AIDS when other AIDS-defining diagnoses have already been established and CD4 counts measure <60/mm³. MAI may be excreted in the stool of AIDS patients without GI symptoms.

Virulence factors for MAI are not well established. The organisms penetrate the gastrointestinal mucosa by unknown mechanisms and are phagocytosed by macrophages in the lamina propria. The macrophages cannot kill
Infectious Diseases

the bacteria and they become stuffed with mycobacteria as they multiply within the cells. With continued bacterial replication the host cell ruptures. The process leads to the presence of sheets of macrophages laden with AFB. The bacteria spread through the submucosal tissues, where the lymphatic drainage carries them to the regional lymph nodes. In the lymph nodes, the same process is again repeated. The mycobacteria replicate in macrophages, eventually breaking loose and again forming sheets of infected cells that eventually replace the normal histology of the lymph node. Tissue destruction is rare and most signs and symptoms of MAI result from the elaboration of cytokines (365).

Symptomatic MAI infections typically present indolently with nausea, chronic diarrhea, abdominal pain, malabsorption resembling Whipple disease, fever, sweats, chills, weight loss, lymphadenopathy, hepatosplenomegaly, and pancytopenia. Obstructive jaundice develops secondary to massive involvement of the peripancreatic and porta hepatis lymph nodes. Intestinal obstruction may result from intussusception secondary to hyperplasia of Peyer patches and lymph node involvement (366). Death may result from malnutrition or superinfections. MAI also produces clinical and radiologic pictures resembling Crohn disease, especially in patients with terminal ileitis. At the time of autopsy, up to 60% of patients with MAI infection have GI involvement, even though the organism is rarely recognized antemortem (366). Numerous bacilli are seen in acid-fast–stained sections, both within macrophages and extracellularly.

MAI infections occur throughout the GI tract but they are most common in the duodenum (365). The mucosa appears edematous, erythematous, and friable, sometimes with multiple yellowish linear and oval erosions and/or 2- to 3-mm white or erythematous maculopapular nodules and prominent mucosal folds (Fig. 6.145). Fine white mucosal nodules may also be present. Regional lymph nodes become enlarged (Fig. 6.145). Hematoxylin and eosin (H&E)-stained sections reveal an atrophic mucosa with villous blunting, distortion, and widening due to a diffuse lamina propria infiltrate composed of large numbers of plump PAS-positive macrophages with granular or foamy cytoplasm. The glandular architecture usually remains intact, although the crypts become widely separated by a diffuse interstitial infiltrate of large cells with pale cytoplasm. Lymphocytes, plasma cells, and neutrophils are sparse, if present at all. Regional lymph nodes contain similar infiltrates. Occasionally, one sees poorly circumscribed epithelioid granulomas that contain lymphocytes and rare multinucleated giant cells. Small areas of necrosis may be present in up to 30% of cases (367).

When the changes are marked, the infiltrates are easily recognized on H&E stains using low-power microscopy (Fig. 6.146). The organism may also be detectable in duodenal brushings. Detection of focal involvement may require the use of special stains. MAI histologically resembles Whipple disease (see below), and the mucosa in both diseases contains macrophages with PAS-positive cytoplasmic granules. However, mycobacteria are several times larger than the Whipple bacillus and differ from Whipple bacillus in that they are acid fast. In contrast to traditional tuberculous infections, the macrophages in MAI teem with acid-fast microorganisms. The organisms form tight clusters in the cytoplasm. Giant cells and areas of caseous necrosis are usually absent in MAI.

**Actinomycosis**

*Actinomyces israelii* is a filamentous bacterium that is part of the normal oral flora. Abdominal infections result when swallowed organisms escape destruction in the stomach. *A. israelii* can cause serious small intestinal infections, particularly at the ileocecal valve. Changes in bowel habits, low-grade fever, malaise, weight loss, abdominal pain, and a palpable abdominal mass may lead to a misdiagnosis of carcinoma. The affected bowel appears thickened with multiple suppurative foci and scar tissue. Infections usually involve the full thickness of the bowel wall with extension into surrounding tissues. Ulceration may be minimal, but fistulae often develop. Histologically, there is extensive fibrosis and granulation tissue containing foamy histiocytes, abscesses, and fistulous tracts. The typical bacterial colonies stain darkly with hematoxylin, often exhibiting a classic sulfur granule arrangement.
**Brucellosis**

Brucellosis, a fairly common disease in some parts of the world, is transmitted to humans via consumption of contaminated raw milk, through contact with the afterbirth products of infected animals, via transplacental transmission (368), or possibly via breast milk (369). In the United States, the disease usually presents in Hispanics, possibly related to the illegal importation of unpasteurized dairy products from Mexico, where the disease is endemic. Brucellosis is caused by *Brucella melitensis*, *Brucella abortus*, *Brucella suis*, and *Brucella canis* (370). Bacteria colonize the inoculation site or secondary sites causing chronic granulomatous infections.

The organism differs from other bacteria in that it does not exhibit the classic virulence factors such as exotoxin or endotoxin production (370). Rather, it has a tendency to invade and persist in the human host through inhibition of apoptosis (371). The bacteria invade the mucosa after which phagocytes ingest the organism. After ingestion, most bacteria are eliminated by phagolysosome fusion. Surviving bacteria gradually evolve in bacteria-containing compartments in which rapid acidification occurs. Replication takes place in the endoplasmic reticulum, following which the bacteria are released with the help of a hemolysin and induced cell necrosis. Following their release they are transferred to the regional lymph nodes and then seeded throughout the body (370).

The disease has protean manifestations, with fevers, malodorous perspiration, and osteoarticular disease being the most common presentations. The reproductive system is also commonly affected (370). It rarely affects the small intestine (372). The changes consist of a chronic nonspecific inflammation and vasculitis. The diagnosis of the disease requires isolation of the bacterium from blood or tissue (370).

**Listeriosis**

*Listeria monocytogenes* is a Gram-positive bacterium that can be a serious food-borne pathogen. It primarily affects pregnant women, neonates, immunodeficient persons, and the elderly (373). The organism can be isolated from the intestinal tracts of humans, but it is more commonly found in the GI tract of ruminants. The disease follows consumption of contaminated salads, Mexican-style cheese, raw milk, ice cream, raw meat, sausages, and seafood (374,375). Once ingested, the bacteria breach the intestinal barrier, sometimes causing gastroenteritis in their human hosts. The organisms then travel throughout the body causing sepsisemia, meningitis, intrauterine infections, and, occasionally, diarrhea (375). *Listeria* enters the gut epithelium through the binding of its surface protein internalin to the transmembrane protein E-cadherin expressed on epithelial basolateral surfaces (376). *Listeria* bacteria are obligate intracellular pathogens that inhabit the cytoplasm. The secreted pore-forming protein listeriolysin O of the organism is an essential virulence determinant that allows
Whipple disease is an uncommon multisystem disease (Fig. 6.147) that results from a systemic infection with the recently identified bacterium that was originally named *Tropheryma whippeli* (377). Subsequently, the name was changed slightly to *Tropheryma whippeli*. In autopsy studies its frequency is <0.1%. Whipple disease occurs in people of all ages throughout the world, but the typical patient is a middle-aged white male (378). Whipple disease may occur in regional clusters or in sibling pairs, but the spread of Whipple disease and the role of genetic susceptibility remain obscure. Sequencing studies suggest that immune evasion and host interaction play an important role in the lifestyle of this persistent bacterial pathogen. Persistent monocytic or macrophage dysfunction may predispose to the infection since the macrophages appear to be unable to degrade the bacteria once they are phagocytosed (379). This inability to degrade bacterial antigens may relate to decreased production of interleukin (IL)-12, which may lead to decreased interferon-γ production by T cells and defective macrophage activation. A decrease in IL-12 might prevent the development of an effective type 1 helper T-cell immune response (378). Additionally, the bacterium has a unique cell wall and it localizes in the lamina propria, where it elicits a cellular response that consists almost entirely of macrophages with the accumulation of bacterial wall remnants in these cells. Replication of the organism in the macrophages associates with apoptosis of the host cell with expression and release of IL-16. Elevated serum IL-16 levels and markers of apoptosis correlate with the activity of Whipple disease, decreasing to normal levels after successful therapy (378).

**FIG. 6.147.** Diagram showing the various manifestations of Whipple disease.
Whipple disease is characterized by two stages: A prodromal stage and a much longer steady-state stage. The prodromal stage is characterized by the presence of migrating polyarthritis and arthritis. The steady state is typified by diarrhea, abdominal pain, weight loss, malabsorption, low-grade fever, dermal hyperpigmentation, pericarditis, aortic valve vegetations, peripheral lymphadenopathy, anemia, and edema. The diarrhea is usually watery, malodorous, and often associated with steatorrhea (380,381). Lymphadenopathy affects approximately 50% of patients. Central nervous system disease affects approximately 10% of patients. The average time between the prodromal and steady-state stage is 6 years (378). However, if a patient had received previous immunosuppressive therapy, a more rapid clinical progression can occur. Macrophage infiltrations of the endocardium lead to valvular stenosis or insufficiency. The abdomen may be distended or slightly tender, and a periumbilical mass representing the enlarged mesenteric lymph nodes is sometimes palpable. Hepatosplenomegaly affects some patients. Approximately 15% of patients do not have the classic signs and symptoms of the disease. The disease is fatal if left untreated (378).

Whipple disease frequently involves the jejunum and ileum, but it usually spares the duodenum (381). The edematous mucosa acquires a coarse, granular appearance and it may contain yellow-white plaques. The intestinal wall thickens and subepithelial yellowish lipid deposits are seen. One may also see rare mucosal ulcers and petechial hemorrhages (Figs. 6.148 and 6.149) (381). Mesenteric and retroperitoneal nodes become grossly enlarged and pale, sometimes measuring as much as 3 to 4 cm in diameter (Fig. 6.150). Yellowish perilobular plaques and massive infiltration of the mesenteric fat are characteristic of late-stage disease. The diagnosis depends on the demonstration of multiple rounded, rod, or sickle-shaped PAS-positive diastase-resistant inclusions stuffing lamina propria macrophages. Some bacilli are seen within and between epithelial cells (379). PAS-positive material is also seen in smooth muscle, endothelium, and fibroblasts. The villi appear blunted and distorted by macrophage collections (Fig. 6.151). In severe cases, there may be subtotal or total villous atrophy. Most commonly, the macrophages lie just beneath the luminal epithelial basement membrane and decrease in number as one progresses toward the submucosa. This pattern of involvement supports the concept that the bacteria invade the tissues from the intestinal lumen. Lymphocytes, neutrophils, eosinophils, and macrophages may infiltrate among the macrophages. Rarely, one sees necrosis and fibrosis. Widespread fatty deposits and granulomas are present in the mucosa and intra-abdominal lymph nodes. The lymph nodes lose their normal architecture and become fibrotic. Three types of granulomas are seen (i.e., foreign body, lipogranulomas, and epithelioid granulomas). Granulomas may also be present in other tissues such as spleen, muscles, bronchial mucosa, lung parenchyma, kidney, GI mucosa, and bone marrow. Lymphatic obstruction causes dilation of the lacteals. Although the macrophages may resemble one another in several diseases (Table 6.16), fatty deposits are usually only present in Whipple disease. MAI infections are compared with Whipple disease in Table 6.17. In one study, the histology was characteristic with these features in only 90% of patients (382). The diagnosis may be confirmed using antibodies to the bacillus or by PCR reactions (377).
FIG. 6.149. Whipple disease. A: Hyperemic bowel, indurated mesentery, and prominent serosal lymphatic channels. B: Small bowel involvement demonstrating marked obliteration of the normal architecture with thickening of the mucosa and loss of normal crypts and villi. C: Same area stained with a periodic acid–Schiff (PAS) stain demonstrating the collections of dark fuchsinophilic macrophages within the mucosa. D: High magnification of the mucosal infiltrate showing histiocytic cells. E: Higher magnification of the infiltrate stained with PAS stain.

Treatment may affect the histology of the disease, with the principal changes consisting of a decrease in the number of PAS-positive macrophages and the pattern of mucosal inflammation changing from diffuse to patchy. In addition, the cytologic aspects of the PAS-positive macrophages change (382).

<table>
<thead>
<tr>
<th>TABLE 6.16 Macrophage Collections in the Lamina Propria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAS</strong></td>
</tr>
<tr>
<td>MAI infections</td>
</tr>
<tr>
<td>Whipple disease</td>
</tr>
<tr>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>T-cell defects</td>
</tr>
<tr>
<td>Transplant patients</td>
</tr>
<tr>
<td>Xanthomas</td>
</tr>
<tr>
<td>Storage disease</td>
</tr>
<tr>
<td>Combined immune deficiency</td>
</tr>
<tr>
<td>MAI, Mycobacterium avium-intracellulare; PAS, periodic acid–Schiff.</td>
</tr>
</tbody>
</table>

Tropical Sprue
Infectious Diseases

Tropical sprue results from one or more of the following: (a) a nutritional deficiency, (b) a transmissible organism, and/or (c) a toxin elaborated by a microorganism or contained in the diet. Most believe the disease to be infectious in nature.

P.378

(Table 6.18). Several microorganisms are the suspected pathogen, but none is common to all patients. Characteristic clinical features include the presence of nutritional deficiencies, anorexia, abdominal distention, and persistent diarrhea. Patients develop pallor, weakness, oral edema, and night blindness. Many patients develop milk intolerance because of a lactase deficiency; other patients develop alcohol intolerance (383). When severe, chronic diarrhea, steatorrhea, macrocytic anemia, glossitis, and emaciation occur, all due to fat, carbohydrate, vitamin B₁₂, and folic acid malabsorption.

P.379

<p>| TABLE 6.17 Mycobacterium Avium-Intracellulare (MAI) Infections Versus Whipple Disease |
|----------------------------------------|----------------------------------------|</p>
<table>
<thead>
<tr>
<th>MAI</th>
<th>Whipple Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villi</td>
<td>Widened</td>
</tr>
<tr>
<td>Lacteals</td>
<td>Not dilated</td>
</tr>
<tr>
<td>PAS</td>
<td>+</td>
</tr>
<tr>
<td>AFB</td>
<td>+</td>
</tr>
<tr>
<td>Appearance</td>
<td>Yellow–white granular appearance of small bowel</td>
</tr>
<tr>
<td>Lipid deposits</td>
<td>-</td>
</tr>
<tr>
<td>Response to tetracycline</td>
<td>None</td>
</tr>
<tr>
<td>Malabsorption, fever, cachexia</td>
<td>+</td>
</tr>
<tr>
<td>Migrating arthritis</td>
<td>-</td>
</tr>
</tbody>
</table>

PAS, periodic acid–Schiff; AFB, acid-fast bacillus.
FIG. 6.150. Whipple disease in the mesenteric lymph nodes. A: Gross appearance with yellowish discoloration. B: Histiocytic collections and fatty replacement of lymph nodes. The normal underlying lymph node architecture has been destroyed. C: Histiocytic cells filled with foamy cytoplasm.
FIG. 6.151. Whipple disease. A: Whole mount section showing Whipple disease occupying the mucosa and the submucosa. B: Higher magnification of the base of the mucosa with the histiocytic infiltrates and prominent lipid collections. The histiocytic cells resemble those seen in patients with *Mycobacterium avium-intracellulare* (MAI) infections. However, the presence of the open spaces resulting from the organic chemical extraction of fats only occurs in Whipple disease and is virtually never seen in MAI infection. C: Higher magnification of the lipid-filled histiocytes.

**TABLE 6.18 Factors Favoring an Infectious Origin of Tropical Sprue**
Tropical sprue has a striking geographic distribution affecting four groups of individuals: (a) indigenous populations of the world where the disease is endemic and epidemic, (b) travelers and tourists from temperate climates returning from visits to endemic areas, (c) Caucasian ex-residents of endemic areas returning to live in temperate zones, and (d) inhabitants of endemic areas who migrate to temperate climates. Most expatriates can pinpoint the disease onset, which usually consists of acute, watery, nonbloody diarrhea; malaise; fever; and weakness (383). Diagnostic evaluation of tropical sprue requires its differentiation from parasitic diarrheal diseases. In contrast to bacterial or viral infections, which are short lived, tropical sprue usually fails to improve after returning to a temperate climate. Jejunal biopsies are necessary to establish the presence of the characteristic morphologic abnormalities and to exclude other disorders such as celiac disease, Whipple disease, or lymphoma. The lesion first appears in the jejunum, spreading distally to involve the ileum. Early on, the jejunal mucosa appears normal or only slightly abnormal with increased numbers of intraepithelial lymphocytes. Chronic tropical sprue occurs if the acute phase does not completely remit. Histologic features of tropical sprue consist of villous atrophy, crypt hyperplasia, and epithelial infiltration by chronic inflammatory cells, particularly plasma cells, lymphocytes, eosinophils, and histiocytes. The villi appear thickened, shortened, and broadened to form leaflike structures. Less than 10% of patients develop a completely flattened mucosa (Fig. 6.152). Enterocytes acquire abnormal shapes and orientations. A marked mononuclear infiltration develops in the lamina propria and epithelium. Lymphocytic infiltrates are distributed focally in the upper crypt and crypt villus in zones. Nuclei of crypt enterocytes appear megaloblastic. The basement membrane usually thickens and creates an increased collagen table.

Other Bacterial Infections

Extranodal cat-scratch disease, which is caused by *Bartonella henselae* infection, rarely involves the bowel but it may produce changes histologically identical to those seen in typhoid enteritis. The presence of a neutrophil-rich, macrophage-poor quality to the necrotic areas provides a clue to the diagnosis, as does the identification of microorganisms on a Warthin-Starry or other silver stain. Life-threatening chronic enteritis may complicate Gram-negative *Stenotrophomonas maltophilia* infections (384). To date, it only causes diarrheal disease in immunocompromised hosts or those with malignancies. The infection is characterized by small intestinal erosions.
**Infectious Diseases**

**FIG. 6.152. Early tropical sprue with prominent crypt hyperplasia.**

*Bacillus cereus* is a spore-forming Gram-positive rod that causes both gastrointestinal and nongastrointestinal infections. *B. cereus* is responsible for an increasing number of food-borne diseases in industrialized countries (385). The incidence of *B. cereus* differs geographically and causes from 0.8% to 17.8% of bacterial food poisonings; in the United States it has only been reported in 1.3% of food poisonings (386). Many diverse types of foods can become contaminated as summarized in reference 385. Patients develop abdominal pain, cramps, and watery diarrhea after an 8- to 16-hour incubation period. Symptoms last for 12 to 24 hours. Vegetative cells of the bacterium in the small intestine produce an enterotoxin and the emetic toxin can be isolated directly from the food products (387).

**Fungal Diseases**

**Candida Infections**

Small intestinal candidal infections affect as many as 20% of autopsied patients with disseminated *Candida* infections (388). However, it is extremely rare to find an infection limited to the small bowel (388). Historically, candidemia affects patients on antibiotics, hemodialysis, or chemothereapeutic agents; immunocompromised individuals; immunocompetent patients with serious postoperative complications, cancer, and penetrating abdominal trauma; and patients with indwelling vascular access devices. More recently, increasing numbers of cases result from nosocomial infections (389). Symptoms are more common in hospitalized patients, particularly in children. Rarely, *Candida* species associate with neonatal necrotizing enterocolitis (390).

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is an autosomal recessive disease characterized by (a) variable endocrine failure involving parathyroid glands, the adrenal cortex, gonads, pancreatic β cells, gastric parietal cells, and the thyroid gland; (b) chronic mucocutaneous candidiasis; and (c) dystrophy of dental enamel and nails, alopecia, vitiligo, keratopathy, and hepatitis. Eighteen percent of patients experience malabsorption (391). Patients develop candidiasis sometime during the course of their disease. Probably all species of *Candida* infect the immunocompromised host, although there is a higher frequency of disseminated *Candida tropicalis* than *Candida albicans*. The greater virulence of *C. tropicalis* causes their increased invasiveness (392). These two infections are compared in Table 6.19.

P.381

<table>
<thead>
<tr>
<th>TABLE 6.19 Comparison of Candida tropicalis and Candida albicans</th>
</tr>
</thead>
</table>
Infectious Diseases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C. tropicalis</th>
<th>C. albicans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simultaneous involvement of stomach, small intestine, colon</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Submucosal involvement</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Necrotic band at invasive border in bowel wall</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Less common</td>
<td>Common</td>
</tr>
</tbody>
</table>

Candida has difficulty colonizing nonsquamous cell sites such as the small intestine. In the small bowel, the rapid passage of feces due to peristalsis and the prevention of Candida mucosal interactions by bacterial antagonism reduce the likelihood of fungal colonization (393). Symptoms due to gastrointestinal Candida infections primarily relate to tissue invasion, although hypersensitivity mechanisms and possibly byproducts of fungal growth may induce functional abnormalities.

Fungal involvement falls into two broad categories: Noninvasive (Fig. 6.153) and invasive disease (Fig. 6.154). In noninvasive infection, the fungus grows in devitalized tissues. Candida commonly colonizes blind loops, sites of bacterial stasis, and necrotic areas. The fungus does not cause damage; the fungal spores and hyphae just lie in the fibrinopurulent exudate overlying the necrotic or devitalized tissues without invading intact tissues. Patients present with nausea, acute and chronic diarrhea, abdominal pain, and a host of allergic reactions. Invasive infections affect immunocompromised or chronically debilitated patients or patients in whom the mucosal integrity is destroyed. Such patients develop systemic fungal infections. The organism often invades the vasculature (Fig. 6.155), leading to ischemia and candidal sepsis. If the patient had pre-existing ischemia, the disease may worsen. Monilial enteritis may involve multiple intestinal sites, and multiple candidal ulcers or perforations can be seen. Histologically, Candida organisms appear as 4- to 6-μm budding yeastlike forms admixed with nonseptate pseudohyphae that stain positively with PAS and silver stains (Fig. 6.154).

FIG. 6.153. Candidal colonization of necrotic intestinal tissues. Numerous candidal spores and young hyphae are present.

Histoplasmosis

*Histoplasma capsulatum* is a dimorphic fungus with a worldwide distribution. It is the most common systemic endemic mycosis in the United States, occurring in the central regions of the country from the Gulf Coast to the Great Lakes. The fungus grows in soil that contains a high nitrogen content, particularly in soil enriched by bird and bat guano. Macrophages ingest the yeast after opsonization with antibody and/or complement or following direct binding of the organism to integrins on the surface of phagocytes (394) via the fungal adhesin HSP60s (395). The organism is internalized via a phagosome that subsequently fuses with lysosomes within the macrophage cytoplasm. Once inside the lysosome, Histoplasma employs several mechanisms to escape destruction. The major Histoplasma-secreted antigen, the M antigen, is thought to be a hydrogen peroxide–degrading catalase (396) that may neutralize the harmful effect of host cell–generated hydrogen peroxide. Survival of intact viable fungus in the hostile environment of phagolysosomes within the macrophages requires Histoplasma protein synthesis, indicating an active role of the organism in promoting its own survival. It may accomplish this by moderating the microenvironmental pH, reducing its acidity. This function may occur through a fungal protein pump (397). Additionally, the mode of entry of the Histoplasma into macrophages via alternative nonopsonophagocytic mechanisms may help the organism avoid or suppress host defenses against it. Heavy inhalation of spores results in systemic illnesses, even in immunocompetent individuals. Immunocompromised patients develop particularly severe infections. Gastrointestinal involvement is frequent in disseminated disease and may affect any site, including the esophagus, stomach, and small and large bowel. Patients present with crampy abdominal pain, nausea, vomiting, diarrhea, dysphagia, anorexia, vomiting, hematemesis,
Infectious Diseases

Intestinal ulceration develops in disseminated disease, often leading to perforation and peritonitis. Pulmonary symptoms are uncommon in patients with GI disease (398). Terminal ileal involvement predominates in one third of the cases. In severe disease, perforation and peritonitis may occur. Gastrointestinal masses or ulcers may mimic inflammatory bowel disease or carcinoma. Systemic manifestations often accompany these symptoms including gradual weight loss, fatigue, and weakness. AIDS patients with disseminated histoplasmosis often develop acute severe symptoms associated with shock, respiratory failure, and disseminated intravascular coagulation (399).

FIG. 6.154. Superficially invasive candidiasis. A: Low magnification showing a prominent monilial membrane overlying the ulcerated surface. The branching hyphae are beginning to invade the tissues. B: Higher magnification. A and B are stained with Grocott stain.

Grossly, ulcers, localized and diffuse granulomas, pseudopolyps (Fig. 6.156), and areas resembling xanthomas are present. The lesions usually assume the form of discrete, yellowish, raised plaques that undergo secondary ulceration and produce widespread tissue destruction and even perforation. The histologic response ranges from little response (in immunocompromised patients or those treated with cytotoxic drugs) to severe mononuclear cell infiltrates with fibrosis. The organism lies within well-formed granulomas (Fig. 6.157) or in scattered lamina propria macrophages, producing a pattern resembling Whipple disease. However, the organisms are large, round, and easily distinguishable from Whipple bacilli. In severe disease, fungi fill the macrophages. The capsule of H. capsulatum is PAS positive and diastase resistant.

FIG. 6.155. Invasive Candida in a vessel. The vascular wall is partially destroyed in its lower margin. Numerous clear spaces (arrows) correspond to the cross section of hyphae.

Other Fungal Infections

Aspergillus species are ubiquitous environmental pathogens occurring worldwide. They pose particular problems in hospitalized populations when patients are exposed to organisms present in the ventilation or near construction sites. The infection generally affects severely debilitated or immunocompromised hosts, particularly those with severe neutropenia. The fungi tend to invade vessels, causing vasculitis, thrombosis, ischemia, and infarction (Figs. 6.158 and 6.159). When the tissues become ischemic, perforation and peritonitis develop. Identification of the characteristic hyphae leads to the diagnosis.

Mucor is widely distributed in nature and belongs to the phycomycetes with nonseptate hyphae. Mucor infections...
Preferentially affect chronically debilitated individuals, diabetics, and severely malnourished children (400). Histologically, the pleomorphic, irregularly right-angled branched hyphae of *Mucor* appear broad and aseptate, measuring 10 to 20 µm in diameter. They are usually well seen in H&E-stained sections. The fungus tends to invade blood vessels, causing thrombosis and ischemia. *Mucor* produces discrete mucosal erosions and deep ulcers, causing hemorrhage, necrosis, and perforation as the infection spreads into the bowel wall. Histologically, the ulcer bases contain necrotic tissue with a surrounding rim of neutrophils and occasional giant cells, unless patients are on chemotherapy, in which case the inflammation may be negligible.

*FIG. 6.156.* Histoplasmosis. Intestinal resection specimen showing nodular ulcerated lesions diffusely throughout the bowel wall obliterating the normal mucosal fold pattern.

*FIG. 6.157.* Histologic section of the lesion shown in Figure 6.156 indicating the presence of a submucosal granuloma.

*Paracoccidioidomycosis* infects both the large and small intestines (401). The ulcerative lesions of paracoccidioidomycosis have a characteristic rolled border with a white exudative base and small hemorrhagic dots. These are due to the formation of multiple granulomas. The draining lymph nodes are often involved. The fungi are easily seen in H&E-stained sections due to their large size, but they can be highlighted by fungal stains. The fungi are often surrounded by a granulomatous reaction combined with pyogenic inflammation. The distinctive feature of the fungus in tissue is an occasional large cell that, when hemisected, reveals peripheral buds protruding from a thin-walled, round mother cell that sometimes resemble a ship's wheel.
Infectious Diseases

Aspergillosis infection in a patient with acute myelogenous leukemia. The irregular, necrotic areas outlined by the arrows represent areas of ischemic necrosis due to invasive aspergillosis. The mucosal lesion is highlighted by the double arrows.

Penicillium marneffei is a thermally dimorphic fungus that can cause disseminated infections in individuals residing in, or traveling to, areas where the organism is endemic including Southeast Asia, Southern China, and Hong Kong. The disease infects both immunocompetent and immunocompromised hosts, but most cases occur in AIDS patients. It is the third most common opportunistic infection in HIV-infected patients in Thailand. The most common manifestations are fever, anemia, weight loss, and skin lesions, but GI symptoms are also common. The organisms infect the gut from the esophagus to the colon. Endoscopy demonstrates the presence of mucosal ulcers or bleeding tumorlike masses. Biopsies from the margins of the ulcers show lymphocytes and macrophages distended with yeasts in a pattern mimicking that of histoplasmosis. However, P. marneffei shows much more morphologic variation than Histoplasma. The demonstration of characteristic central septation and elongated sausage-shaped forms by silver stains and the absence of buds attached by a narrow neck distinguish P. marneffei from H. capsulatum.

Viral Infections

Numerous viral classes cause gastroenteritis; some are compared in Table 6.21. Diagnostic methods used to identify GI viral infections include viral culture, electron microscopy, immunoelectron microscopy, enzyme-linked immunosorbent assay (ELISA) of stool specimens, genetic probes, and, rarely, biopsies.

Rotavirus Infections

Rotaviruses are a prominent cause of severe diarrhea in children under the age of 2 years. Most infected patients are between 5 months and 4 years in age. Annually, they account for an estimated 140 million cases and 1 million deaths in young children. Child daycare increases the risk of diarrhea due to rotavirus infections. Rotavirus infections also affect immunosuppressed adults and transplant and geriatric patients. The infection is highly contagious so that it only takes a small inoculum to infect a child. The viruses survive well on environmental surfaces and are difficult to inactivate. Rotaviruses are cosmopolitan in their distribution. Patients develop fever, severe vomiting, and watery diarrhea, often leading to dehydration and acidosis. Fatal cases exhibit severe cardiac and central nervous system involvement.

Viral Infections

Numerous viral classes cause gastroenteritis; some are compared in Table 6.21. Diagnostic methods used to identify GI viral infections include viral culture, electron microscopy, immunoelectron microscopy, enzyme-linked immunosorbent assay (ELISA) of stool specimens, genetic probes, and, rarely, biopsies.

Rotavirus Infections

Rotaviruses are a prominent cause of severe diarrhea in children under the age of 2 years. Most infected patients are between 5 months and 4 years in age. Annually, they account for an estimated 140 million cases and 1 million deaths in young children. Child daycare increases the risk of diarrhea due to rotavirus infections. Rotavirus infections also affect immunosuppressed adults and transplant and geriatric patients. The infection is highly contagious so that it only takes a small inoculum to infect a child. The viruses survive well on environmental surfaces and are difficult to inactivate. Rotaviruses are cosmopolitan in their distribution. Patients develop fever, severe vomiting, and watery diarrhea, often leading to dehydration and acidosis. Fatal cases exhibit severe cardiac and central nervous system involvement.

TABLE 6.20 Etiologies of Viral Enteritis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>Prominent cause of severe diarrhea in children under the age of 2 years.</td>
</tr>
<tr>
<td></td>
<td>Most infected patients are between 5 months and 4 years in age.</td>
</tr>
<tr>
<td></td>
<td>Annually, they account for an estimated 140 million cases and 1 million deaths in young children.</td>
</tr>
<tr>
<td></td>
<td>Child daycare increases the risk of diarrhea due to rotavirus infections.</td>
</tr>
<tr>
<td></td>
<td>Rotavirus infections also affect immunosuppressed adults and transplant and geriatric patients.</td>
</tr>
<tr>
<td></td>
<td>The infection is highly contagious so that it only takes a small inoculum to infect a child.</td>
</tr>
<tr>
<td></td>
<td>The viruses survive well on environmental surfaces and are difficult to inactivate.</td>
</tr>
<tr>
<td></td>
<td>Rotaviruses are cosmopolitan in their distribution.</td>
</tr>
<tr>
<td></td>
<td>Patients develop fever, severe vomiting, and watery diarrhea, often leading to dehydration and acidosis.</td>
</tr>
<tr>
<td></td>
<td>Fatal cases exhibit severe cardiac and central nervous system involvement.</td>
</tr>
<tr>
<td>Virus Family</td>
<td>Disease</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Rotavirus family of viruses</td>
<td>Coronavirus</td>
</tr>
<tr>
<td>Norwalk family of viruses</td>
<td>Dengue fever</td>
</tr>
<tr>
<td>Reovirus</td>
<td>Measles</td>
</tr>
<tr>
<td>Echoviruses</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Parvoviruses</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Toroviruses</td>
</tr>
<tr>
<td>Calicivirus</td>
<td>Reoviruses</td>
</tr>
<tr>
<td>Astroivirus</td>
<td>Pestiviruses</td>
</tr>
</tbody>
</table>

![Image A](image1.png)
![Image B](image2.png)
**TABLE 6.21 Virologic Characteristics of Human Gastroenteritis Viruses**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Virion Diameter (nm)</th>
<th>Virologic Features</th>
<th>Genomic Nucleic Acid</th>
<th>Medical Importance Demonstrated</th>
<th>Epidemiologic Characteristics</th>
<th>Clinical Characteristics</th>
<th>Laboratory diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus, group A</td>
<td>70–75</td>
<td>Double-shelled, wheelike capsid; segmented; four common serotypes</td>
<td>RNA</td>
<td>Yes</td>
<td>Major cause of endemic severe diarrhea in infants and young children worldwide (in winter in temperate zone)</td>
<td>Dehydrating diarrhea for 5–8 days; vomiting and fever very common</td>
<td>Immunoassay, electron microscopy, PAGE</td>
</tr>
<tr>
<td>Enteric adenovirus</td>
<td>70–80</td>
<td>Morphologically like other adenoviruses; types 40 and 41 cause gastroenteritis</td>
<td>DNA</td>
<td>Yes</td>
<td>Endemic diarrhea of infants and young children</td>
<td>Prolonged diarrhea lasting 5–12 days; vomiting and fever</td>
<td>Immunoassay, electron microscopy, PAGE</td>
</tr>
<tr>
<td>Norwalk virus</td>
<td>27–32</td>
<td>Round with ragged surface outline; single structural protein similar to caliciviruses</td>
<td>RNA</td>
<td>Yes</td>
<td>Epidemics of vomiting and diarrhea in older children and adults; occurs in families, communities, and nursing homes; often associated with shellfish, other food, or water</td>
<td>Acute vomiting, diarrhea, fever, myalgia, and headache lasting 1–2 days</td>
<td>Immunoassay, immune electron microscopy</td>
</tr>
<tr>
<td>Norwalk-like viruses</td>
<td>27–35</td>
<td>Examples are Snow Mountain, Hawaii, Taunton, and Otofuke</td>
<td>RNA</td>
<td>Yes</td>
<td>Similar to characteristics of Norwalk virus</td>
<td>Acute vomiting, diarrhea, fever, myalgia, and headache lasting 1–2 days</td>
<td>Immunoassay, electron microscopy</td>
</tr>
<tr>
<td>Calicivirus</td>
<td>27–38</td>
<td>Round, classically structured, cup-shaped indentations on surface</td>
<td>RNA</td>
<td>Partially</td>
<td>Usually pediatric diarrhea; associated with shellfish and other food in adults</td>
<td>Rotaviruslike illness in children; Norwalk-like in adults</td>
<td>Immunoassay, electron microscopy</td>
</tr>
<tr>
<td>Astrovirus</td>
<td>27–32</td>
<td>Round, classically structured, unbroken surface with pointed star</td>
<td>RNA</td>
<td>Partially</td>
<td>Diarrhea in children and nursing homes</td>
<td>Watery diarrhea, often lasting 2–3 days, occasionally longer</td>
<td>Immunoassay, electron microscopy</td>
</tr>
</tbody>
</table>

PAGE, polyacrylamide gel electrophoresis.

The infection usually spreads from the proximal small bowel to the ileum over a period of 1 to 2 days. Rotaviruses infect mature enterocytes on the villous tips and differentiated enterocytes in the dome epithelium overlying Peyer patches, particularly M cells (408). The viruses mature in enterocytes, multiplying within the endoplasmic reticulum. As the viral particles accumulate, they lyse the cells, causing epithelial shedding, crypt hyperplasia, and round cell infiltration in the lamina propria (408). The crypt depth:villous height ratio increases. Severe infection causes gross destruction of villous architecture, leading to malabsorption. The changes persist for 3 to 8
weeks. The diagnosis is usually made by examining the stool. Negative contrast electron microscopy demonstrates the presence of 70-nm wheel-like particles (Fig. 6.160). Immunoelectron microscopy increases the sensitivity of conventional ultrastructural examination. Other diagnostic tests include immunoelectrophoresis, complement fixation, viral RNA electrophoresis, radioimmunoassay, and rapid latex agglutination technique. PCR amplification provides a way of identifying the organism in stool specimens. There is also an antibody directed against the virus that can detect it in tissues.


In 1998, a tetravalent rotavirus vaccine was licensed in the United States for vaccination of infants, following the demonstration of its efficacy in a trial in South America (409). Following that, the American Academy of Pediatrics and the American Academy of Family Medicine recommended routine vaccination of healthy infants. To date, the only complication has been rare cases of intussusception (410). Since then additional highly effective vaccines have been developed that do not seem to be associated with an increased rate of intussusception (411).
Caliciviruses cause more than 90% of outbreaks of acute gastrointestinal illness in the United States (412). Norwalk virus is the prototype of the human caliciviruses and is found in human feces by immunoelectron microscopy (413). The virus has a cosmopolitan distribution, infecting adults and school-age children, but not infants and young children. Norwalk virus and related viruses cause approximately 40% of gastroenteritis outbreaks in recreational camps and the military; on cruise ships; in communities or families; at elementary schools, colleges, and nursing homes; in hospital wards; in cafeterias; and among members of sports teams. The disease mainly spreads by person-to-person contact and by ingestion of contaminated drinking or swimming water, poorly cooked or raw shellfish, and contaminated food (414). Air-borne transmission also occurs. The virus has an incubation period of 12 to 48 hours, and the disease runs its course in 1 to 2 days. Symptoms of Norwalk virus infection include low-grade fever and combinations of diarrhea, anorexia, malabsorption, nausea, vomiting, abdominal cramps, malaise, myalgia, and headache. Unlike rotavirus infections, the gastroenteritis induced by Norwalk viruses is more epidemic in nature, usually resulting in shorter and milder illness, and the infections occur throughout the year.

Norwalk viruses invade the upper intestinal mucosa by binding to specific histo-blood group antigens present on the epithelium (415). Damage is limited to the small intestine in the area of the duodenal–jejunal junction. Volunteers who received the Norwalk agent developed histologic abnormalities within 12 to 48 hours following viral inoculation. These included mucosal inflammation, enterocyte changes, villous shortening, crypt hyperplasia, and increased epithelial mitoses. The lamina propria cellularity increased, containing both mononuclear cells and neutrophils. The changes persisted for at least 4 days and cleared by 6 to 8 weeks after the acute illness (416). Diagnostic tests include immunoelectron microscopy, radioimmunoassay for the virus and its antibodies, and PCR for the detection of Norwalk virus DNA.

**Enteric Adenovirus Infections**

Enteric adenovirus types 40 and 41 are readily transmitted from child to child and are the second most common cause of viral diarrhea in infants and young children requiring hospitalization. The virus has a worldwide distribution. Adenoviral illnesses usually affect children younger than 2 years old, particularly in the first year of life (417), and they may originate in daycare centers. Severe infections affect immunodeficient individuals and bone marrow transplant recipients, sometimes causing death. The infection also affects children following small bowel transplantation (418). The infections do not demonstrate seasonality. Adenovirus infections typically last from 5 to 12 days, producing protracted, watery diarrhea. Vomiting and fever are less prominent than with rotavirus infections (417). Rare infections associate with fatal disease and intussusception. The diagnosis is usually established by ultrastructural examination of the stool, viral cultures, radioimmunoassay, or the use of DNA probes. Ultrastructurally, the epithelial cells contain irregular hexagonal virions averaging 73 to 80 nm in diameter, often forming paracrystalline arrays.

Adenovirus infections tend to localize to the ileum because of the viral proclivity to infect lymphoid tissues (Fig. 6.77). Pathologists are unlikely to receive a specimen from a patient infected with an adenovirus unless the patient develops an intussusception, in which case the associated lymphoid hyperplasia acts as the lead point. Histologic changes are relatively nonspecific and include villous atrophy and inflammation. Neutrophils and mononuclear cells infiltrate the epithelium and lamina propria. Most of the changes remain confined to the villi, but rare glands also become necrotic and inflamed. Many villous epithelial cells contain intranuclear eosinophilic inclusions surrounded by a clear halo. In situ hybridization (Fig. 6.77) or PCR confirms the viral presence. Patients with intussusceptions may have ischemic changes superimposed on the viral changes.

**Astrovirus Infections**

Astroviruses occur worldwide and may be associated with both epidemic gastroenteritis and endemic childhood diarrhea (419). Astroviruses cause diarrheal outbreaks in newborn nurseries and pediatric wards, in community settings, and in nursing homes. Outbreaks sometimes affect daycare workers. Diarrhea due to astrovirus infections is more common in young children up to age 7 than in adults. Infants who are younger than 1 year of age are particularly vulnerable. Diarrhea usually develops in the winter months (420). Clinically, the infections resemble rotaviral illness, although the disease is less severe. The virus infects the enterocytes along the upper parts of the villi and subepithelial macrophages. The viral particles are then released when the desquamated cells are released into the intestinal lumen and disintegrate. The epithelium restores itself within 5 days (421). Ultrastructurally, astroviruses measure 27 to 30 nm in diameter and exhibit a very characteristic five- or six-pointed star-shaped surface structure without a central hollow. Astroviral antibodies are detectable using indirect fluorescence. Most children acquire antiviral antibodies by age 5 years.

**Cytomegalovirus Infections**

CMV, a ubiquitous herpes virus, causes diverse clinical symptoms in many organs. Populations at highest risk for disseminated GI infection include neonates, allograft recipients, HIV-infected individuals, immunosuppressed patients, pregnant women, the very young or very old, or those with malnutrition or malignancy. Patients who undergo intestinal transplantation for short bowel syndrome are particularly vulnerable to CMV infections (422). In these patients, PCR analysis of intestinal biopsies may be useful for preemptive therapy in the selected patients (423).

The presentation of CMV enteritis in patients with isolated GI involvement ranges from mild anorexia to frank hemorrhage and perforation. The usual clinical manifestations are nonspecific and include fever, abdominal pain, diarrhea, vomiting, anorexia, weight loss, diarrhea, GI bleeding, and, occasionally, perforation. Mortality in CMV enteritis is adversely associated with age older than 65 and increased time to the institution of therapy but is not affected by the anatomic site of the infection (424). The entire small bowel may be involved, although some patients have limited ileocecal involvement. Histologically, the changes range from isolated inclusions with no accompanying tissue reaction to frank ulceration, toxic megacolon, and perforation. The pathologic features of CMV are discussed further in Chapter 13.

**HIV Infections**

More than 30 million people are infected with HIV-1 worldwide. Epidemiologically, the major risk groups for developing AIDS vary depending on geographic locale. In Africa and Asia, the major risk group is sexually active heterosexuals; women are more often infected than men (425). In contrast, in the United States, over 70% of cases affect homosexual or bisexual men. Another 15% develop in intravenous drug users. Other high-risk groups include prostitutes, hemophiliacs, children born to HIV-positive mothers, patients transfused with infected blood or blood products, and heterosexual contacts of any of the above groups (426). HIV-infected mothers pass the virus transplacentally, at the time of delivery through the birth canal, or through breast milk. AIDS especially affects Hispanics and African Americans (427). The AIDS patient population in the United States is disproportionately male, black, and poor. Women represented 18% of all cases in the United States in 1994. Sexual transmission is now the dominant route by which women become infected (428).

Substantial declines have occurred in AIDS incidence and death in recent years, probably due to an increased awareness in at-risk populations and the introduction of highly active antiretroviral treatment (HAART). Gastrointestinal complications were universally recognized during the course of HIV infection; however, in the era of HAART, these complications have dramatically decreased. There is a substantial reduction in the number of opportunistic infections associated with HIV infection in patients on HAART (429). Although substantially effective in suppressing opportunistic infections, the antiretroviral medications associate with GI side...
Infectious Diseases

effects in up to 10% of cases. Currently, drug-induced side effects and nonopportunistic diseases are among the most common causes of GI symptoms in HIV-positive patients (430). Multiple enteric pathogenic bacteria also cause diarrhea in AIDS patients. Patients may have one or more infections, including *C. jejuni* or *C. fetus*, *Enterobacter aerogenes*, *Salmonella*, *S. flexneri*, *Klebsiella*, other Gram-negative bacilli, and *M. avium*. The most common virus to be detected is CMV. Patients may also have fungal or parasitic infections. The degree of inflammation seen in AIDS enteropathy correlates with mucosal levels of p24 antigen and clinical symptoms, supporting an etiologic role for HIV.

Disruption of the villous architecture with a reduction in villous height and crypt hyperplasia commonly occurs in patients with HIV enteropathy. This change alters the crypt:villus ratio and results in a decreased surface area in the small bowel. In addition, the epithelium converts from a columnar to a cuboidal morphology, consistent with epithelial cell injury. These epithelial changes associate with lamina propria inflammation, intraepithelial lymphocytosis, epithelial vacuolization, and increased apoptoses (Fig. 6.161) (431).

Some of the epithelial changes result from concomitant infections, and others are thought to be immune mediated. HIV can be found within the intestinal mucosa and the virus itself may be important in the enteropathy. In addition, nutritional factors may cause the enteropathy secondary to deficiencies of key nutrients (431). Other aspects of intestinal HIV infections are discussed in Chapter 13.

**FIG. 6.161.** HIV enteropathy. Small intestinal mucosa with increased number of intraepithelial lymphocytes and apoptosis within the epithelium as well as in the lamina propria mononuclear cells. The apoptotic areas are outlined by circles.

P.389

Parasitic Infections

Protozoans and helminths are responsible for considerable human morbidity and mortality (Table 6.22). Intestinal parasites infect more than 25% of the world's population. The infections are most frequent in developing countries due to overcrowding, poor nutrition, and inadequate sanitation. In a 1987 survey of 216,275 stool specimens examined by state diagnostic laboratories in the United States, parasites were found in 20.1%. Percentages were highest for protozoans (*Giardia lamblia*) (7.2%), *Entamoeba coli*, and *Endolimax nana* (4.2% each), *Blastocystis hominis* (2.6%), *Entamoeba histolytica* (0.9%), and *Cryptosporidium* spp. (0.2%). The most commonly identified helminths were nematodes: Hookworm (1.5%), *Trichuris trichiura* (1.2%), and *Ascaris lumbricoides* (0.8%). Other less commonly identified helminths included *Clonorchis* and *Opisthorchis* spp. (0.6%), *Strongyloides stercoralis* (0.4%), *Hymenolepis nana* (0.4%), *Enterobius vermicularis* (0.4%), and *Tinea* spp. (0.1%) (432,433).

**TABLE 6.22 Small Intestinal Parasite Infections**

---

file:///F|/Gastro/Chapter%206%20Infectious%20Diseases.htm (34 of 56)2/4/2009 2:05:31 PM
<table>
<thead>
<tr>
<th>Protozoa</th>
<th>Helminths</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Giardia lamblia</em></td>
<td>Nematodes (round worms)</td>
</tr>
<tr>
<td>Cryptosporidium parvum</td>
<td>Ascaris lumbricoide</td>
</tr>
<tr>
<td><em>Isospora belli</em></td>
<td>Trichuris trichiura</td>
</tr>
<tr>
<td>Sarcocystis species</td>
<td>Capillaria philippinensis</td>
</tr>
<tr>
<td>Coccidianlike bodies</td>
<td>Enterobius vermicularis</td>
</tr>
<tr>
<td>Microsporidia</td>
<td>Trichostrongylus species</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Trichinella species</td>
</tr>
<tr>
<td>Visceral leishmaniasis</td>
<td>Toxocara infections</td>
</tr>
<tr>
<td></td>
<td>Angiostrongylus costaricensis</td>
</tr>
<tr>
<td></td>
<td>Anisakis species</td>
</tr>
<tr>
<td></td>
<td>Cestodes (tapeworms)</td>
</tr>
<tr>
<td></td>
<td><em>Taenia saginata</em></td>
</tr>
<tr>
<td></td>
<td><em>Taenia solium</em></td>
</tr>
<tr>
<td></td>
<td><em>Diphyllobothrium latum</em></td>
</tr>
<tr>
<td></td>
<td><em>Hymenolepis nana</em></td>
</tr>
<tr>
<td></td>
<td>Trematodes</td>
</tr>
<tr>
<td></td>
<td>Schistosomal species</td>
</tr>
<tr>
<td></td>
<td>Intestinal flukes</td>
</tr>
<tr>
<td></td>
<td><em>Fasciolopsis buski</em></td>
</tr>
<tr>
<td></td>
<td><em>Echinostoma caprovi</em></td>
</tr>
<tr>
<td></td>
<td><em>Heterophyes heterophyes</em></td>
</tr>
<tr>
<td></td>
<td><em>Metagonimus yokogawai</em></td>
</tr>
</tbody>
</table>

Parasites have complex life cycles, with each stage exhibiting unique biochemical, antigenic, and morphologic features. Humans acquire protozoan and helminthic infections via multiple routes, including ingestion, direct penetration of the intact skin, or insect bites. The parasites then inhabit specific locations within their hosts. They reside intracellularly, intravascularly, in tissues, or in the GI lumen. Humans serve as both intermediate and definitive hosts for many parasites. Passage through intermediate hosts plays a significant role in the life cycle of many parasites.

**Protozoal Infections**

**Giardia**

*G. lamblia* has a worldwide distribution and is the most commonly reported parasitic disease in the United States and Canada (434). It is a leading cause of water-borne diarrheal outbreaks. *Giardia* infections increase in the summer and fall. In the United States, giardiasis commonly occurs in residents of, and travelers to, the Rocky Mountains. The surface waters become contaminated by the fecal material from wild animals. Most community-acquired infections occur where surface water (streams, rivers, and lakes) serves as the principal water source and chlorination is the principal disinfection method. Cysts remain viable in cold or tepid water for 1 to 3 months and can survive the chlorine concentrations present in municipal water systems. *Giardia* oocysts can also be found in the soil in up to 40% of parks, places where children commonly play (435). Infections occur by fecal–oral transmission, ingestion of contaminated food or drink, and person-to-person transmission in daycare centers and among homosexuals (436). *Giardia* also spreads among participants in swimming
Infectious Diseases

classes (437). Domestic pets, especially dogs, carry the organism (438). Patients with hypogammaglobulinemia, immunodeficiency syndromes, hypochlorhydria, or achlorhydria have an increased risk of acquiring the infection.

The infections may remain self-limited and asymptomatic or may last for years, causing severe diarrhea, cramps, malabsorption, and failure to thrive in children. The most common presentation is the onset of 5 to 7 days of acute diarrhea following an incubation period of 1 to 3 weeks. The acute illness varies in severity. Some patients experience an abrupt, explosive onset of frequent watery, foul-smelling stools, whereas others have only a few loose bowel movements. Other patients present with abdominal cramps, abdominal pain or distention, passage of flatus, lassitude, progressive weight loss, and malabsorption (439). Less often, fever and vomiting develop. Patients with chronic giardiasis have intermittent diarrhea that is less severe than that seen in the acute illness. Occasionally, allergic and other inflammatory phenomena develop.

\[ \text{P.390} \]

Giardia exists in two morphologic forms: The motile trophozoite or feeding stage and the infective cyst (Fig. 6.162). Following ingestion, the cysts excyst in the duodenum, forming two daughter trophozoites. The oval, thick-walled cysts of G. lamblia initially contain two nuclei. These divide, forming four nuclei as the cysts pass through the intestinal tract. Mature cysts are shed in the stool. The cytoplasm often retracts from the cyst wall, imparting a double-walled appearance.

Giardia can be diagnosed by examining stool, duodenal aspirates, or duodenal biopsies. The diagnosis is most commonly made by finding characteristic cysts in the stool. However, stool examinations are only diagnostic in some patients with known infections. In contrast, most duodenal aspirates are positive. The number of trophozoites in these aspirates tends to be high during the acute phase of the infection and declines with the clearance phase (440). The sensitivity of Giardia detection increases if both stool specimens and duodenal aspirates are examined. Immunologic tests specific for the organism can supplement stool examination since most individuals develop antibodies to the parasite.

Giardia organisms are pear shaped, about the size of an epithelial cell nucleus, with two nuclei. One nucleus is visible when seen in profile. The parasites are often numerous. In H&E sections, Giardia appears gray or faintly basophilic (Figs. 6.163 and 6.164). The organism attaches itself to the microvilli of absorptive cells with its ventral suction disc and feeds through its dorsal surface. Giardia covers the enterocyte surface (Fig. 6.164), interfering with the microvillus layer and preventing interaction of digestive enzymes with luminal substrates. Rarely, trophozoites are found in the mucosa and lamina propria.

Infectious Diseases

FIG. 6.163. Giardiasis. The *Giardia lamblia* trophozoites seen here in a trichrome-stained smear are distinguished by their pear shape and paired nuclei resembling eyeglasses.

Small intestinal biopsies from immunocompetent patients show one of three patterns: (a) no alterations even though organisms are present; (b) a normal villous architecture, but increased numbers of intraepithelial lymphocytes and immunoglobulin-containing cells in the lamina propria with a relative increase in the number of IgA- and IgG-containing cells; and (c) complete villous atrophy with brush border enzyme deficiencies, crypt hyperplasia, variable inflammation, large numbers of intraepithelial lymphocytes, and IgA- and IgM-containing cells in the lamina propria. Focally, neutrophils infiltrate the mucosa. The cellular infiltrate of the lamina propria tends to be highest in individuals with high trophozoite counts (440). A flat mucosa similar to that seen in celiac disease may occur, but it is rare. The incidence of partial villous atrophy ranges from 23% to 50% depending on a number of factors, including geography and the phase of the infection. When trophozoite numbers decline, the crypts lengthen to repair the villous atrophy. Patients may develop nodular lymphoid hyperplasia. Patients whose biopsies lack lamina propria plasma cells usually have coexisting hypogammaglobulinemia. Rarely, the organisms may be seen in the stomach or colon (439).

 Cryptosporidial Infections

*Cryptosporidium*, a coccidial organism, infects the gastrointestinal epithelium, causing a diarrhea that is self-limited in immunocompetent persons but is potentially life threatening in those with AIDS (441). It accounts for 6% of all diarrheal diseases in immunocompetent persons and is found in up to 24% of persons with AIDS and diarrhea worldwide (442). HIV-positive patients with self-limited infections have significantly higher CD4 counts than patients with persistent infections. The latter frequently have CD4 counts measuring <100 cells/mm³; they usually measure <50 cells/mm³. Although *Cryptosporidium parvum* is the most common species in humans, *Cryptosporidium felis, Cryptosporidium muris*, and *Cryptosporidium meleagridis* have also been identified in immunocompromised persons (443,444). *C. parvum* causes self-limited diarrhea in children, animal handlers, residents of developing countries, and travelers to tropical countries (445). Cryptosporidia have been added to the growing list of organisms causing diarrhea in daycare centers. Food, water, and other sources play a role in oocyst transmission (446). The organism is transmitted by fecal–oral or hand–mouth contamination, person to person, via pets, via contaminated food, and by water-borne outbreaks. Many community infections originate from public water sources, even when they are chlorinated since the cryptosporidia are resistant to chlorine treatment.
Infectious Diseases

FIG. 6.164. Duodenal biopsy in a patient with giardiasis. A: Shows many trophozoites demonstrating their typical flattened appearance. B: Shows numerous trophozoites seen on their sides adherent to the glycocalyx of the enterocytes.

Humans are infected once they ingest the oocysts, which preferentially migrate to the GI tract where they begin their life cycle releasing infective sporozoites. Cryptosporidia can complete all stages of their development (sexual and asexual) within a single host cell (441). The sporozoite attaches to the apical membrane of enterocytes in a process mediated by specific ligands on the host cell (447). This attachment induces reorganization of the host cell actin cytoskeleton and protrusion of the host cell membrane around the sporozoite to form a vacuole in which the organisms remain intracellular but extracytoplasmic (447). At the base of each vacuole an electron-dense band of host cell cytoskeletal elements facilitates the uptake of nutrients by the parasite from the host cell. The internalized sporozoite then matures and undergoes asexual reproduction to produce merozoites. After release into the intestinal lumen, the merozoites can either infect other epithelial cells or mature into gametocytes, the sexual form of the parasite. The life cycle is repeated after fertilization occurs in the intestinal tract, yielding thin-walled oocysts that sporulate to release sporozoites again. This cycle leads to autoinfection and heavy persistent infections with massive shedding of oocysts in the feces of an infected patient (441).

In immunocompetent individuals, the disease usually presents as an acute, mild to moderate, self-limited illness lasting 3 to 4 days (446), although it may persist for up to 4 weeks. Patients have nonspecific clinical manifestations including passage of watery, nonbloody stools; vomiting; anorexia; abdominal cramps and pain; and possibly malabsorption and weight loss. AIDS patients, unlike immunocompetent patients, cannot clear the organism, so that the infection often persists for the remainder of the patient's life. Patients with proximal small intestinal infections typically begin with a mild diarrhea that progresses to voluminous, debilitating, watery diarrhea associated with dehydration, malabsorption, and profound weight loss. Secondary malabsorption often occurs and is related to a decreased absorptive surface area in heavily infested individuals. Gastroduodenal involvement may produce partial gastric outlet obstruction. AIDS patients often have coexisting gastrointestinal infections; the intensity of the symptoms and histologic findings reflect the nature and intensity of all of the organisms that are present.

The clinical diagnosis primarily relies on detection of 5-µm acid-fast oocysts in fresh stools (Fig. 6.165). Immunofluorescence methods provide enhanced sensitivity and specificity over conventional staining methods. Enzyme immunoassay kits are simple, rapid, and less subjective ways to detect cryptosporidia in fecal samples (448).

Cryptosporidia can involve the esophagus, stomach, bile ducts, and intestines. The diagnosis of cryptosporidial infection requires close scrutiny of all epithelial surfaces, including those in the lumina of intestinal glands for the presence of the characteristic organisms (Fig. 6.165). The organisms can be recognized as clusters of spherical or ovoid basophilic (bluish) or golden brown bodies measuring 2 to 4 µm in diameter attached to the epithelial surfaces. The sensitivity of endoscopy with mucosal biopsy in detecting the organism varies by anatomic location as follows: Stomach (11%), duodenum (53%), terminal ileum (91%), and colon (60%) (449). Low-density infections may associate with normal duodenal histology, whereas severe inflammation and villous atrophy complicate high-density infections. The mucosa may contain acute inflammation and an intraepithelial lymphocytosis. The infected cells show a range in cell injury from only minimal injury and fragments of organisms in the cells to focal necrosis that results in variable villous and crypt atrophy. In tissue sections, cryptosporidia are best seen with a modified Kinyoun stain. The organism stains deep blue with Giemsa and Gram stains, positively with PAS stains, and negatively with the Gomori methenamine silver (GMS) stain. A combined acid fast–trichrome stain may be useful in detecting the organism (450). A fluorescein-labeled IgG monoclonal antibody to the wall of cryptosporidial oocysts is very sensitive and can detect small
Infectious Diseases

Microsporidial Infections

Microsporidia constitute a separate phylum of ubiquitous, spore-forming, obligate intracellular protozoans that cause a wide range of diseases, including enteritis and encephalitis. Distinctive features of the phylum *Microspora* include (a) a lack of mitochondria; (b) a merogonic and sporogonic life cycle, which gives rise to generations of sporoblasts that become mature spores; and (c) spores with a coiled polar filament; the number of coils is unique to each species (451). Microsporidiosis has an extensive host range, including most invertebrates and all classes of vertebrates. Microsporidia are pathogens in birds, arthropods, fish, and a few mammals. Most animals acquire the infection through ingestion. Microsporidia are primarily water borne, but food-borne disease also occurs. These infections predominantly, but not exclusively, affect severely immunocompromised persons with AIDS. The prevalence of microsporidial infection in AIDS patients varies from 15% to 39% (452,453). Patients with microsporidial infections are usually homosexual with a history of foreign travel or residence in tropical regions. Microsporidia contribute significantly to the overall morbidity in HIV-infected patients. Human infections result from the following organisms: *Enterocytozoon bieneusi*, *Enterocytozoon bieneusi*, and *Encephalitozoon hellem*. There are three currently recognized *Encephalitozoon* species: *Encephalitozoon hellem*, *Encephalitozoon cuniculi*, and *Encephalitozoon intestinalis*. *Enterocytozoon* and *Encephalitozoon* account for most microsporidial infections.

The clinical manifestations of microsporidiosis are diverse and include intestinal, biliary, pulmonary, ocular, muscular, and renal disease (453). The organisms also cause asymptomatic disease. Endoscopically, patients with microsporidial infections do not usually demonstrate discrete ulcerations or mass lesions, but the villi often appear abnormal under the dissecting microscope. *E. hellem* and *E. intestinalis* behave more like classic mammalian microsporidia. *E. cuniculi*, *E. hellem*, and *E. intestinalis* not only spread contiguously, but also infect macrophages and disseminate from their points of entry to the respiratory tract and other organs (454).

**Enterocytozoon bieneusi Infection**

The cardinal features of *E. bieneusi* infections are persistent diarrhea with increased fecal volumes measuring up to several liters per 24 hours. The chronic diarrhea (lasting up to 30 months) causes severe wasting (451) and fluid and electrolyte imbalance. Its prevalence ranges from 10% to 34% in AIDS patients with diarrhea. Patients with microsporidial infections are usually men having sex with men with a history of foreign travel or residence in tropical regions. CD4 counts typically measure <50 cells/mm³. Although *E. bieneusi* infects the entire length of the small intestine, it preferentially involves the proximal small intestine. The lesion may go undetected if the infection does not produce enteritis, ulceration, or other histologic abnormalities. The infection is usually focal and spores may be very sparse. Mucosal biopsies may show an increase in mucosal macrophages or plasma cells.

Two phases of the life cycle of *E. bieneusi* are identified ultrastructurally: (a) a proliferative phase (merogony) and (b) a spore-forming phase (sporogony). During the proliferative phase, the organisms appear as small, electron-lucent round objects containing one to six nuclei. The spore-forming phase begins with the presence of stacks of electron-dense discs that later aggregate end to end to form the curved profiles of polar tubes. The nuclei continue to divide, resulting in larger organisms with up to 12 nuclei surrounded by several coils of the polar tube. These large multinucleated forms break up into sporoblasts (immature spores) that then develop into mature spores. The mature spores are very electron dense with a single nucleus and possess an exceptional tubular extrusion apparatus for injecting spore contents, termed *sporoplasm*, into host cells. It consists of several coils of polar tube, an anchoring tube, and a polarplast. Each spore also contains a posterior polar vacule and a polar filament with five to seven overlapping coils of the polar tubules that appear in cross section as a series of doublets. Spores are infective when released in the feces. Intracellularly, spores differentiate into trophozoites that undergo asexual multiplication to form merozoites. The merozoites invade new host cells and certain types develop into male and female microgametes. Fertilization produces oocysts that are either excreted or produce sporozoites in situ to repeat the cycle.

Microsporidia can be diagnosed by identifying the spores in the stools, small bowel biopsies, intestinal aspirates, or mucosal brushings with touch preparations. Stool examination for spores using the modified chromohemate stain is the simplest method and perhaps the most sensitive for diagnosing the intestinal infection (455).

---

**FIG. 6.165. Cryptosporidium.** A: The cryptosporidial organisms appear as small (2 to 3 µm) round hematoxylinophilic bodies adjacent to or attached to the mucosal surface. B: In cryptosporidial diarrhea, the diagnosis can be made by demonstrating characteristic oocysts in the stools on modified acid-fast stains of the smear preparation. The oocysts typically measure 3 to 6 µm in diameter and stain bright pink-red and have a discernible outer wall.

Cryptosporidia can be easily overlooked or mistaken for mucous droplets. Conversely, cellular debris and mucus clinging to the epithelium can be mistaken for cryptosporidia. However, unlike the apical mucin droplets that they resemble, cryptosporidia are mucicarmine negative. There is currently no effective treatment for the disease (441).
Infectious Diseases

Typically, the parasite has a focal distribution in the duodenal mucosa, although massive infestations may occur (Fig. 6.166). The degree of cellular injury parallels the intensity of the infection. Some patients develop villous atrophy, crypt hyperplasia, intraepithelial lymphocytosis, and loss of brush border enzyme activity. Involved villi may appear blunted or have a bulbous shape. The enterocytes may contain irregular hyperchromatic nuclei and a vacuolated cytoplasm. In heavy infections, disorganized aggregates of crowded, irregularly shaped, degenerating necrotic cells often containing merozoites and spores populate the villous tips. The tips of the villi and strips of infected mucosa eventually slough into the lumen. A variable lymphocytic infiltrate accompanies the epithelial changes, but neutrophils are usually absent. The organisms lie clustered in the supranuclear cytoplasm and may indent the enterocyte nucleus, making them easier to identify when screening at low power. The clustered, dark, refractile, oval spores measure approximately 0.7 to 1.0 µm in width and 1 to 1.6 µm in length and are less frequent than the parasite. They are surrounded by an inner unit membrane, an electron-lucent endospore, and a thin electron-dense exospore. Spores are often seen in degenerating enterocytes.

A helpful diagnostic feature is the presence of a PAS-positive polar cap at one end of the spore. The spores are also positive with acid-fast stains. Gram stains also are useful for detecting the organism. They are readily identified because of the contrasting dark blue or reddish staining against a brown-yellow background. Some use Warthin-Starry, modified trichrome, or Giemsa stains to identify the parasite. A combined acid-fast–trichrome stain may be useful in detecting the organism (450). The use of semithin sections (Fig. 6.167) gives better histologic definition and is helpful in identifying the organism in individuals with sparse infections and in identifying the earlier stages of the parasitic development because of the visualization of the characteristic clefts. The diagnosis is based on the ultrastructural features of the spores in the proliferative forms, the method of division, and the nature of the host cell–parasite interface. Ultrastructural examination is particularly useful in differentiating between intestinal microsporidiosis due to *E. bieneusi* and *E. intestinalis* as described in reference 455. The organism may also be detected by the use of antibodies or PCR amplification of small-subunit RNA.
Infectious Diseases

FIG. 6.166. Microsporidia. A: Medium-power hematoxylin and eosin–stained section showing a small intestinal mucosa with atrophy and a minimal increase in chronic inflammatory cells. B: Higher magnification shows a flattened epithelium with mild increased basophilia (arrows). C: Gram stain showing parasitophorous vesicles (arrow) containing a large number of organisms. D: Giemsa-stained specimen showing the azure blue organisms within the epithelium (arrow).

FIG. 6.167. Microsporidia. Thick Epon-embedded section stained with toluidine blue demonstrating numerous parasitophorous vesicles (arrows) in a supranuclear location.

Microsporidia are often missed, even on careful examination, because of their small size, intracellular location, and poor staining with usual tissue stains. The stains discussed above may produce distinctive contrasts between the very small microsporidial spores and other cellular contents and background debris. Because of the propensity of some microsporidia to disseminate and because of their differences in drug sensitivities, there is an increasing demand for pathologists and microbiologists to classify the microsporidia. The infection can be treated with fumagillin (456).
**Enterocytozoon intestinalis Infection**

*Enterocytozoon intestinalis* is the second most prevalent microsporidian infection reported in AIDS patients. *E. intestinalis* produced severe diarrhea, a wasting syndrome, and systemic disease. The initial symptoms usually localize to the GI tract, but the organisms can disseminate and infect hepatobiliary, respiratory, and urologic tissues leading to renal failure and rhinosinusitis (457).

*E. intestinalis* has a life cycle with four stages: Meront, sporont, sporoblast, and spore. Like *E. bieneusi*, the spores contain a polar tube that injects membrane-bound sporoplasm into uninfected host cells. The earliest stage, the meront, is an ovoid, uninucleate organism measuring 2.7 x 1.5 µm that replicates by binary fission. The nuclear division sometimes outstrips cytoplasmic division, leading to binucleate and tetranucleate forms. As a result, a cluster of organisms aggregates within a vacuole in the host cell cytoplasm. The second stage, the sporont, divides by binary fission, each producing two or four sporoblasts (455). Sporoblasts are uninucleate organisms that develop a polar tube and as these mature, these organelles become more conspicuous. Transformation to the final or fourth stage of the spore is marked by the development of a thick coat. The spores measure approximately 2.0 x 1.2 µm in size and contain a single nucleus and a polar tube, as well as some other organelles. They infect target cells by sticking to the cell membrane by means of the anterior attachment organ and injecting sporoblasts into the host cell via the polar tube. This is followed by merogony. *E. bieneusi* and *E. intestinalis* may be differentiated by their location in the intestine. *E. bieneusi* only infects the epithelial cells, usually at the villous tips. In contrast, *E. intestinalis* also infects the epithelium at the tips of the villi and deeper in the crypts and also infects fibroblasts, macrophages, and endothelial cells in the lamina propria.

Histologically, one sees the typical features of a microsporidia. The degree of villous blunting and inflammation varies considerably, and may be present or absent. Ultrastructurally, parasites in various stages of development cluster in parasitophorous vacuoles that appear to undergo septation by a fibrillar matrix so that each spore appears to lie in its own compartment. The spores contain a polar filament with five to seven coils.

**Isospora belli Infection**

Most *Isospora belli* infections affect patients in tropical and subtropical countries, particularly in Africa and South America. *I. belli* accounts for diarrhea in 15% of Haitian and 0.2% of U.S. patients with AIDS. The organism spreads by ingestion of contaminated food or water or via homosexual transmission. In the immunocompetent host, the disease manifests itself as a self-limited malabsorption lasting 3 to 5 weeks (458). Fever, malaise, colicky abdominal pain, nausea, weight loss, and watery diarrhea usually occur in immunocompromised patients. The diarrhea in AIDS patients may last for months and is more severe than that which affects the immunocompetent host, and these patients may become wasted (459). About 50% of patients develop peripheral eosinophilia. Malabsorption appears later in the disease course. Symptoms resemble those seen in cryptosporidial infections, but the distinction between the two infections is important because *Isospora* infections are easily treated by appropriate antibiotic therapy. Like cryptosporidiosis, *I. belli* infections follow ingestion of infective forms (sporulated oocysts). Excretion occurs in the proximal small bowel, resulting in the release of eight sporozoites from each cyst. The latter invade epithelial cells and mature into trophozoites. During the schizogonous (asexual) phase, each trophozoite divides into numerous merozoites, which, when released from parasitized cells, invade other epithelial cells. Each merozoite may then pass through one or more repetitive cycles of asexual division or proceed to the sexual phase by maturing into macro- (female) and micro- (male) gametes. Zygotes, resulting from fertilization of the gametes, mature into oocysts that are then released into the bowel lumen. These then pass into the stools (Fig. 6.168), or during their transit in the bowel, undergo sporulation, and release trophozoites that parasitize enterocytes downstream to start the cycle over again. All stages of both asexual (trophozoite, schizont, and merozoite) and sexual (macrogametocyte) phases of the life cycle of the parasite are found in the epithelial cytoplasm, always enclosed within a parasitophorous vacuole. The nonsporulated (immature) oocysts excrated in stool mature into infective mature oocysts within 48 to 72 hours but can also remain dormant for long periods.

Because patients with isosporiasis intermittently shed oocysts, multiple stool specimens should be examined to increase the likelihood of detecting the organism. The oocysts are concentrated from fresh stool samples by sucrose flotation and highlighted by the Kinyoun acid-fast stain. *Isospora* oocysts are larger (25 to 30 µm in length) than *Cryptosporidium* (4 to 5 µm), with a thin wall enveloping two large sporoblasts or a single large zygote (an immature oocyst) when shed in the feces. Fecal specimens are best examined after 1 to 2 days at room temperature, allowing oocysts to mature. Although the organism preferentially infects the small bowel, it can spread to the stomach, esophagus, biliary tree, and large intestine, but it only rarely disseminates to extraintestinal lymph nodes, liver, or spleen.

This pathogen can be seen within enterocytes of the small intestine or, less commonly, in the colonic mucosa. *I. belli* causes moderate mucosal villous atrophy, crypt hyperplasia, and lamina propria infiltration by lymphocytes, plasma cells, neutrophils, and eosinophils. Eosinophils may be so plentiful as to suggest a diagnosis of eosinophilic enteritis. The flattened mucosa may show clubbed villous tips, marked dilation of the vascular spaces, and excessive collagen deposits in the lamina propria. The epithelium generally appears well preserved except for foci of vacuolization. Closer examination usually discloses the presence of organisms in different stages of sexual and asexual life cycles. The parasitized cells are destroyed and adjacent cells are left intact, appearing normal. Occasional extracellular merozoites may be seen in the intestinal lumen and in the lamina propria near or within lymphatic vessels (460). Rarely, schizonts are present in the lamina propria and the submucosa. Mesenteric lymph nodes may also become involved.
Infectious Diseases

FIG. 6.168. *Isospora*. The relatively large (15 to 20 µm) oocyst of *Isospora* is thin walled and contains sporocysts after sporulation. The organisms are difficult to see on routine H&E sections, but Giemsa staining highlights them. Often one sees large numbers of unsuspected coccidial organisms within the epithelium. The organisms stain faintly with H&E, and dark blue with Giemsa or H&E plus Alcian blue. They are also strongly PAS positive but are difficult to differentiate from host goblet cells. The large schizont stage is best seen in overstained Giemsa preparations. The merozoite has a banana shape and occurs at all levels in the enterocyte cytoplasm. The central nucleus, large nucleolus, perinuclear halo, and location within a thick parasitophorous (PAS-negative) vacuole give it a characteristic appearance. Free merozoites and gametocytes are more difficult to detect than intracellular organisms.

Eimeria Infections

*Eimeria* infections resemble other coccidial infections. The clinical features and histologic features are essentially similar. The terminal web of microfilaments in the epithelial cells infected by the merozoites of *Eimeria tenella* becomes disrupted and cell extensions are present on the enterocyte surface. Marked morphologic alterations result in microvillous loss and extensive cytoplasmic bulging into the crypt lumen. Invasion of enterocytes and invasion of goblet cells also occurs. Large numbers of mast cells infiltrate the mucosa. Merozoites are also found within mast cells and lymphocytes in the lumen (461). Ultrastructurally, the organism lacks the crystallloid body found in *Isospora*.

Cyclospora Infection

*Cyclospora* infections affect up to 11% of Haitian AIDS patients (462), and they also commonly affect North American travelers returning from Haiti and Mexico. The organisms have been implicated in large diarrheal outbreaks and community infections originate from public water sources since the organism can withstand the chlorination process. The illness develops in both normal and immunocompromised individuals, and is characterized by severe intermittent watery diarrhea, nausea, and anorexia and fatigue, which wax and wane for weeks to months before spontaneous recovery (463). Resolution occurs abruptly after 2 to 12 weeks of illness and the organism disappears from stool specimens. The symptoms resemble those seen in patients with *Isospora* or cryptosporidial infections.

### Table 6.23 Comparison of Helminths

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nematodes</th>
<th>Cestodes</th>
<th>Flukes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape</td>
<td>Round, without segments</td>
<td>Tapelike, segmented</td>
<td>Leaflike, without segments</td>
</tr>
<tr>
<td>Body cavity</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sexes</td>
<td>Separate</td>
<td>Hermaphroditic</td>
<td>Hermaphroditic</td>
</tr>
<tr>
<td>Hooklets</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Suckers</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Infectious Diseases

The cysts measure 10 µm in diameter and in freshly passed stool are readily identified by their blue autofluorescence under ultraviolet light (463). This identification method may be more sensitive and reliable than the modified acid-fast stain or iodine stains. The organisms stain with modified acid-fast stain but not with hematoxylin, methenamine silver, or PAS stain.

The organism is not usually found in intestinal biopsies, although it is found in duodenal aspirates (463). Patients with these infections exhibit mild to moderate acute and chronic inflammation, surface epithelial disarray, variable villous atrophy and crypt hyperplasia, increased plasma cells in the lamina propria, and focal neutrophilic infiltrates. Surface enterocytes, especially their villous tips, appear focally vacuolated and lose their brush border. The enterocytes become columnar in shape and crypts become hyperplastic.

Helminthic Infections

Table 6.23 compares nematodes (round worms), trematodes (flukes), and cestodes (tapeworms).

Ascaris Infections

*Ascaris* infections are the most prevalent intestinal helminth, infecting approximately 25% of the human population (464). The worms have a worldwide distribution, although they are most common in tropical and subtropical regions of Asia, Africa, and America. Ascariasis is acquired by ingesting mature eggs from contaminated soil when children play on the ground or when ova are ingested in fecally contaminated food and water (Fig. 6.169). The number of worms harbored determines morbidity and transmission dynamics. The balance between exposure rates and rate of loss of the infection due to host immune defenses determines the intensity of infection. Environmental factors also play a role in disease transmission. *Ascaris* eggs remain dormant under dry conditions.

*Ascaris lumbricoides* is the largest of the round worms, measuring up to 40 cm in length. These worms have a lifespan of 1 year or less and females generally live longer than males. The worm has a constricted area known as a vulvar waist (genital girdle) located at the junction of the anterior and middle thirds of the body. A coiled tail forms copulatory spicules. Each female releases about 200,000 ova. Fertile eggs are ovoid, measure 6 to 40 µm in length, have a golden brown color due to bile staining, and consist of an albuminous outer coat, a thick inner shell, and one or more yolk cells. Infertile eggs are longer, measuring 40 to 90 µm with irregular albuminous coats and no yolk cells. The organisms mature inside their egg shells before becoming infective. Eggs become infective in soil 3 to 4 weeks after excretion. It takes 2 to 3 weeks following ingestion for infective larvae to develop in the intestine and to penetrate the mucosa, reaching the portal venous system. Following migration, the adult worms (one to several hundred) develop in the small intestine (usually midjejunum), where they anchor themselves to mucosal surfaces (Fig. 6.170).
Infectious Diseases

FIG. 6.169. Life cycle of the *Ascaris lumbricoides* (see text).

FIG. 6.170. *Ascaris lumbricoides*. A: This organism measures up to 35 cm in length, much larger than other intestinal roundworms, and resembles an earthworm. B: Diagnosis of *Ascaris* infection is usually made by demonstration in the stool of the characteristic egg with its corrugated outer surface. (B courtesy of Dr. Dickson Despommier, Department of Parasitology, Columbia University, NY.)

Clinical features include epigastric pain resembling peptic ulcer disease, duodenitis, and malnutrition. When present in large numbers, clumps of *Ascaris* obstruct the small intestinal lumen, causing an acute abdomen. Masses of worms also obstruct the common bile and pancreatic ducts, which leads to perforation and volvulus. When these long worms migrate into the common bile duct and pancreatic duct, they produce cholangitis and pancreatitis. In severe cases, the liver may be involved. Ascariasis has particularly adverse effects in malnourished populations. The worms may be evident within the intestinal lumen. Once the infection clears, one may only see residual traces of their presence. These may present as small polypoid structures lying within the submucosa and surrounded by fibrotic reactive tissue (Fig. 6.171).

Hookworm Infections

Hookworm infections rank second to ascariasis in incidence of intestinal helminthic infections. The parasites infect approximately 900 million individuals worldwide (465). The most significant nematodes in the hookworm group include *Ancylostoma duodenale* and *Necator americanus*. Hookworms cause chronic blood loss, intestinal malabsorption, abdominal pain, and bloody diarrhea. Patients with chronic infections present with iron deficiency anemia (which may be severe when the worm burden is high and iron intake is limited), hypoalbuminemia, blood loss, and vague abdominal discomfort or pain. Patients often have peripheral eosinophilia as well as eosinophilic enteritis. The eosinophilia results from an allergic response to larval secretions.

*Ancylostoma caninum* (dog hookworm) causes disease in patients who own dogs. Infectious filariform larvae invade the skin through bare feet or other exposed skin surfaces (Fig. 6.172). A purpuric, papular, or vesicular eruption develops at the entry site. After passing through a series of developmental stages, the hookworm migrates through the lungs, occasionally causing pulmonary symptoms, infiltrates, and eosinophilia. Adult worms, measuring 8 to 10 mm in length, emerge in the proximal small intestine and anchor themselves to the mucosa (Fig. 6.173). *A. caninum* is often diagnosed by identifying the 1-cm long worm in GI biopsies or duodenal aspirates, especially in patients with heavy parasitic infections. The mucosa may appear hemorrhagic, eroded, congested, and edematous. The diagnosis is also made by stool examination and identification of characteristic ova (Fig. 6.173). Histologically, besides the presence of the worm, the most significant pathologic findings are a focal or diffuse eosinophilia and mural edema. Increased numbers of lamina propria eosinophils are particularly prominent near areas of parasitic attachment. Ulcers result from the hookworm bite sites. Some patients develop focal crypt hyperplasia, villous atrophy, and inflammation. Patients may exhibit regional lymphadenopathy due to the presence of granulomas with central eosinophilic degranulation and degradation products. The worms are often found within the short stenotic ileal segments.

Strongyloidiasis

Infections by *Strongyloides stercoralis* are widely prevalent throughout the world. Five million people harbor the nematode (466). Infections are most likely to occur in areas where waste is used as fertilizer. Principally found in tropical and subtropical areas, *S. stercoralis* is also endemic elsewhere. In the United States, the highest prevalence of strongyloidiasis occurs in Kentucky and eastern Tennessee (467). Endemic areas are also present in central and southern Europe (468). *Strongyloides*, the most common intestinal parasite in Southeast Asia, causes chronic debilitating illnesses. Individuals or military personnel returning from this area may experience symptoms for a long time (469). Prisoners of war are particularly prone to develop these infections. In the United States, parasitic infections emerged in World War II and Vietnamese veterans years after exposure. Disseminated strongyloidiasis becomes manifest as the veteran population ages or undergoes immunosuppressive and/or cytotoxic therapy for other disorders. Disseminated hyperinfection affects subjects with immunocompromised T-cell immunity associated with steroid use, neoplasms, malnutrition, aging, or AIDS.
The rhabditiform larvae are found in soil contaminated by human feces where they go through four stages to become male (0.7 mm in length) and female (1 to 2 mm in length) adults. If the climatic conditions are unfavorable, the rhabditoid larvae change directly into filariform or strongyloid larvae, measuring approximately 400 µm in length. These are incapable of surviving for more than a couple of weeks in the external environment but they can continue development in humans (Fig. 6.174). The filariform larvae enter humans by penetrating the skin. The larvae reach the lungs through vessels. In the lung, they pass through the alveoli, reaching the bronchi, trachea, and larynx. They then enter the esophagus and migrate to the duodenum and jejunum, their preferred sites, where they transform into adults. After fertilizing the females, males are rapidly expelled with the feces, whereas the females penetrate the intestinal mucosa. Here they deposit up to 30 eggs a day. These develop into rhabditoid larvae. Only when they hatch do they leave the mucous membrane to reach the intestinal lumen from which they are excreted with the feces. It is for this reason that eggs are very rarely found in the stools. The rhabditoid larvae can transform into filariform larvae within 24 hours and then may rein invade the host either through the intestinal mucosa (internal autoinfection) or through the perianal skin (external autoinfection).

Adult females inhabit the duodenal and jejunal mucosa. However, adults can be found throughout both the small and large intestine in heavy infections. The worm perpetuates itself in the host for decades by autoinfection. Chronic infection results from the inability of the host to eliminate the adult worms from the small bowel, the inability to prevent colonic reinfection by filariform larvae, or the inability to destroy larvae that are in transit back to the intestine. Most filariform larvae lie within the intestinal lymphatics, and they concentrate in the mesenteric and retroperitoneal lymph nodes. Larvae may be found in many tissues.
Strongyloides infections range from asymptomatic cases to the presence of severe disease, especially in patients with heavy infections. Symptoms include diarrhea, malabsorption, weight loss, eosinophilia, abdominal pain, nausea, vomiting, constipation, gastrointestinal bleeding, and pruritus ani (469). A rash (creeping eruptions) results from dermal penetration. Patients with disseminated strongyloidiasis show the heaviest parasite burden in the proximal small intestine and lungs. Some patients die secondary to extensive small and large intestinal ulceration. Hyperinfection syndrome is diagnosed by finding parasites on stool examination, duodenal aspiration, sputum, bronchoalveolar lavages, cerebrospinal fluid, ascites fluid, or urine, or in biopsies. Serologic tests also detect the disease.

The intestines acquire hemorrhagic and ragged mucosal surfaces covered by a friable, greenish tan pseudomembrane. Larvae, adult worms, and eggs may be seen within the crypts. At the time of laparotomy or autopsy, one may find a mass in or attached to the bowel wall, often wrapped around the greater omentum. The lesions frequently center around the ileocecal valve. Occasionally, the changes mimic Crohn disease. Biopsies show cross section of the worms. The posterior regions of the adult females exhibit a characteristic single intestine and double reproductive tubes (Fig. 6.175). The mucosa may show superficial segmental ulceration and the lamina propria may appear congested and edematous, containing numerous neutrophils and eosinophils early in the infection. Later, mononuclear cells, including lymphocytes and plasma cells, infiltrate the mucosa. If the inflammation becomes transmural, peritonitis develops. Most acute lesions affect the small intestine but similar changes occur both in the stomach and colon. Crypt hyperplasia with varying degrees of villous atrophy associates with inflammation of the lamina propria. In patients with severe malabsorption, the intestinal villi become atrophic, swollen, or fused, and one may see granulomas and fibrosis. Crypt distortion and erosions relate to the presence of adult worms, rhabditiform larvae, and ova. Some patients develop inflammatory pseudotumors or "helminthomas," usually in the ileocecal area. Smaller granulomas with necrotic centers are characterized by a cuff of eosinophils (Fig. 6.176). The presence of Charcot-Leyden crystals in the necrotic center should alert the examiner to the possibility of chronic hyperinfective strongyloidiasis. Worm tracks can be found within the masses as the worms try to migrate further into the bowel wall.

FIG. 6.172. Hookworm life cycle (see text).
Infectious Diseases

Angiostrongyloidiasis
Abdominal angiostrongyloidiasis results from infections with the nematode *Angiostrongylus costaricensis*, an organism prevalent in Central and South America. Its life cycle involves a definitive host (wild rodents) and an intermediate host (the slug). Human infections occur when persons ingest vegetables contaminated with third-stage larvae from the slugs. Larvae penetrate the GI wall and mature in lymphatics and lymph nodes to migrate through the vasculature of the ileocecal region. *A. costaricensis* causes an intense eosinophilic necrotizing arteritis associated with thrombosis and ischemic necrosis due to an arteritis and arterial thrombosis and the presence of numerous eosinophilic granulomas (470).

**Capillaria philippinensis Infections**
*Capillaria philippinensis* is a tiny nematode that causes severe diarrhea in humans. Persons infected with this parasite often live in the Philippines and Thailand, where it is common to eat raw freshwater fish. A fish–bird cycle plays a role in the infection. The worms inhabit both the large and small intestines. Male worms measure 1.5 to 3 mm in length and females measure 2.5 to 5 mm in length. Capillarids are closely related to *Trichuris* and *Trichinella* species (471). The organism is diagnosed by the presence of characteristic ova. The barrel-shaped eggs have flattened bipolar plugs (Fig. 6.177).

and the presence of fully developed larvae. The eggs of *C. philippinensis* average 36 × 19 to 45 × 21 µm and they resemble those of *T. trichiura*, which average 50 × 20 µm. Some patients have both infections.

**FIG. 6.173.** Hookworm. A: The first-stage rhabditiform hookworm larva develops from the egg and is usually found in the stool. B: The hookworm egg with its thin shell, bluntly rounded ends, and multilobulated contents is typical of hookworm eggs found in the stool. Eggs of *Necator americanus* and *Ancylostoma duodenale* are indistinguishable. C: Patient with pig bel and incidental *Ascaris* infection and hookworm. The hookworm lies at the tip of the curved tail of the *Ascaris*. (A and B courtesy of Dickson Despommier, Ph.D., Department of Parasitology, Columbia Presbyterian Medical Center, New York, NY. C courtesy of Robin Cooke, M.D., Department of Pathology, Royal Brisbane Hospital, Brisbane, Australia.)
FIG. 6.174. Strongyloidiasis with both external infection as well as autoinfection (see text).

FIG. 6.175. *Strongyloides* infection of the small intestine. *A:* Longitudinal cross section of several worms lying within a crypt. *B:* Transverse cross section showing the paired intestinal tracts (see text).
FIG. 6.176. Prominent eosinophilia in a patient with disseminated strongyloidiasis. Portions of a worm are present (arrows). Note the intense lamina propria eosinophilia.
Dwarf Tapeworm Infections

The proglottids of Taenia saginata can be distinguished from that of Taenia solium by the number of primary lateral uterine branches. This proglottid injected with India ink shows the >15 branches characteristic of T. saginata. (Courtesy of Dickson Despommier, Ph.D., Department of Parasitology, Columbia Presbyterian Medical Center, New York, NY.)

Adult T. saginata, T. solium, and Diphyllobothrium latum are among the largest parasites to infect humans; they can reach lengths of 10 to 15 m. These three worms are acquired via ingestion of larvae. Pea-sized larvae (cysticerci) of the beef and pork tapeworms infect various tissues, including the musculature of cattle and pigs, respectively. Cysts are released into the small intestine of humans when raw or undercooked infected meat is consumed. Ingestion of tissues containing cysts with viable scolecis allows larvae to develop into mature worms. It takes approximately 3 months for T. solium, T. saginata, and D. latum to become gravid. Humans are the only definitive host for the adult stage of T. saginata, which inhabits the upper jejunum for as long as 25 years. The intermediate hosts (cattle and pigs) acquire their infection by ingesting human feces contaminated with tapeworm ova.

Mild epigastric discomfort, nausea, and hunger sensations are the most common symptoms. Weight loss, diarrhea, irritability, and increased appetite also occur. Impacted proglottid segments cause obstruction, jaundice, or pancreatitis, depending on their location.

T. solium, the pork tapeworm, inhabits the human intestinal lumen, its only definitive host. When larvae invade humans, the condition is referred to as cysticercosis. T. solium infections occur most commonly in Mexico, Africa, Southeast Asia, South America, and Eastern Europe. It has recently been found in swine in New Mexico and Colorado. When the eggs of T. solium are ingested either by pigs or humans, the larvae hatch in the small intestine (upper jejunum), penetrate the gut wall, and enter the circulation. They are then carried by the blood to any organ in the body. Once in the capillaries, they encyst. No further development occurs while the cercariae remain encysted. One can distinguish the various species of tapeworms by counting the number of teeth or cutting plates on the buccal cavity. T. saginata has a small unarmed scolex with four prominent suckers and 1,000 to 2,000 proglottid segments.

The proglottids (Fig. 6.178) develop to form the chainlike strobila of the worm. As each proglottid becomes gravid, eggs are released. Adult worms produce up to 20,000 eggs per day, which disseminate into the environment via stool. Once stuck to the mucosa, the worms suck blood from it. The amount of blood lost varies with the parasite species. Because the worms lack a GI tract, adults absorb predigested food across the tegumental surface of each segment (473).

FIG. 6.177. Diagnosis of Capillaria philippinensis infection is made by demonstration of the characteristic egg with subtle flattened polar prominences in the stool. (Courtesy of Dickson Despommier, Ph.D., Department of Parasitology, Columbia Presbyterian Medical Center, New York, NY.)

Disease onset is acute with severe malabsorption and it has a 35% mortality. Patients develop diarrhea, malaise, anorexia, nausea, and vomiting, and they may die of extreme malnutrition, dehydration, or secondary bacterial infections. The period between symptom onset and death is usually 2 to 3 months.

Grossly, the small intestine appears thickened, indurated, and hyperemic and contains large amounts of fluid (472). Thousands of adult worms, larvae, and ova are seen within the jejunum and the upper portion of the ileum. Occasionally, parasites are found in the stomach, esophagus, and colon. Patients with severe infections have many worms embedded in the small bowel mucosa. Histologically, one sees the parasites in the intestinal lumen, within the crypts of Lieberkühn, and in the lamina propria. The intestinal villi develop secondary changes, including villous atrophy, obliteration, and epithelial sloughing. Approximately 50% of biopsies disclose the presence of worms.

Tapeworm Infections

Tape worms are ribbon-shaped, segmented, hermaphroditic worms that inhabit the intestinal tract of many species. Species that commonly infect humans in the West include the beef tapeworm, Taenia saginata, and the pork tapeworm, Taenia solium. Mucosal attachment occurs via suction cups or grooves located on the head or scolex. One can distinguish the various species of tapeworms by counting the number of teeth or cutting plates on the buccal cavity. T. saginata has a small unarmed scolex with four prominent suckers and 1,000 to 2,000 proglottid segments.

The proglottids (Fig. 6.178) develop to form the chainlike strobila of the worm. As each proglottid becomes gravid, eggs are released. Adult worms produce up to 20,000 eggs per day, which disseminate into the environment via stool. Once stuck to the mucosa, the worms suck blood from it. The amount of blood lost varies with the parasite species. Because the worms lack a GI tract, adults absorb predigested food across the tegumental surface of each segment (473).
Hymenolepis nana, the dwarf tapeworm, is the most common autochthonously acquired tapeworm disease in the United States. Most infections affect children and institutionalized individuals. The infection spreads by an oral–fecal route. Feces of infected children and rats are the most common reservoirs. In some countries, 25% of the rural population has an H. nana infection, presumably due to consumption of contaminated water (474). Most infections remain asymptomatic or associate with only mild infections. Proglottids and eggs (Fig. 6.180) are shed into the stool. Some patients develop severe crampy abdominal pain, diarrhea, constipation, vomiting, weakness, or weight loss. A small percentage of patients develop anemia. About 40% of patients with the infection have low vitamin B₁₂ levels because the tapeworm successfully competes with the host for the vitamin.

**FIG. 6.179.** The *Diphyllobothrium* egg passed in the stool is ovoid with a barely discernible operculum. It resembles the egg of *Paragonimus westermani*, which is larger. (Courtesy of Dickson Despommier, Ph.D., Department of Parasitology, Columbia Presbyterian Medical Center, New York, NY.)

**FIG. 6.180.** *Hymenolepis nana* egg passed in the stool is distinguished by the presence of six hooklets on the embryo and the polar filaments that encircle the embryo. (Courtesy of Dickson Despommier, Ph.D., Department of Parasitology, Columbia Presbyterian Medical Center, New York, NY.)

### Fascioliasis
Fascioliasis results from infections by the large fluke *Fasciolopsis buski*. Fascioliasis infections usually affect the biliary tree but occasionally they present in other organs (475). The diagnosis is made by finding ova in the stool (Fig. 6.181) (475). The disorder remains mainly confined to Southeast Asia, but with the travel patterns of many individuals, it is seen in other countries. Several flukes, including *F. buski*, are acquired when people ingest contaminated water plants such as the water chestnuts (Fig. 6.182).

*F. buski* inhabits the upper intestine. The hermaphroditic, 20-mm-diameter, flat flukes produce unembryonated ova that hatch 3 to 7 weeks later in water having a temperature of 80°C to 90°C. After infective forms of the
organism are ingested, the parasites enter the peritoneal cavity through the intestinal wall, reach the liver where the young flukes enter the parenchyma through the capsule, and find a bile duct where they grow to adulthood. Aberrant localization of *Fasciolopsis* and other flukes occur while the parasite is migrating within the host tissues to its normal location (476). The life cycle is shown in Figure 6.182. Pigs and humans act as the reservoirs for the infections.

**FIG. 6.181.** The adult *Fasciolopsis hepatica* resides in the hepatic bile ducts and passes eggs, which may be found in the stool. The egg seen here is large (130 to 150 μm), is ovoid, and has a barely discernible operculum. (Courtesy of Dickson Despommier, Ph.D., Department of Parasitology, Columbia University, New York, NY.)
The infection usually remains asymptomatic. However, patients with hundreds or thousands of flukes may develop intestinal obstruction, allergic responses to parasitic metabolites, or mucosal injury. Symptoms include nausea, diarrhea, epigastric pain, and GI hemorrhage. Histologically, the most severe lesions affect the duodenum and jejunum. Exceptionally, the ileum, stomach, and colon become involved. Large adults attach themselves to the intestinal mucosa, eliciting an intense inflammatory reaction with abscess formation. One may see cystic masses containing necrotic material, inflammatory debris, and hemosiderin-tinged exudates without grossly recognizable parasites. Eosinophils may surround dead worms. Other presentations include the presence of masses in the anterior abdominal wall, periumbilical area or iliac fossa, or intestinal intussusception. Peripheral eosinophilia is frequently present.

**Schistosomiasis**

Schistosomal infections occur within both the small and large intestine. Pathologists are much more likely to encounter the organism in colonic specimens than small intestinal ones; therefore, this infection is discussed in Chapter 13.

**Helminthomas (Helminthic Pseudotumors)**

Helminthoma is the term used to describe tumorlike inflammatory intestinal swellings caused by penetration of the intestinal wall by nematodes, usually in the area of the ileocecal valve (477). The worms usually belong to the genus *Oesophagostomum* and other closely related species in the *Strongyloides* family. Hookworms *Sparganum* and *Oxyuris* also occasionally bury themselves into the mucosa and submucosa causing circumscribed...
hemorrhages, but they do not usually penetrate the tissues any further (478).

Multiple nodules are present in the terminal ileum, cecum, and ascending colon (Fig. 6.183). Adhesions develop to surrounding structures and the greater omentum is frequently attached to the inflammatory mass. Sometimes the mass resides completely outside the bowel wall. Masses vary in size but usually they measure 4 to 6 cm in diameter. On sectioning, an abscess or fistulous tract is usually present. Often, a worm still resides inside the mass. Occasionally, the tract presents as a sausage-shaped lump resembling a double appendix. Fat necrosis may occur. Patients present with symptoms resembling appendicitis, ileocecal tuberculosis, or Crohn disease or carcinoma. The histologic features of an inflammatory pseudotumor are present, often containing numerous eosinophils.

FIG. 6.183. Cross section through a small intestinal helminthoma. All that remains are nodular concentric fibrous regions containing areas of calcification. The patient had disseminated schistosomiasis and chronic Ascaris infections. The structures of the offending parasites are no longer visible.

Traveler's Diarrhea

Between 20% and 70% of people who travel from the industrialized world to the developing world each year report some illness related to their travel (479,480). Diarrhea is the most common health problem of travelers to developing countries. Its incidence varies depending on the travel destination and the number of dietary indiscretions made by the traveler (481). High-risk destinations include most of the developing countries of Latin America, the Middle East, and Asia. Intermediate destinations include southern European countries and a few Caribbean islands. Low-risk destinations include Canada, northern Europe, Australia, New Zealand, the United States, and a number of Caribbean islands. Various infections are implicated (Table 6.24); these produce a diverse clinical spectrum. The causative agents are identified in 50% to 75% of travelers with diarrhea that lasts <2 weeks. However, as the duration of the diarrhea increases, the likelihood of identifying the causative agent decreases (482). Seasonal variations exist in the etiology of traveler's diarrhea. Acquisition of multiple pathogens is much less common among individuals who travel in the winter than in the fall. Campylobacter strains are the leading cause of traveler's diarrhea in the winter, contrasting with enterotoxigenic E. coli and Salmonella in the fall (483). Because of Mexico's popularity and proximity to the United States, its version of traveler's diarrhea, popularly called "Montezuma's revenge," is the most extensively studied form of traveler's diarrhea in the United States (484).

Traveler's diarrhea occurs slightly more commonly in young people, perhaps due to their more adventurous travel styles or to different eating habits. Traveler's diarrhea is acquired through ingestion of fecally contaminated food and/or water. Both cooked and uncooked foods may be implicated. Particularly risky foods include raw vegetables, salads, raw meat and seafood, and foods left at room temperature and served buffet style. Other high-risk foods include tap water, ice, unpeeled fruits, unpasteurized milk, and dairy products. Episodes of generally self-limited diarrhea develop abruptly during travel or soon after returning home. Host factors that influence the outcome of traveler's diarrhea are listed in Table 6.25.

TABLE 6.24 Causes of Traveler's Diarrhea

<table>
<thead>
<tr>
<th>Cause</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>High</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Low</td>
</tr>
</tbody>
</table>

Traveler's diarrhea is a common problem for travelers. It is acquired through ingestion of fecally contaminated food and/or water. High-risk foods include raw vegetables, salads, raw meat and seafood, and foods left at room temperature and served buffet style. Host factors that influence the outcome of traveler's diarrhea are listed in Table 6.25.
<table>
<thead>
<tr>
<th><strong>Bacterial</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterotoxigenic <em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Salmonella</em></td>
</tr>
<tr>
<td><em>Shigella</em></td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
</tr>
<tr>
<td><em>Vibrio parahaemolyticus</em></td>
</tr>
<tr>
<td><em>Aeromonas hydrophila</em></td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em></td>
</tr>
<tr>
<td><em>Plesiomonas shigelloides</em></td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
</tr>
<tr>
<td><em>Vibrio fluvialis</em></td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
</tr>
<tr>
<td><em>Dientamoeba fragilis</em></td>
</tr>
<tr>
<td><em>Isospora belli</em></td>
</tr>
<tr>
<td><em>Balantidium coli</em></td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em></td>
</tr>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td><em>Rotavirus</em></td>
</tr>
<tr>
<td><em>Norwalk-like virus</em></td>
</tr>
<tr>
<td><em>Adenoviruses</em></td>
</tr>
<tr>
<td><em>Astroviruses</em></td>
</tr>
<tr>
<td><em>Caliciviruses</em></td>
</tr>
<tr>
<td><em>Coronaviruses</em></td>
</tr>
<tr>
<td><em>Enteroviruses</em></td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
</tr>
<tr>
<td><em>Blastomyces hominis</em></td>
</tr>
</tbody>
</table>
Interpretation of Ileal Biopsies

Ileal biopsies are commonly taken when patients undergo colonoscopy. As a result, pathologists often have the opportunity to examine changes that may be present in the ileal mucosa. The most common changes include acute inflammation and evidence of chronic disease. Additionally, there may be changes in the Peyer patches. One common mistake that we see is overinterpretation of increased numbers of intraepithelial lymphocytes that are normally present in the follicle-associated epithelium as either lymphocytic enteritis or, worse yet, as evidence of a lymphoma.

**FIG. 6.204.** Abetalipoproteinemia. *A:* Moderate-power photograph demonstrating the presence of an essentially intact architecture with normal villous and crypt length. The epithelium appears clear due to the presence of marked lipid accumulations within the epithelium. *B:* Higher magnification showing the displacement of the nuclei upward and the clear nature of the cytoplasm.

In an inflamed ileum, the inflammatory cells might include lymphocytes, plasma cells, neutrophils, eosinophils, mast cells, and/or macrophages with or without surface erosions or ulcers. These may be present in the epithelial compartment or the lamina propria. In addition, granulomas, parasites, viral inclusions, or enterocyte changes may be evident.

Acute ileitis due to bacterial infections causes changes similar to those seen in acute self-limited colitis (see Chapter 13). Thus, there is mucosal edema and a polymorphous inflammatory infiltrate that early on is dominated by neutrophils but becomes replaced by mononuclear cells over time. The neutrophils may cause cryptitis or crypt abscesses as well as lamina propria inflammation. The crypt and villous architecture generally remain normal without significant crypt distortion. The epithelium appears variably degenerated or regenerative depending on the stage of the disease. Some drug-induced damage causes similar changes. Some bacterial infections cause characteristic granulomatous lesions (Table 6.15). Viral infections...
often cause prominent lymphoid hyperplasia. Chronic ileitis is recognized by the presence of crypt and villous distortion and by the presence of pyloric metaplasia. A lymphoplasmacytosis is variably present. The most common etiology for chronic ileitis is Crohn disease (see Chapter 11), but it also can result from chronic infections, drug injury, and chronic ischemia. Additionally, many of the disorders discussed earlier in this chapter may cause chronic ileal damage.
Intestinal Goblet Cell Autoantibody-Associated Enteropathy

There is a second form of autoimmune enteropathy that is characterized by the presence of circulating antibodies to goblet cells. These can be demonstrated using the patient's serum applied to sections of normal human intestine that stain the goblet cell mucus. The clinical presentation of these patients is similar to autoimmune enteropathy but the histology is distinctive. Patients with intestinal goblet cell autoantibody-associated enteropathy have a normal intestinal architecture, but the mucosa lacks goblet cells, Paneth cells, and perhaps endocrine cells. The base of the crypts may contain apoptotic figures and mitoses. The lamina propria often appears hypercellular, infiltrated by mononuclear cells and eosinophils (Fig. 6.202). Similar findings occur in both the small bowel and the colon. There may be an increase in crypt (but not surface) IELs and apoptotic bodies (563).
Ischemic Enteritis

When the blood supply to a tissue is interrupted, a sequence of chemical events leads to cellular dysfunction, edema, and ultimately cell death. Tissue anoxia results in anaerobic metabolism and lactic acidosis. Fewer high-energy bonds are created, and the cell is deprived of the energy needed to maintain homeostasis (182) (Fig. 6.92). Ischemic injury forms a continuum of changes that range from increased mucosal permeability to frank necrosis. The clinical severity of ischemic enteritis varies widely from massive and sometimes fatal hemorrhagic infarctions to silent transient minimal ischemic episodes. Vascular occlusion and periods of hypotension or vasoconstriction account for most cases of intestinal ischemia. The ischemia may therefore be caused by diseases intrinsic or extrinsic to the bowel. Small intestinal ischemic necrosis predominantly affects elderly individuals with underlying cardiovascular disease. However, intestinal ischemia may affect individuals of any age, including infants. Intestinal ischemia complicates peripheral vascular disease, various vasculopathies, some infections, intussusception and torsion, and certain drug therapies.
The pathogenesis of duodenal ulcer disease is multifactorial and involves host factors as well as environmental factors. Most patients exhibit increased acid secretion, increased parietal cell mass, and increased pepsinogen production. Environmental agents such as steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, or Helicobacter pylori further contribute to the injury by breaking down mucosal defenses.

All forms of ischemic damage (see Table 6.5) share the underlying feature that the blood supply fails to meet the local tissue demands required to fulfill normal functions and/or maintain normal structure. Prolonged cessation of blood flow inevitably results in cell death because of the diminished delivery of oxygen and metabolic substrates and the accumulation of potentially cytotoxic end products of anaerobic metabolism. Small intestinal blood supply has to be reduced by >50% to induce detectable tissue injury (183). The extent and duration of the ischemia depends on several factors, including the nature of the intestinal vasculature, luminal bacterial virulence, and the duration of the ischemic episode. The first detectable sign of ischemic injury is increased capillary permeability. With continuing ischemia, detectable epithelial cell injury occurs. Mucosal cells are shed at an increased rate, and damage to the plasma membrane of unshed cells results in leakage of cytoplasmic digestive enzymes and trypsic digestion of the mucosa. Arteriolar spasm and decreased perfusion pressure accentuate the extent of the ischemic damage. Necrosis and subsequent bacterial invasion develop when the mucosal barrier becomes defective. The basic pathologic response to ischemia is mucosal coagulative necrosis. If reflow is re-established, acute inflammation develops.

No single process represents the critical event in ischemic injury. Depletion of cellular energy stores and accumulation of toxic metabolites both contribute to cell death. Re-establishing the blood flow (reperfusion) is required to reverse the injury because it allows cellular regeneration and washout of toxic metabolites. However, reperfusion of ischemic tissues also paradoxically injures the tissues (Fig. 6.93) (184). In fact, most of the injury that occurs in intestinal ischemia occurs during the reperfusion period due to the production of reactive oxygen metabolites by activated neutrophils and other inflammatory cells. The severity of reperfusion injury depends on the duration of the preceding hypoxia, with it being more severe following partial rather than total intestinal ischemia (185). The sudden reintroduction of oxygen into the anoxic tissues unleashes oxygen-free radical cascades that overwhelm endogenous defenses. Many derive from the hypoxanthine-xanthine oxidase system (186). Superoxide and hydrogen peroxide increase mucosal and vascular permeability, recruit and activate neutrophils, and act as the precursors of more damaging hydroxyl radicals via the Fenton and myeloperoxidase reactions (Fig. 6.93) (186). Aggressive luminal factors (such as pancreatic proteases, especially trypsin) contribute to the mucosal damage and potentiate bacterial translocation and sepsis.

Neutrophil–endothelial cell interactions are a prerequisite for ischemic microvascular injury (187). The hypoxia induces endothelial cells to produce various adhesion molecules, including integrins, members of the immunoglobulin superfamily, and selectins. These powerful chemoattractants attract leukocytes and platelets to reperfused sites and promote their adherence, transendothelial migration, and activation. As a result, one sees a massive mucosal influx of neutrophils. The infiltrating neutrophils are also a major source of reactive oxygen metabolites (ROMs), including O₂⁻, H₂O₂, OH⁻, HOCl, and certain n-chloramines.
**FIG. 6.89.** Gross appearance of peptic duodenal ulcers. *A* and *B* derive from the same specimen dissected at the time of autopsy. The patient had numerous ulcerations involving the stomach, esophagus, and duodenum. The plastic *arrow* is inserted through a perforating duodenal ulcer. *B:* Higher magnification of a different ulcer showing the presence of a granular base. The specimen illustrated in *A* and *B* is from a patient with Zollinger-Ellison syndrome. *C:* Image from a different patient showing the presence of a large visible vessel containing a probe.

Acute mesenteric infarctions result from mesenteric arterial occlusion (Fig. 6.94), nonocclusive low-flow states, mesenteric vein thrombosis (Fig. 6.95), or vasculitis.

Mesenteric artery thrombosis and embolization (Figs. 6.96 and 6.97) occur with about equal frequency. Thrombi almost invariably overlie atheromatous plaques occupying the proximal few centimeters of the vessel. In contrast, emboli lodge at bifurcation points or in a distal branch. Ischemia also complicates numerous other conditions that ultimately obliterate the intestinal vascular supply (Table 6.5).

**TABLE 6.5 Causes of Intestinal Ischemia**

*FIG. 6.90.** Duodenal ulcer. *A:* An ulcer with typical overhanging margins is seen. It has the same zones as gastric peptic ulcers (see Chapter 4). *B:* Ulceration extends deep into the duodenal wall. Brunner gland hyperplasia is seen.
Ischemic Enteritis

Acute vascular occlusion
  Arterial or venous thrombosis
  Embolus
Low-flow states (low cardiac output, hypotension/shock)
Atherosclerosis
Mechanical
  Intussusception
  Volvulus
  Hernias
Necrotizing enterocolitis
Vasculitides and vasculopathies
Hypercoagulable states
Drugs
  Oral contraceptives
  Cocaine
  Digitalis and vasopressors
  Potassium chloride
Vascular compression
  Volvulus
  Intussusception
  Celiac axis compression
Amyloidosis
Collagen vascular diseases
Radiation damage
Diabetes mellitus

Ischemia in Low Flow States (Nonocclusive Ischemia)

Low flow states usually result from decreased cardiac output following primary cardiac disease (infarction or arrhythmia), hypovolemia, shock, vascular shunting, or a combination of low mesenteric flow and mesenteric arterial vasoconstriction. Patients who develop low-flow states are typically elderly and they often have concomitant atherosclerotic vascular disease. Even though the blood supply to the superficial mucosa is fairly well maintained during shock, hypoxic injury still develops within 1 to 2 hours. Several pathogenic mechanisms account for the ischemic necrosis including vasoconstriction with increased resistance to blood flow, redistribution of the blood flow away from the mucosa, increased capillary filtration via relaxation of the precapillary sphincter smooth muscle fibers, and intestinal countercurrent mechanisms in the villi that shunt oxygen away from the villous tips (Fig. 6.98) (188). This explains why the villous tips become anoxic first and explains why early and minimal injury always occurs first at the villous tip (Fig. 6.99).

Arterial Occlusive Disease

Arterial occlusive disease occurs secondary to narrowing, thrombosis, embolism, or hemorrhage under an atheromatous plaque. Occlusions also result from aortic aneurysms, aortic
Ischemic Enteritis

dissections, obstruction by mural thrombi, and tumors that externally compress the vessels. The occlusion may involve one or all of the intestinal arterial trees. Atheromatous occlusion progresses slowly enough for collateral circulation to develop, and as a result patients often have severe disease involving all the mesenteric arteries before they become symptomatic. Intestinal infarction secondary to atheromatous occlusion of a single vessel is rare (189). (About 50% of patients over the age of 50 have atheromatous narrowing or occlusion of the celiac axis.) The disease is most likely to be most severe in patients with diabetes. The superior mesenteric artery is affected more commonly than the inferior mesenteric artery. The most severe atherosclerotic lesions affect the proximal 2 cm of the superior and inferior mesenteric arteries. Embolic occlusion accounts for one third of cases of mesenteric vascular occlusion (190). Massive, acute, and often fatal embolism usually results from migration of an intracardiac mural thrombus complicating heart disease. Cholesterol emboli migrate from aortic plaques, especially following catheterization, resulting in localized or widespread intra-abdominal ischemia. Valvular endocarditis may shed small mycotic emboli. Intestinal damage develops within minutes of total circulatory arrest.

FIG. 6.91. Penetrating duodenal ulcer. A: The bottom of an ulcer bed has eroded a large extraintestinal vessel. The structure at the base is the pancreas, the periphery of which has become fibrotic due to the inflammatory response. B: Erosion into the serosal fat, exposing several branches of a major vessel.
Ischemic Enteritis

FIG. 6.92. Intestinal ischemia. Intestinal ischemia develops when insufficient arterial blood reaches the intestinal mucosa through the presence of a thrombus, an embolus, an atheromatous plaque, a vascular spasm, low-flow states, or obstruction of venous outflow. As a result, oxidative metabolism becomes impaired, leading to decreased adenosine triphosphate (ATP), increased glycolysis, acidosis, and changes in nuclear chromatin, as well as in other cellular organelles. The decreased ATP also leads to decreased functioning of the sodium-potassium pump with an influx of calcium ions and water and an efflux of potassium. As a result, the cells swell, as do intracellular organelles. As the organelles become damaged, ribosomes decrease and protein synthesis decreases, interfering with reparative processes.
During ischemia, cellular adenosine triphosphate (ATP) is converted to adenosine monophosphate and further catabolized to hypoxanthine, which serves as an oxidizable substrate for xanthine oxidase. The enzyme xanthine oxidase (XO) is the rate-limiting enzyme in nucleic acid degradation. XO generates H_2O_2 and O_2^- during the oxidation of hypoxanthine or xanthine. Free radicals are also generated via the Fenton reaction, especially during cell reperfusion. The free radicals recruit polymorphonuclear leukocytes (PMNs) to the reperfused area. The neutrophils adhere to the endothelial cells secondary to increased transcription of integrins and adhesion molecules on both neutrophils and endothelial cells. Free radicals also diffuse into the local tissues, causing abnormalities in the enterocytes with lipid peroxidation of membranes and damage to DNA, RNA, and proteins, and alterations in cellular transport mechanisms.
Ischemic Enteritis

FIG. 6.94. Thrombosed superior mesenteric artery. The *arrowhead* points to the orifice of the superior mesenteric artery as it exits the aorta.

Sudden occlusion of the superior mesenteric artery produces hemorrhagic infarction in the area supplied by the occluded vessel (as modified by the presence of a collateral blood supply). The infarcted area may extend from the proximal jejunum to the transverse colon, producing a pattern of ischemic enterocolitis (36). However, usually a small area is involved, and there is a sharp dividing line between the normal and ischemic parts of the bowel (Fig. 6.100).

Generally, one has little difficulty in diagnosing patients with acute, diffuse, transmural ischemic necrosis. These patients abruptly become symptomatic. The most common manifestation is poorly localized colicky abdominal pain that becomes constant and unremitting as the disease progresses. The pain results from spasm of the muscularis propria. Diarrhea develops and stools become overtly bloody. As the ischemic muscle loses its contractile functions, much of the spasm ceases. The patient then experiences abdominal tenderness, positive rebound signs, and evidence of peripheral circulatory collapse. At this point, the bowel is usually beyond recovery and requires surgical resection. With further disease progression, the abdomen distends and bowel signs disappear. As the ischemia persists and infarction develops, the patients often develop an elevated white blood count, fever, and signs of peritonitis.
Ischemic Enteritis

FIG. 6.95. Intestinal infarction secondary to portal vein thrombosis. A: Gross photograph of the junction of the infarcted intestinal segment with normal mucosa. There is a sharp line of demarcation between the infarcted tissue (black tissue on the left) and the viable, noninfarcted tissue on the right. B: Dissection through the peri-intestinal fat showing a branch of the portal venous system, which has been opened and contains a long thrombus (arrows).

FIG. 6.96. Histologic section through the portal vein showing the presence of an organized thrombus.

Mesenteric Venous Thrombosis

Mesenteric venous thrombosis is a relatively rare disease primarily affecting the elderly in their 6th and 7th decades of life (191). The prevalence of mesenteric vein thrombosis ranges from 0.003% in the general hospital population to 0.05% of autopsied populations (192). Venous thrombosis accounts for 5% to 15% of all cases of mesenteric ischemia and infarction (Fig. 6.101) (193). Multiple etiologic factors may exist in any one patient. For example, a patient requiring splenectomy may have a pre-existing abnormality involving the coagulation system, experience intraoperative trauma to regional veins, and develop a transient thrombocytosis caused by the splenectomy. Its presence in younger persons suggests that the patient has a hypercoagulable state. Twenty-five to fifty percent of cases have no predisposing cause; these are classified as primary venous thrombosis. Regardless of the cause of the thrombosis, egress of blood from the intestine becomes impaired, causing the mesenteric arterial pressure to rise and arterial blood flow to slow, leading to the development of ischemia. Increased intraluminal pressure further interferes with mucosal viability.

Approximately 95% of all mesenteric thromboses involve the superior mesenteric vein and lead to ischemia or infarction of the small bowel or proximal colon (191). In a small number of cases, the thrombosis develops over an extended period, permitting the development of collateral venous drainage from the involved intestinal segments. Depending on the cause, mesenteric venous thrombosis may begin in the portal vein and extend back into the mesenteric vein and its branches, or it may begin in smaller peripheral mesenteric venous branches.
Ischemic Enteritis

and proceed up into the portal vein.

P.333

Propagating portal vein thrombosis causes portal hypertension. Thrombi often arise in the distal arcades and propagate proximally.

FIG. 6.97. Atheromatous emboli. A: Cross section through the superior mesenteric artery demonstrating the presence of a large atheromatous embolus. B: Emboli extend into the smaller vessels just beneath the muscularis mucosae (arrows).

Patients present with a constellation of nonspecific findings. The clinical presentation is characterized by gradually increasing colicky abdominal pain. With increased blockage of the collaterals by new thromboses, the patient develops nausea and vomiting, an acute abdomen, and rectal bleeding. At this time, surgical intervention is required. Involvement of the splenic or portal vein with a propagating thrombus may result in portal hypertension (191). Patients with venous occlusion tend to have a subacute course producing days or weeks of abdominal pain. Bloody ascites is common.
FIG. 6.98. Diagram of countercurrent mechanism demonstrating shunting that occurs at the villous base. It diverts oxygen from the villous tips to the base of the crypts during anoxic periods.
FIG. 6.99. Early ischemia demonstrating marked capillary congestion and loss of epithelium from the villous tips. One of these denuded villus tips is indicated by the star. Taken in isolation, the changes may resemble those seen in autolysis. No reperfusion has occurred and therefore acute inflammatory cells are absent.
Ischemic Enteritis

**FIG. 6.100.** Small bowel ischemia. A: Hyperemic infarcted areas with adjacent friable pink-tan mucosa. B: Area of infarction with gradual hyperemia of adjacent lesser involved mucosa.

The diagnosis of mesenteric venous thrombosis is usually made during laparotomy for an acute abdomen. At the time of surgery, the serosal and mucosal surfaces appear mottled, hemorrhagic, and discolored with fibrinous exudates deposited on them. The bowel appears thinned in areas of transmural hemorrhagic infarction. Adjacent areas show patchy ischemia. The mesentery usually appears thickened, hemorrhagic, and edematous, and it contains numerous cordlike thrombosed veins. The arteries usually appear normal. Numerous recent, organizing, and partially recanalized thrombi are observable in the mesenteric venous vasculature, and the bowel wall shows intramural hemorrhage and variable degrees of edema and ischemic necrosis with ulceration and acute inflammation. The thrombosis occurs in the absence of phlebitis. The arteries remain uninvolved. Patients may develop Budd-Chiari syndrome.

**Mechanical Obstruction of Venous Return**

Venous return becomes impeded when the bowel undergoes torsion, volvulus, or intussusception, or when it becomes strangulated and herniates. External compression of the vasculature causes obstruction of the relatively thin-walled and low-pressure venous system before the arterial supply is affected. As a result, the bowel becomes congested with blood, hemorrhagic, and edematous. Ischemic necrosis then develops rapidly. The histologic features resemble those of mesenteric venous thrombosis, except that thrombi are absent.

**Gross Features of Ischemic Injury**

The pathologic features of intestinal ischemia are similar, no matter what the underlying cause. Ischemia characteristically appears segmental in nature. Early on, the ischemic bowel is edematous and pale with submucosal congestion, hemorrhage, and focal mucosal sloughing (Fig. 6.102). As the disease progresses, the serosa becomes dusky and purple or dark red due to the presence of large amounts of intraluminal blood. The serosa loses its normal glistening appearance and appears dull. The mucosa appears necrotic, nodular, and ulcerated. Extensive submucosal hemorrhage may be present. In early lesions, only the mucosa and sometimes the submucosa are affected; the muscularis propria usually remains normal. As the necrosis progresses, all of the bowel wall layers become damaged and the serosa becomes purplish green. With increasing damage, the intestinal wall thins and becomes friable and membranous exudates form. If the ischemia results from mesenteric venous thrombosis, one sees old and new thrombi extruding from the veins. Ulcers may be present that may be superficial or deep. Perforation may develop. Patients with chronic damage may have mural fibrosis and strictures.

**Histologic Features of Ischemic Injury**

The histologic features of ischemia depend on whether the changes are acute and minimal or whether they result from transmural infarction. They also depend on whether there is a total vascular occlusion without reperfusion or whether the blood flow is merely reduced below the local needs and reflow has occurred. Therefore, ischemic lesions vary from patchy congestion and ulceration to extensive infarction, gangrene, and perforation.

Most pathologists encounter small intestinal ischemia when they examine large resected segments of necrotic bowel. In this situation, it is easy to diagnose the ischemia. Diagnostic difficulties only occur when one encounters early lesions or when complications develop. Biopsies to establish a diagnosis of ischemia or to rule out other etiologies of enterocolitis are much less common than colonic biopsies for the same purposes. Therefore, the biopsy features of intestinal ischemia are extensively discussed in Chapter 13.
FIG. 6.101. Portal vein thrombosis in a patient with protein S deficiency. The histologic features derive from the specimen illustrated in Figure 6.95. A: The patient developed ischemia with reperfusion injury. There is glandular dropout, loss of villous epithelium, villous congestion, and inflammation. B: Higher magnification of the submucosa showing the presence of a congested and a thrombosed (star) submucosal vein. C: Higher magnification of one of the vessels showing the lines of Zahn in the thrombus. D: The mesenteric fat contains numerous thrombosed branches of the portal vascular system.
Because the mucosa is the most vulnerable part of the intestinal wall, it is damaged first (Fig. 6.103). Early epithelial damage results from loss of energy-dependent processes, causing intercellular edema, and epithelial detachment. Membrane-enclosed cytoplasmic blebs develop on the basal side of the enterocytes where they attach to the basement membrane. This begins the epithelial detachment process. This process starts before the enterocytes display signs of irreversible damage. The process advances from the villous tips to the crypt bases. With more severe or more prolonged ischemia, or both, the epithelium lining the sides of the villi lifts off the basement membrane until the epithelial cells are lost completely (Fig. 6.104). Within 1 hour of total vascular occlusion the upper two thirds of the villi becomes denuded. Then, the villous core disintegrates. The crypt cells often remain intact with little histologic evidence of damage. In other cases, one sees crypt hypoplasia–villous atrophy interfering with normal cellular turnover. Occasionally, crypt dilation becomes prominent. Later, the epithelial cells become markedly attenuated and the crypts appear compressed and atrophic as the lamina propria swells and hemorrhages. After 5 hours of total acute occlusion, almost the entire intestinal wall appears necrotic.

**FIG. 6.102.** Gross features of intestinal ischemia. *A:* Unopened specimen with a perforation (arrow). *B:* Opened specimen showing a localized area of ischemia (arrow).
**FIG. 6.103.** Ischemic enteritis. *A:* Medium magnification showing loss of superficial epithelial lining from the villi. Large numbers of the crypts are identifiable only by residual cells at the base of the glands. *B:* Higher magnification of the superficial area showing edema, vascular congestion, and degeneration and sloughing of the epithelium from the tips (*arrow*).
FIG. 6.104. Intestinal infarction. **A:** The small intestine is completely necrotic with transmural coagulative necrosis. The ghosts of the preexisting villous cores are present *(stars)*. Ghosts of dead enterocytes are indicated by the *arrow*. There is no inflammation because reperfusion did not occur. **B:** Coagulative necrosis associated with anoxia. Sections of several crypts are indicated by the *stars*. The epithelium is sloughing and the nuclei lack their typical basophilia. This photograph shows the increased sensitivity of the epithelium to anoxic effects. The underlying stroma still contains intact nuclei in the stromal cells.

In cases of total occlusion, the capillaries appear congested with red cell extravasation and coagulation necrosis unaccompanied by acute inflammation. The pathologic findings are definitive but mimic autolysis because of the absence of neutrophilic infiltrates. Longer periods of ischemia eventually destroy the crypt bases and the underlying musculature. Overt perforation occurs when the ischemic process involves the entire thickness of the bowel wall. The presence of fibrin thrombi in mucosal capillaries serves as a useful diagnostic feature of ischemia (Fig. 6.105), but it only becomes evident once epithelial breakdown occurs. In severe injury the crypts drop out completely, and if the damage heals the area becomes fibrotic. The degree of fibrosis that develops depends on the extent of the ischemic damage.

If partial blood flow is maintained, then the effects of the reperfusion are superimposed on the ischemic damage. Early stromal changes consist of edema of the lamina propria, often associated with hemorrhage and emigration of neutrophils through the epithelial surface, especially at the villous tips. There is often prominent telangiectasia. A pseudomembrane composed of necrotic epithelium, fibrin, and inflammatory cells develops (Fig. 6.106). In cases of severe injury, the ischemic process extends into the submucosa and muscularis propria and serosa (Fig. 6.106). If the ischemia only affects a small segment, collateral circulation may allow healing to begin even as the infarction is proceeding at a smaller focus, resulting in regenerative changes superimposed on degenerative ones.
FIG. 6.105. Ischemia with focal fibrin thrombi in the vasculature.
Ischemic Enteritis

FIG. 6.106. Acute ischemia. A: Early hemorrhagic necrosis of the tips of the folds is seen. The epithelium is extensively denuded. B: Extensive hemorrhagic infarction of the tip of the folds. The entire mucosal structure is completely infarcted. A pseudomembrane covers the surface of the bowel. The submucosal structures are edematous and hemorrhagic. C: Marked necrosis is seen in the small bowel. The mucosa appears hemorrhagic and telangiectatic. An organizing thrombus is seen in the underlying blood vessel. D: Severe extensive transmural infarction of the small bowel.

It is unusual for the etiology of the ischemic damage to be evident from an intestinal resection or biopsy specimen, unless one finds a vasculitis or thrombi. It is important to make a distinction between the damaged vessels that result from ischemia and ulceration and primary vascular disease. In trying to make this distinction, one must examine those parts of the intestine that are not ulcerated or show only minimal signs of ischemic damage to establish whether underlying vascular disease or another change is present.

Isolated intramucosal goblet cells may be present in patients with subacute ischemic enteritis and these may mimic signet ring cell carcinoma, particularly since gastrointestinal signet ring cell tumors may have a deceptively benign appearance (194). These are typically found in areas of extensive necrosis with mucosal sloughing. They typically lie within the crypt lumens along with inflammatory debris, near dying cells of the crypt. There is often continuity between the dying cells and the sloughed signet ring–like cells at the crypt bases. The
signet ring–like cells represent degenerating goblet cells and are usually accompanied by
other dying cells with the features of enterocytes, endocrine cells, and Paneth cells. These cells are confined to the ischemic areas in the partially viable mucosa.

**Recovery from Ischemic Damage**

Even when the villi are extremely damaged, healing begins quite rapidly if the tissues become adequately reoxygenated (195). Recovery takes place in several phases. In the first phase, a new epithelial layer regenerates from the crypts and the lower third of the villi (Fig. 6.107). The cells proliferate and migrate upward to cover whatever residual villous core remains. If the villous cores are completely destroyed, the mucosa will become simplified, resembling colonic tissue, or even appear as an area completely lacking crypts. After 12 hours, a flat epithelium is present, but by 24 hours the epithelium and cells appear cuboidal or columnar and incipient development of small intestinal villi is apparent. After 8 days, the regenerated small intestinal mucosa shows a variably normal morphology (196), depending on the extent of the original injury and architectural loss.

**Complications**

Reparative changes following ischemia can lead to stricture formation as early as 2 to 8 weeks after the initial injury. Transmural infarction with serosal ischemia induces adhesions between adjacent structures. Extensive intestinal infarction leads to systemic acidosis and hypotension, with secondary cardiac, renal, or pulmonary failure; sepsis; strictures; and death (Fig. 6.108).
Ischemic Enteritis

**FIG. 6.107.** Early regenerative changes following ischemic damage. The villi have become completely denuded. The crypts are lined by hyperchromatic cells that are beginning to proliferate and replace the previously destroyed epithelium.

**FIG. 6.108.** Ischemic stricture.

Ischemic strictures may be single or multiple and can measure many centimeters in length. They are usually sharply delimited concentric lesions. The bowel wall appears thickened, fibrotic, and whitish in color. There is usually mucosal necrosis. The submucosa may contain granulation tissue and abundant new vessels. The mucosa may be ulcerated, contain inflammatory polyps, or appear healed with distortion of the mucosal folds. There may also be fissures. The wall shows scattered inflammation and lymphoid aggregates may present throughout the bowel wall. All of these features mimic the strictures present in patients with Crohn disease. Hemosiderin deposits may be present in areas of previous hemorrhage and may serve to distinguish ischemia from Crohn disease. Other features that help distinguish between the two entities are listed in Table 6.6.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) affects all age groups, ranging from premature neonates to the very elderly. Ischemia is the underlying cause of the pathologic process, but the mechanisms are poorly defined and vascular occlusion is not usually demonstrable. Often there is a coexisting bacterial infection. Frequently this is due to *Clostridium* species. Disseminated intravascular coagulation may occur secondary to the presence of bacterial toxins.

| TABLE 6.6 Ischemic Strictures Versus Crohn Disease |

P.340
Neonatal Necrotizing Enterocolitis

Neonatal NEC is a devastating neonatal disease with a rapid onset that affects 6% of all premature infants (197). Twenty to forty percent of cases are fatal. Surviving babies suffer from short bowel syndrome and/or malabsorption later in life. Stricture formation occurs as early as 5 weeks after the acute episode in infants who survive. Four major factors play critical roles in the pathogenesis of neonatal NEC, including prematurity, establishment of enteral feeding, intestinal mucosal ischemia, and the presence of luminal bacteria (Fig. 6.109). Some patients have a Paneth cell deficiency (198). Contributing factors include intestinal dysfunction and endotoxemia. In most cases the intestinal ischemia results from decreased cardiac output due to fetal asphyxia.

The neonatal intestine has a limited capacity to maintain oxygen uptake during periods of reduced perfusion pressure and arterial hypoxia, especially during feeding (199). Additionally, the enzymatic composition of the immature neonatal intestine does not allow complete digestion of fats, carbohydrates, and casein, leaving a large amount of protein in the intestinal lumen in the form of curd. This favors intestinal bacterial growth, particularly those that produce potent toxins. Mucosal injury permits proteins and bacterial toxins to pass into the portal circulation and then into the liver, injuring hepatocytes and Kupffer cells. If liver function becomes sufficiently impaired, endotoxin enters the systemic circulation, causing shock. Gram-negative bacterial colonization also occurs, further intensifying the circulatory insufficiency and the shock (197). The terminal ileum and right colon are preferentially affected.

The gross findings of neonatal NEC may be dramatic, with the affected bowel segments appearing dilated, necrotic, hemorrhagic, friable, and gangrenous (Fig. 6.110). The external surface shows shaggy serosal exudates and adhesions between adjacent loops of bowel. Because the injury is ischemic in nature, the changes are either diffuse or focal. Pneumatosis intestinalis may be present (Figs. 6.110 and 6.111).

Tropical Necrotizing Enterocolitis

Tropical necrotizing enterocolitis affects patients of all ages in tropical and subtropical areas. Dietary factors and infections contribute to its pathogenesis. Ischemia is always the initial insult. Pig bel, seen in Papua, New Guinea (Fig. 6.111), represents an example of this group of lesions. This entity is described further in a later section.
FIG. 6.109. Pathogenesis of neonatal enterocolitis. Multiple factors play a role in the etiology of this pediatric disorder. Common to most cases is a period of hypoxia leading to ischemia. Coexisting hypovolemia leads to low-flow states and complicates the underlying anoxia. Umbilical vein catheterization may cause localized vasospasm and further compromise luminal flow. At the same time as anoxic injury is progressing, the small intestinal epithelium loses its normal barrier function and bacteria that are present gain access to the underlying tissues, leading to sepsis and shock.
FIG. 6.110. Necrotizing enterocolitis. A: Resection specimen from a child with severe necrotizing enterocolitis. The bowel is dusky in many areas, representing areas of hemorrhagic infarction. In addition, multiple areas of transmural gangrene with pseudomembrane formation are represented by the multifocal whitish areas. B: Pneumatosis intestinalis is present in area of stricture. C: Higher power magnification demonstrates the bubbly quality of the mucosal surface representing entrapped air within the bowel wall.
Acute Segmental Obstructing Enteritis

Acute segmental obstructing enteritis is characterized by fever, leukocytosis, copious bilious vomiting, severe abdominal pain, and signs of intestinal obstruction. Many patients eventually recover from the disorder following antibiotic treatment. The disease may be self-limited. Some patients undergo surgical exploration with the demonstration of segmental ischemia. This pediatric disorder may account for some subsequent cases of shortened bowel syndrome with segmental transmural fibrosis (200).

Celiac Axis Compression Syndrome

Celiac axis compression syndrome (mesenteric vessel compression) results in abdominal pain, vascular narrowing, and ischemia. It results from mesenteric vessel compression (Table 6.7). The intestines develop typical ischemic injury. If the compression results from a neoplasm compressing the vasculature, the tumors may also extend into the bowel wall.

Intestinal Ischemia Following Atheromatous Embolization
Ischemic Enteritis

Cholesterol emboli arising from complicated atheromatous plaques produce a wide range of clinical syndromes depending on the organs and size of the vessels involved. Emboli usually arise from the aorta and patients present with abdominal pain and melena secondary to intestinal ischemia. Abdominal aortic catheterization in such patients sometimes results in a showering of atheromatous emboli throughout the abdominal arterial circulation. Such an unfortunate event may produce dramatic changes not only in the GI tract, but also in the spleen, kidneys, and adrenals. Because the emboli lodge in small vessels, it is rare for full-thickness infarction to develop due to the presence of collateral circulation. Patients with healed disease develop strictures. The vessels in the affected areas undergo various changes. Initially, they are plugged by atheromatous emboli, cholesterol crystals, or amorphous debris. This elicits a foreign body giant cell reaction followed by concentric intimal fibrosis, luminal reduction, and variable degrees of recanalization (Fig. 6.112) (201).

**TABLE 6.7 Mesenteric Vessel Compression**

<table>
<thead>
<tr>
<th>Retroperitoneal hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneal fibrosis</td>
</tr>
<tr>
<td>Retroperitoneal tumors</td>
</tr>
<tr>
<td>Enlarged mesenteric lymph nodes</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Infectious processes</td>
</tr>
</tbody>
</table>
Ischemic Enteritis

**FIG. 6.112.** Ischemia due to atheromatous emboli. A: A portion of ischemic small intestine with focal complete loss of the epithelium (*arrows*). The vessels are extremely dilated. One vessel contains an embolus with slitlike spaces corresponding to cholesterol emboli (*arrow*). B: Higher magnification of the cholesterol clefts in the emboli in a medium-sized vessel.

P.343

**Bowel Infarctions in Dialysis Patients**

Patients with end-stage renal disease who undergo dialysis are at increased risk for nonocclusive intestinal infarction due to the presence of hypertension, severe underlying heart disease, and the frequent removal of large volumes of fluid during ultrafiltration dialysis. Patients develop a hypotensive episode; an anion gap and metabolic acidosis are frequently present. Multiple infarctions may develop.

**Gastrointestinal Ischemia in Vasculitis**

Vascular inflammation complicates many disorders leading to ischemic enteritis, perforation, hemorrhage, infarcts, ulcers, and strictures. Both the small and large intestine may be involved. Larger vessel disease is exemplified by polyarteritis nodosa. The intestines are also affected by other forms of vasculitis, including Henoch-Schönlein disease, Wegener granulomatosis, and Churg-Strauss disorder. Venous disease leading to ischemia not caused by primary thrombotic processes may occur in systemic lupus erythematosus (202), Behçet disease (203), necrotizing giant cell granulomatous phlebitis (204), enterocolic lymphocytic phlebitis (205), and idiopathic myointimal hyperplasia of mesenteric veins (206). Vasculitides are often classified based on the size of the vessels that are involved as shown in Table 6.8.

**Polyarteritis Nodosa**

Twenty-five to seventy-nine percent of patients with polyarteritis nodosa (PAN) present with abdominal pain, diarrhea, positive fecal occult blood, nausea, vomiting, and hematemesis...
Ischemic Enteritis

(207) Steatorrhea, perforation, strictures, ulcerative enteritis, ischemia, and intussusceptions may all occur (208). Thirty-six percent of patients with PAN exhibit only GI manifestations. Males are afflicted four times more often than women, most commonly between the ages of 20 and 40. Patients often have other autoimmune diseases, with rheumatoid arthritis and systemic lupus erythematosus being the most common. Deposition of immune complexes in the blood vessels leads to fibrinoid necrosis and thrombotic, occlusive, ischemic, and hemorrhagic events in the affected tissues. Microaneurysms and vascular stenoses develop in the medium-sized mesenteric arteries. The mesenteric vessels are involved in 25% to 30% of cases. Nodular swellings along the course of the mesenteric arteries represent a characteristic but uncommon finding.

A resection specimen often shows patchy necrosis, well-demarcated mucosal ulcers along the antimesenteric border, strictures, and possibly perforation. The major histologic findings usually remain confined to the smaller mesenteric arteries as well as small and medium-sized submucosal arteries. Vascular edema occurs first, followed by acute inflammation of all layers of the vessel walls (Fig. 6.113). Fibrinoid necrosis of the media and elastic intima occurs later, causing stretching and fragmentation. This predisposes the abnormal vessel to undergo thrombosis and luminal narrowing. Elastic tissue destruction results in aneurysmal dilation or rupture. The whole circumference of the artery may be involved, but more often the involvement is eccentric or segmental in nature. Elastic tissue stains demonstrate disruption and dissolution of the elastic fibers. Lymphocytes, histiocytes, polymorphonuclear cells, and eosinophils infiltrate the intestinal wall in response to the vasculitis. Giant cells are absent.

### TABLE 6.8 Gastrointestinal Vasculitis

<table>
<thead>
<tr>
<th>Affecting large vessels</th>
<th>Predominantly affecting large and medium-sized vessels</th>
<th>Predominantly affecting small and medium-sized blood vessels</th>
<th>Predominantly affecting small-sized vessels, ANCA-associated</th>
<th>Predominantly affecting small vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu arteritis</td>
<td>Crohn disease</td>
<td>Radiation damage</td>
<td>Wegener granulomatosis</td>
<td>Henoch-Schönlein syndrome</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td></td>
<td>Polyarteritis nodosa</td>
<td>Churg-Strauss syndrome</td>
<td>Behçet syndrome</td>
</tr>
<tr>
<td>Polyarteritis rheumatica</td>
<td></td>
<td>Kawasaki disease</td>
<td>Microscopic polyangiitis</td>
<td>Hypersensitivity vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arterial fibromuscular dysplasia of childhood</td>
<td></td>
<td>Thromboangiitis obliteransa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Buerger disease</td>
<td></td>
<td>Leukocytoclastic vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fungal vasculitis</td>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Danlos-Ehlers syndrome</td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypocomplementemic vasculitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cytomegalovirus vasculitis</td>
</tr>
</tbody>
</table>

file:///F|/Gastro/Chapter%206%20Ischemic%20Enteritis.htm (29 of 42)2/4/2009 2:05:34 PM
### Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is a multisystemic disorder characterized by a symmetric, nontraumatic, nonthrombotic, painless purpuric rash largely involving the skin of the legs and buttocks with arthritis, nephritis, hematuria, and GI injury (209). The disorder is primarily a pediatric disease characterized by IgA immune complex deposits beneath the vascular basement membranes. Antigenic stimulation may result from respiratory tract infections, stings, immunizations, and drugs. The gut is involved in up to 85% of patients. Patients may initially manifest isolated GI disease but subsequently other organs become involved. Any bowel segment may be involved but the jejunum and ileum are most frequently affected. Patients present with acute abdominal symptoms, including pain and GI bleeding (210).
Ischemic Enteritis

**FIG. 6.113. Polyarteritis nodosa.** The vessels are inflamed.

**FIG. 6.114. Henoch-Schönlein purpura.**

- **A:** A leukocytoclastic vasculitis is seen in a submucosal vessel.
- **B:** Low-power photograph demonstrating the presence of mucosa on the right side of the photograph and distorted, penetrating vessels with fibrosis and inflammation.
- **C:** Higher magnification of the penetrating vessel.

Grossly, the bowel exhibits small, superficial infarcts with diffuse edema, mottling, congestion, and hemorrhage. A white purulent exudate covers an erythematous mucosa (211). Erosions and ulcers may be present. Several ischemic areas of varying ages may be present. Transmural infarctions and perforations are rare. The mesentery may appear focally congested.

Histologically, there is vascular congestion, hemorrhage, necrosis, and inflammation (Fig. 6.114). The necrotizing small vessel vasculitis predominantly affects capillary venules in the mucosa and upper submucosa, sparing larger mesenteric vessels. The venules of involved portions of the bowel demonstrate an acute leukocytoclastic vasculitis, fibrinoid necrosis of the vascular walls, and polymorphonuclear leukocytic infiltrates in surrounding tissues (211). Fibrinoid necrosis can be seen within the lumens of involved venules subjacent to the areas of ischemic mucosal necrosis (Fig. 6.115) (211). The demonstration of IgA deposits in the vascular walls by immunofluorescence is diagnostic.

**Hypersensitivity Vasculitis**

Hypersensitivity vasculitis involves inflammation of the small blood vessels (arterioles, capillaries, and venules) and represents an allergic response to a precipitating antigen such as a drug, vaccine, microorganism, or foreign protein. Immune complexes deposit in the walls of small vessels, activating the complement cascade. Neutrophils infiltrate the vessel walls, releasing lysosomal enzymes, which results in fibrin deposition and necrosis (212). Biopsies usually show ischemia, fragmentation of white cells (leukocytoclastic), and fibrinoid necrosis of the walls of the small blood vessels. Specific involvement of small vessels in contrast to medium-sized muscular arteries distinguishes hypersensitivity vasculitis from polyarteritis nodosa, the two kinds of vasculitis that most frequently involve the GI tract.
Wegener Granulomatosis

Persistent inflammatory sinonasal disease coexisting with systemic fevers, malaise, and migratory arthritis typifies the clinical presentation of Wegener granulomatosis. The disease, which affects males and females equally, classically involves the upper and lower respiratory tracts and the kidney, but it may affect any organ system. Wegener granulomatosis is characterized by a granulomatous vasculitis involving small or medium-sized arteries and veins. The granulomatous inflammation consists of palisading epithelioid histiocytes arranged around necrotic foci (213). Multinucleated giant cells constitute a prominent feature of the vascular inflammatory infiltrate. Antineutrophilic cytoplasmic antibodies (c-ANCAs) are diagnostic, especially in patients with concomitant renal disease.

Sjögren Syndrome

Sjögren syndrome associates with hypersensitivity vasculitis. The major histologic findings fit into four major vasculitic categories: Acute necrotizing vasculitis, leukocytoclastic vasculitis, lymphocytic vasculitis, and endarteritis obliterans. The acute necrotizing vasculitis affects small and medium-sized arteries. The entire vascular wall becomes infiltrated with acute and, to a lesser extent, chronic inflammatory cells. Fibrinoid necrosis of the walls is characteristically present. The lesions simulate those seen in PAN during the acute phase, but they lack the aneurysmal formation seen in PAN. Patients with leukocytoclastic vasculitis demonstrate a polymorphonuclear infiltration in capillaries and venules and fibrinoid necrosis of the vessel wall with extravasated red blood cells. Patients with lymphocytic vasculitis exhibit a lymphoplasmacytic infiltrate in capillaries and venules. Vascular wall necrosis is absent. The noninflammatory obliterative vasculitis affects medium-sized vessels.
**Rheumatoid Arthritis and Other Collagen Vascular Diseases**

Approximately 10% of patients with *rheumatoid arthritis* (RA) have GI involvement. Patients with vasculitis usually have severe arthritis, rheumatoid nodules, and high titers of rheumatoid factor. They usually display signs of cutaneous vasculitis. Patients also develop complications from their NSAID or gold therapy. Intestinal infarction in RA patients usually results from the presence of a systemic vasculitis that also involves the vessels of the intestinal wall or mesenteries (Fig. 6.116). Occasionally, RA patients also have proliferative endarteritis characterized by intimal proliferation without vascular wall necrosis or inflammation. RA may also manifest as polyneuropathy, or skin infarction with ulceration, and digital gangrene. In severe cases, the vasculitis affects virtually any organ (214). GI tract involvement is rare but catastrophic when it occurs. GI bleeding, intraperitoneal bleeding, ischemic mucosal ulceration, small and large bowel infarction, bowel perforation, and pancolitis have all been reported. Patients with *scleroderma*, especially the form associated with Raynaud disease, may develop ischemic enterocolitis on the basis of an underlying vasculitis.

Arteritis and venulitis in *systemic lupus erythematosus* may result in massive lower intestinal hemorrhage. Histologic examination shows mucosal ulceration with necrotizing vasculitis (215). Rare complications include infarction and sepsis. Fibrinoid necrosis may be present. Hemorrhagic blebs result from intramucosal hemorrhage oozing from ruptured mucosal capillaries.

**Ehlers-Danlos Syndrome**

Ehlers-Danlos syndrome is an autosomal dominant disorder with abnormalities affecting the cardiovascular, gastrointestinal, and respiratory systems. Vessels become very fragile in the type IV form of the disease. The disorder results from a deficiency in type III collagen. GI vascular involvement presents with intramural hemorrhage, massive bleeding, ischemic necrosis, and perforation (216). The cardinal

P.346

histologic features include arterial dilation with aneurysm formation and aneurysmal rupture, usually limited to medium-sized and smaller arteries (the muscular arteries), although multiple aneurysmal dilations may also affect major muscular arteries, including those in the mesentery. Collagen fibers appear disorderly and loose, disrupting the media of the muscular arteries. Medial hemorrhages occur at the site of the structural damage. Increased acid mucopolysaccharides deposit around the abnormal collagen defects in the arterial walls, suggesting the presence of interactions between the two. Muscular and collagen fiber abnormalities also lead to disintegration of the muscularis mucosae, which becomes practically unrecognizable, especially in the small intestine, and diverticula may develop.
Ischemic Enteritis

**FIG. 6.116.** Vasculitis in rheumatoid arthritis. A and B come from the same resection specimen that was removed for ischemic enterocolitis. A: Cross section through a small arteriole demonstrating the presence of prominent, predominantly concentric perivascular inflammation with a necrotizing vasculitis. Prominent fibrin deposition is present within the lumen. Desquamating cells are seen. B: Another vessel with an endoluminal proliferation and occlusion by proliferating reactive cells. Inflammatory cells surround the bottom portion of the photograph.

### Kawasaki Disease

Kawasaki disease is an acute systemic vasculitis of early childhood characterized by fever, rash, mucosal inflammation, and coronary artery damage (217). Most patients are under age 3. The acute phase of the illness is marked by a profound immunoregulatory change that includes a reduction in CD8+ cells, an increase in activated (DR+) circulating CD4+ cells, and marked polyclonal B-cell activation in the peripheral blood. GI tract involvement, manifesting as diarrhea and/or protein-losing enteropathy, is often the initial symptom.

### Diffuse Hemorrhagic Gastroenteropathy

Diffuse hemorrhagic gastroenteropathy presents as a small vessel vasculopathy that involves the gastric and small intestinal mucosa, which appear diffusely hemorrhagic (218). Biopsies demonstrate luminal narrowing of capillaries and postcapillary venules in the lamina propria due to swelling and proliferation of endothelial cells, neutrophilic margination, and emigration and partial vascular occlusion by fibrin thrombi. These changes remain restricted to the mucosa and are not found in the submucosa, muscularis propria, or serosa. The endothelial cells are histologically abnormal in that they show redundant basal lamina and abnormal endothelial cells with myoid features (218).

### Segmental Mediolytic Arteritis

GI segmental mediolytic arteritis (SMA) affects the abdominal muscular arteries and arterioles in the serosa and bowel wall of elderly patients. The lesion results from an inappropriate
vasospastic response to shock or severe hypoxemia (219). Histologically, SMA is characterized by transformation of the arterial smooth muscle cytoplasmic contents into a maze of dilated vacuoles containing edema fluid. The vacuoles rupture, disrupting the smooth muscle cells. Fibrin deposits and hemorrhage occur at the adventitial–medial junction within the media. Inflammation is inconstant and limited to the periadventitial tissues. Transmural medial lysis leads to the formation of arterial wall gaps that become bridged by a serofibrinous layer (219).

**Mesenteric Inflammatory Veno-occlusive Disease (Lymphocytic Phlebitis)**

Nonthrombotic mesenteric occlusion is a rare cause of intestinal infarction. Patients are typically hypertensive, elderly individuals with a recent onset of abdominal symptoms. The patients often lack evidence of systemic diseases. It complicates rutoside therapy, a drug used to treat varicose veins in Europe. Histologically, there are prominent, dense, perivascular sheets of lymphocytes in both the grossly abnormal ischemic areas as well as in grossly normal areas. The disorder selectively affects veins and venules in the submucosa, subserosa, and peri-intestinal tissues (220). Arteries and arterioles remain completely unaffected. The phlebitis exhibits various stages of progression. Some veins have lymphocytic infiltrates in their walls without luminal compromise; others have intense transmural lymphocytic infiltrates accompanied by subintimal, focally occlusive fibroproliferative lesions and intraluminal thrombi (Fig. 6.117). Some veins recanalize. Sparse neutrophilic or eosinophilic infiltrates may accompany the lymphocytes (220,221). Focally necrotic areas and isolated giant cells may be present in the fibroproliferative process. The differential diagnosis of enterocolitic lymphocytic phlebitis includes a drug-induced hypersensitivity reaction, vasculitis affecting small veins as seen in systemic lupus erythematosus and Behçet disease, secondary effects of enterocolic inflammation, a benign lymphoproliferative disorder, myointimal hyperplasia of mesenteric veins, and necrotizing granulomatous phlebitis. Idiopathic myointimal hyperplasia of mesenteric veins may represent an end stage of lymphocytic phlebitis. Idiopathic myointimal hyperplasia of mesenteric veins is characterized by the presence of bizarre, thick-walled, hypertrophic veins in the submucosa and mesentery. It develops in patients with venous hypertension. Veins become arterialized. Patients often recover following surgery, suggesting that the process is self-limited or indolent in nature (220,221). It is often very difficult to be certain whether the inflammatory venous changes are the cause or the result of the ischemia.
**Cryptogenic Multifocal Ulcerating and Stenosing Enteritis**

The lesions of cryptogenic multifocal ulcerous stenosis enteritis (CMUSE) are isolated to the intestines. Its pathophysiology is unknown, although there is an association with a complement 2 deficiency and a possible relationship with polyarteritis nodosa (222,223). One hundred percent of patients have intestinal symptoms; 70% exhibit extraintestinal symptoms. Twenty percent of patients experience weight loss and 10% experience fever, altered well-being, polyarteritis, and mesenteric artery aneurysms (222,223). Asthma and sicca syndrome may coexist with the disease. Characteristic digestive lesions include 1- to 25-cm jejunal or proximal ileal areas of stenosis. The remainder of the small intestine appears normal. In all cases, the ulcers are superficial, affecting only the mucosa and submucosa. The stenoses associate with nonspecific inflammatory infiltrates containing eosinophils. Fifty-five percent of cases exhibit vascular wall degeneration with fibrous endarteritis. Patients who undergo surgical resection may experience a complete recovery. However, many patients require steroid therapy. CMUSE differs from chronic ulcerative nongranulomatous jejunitis because of the absence of villous atrophy and malabsorption.

**Thromboangiitis Obliterans**

Most patients with thromboangiitis obliterans (Buerger disease) are heavy-smoking men who present with progressive peripheral arteriolar disease and migratory thrombophlebitis. Buerger disease has a worldwide distribution but it is more prevalent in the Middle East and Far East than in North America or Western Europe (224). The disease typically affects small and medium-sized arteries and veins of the upper and lower extremities and patients have a history of recurrent episodes of thrombophlebitis involving both the upper and lower extremities. GI vascular lesions affect the smaller submucosal and serosal vessels. Larger mesenteric vascular involvement, although rare (225), causes low-grade intestinal ischemia.
Ischemic Enteritis

with crampy abdominal pain or an acute abdominal emergency secondary to ischemic necrosis, skip ulcers, and intestinal perforation (225). The lesion occasionally affects the small bowel.

**FIG. 6.118.** Buerger disease. A through C show portions of a medium-sized vessel from a small intestinal resection in a patient with Buerger disease. **A:** Complete obliteration of the lumen by loose, edematous tissue. **B:** Cross section through another vessel demonstrating almost complete occlusion (van Gieson stain). It shows reduplication of the internal elastic membrane. The material within the vascular lumen represents an area of recanalizing thrombus. Several dilated vascular structures are seen (*arrows*). **C:** Higher magnification of the material within the central portion of the vessel shown in A demonstrating the presence of a loose reparative tissue containing numerous proliferating capillaries.

The histologic features reflect disease stage. During the acute stage, the thrombosis is accompanied by angiitis and microabscesses within the thrombus. There is a highly cellular and inflammatory thrombus with relative sparing of the vessel wall. GI lesions demonstrate endothelial cell proliferation, concentric vascular intimal thickening, mild fibrosis, marked transmural inflammation or degeneration (Fig. 6.118), and organizing thrombi. There is usually interruption of the internal elastic lamina. Subacute lesions appear less distinctive than the acute ones, and end-stage lesions may be difficult to distinguish from old organized thrombi. There may be mild perivascular inflammation. The internal elastic lamina is intact (distinguishing the lesion from other forms of vasculitis) and it and the media lack atheromas or calcification. Patients may have superimposed areas of acute and/or chronic ischemia. The absence of medial necrosis and

P.349

the involvement of medium-sized vessels distinguish these lesions from those seen in polyarteritis nodosa.
Ischemic Enteritis

FIG. 6.119. Cytomegalovirus (CMV) vasculitis. A: A biopsy from the terminal ileum showing large abnormal vascular structures within the submucosa (arrows). The superficial portion of the mucosa is completely denuded and ulcerated. B: Immunostain of one of the smaller vessels from the specimen utilizing a dual stain for vessels (factor VIII–related antigen) and CMV. The CMV-infected cell is an endothelial cell (arrow). A second infected cell is seen at the top right-hand portion of the photograph (double arrows). This cell represents a mononuclear cell. C: CMV enterocolitis. The specimen demonstrates a loose, vaguely granulomatous appearance due to the collections of histiocytes that are obliterating underlying vascular structures. CMV immunostains disclosed the presence of immunoreactive cells in the surrounding tissues.

**Vascular Diseases Caused by Infections**

Several infections involve the GI vasculature, damaging the vessel walls and inducing secondary ischemia. Fungi and cytomegalovirus (CMV) are the most frequent offenders. Debilitated patients with *Aspergillosis* and *Candidiasis* may develop fungal vascular invasion and mycotic aneurysms. The fungi completely occlude the vascular lumens, becoming coated with platelets and fibrin, and eventually the vessels thrombose. The intravascular fungi induce an inflammatory response that leads to secondary damage of the vascular wall and extravasation of red blood cells and vasculitis.

CMV is notorious for its ability to invade endothelial cells, causing endothelialitis and predisposing the vessels to thrombosis. A granulomatous-like lesion characterized by histiocytic collections without giant cells may surround the vascular wall (Fig. 6.119). Viral inclusions are not always identifiable within the endothelium of the affected vessels, probably due to sampling problems. However, they are present elsewhere in the nearby vicinity. Viral inclusions may be highlighted by immunostains.

**Diabetic Microangiopathy**

The most consistent morphologic feature of diabetic microangiopathy is the presence of arteriosclerosis (Fig. 6.120) and hyalinized PAS-positive thickened vessel walls and variable degrees of luminal narrowing in smaller caliber submucosal vessels (226). The vascular thickening is secondary to the deposition of basement membrane material. The small bowel may be extensively involved, resulting in diarrhea and malabsorption. The vessels are uninflamed and Congo red stains are negative. There is no endothelial proliferation.
**Behçet Disease**

A syndrome of orogenital and ocular inflammation (or ulceration) was first reported in 1937 by Behçet (227). The disease affects both genders of all ages from infants to the elderly. It has high prevalence rates in the area along the ancient Silk Road from Far East Asia to Turkey. The site of organ involvement is somewhat geography dependent, with ileocecal disease being relatively more common in the Japanese (228). Some cases are familial in nature (229), although no predisposing genetic abnormality has been identified. Possible etiologic associations include CMV (230) or Epstein-Barr (231) infections. Others suggest that the presence of high levels of truncated actin in the neutrophils of these patients may be specific for the disease (232,233). Gastrointestinal involvement occurs in about 5% of patients and about 1% to 2% have small intestinal disease (234).

Common wisdom is that the disease results from a vasculitis affecting both small and large vessels. However, more recent data suggest that the disorder is primarily a neutrophilic vasculitis that targets the vasa vasorum (235). Intestinal involvement most commonly affects men in their 4th and 5th decades of life. Patients preferentially develop ulcers in the terminal ileum and cecum. Enlarging ulcers or newly formed ulcers coexist with healed ulcers. The ulcers are localized or diffuse, often penetrating the serosa, leading to intestinal perforation. They have a tendency to irregularly undermine surrounding tissues. Edemalike swelling with crater formation around the ulcer margins produces a characteristic "collar-stud" appearance. Perforation and severe hemorrhage are the most severe complications of the disease.
Ischemic Enteritis


Pathologically, the disease is characterized by a vasculitis that is usually lymphocytic in nature and affects small veins and venules to a greater extent than arteries. Mononuclear infiltrates surround capillaries and venules, and some vessels demonstrate intimal thickening. Occasionally, there may be more severe necrotizing inflammation with leukocytoclasis. Often the vasculitis is difficult to demonstrate, making the diagnosis challenging. Small intestinal involvement typically affects the terminal ileum, particularly in the area of lymphoid aggregates and Peyer patches (236). Behçet ulcers contain nonspecific chronic inflammation, and the submucosal connective tissue appears disrupted (Fig. 6.121). Granulomas are absent. The mucosa around the ulcers is usually normal in appearance. Patients treated surgically have a high rate of recurrent disease (236). The histologic features of recurrent disease resemble the primary disease. The preferred treatments are combined drug therapy with any or all of the following: Steroids, NSAIDs, and immunosuppressive and cytotoxic agents. Thalidomide, tacrolimus interferon, and antitumor necrosis factor monoclonal antibody have all attracted recent attention (237,238).

Often the vasculitis is difficult to demonstrate, making the diagnosis challenging. Small intestinal involvement typically affects the terminal ileum, particularly in the area of lymphoid aggregates and Peyer patches (236). Behçet ulcers contain nonspecific chronic inflammation, and the submucosal connective tissue appears disrupted (Fig. 6.121). Granulomas are absent. The mucosa around the ulcers is usually normal in appearance. Patients treated surgically have a high rate of recurrent disease (236). The histologic features of recurrent disease resemble the primary disease. The preferred treatments are combined drug therapy with any or all of the following: Steroids, NSAIDs, and immunosuppressive and cytotoxic agents. Thalidomide, tacrolimus interferon, and antitumor necrosis factor monoclonal antibody have all attracted recent attention (237,238).

The presence of focal ulcers, fistulae, and strictures and the ileocecal location may mimic Crohn disease, and since the histologic features are nonspecific, one must rely on the clinician to suggest the diagnosis based on the presence of characteristic oral, genital, and eye lesions. The diagnosis of Behçet disease requires the presence of recurrent oral ulceration. Other helpful clinical features include ocular involvement, arthritis, erythema nodosum, and recurrent genital ulceration. Unfortunately, some of these may also be present in Crohn disease as discussed in Chapter 11.

Other Vasculitides

Other disorders affecting mesenteric arteries include Takayasu arteritis (pulseless disease), Crohn disease (see Chapter 11), and cryoglobulinemia. These disorders affect children and adolescents, and are usually heralded by severe abdominal pain. Takayasu disease may associate with inflammatory bowel disease.

Patients with Churg-Strauss syndrome sometimes develop GI involvement. These patients often have allergic rhinitis, nasal polyposis, and asthma as well as eosinophilic pulmonary infiltrates. Peripheral neuropathy is also common (239,240). This small-vessel ANCA-positive vasculitis resembles that seen in several other diseases, but the presence of eosinophils as part of the vasculitic infiltrate or an extravascular infiltrate into the surrounding tissues strongly favors the diagnosis. Extravascular granulomas may be present in this disorder and in Wegener granulomatosis (241). A number of drugs also cause vasculitis and ischemic complications. Köhlemeier-Degos syndrome affects the skin and gastrointestinal tract. The intima of small and medium-sized arteries undergoes progressive occlusive sclerosis leading to small intestinal infarction (242). Necrotizing angiitis may complicate AA amyloid (243).

Gastrointestinal Ischemia Secondary to Thrombotic Events

Hemolytic uremia syndrome (HUS) affects young adults who present with anemia, thrombocytopenia, and renal failure. Patients who develop intestinal involvement present with enterocolitis resulting from intravascular microthrombi. The GI effects of HUS and thrombotic thrombocytopenic purpura (TTP) are similar. HUS is discussed in greater detail in Chapter 13. TTP is an idiopathic disorder consisting of thrombocytopenia, microangiopathic hemolytic anemia (without significant consumption of clotting factors), fever, renal insufficiency, and
Ischemic Enteritis

profound neurologic dysfunction. The condition causes thrombosis of intestinal vessels with secondary ischemic injury (Figs. 6.122 and 6.123). Homocystinuria, a recessively inherited inborn error of metabolism, may simulate Marfan syndrome. Vascular abnormalities develop, characterized by episodic thrombosis followed by fibroelastic reorganization of medium-sized arteries. This results in a fibroblastic intimal proliferation and luminal narrowing in the absence of inflammation or fibrinoid necrosis. Homocysteine in the urine is diagnostic of the disease. Köhlinmeier-Degos disease (malignant atrophic papulosis) primarily affects the skin, but small intestinal disease occurs in about 50% of cases (244). The disease usually presents in young adults, although it has been diagnosed in infancy and after age 55. Young men are primarily affected. Patients may develop severe abdominal pain, sometimes with vomiting, suggesting peritonitis, intestinal obstruction, or pancreatitis. Intestinal perforation is the most common cause of death. Malabsorption due to widespread intestinal involvement also develops (242). The characteristic GI lesions consist of conical infarcts associated with thrombi. The arteries and veins appear thrombosed. Other vessels may show evidence of fibrinoid necrosis and perivascular hemorrhage. The intima of small and medium-sized blood vessels undergoes progressive occlusive sclerosis, leading to localized areas of infarction (242). Larger arteries develop proliferative changes resembling those seen in a thrombotic end arteriopathy.

Patients with hypercoagulable states often have anticardiolipin antibodies (245), lupus anticoagulants (246), protein C or S deficiencies (247), a dysfunction of antithrombin III or heparin cofactor II, (248), Leiden factor V mutations, and fibrinolytic dysfunction (249). These patients can present as a primary abdominal emergency due to the presence of ischemic necrosis. Typically, the patients present with diffuse intravascular venous thrombosis. Exceptionally, a multiple myeloma patient presented with an intestinal infarction due to crystallized immunoglobulins in the vasculature (250).

Patients with various bacterial infections may develop septicemia and widespread disseminated intravascular coagulation manifested by the presence of a petechial rash and mucosal hemorrhages. In severe cases, an entire segment of GI tract may become ischemic. This then predisposes the patient to additional septic events, with seeding of the blood by intestinal bacteria due to the disruption of the mucosal barrier. Toxigenic bacteria, such as enterohemorrhagic Escherichia coli and clostridia, damage capillary endothelial cells, causing severe mural edema, red cell extravasation, and hemorrhage. Ischemic necrosis then develops.

**Handling Resection Specimens for Ischemia**

Intestines are resected in ischemia either due to the presence of a perforation or due to life-threatening complications of intestinal ischemic necrosis. When the bowel infarcts or perforates, the clinician is already aware of the presence of ischemia. However, there are certain pieces of information that the resection specimen provides that the clinician may or may not know and may be extremely useful to future patient management. Sections should always be taken from the resection margins of the specimen whether or not they have been designated as to which is proximal and distal by the surgeons since the presence of nonviable tissue in either resection margin may lead to future surgical complications. Sections should also be taken through the most severely affected portion of the bowel to determine the extent of the ischemic damage and the depth of its involvement in the bowel wall. Perforation sites...
Ischemic Enteritis

should be sampled. Sections should always be taken through the mesenteric vessels to determine whether the following are present: (a) atherosclerotic changes involving the vasculature, (b) other major vessel pathologies, (c) thrombi, and (d) emboli. If a thrombus or embolus is present, an effort should be made to determine its age.

FIG. 6.123. Thrombotic thrombocytopenic purpura. A: Small bowel with ischemia and marked atrophy. Villi are completely obliterated. Focal glandular dropout is present. B: A portion of the submucosa immediately underlying an ulcer. The vessels are markedly dilated and contain laked blood. C: A portion of the submucosa underlying an ulcer. The oval-shaped vessel contains prominent lines of Zahn (arrows).

When one examines the histologic sections from the bowel wall, an effort should be made to determine the cause of the ischemia. Therefore, the submucosal vessels should be examined carefully for the presence of vasculitis, thrombi, or emboli. The mucosa and submucosa should also be examined for the presence of viral inclusions. Special efforts should be made to assess the etiology in individuals who would otherwise not be expected to have intestinal ischemia, particularly in younger patients. An intestinal resection often provides the first clue as to the presence of underlying disease. Perhaps the most difficult disorder to recognize is CMV-induced ischemia in an individual without the traditional risk factors for this infection. Viral inclusions should be sought in mononuclear cells and endothelium. If vaguely granulomatouslike lesions are seen around vessels, one may wish to perform immunostains for the presence of the virus. Subtle viral inclusions are often seen near perforations and/or deep ulcers, and in an individual without an obvious cause for the ischemia, one might want to stain such areas as well. The report should specifically state the viability of the resection margins, the depth of the involvement, and the presence of thrombi, emboli, vasculitides, or CMV.
Lipid Malabsorption

The three major forms of lipid malabsorption are abetalipoproteinemia, familial hypobetalipoproteinemia (565), and diabetes. Several other related syndromes result in lipid accumulations in enterocytes producing histologic patterns indistinguishable from abetalipoproteinemia (Table 6.41) (566). The pathogenesis of several lipid malabsorption syndromes is shown in Figure 6.203.

Abetalipoproteinemia

Abetalipoproteinemia is a recessive genetic disease characterized by the virtual absence of apolipoprotein (apo) B and apo B–containing lipoproteins in plasma. Affected patients are usually individuals of Jewish or Mediterranean descent. Approximately one third of cases result from consanguineous marriages, and family studies suggest an autosomal recessive mode of inheritance (567). The sex ratio is 1:1.

<table>
<thead>
<tr>
<th>TABLE 6.41 Diseases Associated with Fatty Deposits in Enterocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetalipoproteinemia</td>
</tr>
<tr>
<td>Familial hypobetalipoproteinemia</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy</td>
</tr>
<tr>
<td>Cow's milk–sensitive enteropathy (and related entities)</td>
</tr>
<tr>
<td>Anderson disease (chylomicron retention disease)</td>
</tr>
<tr>
<td>Fasting states</td>
</tr>
<tr>
<td>Impaired chylomicron metabolism</td>
</tr>
<tr>
<td>Juvenile nutritional megaloblastic anemia</td>
</tr>
<tr>
<td>Tropical sprue</td>
</tr>
<tr>
<td>Following the ingestion of a fatty meal</td>
</tr>
</tbody>
</table>

In abetalipoproteinemia, chylomicron assembly is defective due to mutations in the microsomal triglyceride transfer protein (MTP) (568). MTP is a resident lipid transfer protein within the endoplasmic reticulum of hepatocytes and enterocytes. The absence of MTP in abetalipoproteinemia results from MTP mutations affecting the large subunit of the protein. The absence of MTP results in an absence of apo B100 and B48 from the plasma, because apo B–containing lipoprotein assembly is disrupted in the liver and intestine.

At birth, infants with abetalipoproteinemia are asymptomatic. Signs and symptoms begin months after birth, once a diet rich in lipids is started. The initial complaints are diarrhea, bloating, vomiting, anemia, weight loss, and failure to thrive. Spinocerebellar degeneration, peripheral neuropathy, and retinitis pigmentosa result from deficiencies in fat-soluble vitamins (vitamin E levels are characteristically extremely low). The gastrointestinal manifestations of the disease often improve with time, in part because affected patients (or their parents) learn to avoid dietary fats.

Acanthocytes are characteristically seen in the peripheral blood. Serum hypolipidemia is present with reduced cholesterol, triglycerides, low-density lipoprotein (LDL), and chylomicrons. Patients have undetectable levels of serum apolipoprotein B.

Small bowel biopsies typically show striking enterocyte vacuolization. Overall, the villous architecture appears normal but the villi are lined by enterocytes containing large amounts of intracellular triglycerides. Enterocyte vacuolization, although characteristic of abetalipoproteinemia disorders (Fig. 6.204), is not entirely diagnostic, since these changes occasionally occur in other settings (Table 6.41) (569). The lipid-engorged, vacuolated enterocytes appear pale and at high magnification contain numerous small, clear, lipid-filled vacuoles that pack the apical and subnuclear cytoplasm. No lipid droplets are present in the intercellular spaces or in the lacteals. The lamina propria appears normal except for the presence of macrophages containing...
bizarre inclusions. Acanthocytes may be seen in the capillaries of the lamina propria.

**FIG. 6.203.** Diagrammatic summary of the block in lipid secretions in abetalipoproteinemia and hypobetalipoproteinemia. A: Hypobetalipoproteinemia. Lipids accumulate within the cell due to defective apo B48 synthesis. In contrast, in abetalipoproteinemia (B), a specific genetic mutation leads to defective microsomal transfer protein and the lack of chylomicron assembly. As a result, intracellular lipids increase. RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum.

**Chylomicron Retention Disease**

Chylomicron retention disease, also known as Anderson disease, is a rare autosomal recessive intestinal lipid transport disorder in which apo B48 is absent. Symptoms begin during the first few months of life and include chronic diarrhea, significant fat malabsorption, and failure to thrive (570). Unlike abetalipoproteinemia, acanthocytosis rarely occurs and neuromuscular manifestations are much less severe. Fasting triglyceride levels are normal but fat-soluble vitamins, especially A and E, are severely decreased. Plasma cholesterol levels are low but do not reach those seen in abetalipoproteinemia. Apo B, apo AI, and apo IV are decreased. Immunoperoxidase localization of apoprotein B in fasting biopsy specimens shows normal to elevated staining of the lipid-laden intestinal epithelial cells (570).

The enterocytes contain large numbers of fat particles (chylomicrons) in the endoplasmic reticulum and the Golgi complex. The defect appears to be in the translocation of Golgi-derived vesicles to the plasma membrane for excretion. Hence, little or no fat is observed in the intercellular spaces and lacteals (570). The ultrastructural features differ from those seen in abetalipoproteinemia in that chylomicrons and larger lipid vacuoles are seen in the apical enterocyte cytoplasm (571).
Lymphatic Lesions

Lymphangiectasia

Intestinal lymphangiectasia is a rare congenital obstructive defect of the lymphatics primarily affecting children and young adults. It is characterized by protein-losing enteropathy, hypoproteinemia, edema, lymphocytopenia, malabsorption, and dilated lacteals. It is part of a generalized disorder of the lymphatic system. Patients also have chylothorax, chyluria, chylous ascites, or asymmetric lymphedema, singly or in combination, depending on the degree of hypoproteinemia (645).

Associations of primary intestinal lymphangiectasia are listed in Table 6.55. Hypoplastic visceral lymphatics obstruct lymph flow, causing increased intestinal lymphatic pressure, thereby dilating lymphatic vessels throughout the small bowel and mesentery. Hypoproteinemia and steatorrhea develop secondary to rupture of the dilated lymphatic vessels with discharge of lymph into the bowel lumen. Loss of major plasma protein components leads to hypoproteinemic edema. Serum levels of albumin, immunoglobulins, and other proteins are decreased. Endoscopically, whitish swollen tips of the villi are fairly characteristic.

The intestinal lumen appears dilated and the valves of Kerckring are swollen and broader than normal due to the presence of the dilated lymphatics. The intestines become edematous with a dusky serosa covered by fibrinous exudates. Serosal lymphatics appear as dilated, yellowish nodules measuring <5 mm in diameter. Villi have enlarged bulblike tips imparting a white pebbly papillary appearance to the mucosal surface (Fig. 6.230). The lymphatic channels are dilated and lined by endothelium, contrasting with the changes seen in its mimics (Whipple disease, pneumatosis, and pseudolipomatosis). The reddish brown pigmentation, characteristic of brown bowel syndrome, is often present. Lymphangiectasia is usually a diffuse process, sometimes involving the colon (646). This contrasts with localized lesions such as lymphangiomas or lymphangitic cysts. The diffuse intestinal involvement precludes surgical intervention.

**TABLE 6.55 Primary Intestinal Lymphangiectasia: Associations**

<table>
<thead>
<tr>
<th>Disease localized to intestinal lymphatics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial</td>
</tr>
<tr>
<td>Sporadic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Widespread lymphatic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milroy disease—congenital hereditary lymphedema</td>
</tr>
<tr>
<td>Widespread lymphatic abnormalities and hypoproteinemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Association with other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Noonan syndrome</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
</tr>
<tr>
<td>Enamel hypoplasia</td>
</tr>
<tr>
<td>Yellow nail syndrome</td>
</tr>
<tr>
<td>Thymic hypoplasia</td>
</tr>
</tbody>
</table>

P.451
Lymphangiectasia

Histologically, lymphangiectatic lesions are microscopic lymphatic hamartomas that preferentially involve the small intestine, where the largest amount of lymphatic tissue is present. Since the lesions can be focal, they often require multiple biopsies to demonstrate their presence. The finding of distended lymphatics in a jejunal biopsy after an overnight fast is diagnostic. The villi appear shortened and broadened. Striking distention of lymphatic channels widens the villi, often causing apparent villous fusion (Fig. 6.230). The lymphatics contain foamy histiocytes; similar cells are seen in the yellowish nodules and lymph nodes. Mesenteric lymphatics are greatly thickened and contain a fragmented elastica interna with medial muscular hypertrophy. Focal acute inflammation may be present. Patients have a reduction in the number of intraepithelial lymphocytes. Lymphangiectasia may be localized to the lamina propria or generalized involving the mucosa, submucosa, serosa, and mesentery. Fat staining of frozen sections may demonstrate the lipid contents of the vacuoles.

Lymphatic Cysts

Single or multiple (Fig. 6.231) lymphatic cysts occur in up to 23% of the small intestines or their mesentery when they are examined at the time of autopsy. Mean patient age is 74, and in one study none was found in individuals younger than 55. The symptomless, submucosal nodules measure up to 1 cm in diameter and contain thick, yellow, creamy fluid. Mesenteric cysts rarely rupture or cause volvulus or obstruction. The usually unilocular cysts are lined by flattened lymphatic endothelial cells and they contain eosinophilic proteinaceous material (Fig. 6.232).

Lymphatic Dilation

Lymphatic dilation complicates obstructions either of the GI tract or of the lymphatic drainage. The dilated lymphatics present
Lymphatic Lesions

as prominent whitish channels running alongside the vascular channels, as illustrated in Figure 6.233. Histologically, one sees diffuse dilation of the lymphatics, which usually is most severe on the serosal surface of the bowel (Fig. 6.234). Secondary causes of lymphangiectasia are listed in Table 6.56.

FIG. 6.231. Multiple lymphatic cysts (arrows).

FIG. 6.232. Lymphatic cysts (star).
Lymphatics and Lymphoid Follicles

Lymphatic drainage starts with the central lacteal, which drains into the submucosal lymphatic plexus (Figs. 6.14 and 6.17). CD 38, a type II transmembrane glycoprotein involved in signaling and adhesion, is a novel marker of small intestinal lacteals (36). The broad proximal villi contain from two to five lacteals, whereas more distal thin villi contain only one. Lacteals measure 5 to 15 µm in diameter and run parallel to one another in the longitudinal direction of the villus. The endothelial lining contains gaps and has overlapping areas with adjacent endothelial cells. Chylomicrons and fatty droplets can pass through the gaps (Fig. 6.18) (37). The wall of the lacteal consists of endothelium and a reticulin fiber sheath to which smooth muscle fibers attach (Figs. 6.17 and 6.19) (38). Villi intermittently contract and shorten due to the activity of the smooth muscle cells. These contractions force lymph from the central lacteal into the basal lymphatics. The central lacteal is also completely surrounded by the subepithelial blood capillary network (Fig. 6.17). Lacteals anastomose with each other, which forms an expanded sinus. In the fasted state, lacteals are difficult to see.

FIG. 6.17. Dilated empty vascular space represents the central lacteal of this villus.
**FIG. 6.18.** The lipolytic products—fatty acids (FAs) and monoglycerides (MGs)—form small molecular aggregates with bile salts, called micelles. The micelles provide an ideal shuttle between the bulk water phase and the water–microvillus interface separated by the unstirred water layer. Phospholipids (PLs) and cholesterol (C) are also transported into the cell after hydrolysis in the lumen. Within the enterocytes, FAs and cholesterol are transported to the endoplasmic reticulum by fatty acid–binding proteins and a sterol carrier protein (SP). The assembled prechylomicron, composed of triglycerides and cholesterol esters, moves to the Golgi stacks, where a final glycosylation occurs. The triglyceride and cholesterol ester core is coated with a thin layer of protein to form the chylomicron. The chylomicrons then migrate to the lateral membrane, cross it by a process of membrane fusion, and enter the extracellular space. The chylomicrons pass through the basement membrane and interstitium of the lamina propria to enter the lacteals. The endothelial cells of the lacteals separate during feeding, facilitating chylomicron translocation. VLDL, very-low-density lipoprotein.

**FIG. 6.19.** Muscle fibers in the lamina propria. They are stained with an antibody to smooth muscle actin and counterstained with hematoxylin.

There are many blind-ending lymphatics in the upper part of the interfollicular area. These gradually fuse and form perifollicular lymphatic sinuses surrounding the lateral surfaces and bottoms of Peyer patch follicles. Between the perifollicular lymphatic networks and the interfollicular area are many high endothelial venules (HEVs) that connect to capillaries in the dome and follicle. The close association of HEVs with perifollicular lymphatics facilitates prompt drainage of fluid and keeps...
macromolecules from leaking out of HEVs during lymphocyte migration into the lymphatics. At the villous base, lymphatics empty into thicker lymphatics that then connect to form a flat, wide sinus (the intravillous lymphatic sinus). From the base of each sinus, several lymphatics descend perpendicularly to drain into submucosal lymphatics that run transversely beneath the muscularis mucosae to form a two-layer meshwork. The submucosal lymphatic plexus drains into large subserosal lymphatics (39) that drain into large conducting mesenteric lymphatics eventually flowing into the cisterna chyli.

Draining lymph nodes consist of the pancreatico lienal group lying along the splenic artery, the pyloric group lying along the gastroduodenal artery, and the superior mesenteric nodes. Small pancreaticoduodenal nodes lie scattered along the artery of the same name. The lymphatics also drain into the small pyloric nodes superiorly and preaortic lumbar nodes inferiorly. Pyloric nodes drain to the hepatic nodes along the common hepatic artery. Others drain to the root of the superior mesenteric lymph nodes, following the distribution of the superior mesenteric artery and draining the areas supplied by it. Small mesenteric lymph nodes lie along the vasa recta of the mesentery, adjacent to the bowel wall, and larger ones lie along the primary arcades and the intestinal arteries. There are about 200 mesenteric lymph nodes. Two major groups of ileocolic lymph nodes drain the terminal ileum and cecum: One near the bowel wall and another at the origin of the ileocolic artery.
Lymphocytic and Collagenous Enteritis

Lymphocytic duodenitis and enteritis are conditions in which the number of intraepithelial lymphocytes is increased in areas away from the lymphoid follicles. IELs are phenotypically heterogeneous. Most are cytotoxic T cells. As already noted, IELs can be increased in a number of disorders, most notably celiac disease (Table 6.40). We use the term lymphocytic enteritis/duodenitis when there is an increase in IELs in the absence of what appears to be celiac disease or other known causes for the change. These patients often have chronic diarrhea and/or malabsorption. The lesion may be accompanied by lymphocytic gastritis and lymphocytic colitis. The IELs lack the atypia present in enteropathy-associated T-cell lymphoma. We do state the various entities in which intraepithelial lymphocytosis occurs in an effort to help the gastroenterologist narrow down a specific etiology. Some patients are eventually shown to have celiac disease, but in other cases the cause never becomes evident.

We have also seen rare examples of severe collagenous enteritis accompanied by collagenous gastritis and collagenous colitis in the absence of celiac disease or a history of exposure to NSAIDs. The collagenous gastritis and colitis showed classic features, but the duodenum showed significant epithelial injury, subluminal collagen deposits, and severe fibrosis of the submucosa, a feature not typically seen in collagenous sprue (Fig. 6.198). The etiology of these changes is uncertain and the patients can become severely malnourished, requiring total parenteral nutrition.
Malabsorption Syndromes

Malabsorption results from premucosal, mucosal, and postmucosal diseases (Table 6.26). In premucosal diseases, defective digestion and absorption results from pancreatic or other systemic diseases and reduced bile salt concentrations. Mucosal defects result from anatomic or biochemical epithelial alterations, the presence of microorganisms, and inflammatory or infiltrative processes. Postmucosal diseases include malabsorption due to lymphatic obstruction, vascular disease, or congestive heart failure. Mucosal diseases are the most common disorders that a surgical pathologist is likely to encounter. Malabsorption syndromes affect patients of all ages and the age incidence depends on the etiology. Celiac disease, the most common cause of malabsorption in developed countries, is detected at almost any age. Infectious disease, lactase deficiency, and nutrient deficiencies are the most common causes of malabsorption in the developing world. In an ideal world, the pathologist should be supplied with relevant clinical information, including results of laboratory or serologic tests, before attempting to arrive at a specific diagnosis. Information that allows the pathologist to make the most useful interpretation of the biopsy specimens is listed in Table 6.27.

<table>
<thead>
<tr>
<th>TABLE 6.25 Host Factors that Influence Outcome of Travelers’ Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Digitalis</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>Immunodeficiency</td>
</tr>
<tr>
<td>Decreased gastric acidity</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Previous high susceptibility to travelers’ diarrhea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 6.26 Causes of Malabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate digestion</td>
</tr>
<tr>
<td>Postgastrectomy steatorrhea</td>
</tr>
<tr>
<td>Deficient activation of pancreatic lipase</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Pancreatic resection</td>
</tr>
<tr>
<td>Reduced intestinal bile salt concentration (with impaired micelle formation)</td>
</tr>
<tr>
<td>Parenchymal liver disease</td>
</tr>
<tr>
<td>Cholestasis (intrahepatic or extrahepatic)</td>
</tr>
<tr>
<td>Blind loop syndrome</td>
</tr>
<tr>
<td>Interrupted enterohepatic circulation of bile salts</td>
</tr>
<tr>
<td>Ileal resection or inflammation</td>
</tr>
<tr>
<td>Drugs that sequester or precipitate bile salts</td>
</tr>
<tr>
<td>Inadequate absorptive surface secondary to surgical procedures</td>
</tr>
<tr>
<td>Lymphatic obstruction</td>
</tr>
<tr>
<td>Intestinal lymphangiectasia</td>
</tr>
<tr>
<td>Whipple disease</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Primary mucosal absorptive defects</td>
</tr>
<tr>
<td>Inflammatory or infiltrative disorders</td>
</tr>
<tr>
<td>Regional enteritis</td>
</tr>
</tbody>
</table>
Small intestinal biopsies can be obtained by either a suction capsule or by forceps after endoscopic visualization. The suction capsule method requires radiographic guidance and is more expensive than the more commonly used forceps biopsy. Focal or patchy lesions can be visualized and biopsied by the endoscopic method. This technique also permits visualization of the gastrointestinal tract and avoids the radiation exposure associated with suction biopsy. However, capsule biopsies are still preferred over endoscopic biopsies by some gastroenterologists, particularly in children younger than 2 years of age.

Either the duodenum or the jejunum is an appropriate site for biopsy, but the biopsy should be procured no more proximal than the second part of the duodenum to avoid artifacts due to prominent Brunner glands or the nonspecific or peptic duodenitis commonly seen in the bulb and proximal duodenum. Unfortunately, more often than not the biopsies derive from the proximal duodenum, a site that is not ideal for the interpretation of villous architecture. It is important to note that the presence of a normal small intestinal biopsy does not exclude many malabsorptive conditions. Conditions with malabsorption and a normal small bowel villous architecture are listed in Tables 6.28 and 6.29.

**TABLE 6.27 Information To Be Provided to Pathologists Interpreting Small Bowel Biopsies for Malabsorption**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small intestinal biopsies can be obtained by</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Suction capsule</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Forceps biopsy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Endoscopic visualization</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Avoids radiation exposure</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Prefer duodenum</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Normal villous architecture</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Conditions included</strong></td>
<td></td>
</tr>
</tbody>
</table>
Certain factors optimize the diagnostic accuracy of the biopsy interpretation, including (a) careful biopsy handling and orientation, (b) provision of accurate clinical information to the pathologist, (c) an understanding by the pathologist of the spectrum of normal intestinal histology, and (d) familiarity with the spectrum of small intestinal diseases that may present as malabsorption.

**Handling of Small Intestinal Biopsies**

It is the clinician who decides when an intestinal biopsy needs to be obtained, but the pathologist and the clinician should work together to decide the best way to utilize and/or fix a given tissue specimen. Once it is decided that histologic interpretation will provide the optimal information, the optimal fixation can be decided, including a decision as to whether it is necessary to perform biochemical, microbiologic, electron microscopic, or immunophenotypic studies.

### TABLE 6.28 Malabsorption with Normal-appearing Proximal Jejunal Biopsy

| Dermatosis other than dermatitis herpetiformis |
| Pancreatitis |
| Alcoholism |
| Cirrhosis |
| Hepatitis |
| Iron deficiency anemia |
| Ulcerative colitis |
| Postgastrectomy without bacterial overgrowth |
| Malignancy outside the gastrointestinal tract |
| Cholera |
| Biliary obstruction |

### TABLE 6.29 Malabsorption with Normal Villi but with Diagnostic Features
### Disease Specific Histologic Features

<table>
<thead>
<tr>
<th>Disease</th>
<th>Specific Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetalipoproteinemia</td>
<td>Vacuolated enterocytes containing lipids involving upper two thirds of the villi; acanthocytes</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Noncaseating granulomas</td>
</tr>
<tr>
<td>X-linked immunodeficiency</td>
<td>Absent lamina propria plasma cells</td>
</tr>
<tr>
<td>Lipid storage disease</td>
<td>Vacuolated ganglion cells, capillaries, and macrophages</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Congo red–positive material in muscularis and blood vessels</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Pigmented vacuolated macrophages in lamina propria</td>
</tr>
<tr>
<td>Melanosis</td>
<td>Brown pigmented macrophages in lamina propria</td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
<td>Mast cell infiltrates in lamina propria</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Iron deposits in epithelium and macrophages</td>
</tr>
<tr>
<td><em>Mycobacterium avium-intracellulare</em></td>
<td>PAS-positive diastase-resistant macrophages containing acid-fast organisms</td>
</tr>
<tr>
<td>PAS, periodic acid–Schiff.</td>
<td></td>
</tr>
</tbody>
</table>

A nonfragmented, well-oriented biopsy specimen aids in establishing an accurate diagnosis. Immediate orientation by the gastroenterologist is ideal, but impractical in regular clinical practice. The optimal method of orienting the specimen is to put the base of the mucosa on filter paper and float it upside down in a bottle of fixative, allowing the specimen to float freely with the villi to hang down in a dependent way, thereby minimizing artifactual distortion. This facilitates a more accurate evaluation of the height of the villi and length of the crypts to determine the ratio of these two measurements. Appropriate orientation can also be achieved by scanning under a dissecting microscope. An initial impression of the villous architecture can also be obtained by this method. However, its applicability in clinical practice is limited. In most institutions, adequate orientation is achieved by asking an experienced histotechnologist to embed the biopsies on edge.

Although Bouin, Hollande, or B5 fixatives yield little shrinkage artifact and optimal nuclear detail, most pathology departments use neutral buffered formalin as the fixative. Adequate fixation for histology and superior preservation of DNA for ancillary studies is possible with formalin fixation. Formalin is also inexpensive and easy to discard. There is a lack of consensus among pathologists regarding the number of slides and levels that should be prepared and examined histologically. Examination of multiple sections and levels increases the likelihood of finding patchy changes and well-oriented villi.

### Evaluating the Small Intestinal Biopsy

When assessing a biopsy, it is usually best to follow a standardized format so as not to miss disease that may cause the underlying clinical syndrome (Fig. 6.184). This includes an examination of (a) villous height, crypt length, and overall architecture; (b) the lumen; (c) the surface epithelium; (d) crypts; (e) lamina propria constituents; (f) the presence of abnormal deposits; and (g) changes in other layers of the bowel wall. The histologic findings may allow the diagnosis of specific diseases (Table 6.30).

#### Villus Assessment

Villus assessment involves evaluating the ratio between crypt length and villous height. Since villi bend in various directions and their structure varies from slender fingerlike to leaflike, one should follow the rule that if a row of four fingerlike villi is present in any section, then the biopsy should be considered to be normal (Fig. 6.185) (485). In adults, villous height is approximately three or more times the length of the crypts, whereas in children this ratio is lower, more typically being 2:1. Villous height is also lower in the elderly. The duodenal crypt:villus ratio is 3:1 to 7:1, whereas the ileal crypt:villus ratio is 4:1. Villi overlying lymphoid aggregates are often stubby or absent, and should not be evaluated in these areas. Tangentially sectioned villi are a common source of misinterpretation since they appear broadened and shortened. Tangential sectioning is recognized by the presence of multilayered nuclei in the crypts or villi or fused villi (Fig. 6.186). Villous changes occur in three different patterns as outlined below.
FIG. 6.184. Diagram of the approach to interpreting a mucosal biopsy. A: Low-power assessment. During this assessment, one determines the overall architecture and whether the villi appear normal or demonstrate one of the mucosal patterns of injury such as the villous atrophy shown on the right. One also examines the biopsy for the presence of abnormal infiltrates, such as the amyloid shown in the submucosa and surrounding the blood vessel. Other assessments are noted in the diagram. B: At higher magnification, one examines the lumen for the presence of bacteria or parasites, as shown by the trophozoites and *Helicobacter pylori*. One looks at the epithelium for evidence of metaplasia such as the two foveolar epithelial cells illustrated on the right. One examines the epithelium for the presence of intraepithelial lymphocytes and the lamina propria for neoplasms or inflammatory infiltrates.

<table>
<thead>
<tr>
<th>TABLE 6.30 Specific Histologic Findings in Small Bowel Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
</tr>
<tr>
<td>Whipple disease</td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Intestinal lymphoma</td>
</tr>
<tr>
<td>Parasitic diseases</td>
</tr>
<tr>
<td>Fungal diseases</td>
</tr>
<tr>
<td>Malabsorption Syndromes</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Macroglobulinemia</td>
</tr>
<tr>
<td>Common variable hypogammaglobulinemia</td>
</tr>
<tr>
<td>Severe B₁₂ or folate deficiency</td>
</tr>
<tr>
<td>Intestinal lymphangiectasia</td>
</tr>
<tr>
<td>Acute radiation enteritis</td>
</tr>
<tr>
<td>Graft vs. host disease</td>
</tr>
<tr>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Transfusional siderosis</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Peptic duodenitis</td>
</tr>
<tr>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Collagenous sprue</td>
</tr>
<tr>
<td>PAS, periodic acid–Schiff.</td>
</tr>
</tbody>
</table>
**Villosus Atrophy and Crypt Hyperplasia.**

This is the most common type of injury pattern seen by surgical pathologists since it is typical of celiac disease, as well as many other disorders (Table 6.31). The villous enterocytes are the target of the injury and are shed more rapidly from the villi than are normal enterocytes, leading to a reduction in the number of enterocytes per unit area of intestinal mucosa. The enterocyte loss is accompanied by increased apoptosis. The epithelial cell loss results in a compensatory crypt hyperplasia with increased mitoses in the crypt bases. When epithelial replacement fails to keep up with the cellular loss, villous atrophy develops and the villus:crypt ratio decreases (Fig. 6.187). As villous height diminishes, the villi become morphologically abnormal. Shortened leaves and ridges replace the normal fingerlike villi, and in severe cases, mucosal mounds surrounding individual crypt openings are all that remain of the villi. Crypt length may increase to such an extent that the total mucosal height may remain normal despite marked villous atrophy. However, it is much more common to see a reduction in total mucosal thickness. (485). A system for grading the degree of villous atrophy is shown in Table 6.32. It is also useful to apply the Marsh classification in celiac disease (see below).
Malabsorption Syndromes

Hypoplastic type
- Malnutrition
- Untreated pernicious anemia
- Paneth cell deficiency
- Hypopituitarism
- Gluten-sensitive enteropathy
- Tropical sprue
- Radiation
- Chemotherapy
- Patients with tumors

Hyperplastic type
- Celiac disease
- Chronic trauma
- Urinary ileal conduits
- Areas adjacent to ulcers
- Patients with glucagonomas
- Following extensive small bowel resections

**TABLE 6.32 Grades of Villous Atrophy**

Mild
- Most villi appear branched, broadened, or fused; some remain normal
- Surface epithelium appears abnormal; loss of polarity; increased intraepithelial lymphocytes
- Increased mitoses outside the normal proliferative compartment
- Increased acute and chronic inflammatory cells in lamina propria

Moderate (partial villous atrophy)
- Villi broadened and shortened
- Cuboidal surface epithelium
- Large numbers of intraepithelial lymphocytes
- Increased mononuclear cells in the lamina propria

Severe (subtotal villous atrophy)
- Villi almost completely absent
- Marked mononuclear cell infiltrates
Villous Atrophy with Crypt Hypoplasia.

In this pattern of injury, the crypt is the primary site of damage. Crypt destruction leads to reduced numbers of cells that can mature and populate the villi. As a result, both villous and crypt atrophy occur. An abnormally low villous height and reduced crypt length give the impression of overall mucosal atrophy. However, the crypt:villus ratio may remain normal because the measurements of both portions of the crypt:villus axis are abnormal and reduced. This pattern is seen in advanced celiac disease, radiation damage, cytotoxic drug-induced injury, and vitamin B₁₂ and folic acid deficiency (Table 6.31).

Villous Hyperplasia.

This unusual pattern is seen following intestinal resection, in patients with glucagonomas, or in areas adjacent to ulcers or stenoses. It has also been recently described in hypertrophic eosinophilic gastroenteropathy (486). As in villous atrophy/crypt hypoplasia, the crypt length:villus height ratio tends to remain normal but, unlike villous atrophy/crypt hypoplasia, the overall height of the mucosa increases. The villi may appear thickened and the lamina propria may contain increased mononuclear cells.

Enterocyte Changes

Enterocyte changes include variations in cell shape and size as well as brush border alterations. Enterocytes may appear cuboidal or flattened due to a reduction in their height. They may also show nuclear irregularity, loss of polarity, basophilia, vacuolization, and syncytial formation. Regenerating superficial cells may become tufted. Neutrophils infiltrating the epithelium suggest inflammatory disorders such as Crohn disease, NSAID-
induced injury, or peptic inflammation. Increased intraepithelial lymphocytes suggest a primary villous abnormality mediated by T lymphocytes or infection. Stainable iron is seen in transfusional siderosis, hemochromatosis, rare abnormalities in iron transport, and AIDS. In abetalipoproteinemia, the enterocytes develop characteristic vacuoles. Foveolar metaplasia occurs in peptic duodenitis. The apical borders of the enterocytes or the intestinal lumen may contain parasites. Enterocytes may also contain viral inclusions. The collagen table immediately underlying the epithelium may appear thickened.

Severe vitamin B₁₂ and folic acid deficiency, acute radiation injuries, and chemotherapy all inhibit DNA synthesis and result in impaired epithelial replacement and macrocytosis (Fig. 6.125). Crypt mitotic activity is reduced, epithelial cells become enlarged, and villous abnormalities varying from mild to complete villous loss ensue. The macrocytosis may be irregularly distributed, varying from crypt to crypt or villus to villus. The mucosa reverts to normal following folic acid or vitamin B₁₂ therapy or cessation of drug therapy. Radiation changes may also revert to normal, depending on the radiation dose and the degree of underlying vascular damage.

**Crypt Changes**

Crypts elongate and exhibit increased mitoses in the hyperplastic pattern of mucosal atrophy (Fig. 6.188), contrasting with shortened crypts and macrocytosis in the hypoplastic pattern of mucosal atrophy. Crypt abscesses may signify the presence of peptic disease, drug injury, infection, or Crohn disease. Increased apoptosis characterizes chemotherapy-induced disease, graft versus host disease (GVHD), AIDS enteropathy, and T-cell–mediated cell injury. Other crypt changes include variations in the number of Paneth cells and endocrine cells. Morphologic abnormalities of Paneth cells occur in acrodermatitis enteropathica (487).

**Lamina Propria Changes**

The lamina propria should be assessed for alterations in the normal cell populations, for changes in the lymphatics and vessels, and for the presence of abnormal deposits. The character of any lamina propria inflammatory infiltrate may help to determine the etiology of the patient's malabsorption. It is important to note that a mild degree of lymphoplasmacytosis is normally seen in duodenal biopsies. A marked increase in chronic inflammatory cells occurs in many conditions including celiac disease, peptic duodenitis, drug injury, infection, and nonspecific chronic duodenitis. Acute inflammation suggests peptic duodenitis, drug-induced injury, and Crohn disease. Crypt abscesses indicate acute enteritis or Crohn disease. Eosinophils (Table 6.33) complicate Crohn disease as well as many other disorders. (There is a recently developed web site creating a database for gastrointestinal eosinophilic disorders at www.cincinnatichildrens.org/ eosinophils.) Viruses or parasites may be present. Mast cells increase in mastocytosis, allergic reactions, and Crohn disease. Plasma
Malabsorption Syndromes

but they become the predominant cell type in patients with celiac disease (Fig. 6.189). When they increase significantly enough to cause villous abnormalities, the diagnosis of a lymphoproliferative disorder should be considered. Increases in lymphocyte populations also complicate many disorders, including celiac disease, Crohn disease, autoimmune diseases, and some infections. When lymphocytes appear atypical, a lymphoma may be present. Lymphoid follicles may be encountered and, when associated with reduced numbers of plasma cells, suggest the presence of an immunodeficiency syndrome. The number of macrophages may be increased in nonspecific inflammatory reactions. If they form, granulomas, Crohn disease, *Yersinia* infection, Whipple disease, histoplasmosis, or a mycobacterial infection should be considered (Table 6.15). Increased mucosal macrophages also complicate storage diseases. Dilated lymphatics characterize lymphangiectasia and intestinal obstruction. Blood vessels become abnormal with radiation, amyloid, certain infections, and thrombotic or embolic disorders.

<table>
<thead>
<tr>
<th>TABLE 6.33 Intestinal Lesions Characterized by Prominent Eosinophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory fibroid polyps</td>
</tr>
<tr>
<td>Parasitic infections</td>
</tr>
<tr>
<td>Lymphomas</td>
</tr>
<tr>
<td>Hodgkin disease</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Allergic enteritis</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy</td>
</tr>
<tr>
<td>Magnesium deficiency</td>
</tr>
<tr>
<td>Vitamin E deficiency</td>
</tr>
<tr>
<td>Selenium deficiency</td>
</tr>
<tr>
<td>Peptic duodenitis</td>
</tr>
<tr>
<td>Inflammatory pseudotumors</td>
</tr>
<tr>
<td>Toxic oil syndrome</td>
</tr>
<tr>
<td>L-Tryptophan–associated myalgia syndrome</td>
</tr>
<tr>
<td>Hypereosinophilic syndrome and eosinophilic leukemia</td>
</tr>
<tr>
<td>Allografts with rejection</td>
</tr>
<tr>
<td>Cow's milk intolerance and related entities</td>
</tr>
<tr>
<td>Granulomas</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>Brown bowel syndrome</td>
</tr>
<tr>
<td>Hyperimmunoglobulinemia E</td>
</tr>
</tbody>
</table>
Malabsorption Syndromes

FIG. 6.189. Lamina propria infiltrates. A: Celiac disease with increased lamina propria plasma cells. B: Foamy histiocytes expanding the lamina propria and compressing the glands and crypts (arrows) in a patient with Mycobacterium avium-intracellulare.

It is also important to determine which cells types are not present in the biopsy. For example, an absence of plasma cells is a strong indicator of immunodeficiency disease, particularly common variable immunodeficiency. A decreased number of chronic inflammatory cells is seen in patients who are on steroids or who have other types of immunodeficiency.

Abnormal Acellular Infiltrates

Abnormal acellular infiltrates may lie in the lamina propria (Table 6.34). In collagenous sprue, collagenous duodenitis, or collagenous enteritis, a dense collagen band underlies the surface epithelium (Fig. 6.190). In Waldenstrom macroglobulinemia, amorphous eosinophilic masses lie within the lamina propria. Amyloidosis causes characteristic eosinophilic deposits.

<table>
<thead>
<tr>
<th>TABLE 6.34 Intestinal Mucosal Deposits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid light chains</td>
</tr>
<tr>
<td>Macroglobulins</td>
</tr>
<tr>
<td>Collagenous sprue and collagenous enterocolitis</td>
</tr>
<tr>
<td>Infantile systemic hyalinosis</td>
</tr>
<tr>
<td>Lipid proteinosis</td>
</tr>
<tr>
<td>Melanosis</td>
</tr>
<tr>
<td>Pseudomelanosis</td>
</tr>
<tr>
<td>Xanthomas</td>
</tr>
<tr>
<td>Storage diseases</td>
</tr>
<tr>
<td>Tangier disease</td>
</tr>
<tr>
<td>Fabry disease</td>
</tr>
<tr>
<td>Tay-Sachs and other gangliosidoses</td>
</tr>
<tr>
<td>Niemann-Pick disease</td>
</tr>
<tr>
<td>Wolman disease</td>
</tr>
<tr>
<td>Cystinosis</td>
</tr>
</tbody>
</table>
Submucosal Changes
The submucosa is not always present in intestinal biopsies, but if it is present it should be evaluated. Changes affecting the submucosa include fibrosis, changes in number or thickness of blood vessels, the presence of thrombi or emboli, alterations in lymphatics and nerves, and the presence of abscesses, granulomas, parasites, amyloid deposits, or neoplastic infiltrates. Of note, it is not uncommon to encounter ganglion cells in the muscularis mucosae or the lower mucosa in the proximal small intestine. Their presence should not be interpreted as representing neuronal dysplasia.

Metaplasias
Patients with small intestinal diseases may develop several types of metaplasia. Intestinal crypts may be replaced by gastric mucous cells of the pyloric type. This process almost always occurs just above the muscularis mucosae and is referred to as *pyloric metaplasia*. Its presence indicates that chronic damage has occurred. The cells of pyloric metaplasia are sometimes referred to as *ulcer-associated cell lineage cells*, or UACL cells (488). Three-dimensional reconstruction studies suggest that these cells form by extrusion from crypt bases with the formation of a coiled acinar component and an elongated ductular component that extends to the surface. Ulceration appears to be cue for the development of UACL cells, suggesting that the lineage has a reparative function. This is supported by the presence of epidermal growth factor/urogastrone and heat-shock protein in the acini (488). The metaplastic cells also produce trefoil factors that help restore mucosal integrity. Pyloric metaplasia can occur throughout the small intestine. In contrast to pyloric metaplasia, the superficial duodenal epithelium undergoes foveolar metaplasia as discussed earlier in this chapter.
Malabsorptive Diarrhea

Malabsorptive diarrhea is a newly discovered autosomal recessive disorder that presents as congenital malabsorptive diarrhea and an almost complete absence of intestinal endocrine cells. The patients present in the first few weeks of life with vomiting, diarrhea, and a severe hyperchloremic metabolic acidosis after the ingestion of standard cow's milk–based formulas. It results from loss of function mutations in the *NEUROG3* gene. The histology of the small intestine shows a normal architecture, but with a severe dysgenesis of the endocrine cells. Enterocytes, Paneth cells, and goblet cells appear normal and there is no intraepithelial or lamina propria infiltration of inflammatory cells. However, there is an almost complete absence of endocrine cells and the rare endocrine cells that are present appear morphologically abnormal. These features can be highlighted using chromogranin immunostains (564).

**FIG. 6.202.** Antigoblet cell antibody enteropathy. The pictures derive from the colon but identical features are seen in the small bowel. *A:* Low magnification of a biopsy that appears reactive with increased cellularity of the lamina propria. Note the complete absence of goblet cells. *B:* Higher magnification showing the details of the lamina propria infiltrate. The crypt contains several apoptotic bodies and mitoses but no goblet cells. *C:* Higher magnification of the base of the crypt showing an absence of endocrine cells and goblet cells along with apoptotic debris. The lamina propria eosinophils are also evident at this magnification.
Microvillous Inclusion Disease

Microvillous inclusion disease (MID) occurs worldwide in infants from varying ethnic backgrounds. The disease may have a familial component as it sometimes occurs in multiple siblings (543). A genetic etiology is further supported by the observation that the disease appears to cluster in infants of Navajo descent (544). The mechanism by which microvillous inclusion disease develops is unknown. The underlying defect is thought to represent a genetic alteration that leads to abnormal trafficking of membrane proteins to the apical surface of differentiated epithelial cells (545).

Infants with microvillous inclusion disease present with severe, watery diarrhea. In some cases, the diarrhea can be so watery that it can be mistaken for urine. The volume of stool output in this disease may exceed that seen in association with cholera (545). As a result, affected infants die of dehydration unless adequate fluid replacement is provided.

Both congenital and late-onset forms of MID exist. Patients with late-onset disease have a better prognosis than those with congenital disease. Patients with the congenital form of the disease present with protracted diarrhea from birth and develop mildly hyperplastic villous atrophy (546). The disorder is worsened by oral feeding. The prognosis is extremely poor in infants because they depend completely on total parenteral nutrition. They usually die before the age of 18 months from liver failure, sepsis, and dehydration. All patients experience decreased absorption of water, electrolytes, and nutrients. The only effective therapy is small intestinal or multivisceral transplantation (547).

Small intestinal biopsies show a diffuse villous atrophy with little or no crypt hyperplasia and normal or decreased numbers of inflammatory cells in the lamina propria (Fig. 6.199). Increased mitoses and apoptoses are present in the crypts (548,549). The relatively intact duodenal crypts appear shortened or mildly dilated. Enterocytes usually retain their columnar shape or are only slightly shortened. The epithelium lining the villi appears disorganized with focally piled-up cells. The surface microvilli are either completely absent or appear markedly shortened and disorganized. The apical cytoplasm contains numerous variably sized vesicular bodies and a few lysosomalike inclusions. Other enterocytes contain targetoid intracytoplasmic microvillous inclusions (Fig. 6.200). These have complete brush borders with a microvillous membrane, surface filamentous coat, microfilaments, and terminal webs. The microvillous inclusions lie close to the apical surface or deeper within the supranuclear cytoplasm. Microvillous inclusions occur in the epithelium of the duodenum, jejunum, ileum, colon, gastric antrum, gallbladder, and renal tubules.
The apical cytoplasmic inclusions can be highlighted by PAS, carcinoembryonic antigen (polyclonal), CD10, villin, or alkaline phosphatase staining (548,549). PAS and CD10 stains demonstrate a discontinuous brush border that is most severely disrupted over the atrophic villous apices. Prominent PAS and CD10 staining is seen in the surface enterocytes. Microvillous inclusions are not present in every cell, and sometimes multiple levels on multiple blocks must be examined in order to make the diagnosis.

**FIG. 6.199.** Microvillous inclusion disease. Children with this disorder manifest with microvillous atrophy and crypt hypoplasia. The brush border appears deficient. (Courtesy of E. Cutz, The Hospital for Sick Children, Toronto, Ontario, Canada.)
A definitive diagnosis depends on ultrastructural demonstration of intracytoplasmic microvillous inclusions and poorly developed brush border microvilli of small and large intestinal surface epithelium (Fig. 6.200) (546). Nearby nonenterocytic cells, such as goblet cells and Paneth cells, appear ultrastructurally normal. MID results from defective brush border assembly and differentiation.
Miscellaneous Lesions

*Duodenal pseudolipomatosis* histologically resembles pseudolipomatosis in the colon and stomach. Numerous clear, rounded, PAS-negative, variably sized vacuoles are present in the lamina propria. These vacuoles can cause expansion of the lamina propria with villous widening and separation of the crypts and Brunner glands (651). The lesion may mimic the fatty deposits seen in Whipple disease or lymphangiectasia. The use of special stains serves to distinguish among these possibilities.
Müllerian Lesions

Müllerian lesions may present as mural small intestinal masses. These include endometriosis, which is discussed in detail in Chapter 13, and endocervicosis. Endocervicosis is the presence of benign endocervical glands in ectopic sites. It most typically involves the pelvic peritoneum and lymph nodes but it can present in the small intestine. In this site it presents as a mural nodule that on cut surface consists of variably shaped glands filled with mucin and lined by endocervical-type epithelium. The glands are surrounded by fibrous tissue or the smooth muscle fibers of the muscularis propria. Endometrial-like stroma is not present. The epithelium, which lacks any nuclear atypia, has a CK7 + CK20- phenotype (650).
Nutritional Disorders

Severe nutritional deficiency can produce marked small intestinal abnormalities. The classic example is kwashiorkor. Malnutrition of this severity seldom occurs in developed countries, but less severe forms may be recognized after gastric surgery or in patients with chronic debilitating diseases. Malnutrition results from a lack of a suitable diet, faulty metabolism, and inadequate absorption of dietary constituents.

Kwashiorkor

Kwashiorkor is one of the most common pediatric illnesses in underdeveloped countries. It affects many African tribes, particularly in eastern and southern Africa, causing high morbidity and mortality. Nutrient malabsorption exacerbates the protein–caloric malnutrition, further damaging the gut, impairing immune competence, and increasing the risk of infections (Fig. 6.211). Diarrheal illnesses are common.

FIG. 6.210. Small intestinal xanthoma. A: Gross photograph showing the prominent submucosal expansion by a clear gelatinouslike fluid collection. B: Histologic features demonstrating the presence of a diffuse histiocytic infiltrate loosely arranged in the submucosa. C: Higher magnification demonstrating the histiocytic cells widely separated from one another.

The small intestinal abnormalities may be indistinguishable from untreated celiac disease. Histologically, the mucosa appears flattened. The crypts appear coiled with a relative increase in length and a lower than normal mitotic index. The crypts are not uniformly altered. They may be atrophic in some areas, whereas in others they appear normal or hyperplastic (581). Epithelial cell height decreases and the nuclei are arranged irregularly. The lamina propria becomes infiltrated with mononuclear cells and the basement membrane thickens (582). The presence of neutrophilic infiltrates suggests a coexisting infection. The
patients respond to a normal diet with concomitant improvement in the appearance of the intestinal mucosa.

**FIG. 6.211.** Kwashiorkor. *A:* Hypoplastic bowel in kwashiorkor visualized at the time of surgery. *B:* Severe villous atrophy.

### Vitamin E Deficiency and Brown Bowel Syndrome

Patients with vitamin E deficiency develop eosinophilic enteritis and brown bowel syndrome. Vitamin E deficiency occurs alone or it complicates other diseases (583,584). Brown bowel syndrome is characterized by lipofuscin deposits in the muscularis propria. Patients range in age from the 20s to the late 70s, with an average age of 51 years. They present with epigastric pain, mild diarrhea, and chronic malabsorption.

Grossly, the bowel is variably orange-brown and is often retrospectively described as being darker than usual by the surgeon. The segmental or diffuse brownish discoloration can be appreciated from the serosal aspect of the GI tract as well as on cut section. The disorder more commonly affects the small intestine and stomach, but it can involve the colon. Occasionally, it involves the entire GI tract. No correlation exists between the degree of pigmentation and the severity of the associated disease.

The mucosa usually appears normal. However, occasionally the villi appear blunted and there may be mild submucosal edema. There is usually no inflammation or fibrosis, although eosinophils may populate the submucosa and muscularis propria. A coarsely autofluorescent, granular, golden brown pigment, known as lipofuscin, fills the smooth muscle cells of the muscularis propria, muscularis mucosae, and vascular walls (Fig. 6.212). The pigment appears round to oval, often lying in a perinuclear or central cellular location. Individual pigment granules vary from barely visible to up to 2 to 3 µm in size. In areas of minimal involvement, the pigment is barely visible. In advanced cases, large lipofuscin deposits result in considerable smooth muscle cell loss. Macrophages also contain pigment, especially in the muscular layer. The pigment granules show various tinctorial qualities (Fig. 6.213; Table 6.43). The Fontana-Masson stain is the most sensitive stain for detecting the pigment, especially when the cells contain scant amounts of pigment. The pigments seen in brown bowel syndrome and in melanosis are compared in Table 6.44.
FIG. 6.212. Brown bowel disease. *A:* Low magnification of the lower portion of the mucosa, submucosa, and muscularis propria demonstrating a subtle change in the tinctorial qualities of the muscle cells on hematoxylin and eosin stain. *B:* Higher magnification of the muscularis propria showing a faint brownish tinge. *C:* Very high magnification demonstrating a fine granular golden brownish pigment within the nuclei.

Ultrastructurally, the cytoplasm of the muscle cells contains irregularly shaped, variably electron-dense, intracellular granular aggregates that concentrate centrally in a perinuclear location, sparing the peripheral cytoplasm (Fig. 6.214). Smooth muscle filaments end abruptly or stretch around the pigment. The deposits sometimes assume the shape of myelin figures enveloped by a single unit membrane. Mitochondrial alterations may be the source of the lipofuscin pigment and therefore the term *smooth muscle mitochondrial myopathy* may apply to the disorder (585).
Zinc Deficiencies and Acrodermatitis Enteropathica

Zinc deficiencies can be divided into two groups: A congenital form called acrodermatitis enteropathica and acquired forms. Acrodermatitis enteropathica is a rare autosomal recessive inborn error of metabolism that results in zinc malabsorption and severe zinc deficiency (586). Zinc is a normal constituent of more than 100 enzymes, and therefore zinc deficiencies have an overall detrimental effect on nucleic acid metabolism and protein and amino acid synthesis, eventually leading to growth arrest (587). Diarrhea and anorexia are common, especially in infancy. Growth retardation, alopecia, weight loss, and recurrent infections are prevalent in toddlers and schoolchildren. Without adequate therapy, the disease often leads to death. Biopsies of zinc-deficient individuals demonstrate focal villous shortening with mild crypt hyperplasia and a slight increase in mixed inflammatory cell infiltrates. Electron microscopy of Paneth cells demonstrates characteristic pleomorphic cytoplasmic inclusion bodies typical of acrodermatitis enteropathica. The ultrastructural abnormalities disappear on zinc therapy.

<table>
<thead>
<tr>
<th>Stain</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Golden yellow</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>Blue</td>
</tr>
<tr>
<td>PAS</td>
<td>Magenta</td>
</tr>
<tr>
<td>Sudan black</td>
<td>Black</td>
</tr>
<tr>
<td>Fontana-Masson</td>
<td>Brown</td>
</tr>
<tr>
<td>Thiazine dye</td>
<td>Intense basophilia</td>
</tr>
<tr>
<td>Nile blue sulfate</td>
<td>Blue</td>
</tr>
<tr>
<td>Ziehl-Nielson (AFB)</td>
<td>Pink</td>
</tr>
<tr>
<td>AFB, acid-fast bacillus; H&amp;E, hematoxylin and eosin; PAS, periodic acid–Schiff.</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 6.44 Brown Bowel Syndrome Versus Melanosis Coli
<table>
<thead>
<tr>
<th>Brown Bowel Syndrome</th>
<th>Melanosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Small bowel in smooth muscle cells</td>
</tr>
<tr>
<td>Associations</td>
<td>Cystic fibrosis, biliary atresia, vitamin E deficiency, hypoalbuminemia</td>
</tr>
<tr>
<td>Staining reactions</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>++++</td>
</tr>
<tr>
<td>Giemsa</td>
<td>+ + +</td>
</tr>
<tr>
<td>Alcian blue</td>
<td>-</td>
</tr>
<tr>
<td>Methenamine silver</td>
<td>+ + +</td>
</tr>
<tr>
<td>Acid-fast</td>
<td>+ +</td>
</tr>
<tr>
<td>Fontana</td>
<td>++++</td>
</tr>
<tr>
<td>Prussian blue</td>
<td>-</td>
</tr>
<tr>
<td>Oil red 0</td>
<td>+</td>
</tr>
</tbody>
</table>

PAS, periodic acid–Schiff.
Pneumatosis Intestinalis

Two forms of this relatively rare condition affect the intestines. The most common form affects patients with obstructive pulmonary disease and results from air dissection through the spaces around the great vessels and their abdominal branches. Patients generally do not have specific intestinal complaints. The second form of the lesion results from the presence of gas-forming bacteria in the bowel wall due to prior mucosal ulceration and secondary bacterial invasion. The second form commonly affects infants suffering from fatal colitis or ileocolitis, or adults with ischemic bowel disease (647). This form often runs a fulminant course. Gas-filled cysts occupy the subserosa, submucosa, or both (Figs. 6.235 and 6.236).

FIG. 6.233. Lymphangiectasia. The blood vessels and lymphatics in this specimen are markedly congested. The lymphatics appear as thin, white structures coursing along the blood vessels, which appear as congested, reddish structures.
Pneumatosis intestinalis (PI) involves the large and/or the small bowel and affects both infants and adults. The clinical features vary, depending on the underlying condition with which it is associated (647). Symptoms from the underlying disease may dominate the picture. Thus, in infants, coexisting necrotizing enterocolitis dominates the clinical and pathologic features. In adults, symptomatic patients develop diarrhea, flatulence, and excessive mucus in the stool. Other symptoms include constipation, rectal bleeding, passage of mucus via rectum, vague abdominal discomfort, abdominal pain, increased flatulence, urgency, malabsorption, and weight loss (647).

Partial bowel obstruction with luminal narrowing leads to symptoms similar to those seen in inflammatory bowel disease. Complications include volvulus, pneumoperitoneum, intestinal obstruction, intussusception, tension, pneumoperitoneum, hemorrhage, and intestinal perforation (647).

**TABLE 6.56 Secondary Causes of Intestinal Lymphangiectasia**
<table>
<thead>
<tr>
<th>Lymph node obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Filariasis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Carcinoma</td>
</tr>
<tr>
<td>Acute inflammation</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Eosinophilic enteritis</td>
</tr>
<tr>
<td>Mesenteric paracolitis</td>
</tr>
<tr>
<td>Infectious enteritis</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Fibrosis</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>Intraluminal precipitates</td>
</tr>
<tr>
<td>Hypobetalipoproteinemia</td>
</tr>
<tr>
<td>Extraluminal compression</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Malrotation</td>
</tr>
<tr>
<td>Retractile mesenteritis</td>
</tr>
<tr>
<td>Malignancy in lymph nodes</td>
</tr>
<tr>
<td>Lymph node infiltration</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Whipple disease</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Increased thoracic duct pressure</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Right heart disease</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td>Atrial septal defect</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
</tr>
<tr>
<td>Behçet disease</td>
</tr>
</tbody>
</table>
Pneumatosis Intestinalis

FIG. 6.235. Gross features of small intestinal pneumatosis intestinalis. The air-filled spaces are clustered on the left side of the photograph.

There are two major theories to explain PI. The mechanical theory suggests that gas is forced into the bowel by one or more several routes: (a) pulmonary, (b) traumatic, (c) mucosal breaks, (d) anastomoses, (e) obstructive, (f) increased pressure, and (g) increased peristalsis. Obstructive pulmonary disease may associate with PI via coughing and pulmonary hyperinflation with alveolar rupture. Air then dissects along large vessels into the retroperitoneum and along the mesenteric vessels into the bowel serosa. Steroids may play a significant role in the development of PI because corticosteroids induce atrophy of Peyer patches. The resultant mucosal defects allow intraluminal air to dissect into the submucosa or subserosa.

The second theory explains another form of the disease. Microorganisms may enter the bowel wall through mucosal defects caused by a breakdown in the mucosal defenses. Once in the tissue, they proliferate and produce gas. Support for the presence of intestinal infections comes from the documented high levels of hydrogen in the intramural gas. Organisms implicated in PI include *C. perfringens*, *E. aerogenes*, and *E. coli* (647). Organisms are not usually detectable in the tissues or around the gas-filled cysts.

Usually, when one has the opportunity to study the gross features of PI it is because the PI complicates another disorder that requires resection. Therefore, the gross features are modified by the underlying disease. The gross appearance depends on the location of the cystic spaces and the underlying disease. PI presents as localized or diffuse cysts involving the mucosa, submucosa, and serosa (Fig. 6.237). Examination of the external surface of the bowel discloses the presence of subserosal cysts. They usually lie near the mesenteric border. Cysts often lie on loops of dilated bowel and range in size from a few millimeters to several centimeters. They can occur singly or in clusters, occasionally appearing like serosal bubbles. Predominantly submucosal cysts may not be appreciated on either the serosal or mucosal surfaces and the bowel may feel crepitant on palpation. They may also cause intraluminal mucosal bulging (Fig. 6.236). Cross sections demonstrate a honeycombed appearance of thin-walled, collapsed cysts ranging in size from 1 mm to several centimeters if the bowel is received fresh.

The cysts can be single or multiple, sessile or pedunculated. When the cysts are multiple, they do not intercommunicate. Histologically, PI begins as simple, generally unlined air-filled submucosal spaces (Fig. 6.237). Rarely, the cysts appear to be partially lined by an endothelial layer. Later, inflammatory cells, including leukocytes, eosinophils, plasma cells, lymphocytes, foreign body cells, and macrophages, surround the cysts. Granulomas form around the cyst (Fig. 6.238). The inflammation and giant cell formation most likely represent a reaction to the intestinal intraluminal contents that find
their way into the mucosa and submucosa. The mucosa usually appears normal, although it may be thinned over a submucosal cyst. As the lesions fibrose, the cysts decrease in size and eventually disappear.

**FIG. 6.236.** *Pneumatosis intestinalis.* The lacy appearance seen on the cut (A) and uncut (B) surfaces is secondary to the gas-filled cysts.
Radiation Injury

The small intestine is more sensitive to radiation injury than is the large intestine. The degree of radiation damage reflects many factors (Table 6.11) (286). Patients who receive radiation often have acute but temporary diarrhea, nausea, vomiting, and abdominal cramps. These symptoms usually subside within weeks, due to rapid mucosal regeneration. A small percentage of patients experience a chronic deteriorating disease course, referred to as severe late radiation enteropathy. It is characterized by diarrhea, pain, malabsorption, small bowel obstruction, acute or chronic GI bleeding, intestinal perforation, and pseudo-obstruction. The intestinal pseudo-obstruction develops secondary to neuromuscular damage, vascular obliteration, and intestinal wall fibrosis (286).

TABLE 6.11 Factors that Enhance Radiation Injury

<table>
<thead>
<tr>
<th>Radiation doses given ≥45,000 rads</th>
</tr>
</thead>
<tbody>
<tr>
<td>The way radiation is given (accelerated fractionation increases the incidence of late radiation enteropathy)</td>
</tr>
<tr>
<td>Presence of other disease</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Severe atherosclerosis</td>
</tr>
<tr>
<td>Previous intestinal injury</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Prior surgery</td>
</tr>
<tr>
<td>Prior radiation</td>
</tr>
<tr>
<td>Adriamycin and other chemotherapeutic affects</td>
</tr>
<tr>
<td>An empty intestinal lumen during radiation therapy</td>
</tr>
</tbody>
</table>

The severity of the acute radiation enteritis determines the severity of subsequent chronic disease. The outcome is mediated by mucosal and vascular damage as well as by host defenses to intraluminal antigens and pathogens. The damage is usually most severe in those parts of the small intestine that are fixed because this part of the gut receives a constant maximal radiation dose. Therefore, the duodenum, proximal jejunum, and terminal ileum are most likely to show maximum damage. Patients with acute ischemic damage have an intestinal mucosa that appears reddened and inflamed, with edema and fibrinous peritonitis. The serosa acquires a matte-white appearance as serosal adhesions develop. Eventually the bowel appears markedly thickened, fibrotic, and indurated with stricture formation (Fig. 6.127). The bowel proximal to the strictures distends. The abnormal bowel merges imperceptibly with the noninjured bowel, making it difficult to identify the exact junction of the injured and uninjured bowel.
FIG. 6.127. Radiation stricture of the small bowel. The bowel superficially resembles Crohn disease (CD), except for the fact that the bowel wall is not as thickened as commonly seen in patients with CD and the specimen lacks creeping fat.

Acute radiation effects are predominantly mucosal in nature and range from mild epithelial degeneration to massive intestinal necrosis and ulceration. Endothelial apoptosis is the primary lesion initiating the bowel damage. Vascular damage ranges from isolated endothelial cell injury to complete capillary and venule obliteration. Capillary endothelium swells and the vessels become telangiectatic. Increases in vascular permeability immediately following radiation lead to edema and fibrin deposition in the interstitial spaces and blood vessel walls. The vascular damage leads to epithelial stem cell dysfunction (287). The acute epithelial changes vary in severity. In some cases, one sees little damage, whereas in others, frank ulceration develops. Morphologic changes include loss of the columnar shape and nuclear polarity of enterocytes, epithelial degeneration, mucosal epithelial denudation, nuclear pyknosis and karyorrhexis, crypt disintegration, mucosal edema (Fig. 6.128), enlarged bizarre nuclei, absent mitoses, mucin depletion, prominent apoptoses in the crypt bases, and crypt abscesses with prominent eosinophilic infiltrates. The decreased mitotic activity occurs early and persists for at least 72 hours following the radiation event. Because of the decreased mitotic activity, there is no cellular migration from the crypt bases to replace cells lost from the mucosal surface. This results in surface erosions, ulcerations, and mucosal atrophy. Paneth cells are often unusually prominent. There is also a relative increase in the number of endocrine cells. Whether this represents a true hyperplasia or an apparent increase in endocrine cells due to endocrine cell sparing from the radiation remains unclear. The lamina propria becomes depleted of lymphocytes and is infiltrated by neutrophils. Later other chronic inflammatory cells appear. Because the mechanisms of radiation injury resemble those seen in ischemia and reperfusion injury, it is not surprising that the histologic features of both ischemia and acute radiation injury overlap. After 7 to 10 days of therapy the epithelial surface may be reduced by up to 40%.

Following the radiation injury there is an increase in the proliferative activity in the crypts, a process regulated in part by increased expression of EGF and TGF-α and -β (288). Areas of villous hypertrophy may surround localized ulcers. Complete structural recovery usually occurs within 2 to 3 weeks of cessation of the therapy but villous atrophy and abnormal crypts may persist, resulting in subclinical malabsorption. Distorted villi and ulcerations are characteristic of advanced injury. TGF-β is produced by the epithelium, inflammatory cells, fibroblasts, endothelium, and smooth muscle cells and contributes to the generation of chronic radiation enteropathy (289). Chronic radiation enteropathy is a progressive disease resulting from the underlying vascular damage that develops months to years following the radiation event. Characteristic changes include fibrosis and hyalinization of the submucosal and serosal connective tissues, the presence of telangiectasia, and hyalinized blood vessels with subendothelial foam cells and mucosal damage (Fig. 6.129). Numerous enlarged,
atypical mesenchymal cells with bizarre hyperchromatic nuclei lie scattered throughout the fibrotic submucosa and serosa. These “swallow-tailed” or “radiation fibroblasts” contain abnormal nuclei, sometimes simulating nuclear inclusions. Muscular arteries develop marked intimal thickening with fibrosis and luminal narrowing that leads to endarteritis obliterans. Smaller vessels exhibit marked hyaline sclerosis and obliterative vasculitis. Progressive vascular damage, with increasing intimal fibrosis, leads to ischemia. Complications of the ischemia include ulcers, strictures, perforation, fistulae, malabsorption, and pseudo-obstruction. Other changes include atrophy of the muscularis propria with interstitial fibrosis. Fibrosis and parenchymal atrophy subsequently replace the tissues and are characteristic of late phases of the disease. Epithelial displacement into the submucosa produces enteritis cystica profunda. Lymphangiectasia results from lymphatic obstruction, presumably due to the submucosal fibrosis. Neuronal proliferation, altered ganglia, and muscular changes are prominent in patients who present with pseudo-obstruction (290). The abnormal motility may facilitate bacterial colonization of the bowel (291). In addition, strictures predispose to intestinal

stasis and the blind loop syndrome. These effects may be augmented in patients with hypochlorhydria secondary to the effects of gastric radiation injury and in those who are partially immunosuppressed by concomitant chemotherapy.

FIG. 6.128. Acute radiation damage. A: The mucosa appears hemorrhagic, necrotic, and telangiectatic. The villi are being sloughed. B: High-power magnification demonstrates the severe hemorrhagic necrosis involving the lamina propria. If one did not have the history of radiation, the features could be interpreted as being ischemic in nature. They share a common pathophysiology (see text).
FIG. 6.129. Chronic radiation damage. A: The mucosal surface appears mildly distorted. The submucosa is markedly thickened and fibrotic. B: High-power magnification demonstrates the presence of small vessels, a fibrotic submucosa, and atypical fibroblasts.

Because of the important role played by TGF-β overexpression in the induction of the chronic damage, the chronic changes may be preventable by the use of interferon treatment (292). Prophylactic use of EGF may also reduce ischemic injury (293). Additionally, the endothelial cell damage can be prevented by treatment with basic fibroblast growth factor (287).
References


P.459


file:///F|/Gastro/Chapter%206%20References.htm (1 of 28)2/4/2009 2:05:42 PM
25. Magnusson EK, Sjernstrom I: Mucosal barrier mechanisms. Interplay between secretory IgA, (sIgA), IgG, and mucins on the surface properties and association of salmonellae with intestine and granulocytes. *Immunology* 1982;45:239.
References


References


P.462
References


References

Child 1960;99:833.


References


351. El-Maraghi NR, Mair NS: The histopathology of enteric infection with Yersinia pseudotuberculosis. *Am J Clin
References


397. Schafer MP, Dean GE: Cloning and sequence analysis of an H*-ATPase-encoding gene from the human


P.467

References


References


P.468

534. Pink IJ, Creamer B: Response to a gluten-free diet of patients with the coeliac syndrome. Lancet 1967;1:300.


References

2003;56:629.
References


608. Washington K, Stenzel TT, Buckley RH, Gottfried MR: Gastrointestinal pathology in patients with common...
References

633. Yamada M, Hatakeyama S, Tsukagoshi H: Gastrointestinal amyloid deposition in AL (primary or myeloma-


638. Hearst J, Elliott K: Identifying the killer in cystic fibrosis. Understanding the genetic defects underlying cystic fibrosis is only half the battle. Identifying the specific bacterium infecting CF patients is just as important. *Nature Med* 1995;1:661.


Small Intestinal Lesions Resembling Graft Versus Host Disease

Changes similar to those found in GVHD sometimes occur in immunosuppressed or immunodeficient patients, without transplants or transfusions. The lesion affects any portion of the GI tract but it most often involves the intestines. Patients have various associated diseases including lymphoma, leukemia, combined immune deficiency, severe T-cell deficiency, and Hodgkin disease (625,626). The signs and symptoms resemble those developing following bone marrow transplantation but they occur more rapidly and tend to be associated with a higher fatality rate. A novel T-lymphocyte population has been identified in patients with combined immunodeficiency and features of GVHD (627).

![Figure 6.220. Apoptosis in graft versus host disease. Note the presence of prominent apoptotic bodies in the bases of the crypts (arrows).](image)

**TABLE 6.51 Situations Associated with Increased Apoptosis**

<table>
<thead>
<tr>
<th>Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft vs. host disease</td>
</tr>
<tr>
<td>Rejection</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Zinc deficiency</td>
</tr>
<tr>
<td>Fasting</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>AIDS enteropathy</td>
</tr>
<tr>
<td>Thymoma</td>
</tr>
<tr>
<td>Certain drugs</td>
</tr>
<tr>
<td>Viral infections</td>
</tr>
<tr>
<td>Cell-mediated immune reactions</td>
</tr>
<tr>
<td>Autoimmune enterocolitis</td>
</tr>
</tbody>
</table>

Histologically, patients demonstrate subtotal villous atrophy during a period of diarrhea. A marked mixed inflammatory
Small Intestinal Lesions Resembling Graft Versus Host Disease

infiltrate develops associated with an unusually high number of neutrophils in the lamina propria. The crypt epithelium shows single-cell necrosis (apoptosis) and numerous intraepithelial neutrophils with crypt abscesses. Lymphoid nodules are also present in the lamina propria. Mast cells may be seen. The vast majority of the cells within the lymphoid nodules manifest the T-cell phenotype and are UCHLI+. A few UCHL1+ cells are also found within the crypt epithelium. Rare B cells are present; plasma cells are absent. Patients, especially those with combined immunodeficiency, show this B-cell absence.

FIG. 6.221. Mucosal cast. Gross photograph of a ropy structure shed from the intestines of a transplant patient. This represented a mucosal cast.
Small Intestinal Mucosal Barrier

The mucosal surfaces are regions where individuals and the environment meet. The gut mucosa is in continuous contact with food antigens, the enteric commensal bacteria that constitute the normal gut flora, and potential pathogens that enter the host through the intestine. The upper intestinal bacterial count is normally low and it increases as one progresses distally. Bacterial numbers are kept low by intestinal motility, mucus, and the antibacterial effects of pancreatic and biliary juice and gastric acid (Fig. 6.4). This resident microflora maintains a stable environment and eliminates pathogenic organisms by producing antimicrobial substances and short-chain fatty acids. It also stimulates mucosal epithelial growth (19).

The small intestinal mucosa forms a barrier to the unimpeded movement of antigens, pathogens, and other noxious substances from the exterior world to the internal environment. A single layer of columnar epithelium, held together by tight junctions, lies on an intact basement membrane. Intercellular tight junctions, which are impermeable to large molecules and bacteria, help maintain epithelial integrity and prevent the entry of foreign material. The tight junctions are specialized membrane domains at the apical pole of the cells that not only create a primary barrier to prevent paracellular transport of solutes (barrier function), but also restrict the lateral diffusion of membrane lipids and proteins to maintain cellular polarity (gate function) (20). The tight junction complexes form a complete ring around the apical pole of the cells. Tight junction permeability is plastic and can be altered by extracellular stimuli including bugs and drugs (21). An unstirred layer, which measures 400 to 500 \( \mu \text{m} \) in thickness, covers the epithelium. Molecules diffuse into this layer (22).
The proximal duodenum transports bicarbonate into an adherent mucus layer in a manner similar to that seen in the stomach, providing a protective barrier from damage caused by pepsin and acid. The alkaline pH environment beneath the mucus layer acts as a buffer and a lubricant. The mucus protects against microbial adherence to the epithelium and resists digestion by intraluminal enzymes. Mucus secretion is stimulated by immune complexes, chemical agents, soluble mediators, histamine, lymphokines, and neurotransmitters (23). Nitric oxide plays an important role in modulating epithelial fluid secretion (24). The secreted mucus contains albumin; immunoglobulin, particularly secretory IgA; α1-antitrypsin; lysozyme; lactoferrin; and EGF. Secretory IgA in the intestinal lumen acts in concert with nonspecific host defenses, including mucin, bacteriocidins, defensins, and lytic cells (25), to protect the host by neutralizing or excluding antigens, toxins, and organisms (26). Granulocytes, macrophages, and Paneth cells act as intramucosal phagocytes.

Intestinal epithelium is vulnerable to enteric pathogens that express specific adhesion molecules, enzymes, and other specialized mechanisms for colonizing epithelial surfaces as described in a later section. As a result, the intestines have evolved protective mechanisms in which the lamina propria reacts to microbes and other foreign material by mounting an immunologic barrier. This immunologic barrier includes the gut-associated lymphoid tissues and the systemic immune system. The mucosa is at the leading edge of the immunologic barrier. The intestinal mucosa contains more lymphoid cells and produces more antibodies than any other site in the body. These immunologic responses lead to a cascade of events aimed at inactivating and removing offending antigens or microbes. Specific immunologic responses include IgA production and lymphocyte sensitization in Peyer patches or in the epithelium (27). Enterocytes can present antigen, express secretory component, and transport immunoglobulin into the intestinal lumen. Enterocytes also can produce and secrete interleukin-like substances that activate T cells in response to luminal antigens (28). Secretory IgA coats microbes and toxins, inhibiting mucosal attachment or interaction, and facilitates their rapid expulsion. IgA also mediates antibody-dependent, cell-mediated cytotoxicity resulting in pathogen killing and also activates complement, mainly via the alternate pathway (29).

Intestinal mucosal function is immature in the newborn. Immaturity of the microvillous membrane, low outputs of gastric acid, decreased proteolytic activity, and altered mucin production all contribute to an impaired intestinal barrier that facilitates macromolecular uptake and sepsis. Intestinal immune mechanisms at this stage are also underdeveloped (Fig. 6.5). IgA concentrations in saliva, stool, and serum are low compared to those seen in adults (30). As a result, neonates are particularly prone to develop enteric infections. After 1 month of age, IgA assumes its role as the main immunoglobulin in the lamina propria. The importance of GI immune defenses is dramatically illustrated in immunocompromised patients, especially those with AIDS, who become overwhelmed by GI infections. Because of the importance of small intestinal barrier functions and transport, small intestinal injury must be repaired as rapidly as possible. The GI mucosa heals by both restitution and proliferation (31). The extracellular matrix,

P.279
Small Intestinal Mucosal Barrier

pericryptal myofibroblasts, and growth factors regulate these processes. Initial phases of mucosal restitution involve rapid migration of linked sheets of enterocytes from the epithelium shouldering the wound over the denuded basement membrane across mucosal defects. Once the migrating cells are free of the shoulder of the wound, they begin to proliferate (Fig. 6.6). Matrix–cytoskeletal links participate in this cellular migration. Surviving epithelial cells phagocytose adjacent dead cells. If the progenitor cells are damaged, as in radiation injury, atrophy results. Conversely, if the surface cells are damaged, cell proliferation increases and the cells migrate out of the crypt at a faster rate, leading to a population of immature cells lining the crypts.

FIG. 6.5. Lamina propria of a newborn. The hypocellular lamina propria contains few lymphocytes and plasma cells.
Systemic Mastocytosis

Systemic mastocytosis is characterized by mast cell proliferation in skin, bones, lymph nodes, and parenchymal organs. Patients usually present with classic dermatologic findings of urticaria pigmentosa. Typical symptoms include pruritus, flushing, tachycardia, asthma, and headache, all thought to result from the release of histamine from the mast cells (612). Fifty to eighty percent of patients have GI symptoms, including peptic ulcers, malabsorption, steatorrhea, nausea, vomiting, copious watery diarrhea, and abdominal pain (613). The clinical features may mimic inflammatory bowel disease. These features occur secondary to gastric hypersecretion or result from the release of histamine and prostaglandins from mast cells. Symptoms are often induced by alcohol consumption. The hyperhistaminemia produces gastric hypersecretion, which can be as marked as that seen in Zollinger-Ellison syndrome (613). Gastric acid levels correlate with the degree of histaminemia and with the presence of acid peptic disease, including peptic duodenitis (613). Mast cell–mediated events include increased intestinal permeability and altered smooth muscle function. Malabsorption occurs secondary to mucosal infiltration.

Histologic changes include mucosal villous atrophy, marked submucosal edema, and clumps of mast cell infiltrates in the lamina propria (Fig. 6.218). Large numbers of mast cells infiltrate the lamina propria, muscularis mucosae, and submucosa, with aggregates of mast cells within the gland lumens and evidence of glandular destruction. Prominent mast cell degranulation is also present. Eosinophils may also be seen. Toluidine blue or Giemsa stains highlight the presence of the mast cells. Mast cell lesions also stain with antibodies to tryptase and CD68. Neoplastic mast cells have aberrant expression of CD2 and CD25 and have a codon 816 c-kit mutation (614).

**FIG. 6.218.** Macrocytosis. A: High magnification of an intraluminal collection of mast cells. B: High magnification showing the presence of large numbers of degranulating lamina propria mast cells.
Thermal Injury

Erosive duodenitis and duodenal ulcers develop in severely burned patients (Fig. 6.126). The inflammatory lesions have an ischemic basis and their pathophysiology resembles that seen in stress ulcers. Gastroduodenal erosions occur within 5 hours of injury (285). Within the first 24 hours the mucosal barrier breaks down, mediated in part by transient intestinal hypoperfusion and increased intestinal permeability. Early ischemia results in enterocyte membrane disruption. Bacterial and luminal endotoxins gain access to the systemic circulation. Another form of thermal injury occurs in GI gunshot wounds. Coagulation necrosis develops along the bullet path, due to the heat.

FIG. 6.126. Curling ulcers in a patient who was caught in a house fire. The arrows mark the gastroduodenal junction. Several large geographic ulcers are present within the duodenum, as evidenced by the dark, irregular, geographic areas. Additionally, smaller punctate ulcers (double arrows) are present. The duodenal mucosa also demonstrates marked hyperemia.
Chapter 7

Epithelial Tumors of the Small Intestine

General Features of Small Intestinal Tumors

Benign and malignant small intestinal tumors are uncommon. Most small bowel malignancies are metastases from tumors arising elsewhere (1). Primary small bowel tumors constitute only 1% to 3% of all primary gastrointestinal (GI) malignancies (1,2,3,4) and <2% of all human malignancies (1). The major malignant tumors that arise in this location include adenocarcinomas, lymphomas (discussed in Chapter 18), carcinoid tumors (discussed in Chapter 17), and GI stromal tumors (discussed in Chapter 19). Data from the Surveillance, Epidemiology, and End Results (SEER) Program found that small bowel tumors had an annual average incidence rate of 9.9 per million people (5). Carcinoid tumors and adenocarcinomas were the most common histologic types with an average annual incidence rate of 3.8 and 3.7 per million people, respectively, followed by stromal tumors and lymphomas (5). The small intestine also gives rise to a number of benign lesions including Brunner gland lesions, adenomas, and a variety of polyps that are often a component of a polyposis syndrome (see Chapter 12). Table 7.1 shows the World Health Organization (WHO) classification of small intestinal tumors (6).

Proliferative Brunner Gland Lesions

Enlarged Brunner gland lesions present endoscopically as a submucosal mass. The enlargement most commonly results from hyperplasia, although rare neoplastic lesions also develop (Fig. 7.1). Brunner gland hamartomas and true Brunner gland adenomas do exist, but adenomas are much less common than reported in the literature. The lesions generally affect older individuals and arise on the posterior wall of the duodenum. They are usually detected at the time of upper endoscopy, although they occasionally become symptomatic causing vomiting, bleeding, or obstruction. Both hamartomas and adenomas usually retain their lobular architecture (Fig. 7.1). Hamartomas have fibrous septa coursing between the hyperplastic lobules. They may be accompanied by ciliated cysts and prominent adipose tissue (7). Prominent ducts can be seen as well. The diagnosis of Brunner gland adenomas is based on both architectural and cytologic features. There may be mild architectural distortion and the glands appear more crowded than usual (Fig. 7.2). Cytologically, the nuclei are enlarged and they may be overlapping. These neoplastic cells merge imperceptibly with more normal-appearing epithelial cells. Mitotic figures are rare. This lesion may associate with peptic duodenitis (Fig. 7.2). Rarely, Brunner gland adenomas develop atypical hyperplasia (Fig. 7.2) or undergo malignant transformation (8,9).

Nonneoplastic Intestinal Epithelial Polyps

A number of nonneoplastic polyps develop in the small intestine, including Peutz-Jeghers polyps and juvenile polyps. These are often part of a polyposis syndrome and occasionally these polyps contain areas of malignancy. They are discussed in Chapter 12. Lymphoid polyps can also develop in the small intestine and they are discussed in Chapter 18.

Intestinal Adenomas

Small intestinal adenomas are rare, constituting <0.05% of all intestinal adenomas (10). Since most adenomas arise near the ampulla of Vater, it is postulated that carcinogens or cocarcinogens present in bile or pancreatic secretions play a role in their development. Bile salts are believed to act as tumor promoters, especially when combined with acid from the stomach (11). However, no specific dietary substance, chemical, or toxin is a demonstrated etiologic agent responsible for adenoma production. The only clear risk factor for developing small intestinal adenomas is the presence of one of the genetically inherited polyposis syndromes (see Chapter 12) or the presence of an underlying condition (Table 7.2). A rare example of fraternal sisters with adult polycystic kidney disease and ampullary adenomas also raises the possibility of a genetic link between autosomal dominant polycystic kidney disease and ampullary adenomas (12).

<table>
<thead>
<tr>
<th>TABLE 7.1 World Health Organization Classification of Small Intestinal Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histologic Type</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Carcinoid Tumor</td>
</tr>
<tr>
<td>GI Stromal Tumor</td>
</tr>
<tr>
<td>Brunner Gland Lesion</td>
</tr>
<tr>
<td>Nonneoplastic Polyp</td>
</tr>
<tr>
<td>Intestinal Adenoma</td>
</tr>
</tbody>
</table>

P.472
### Epithelial tumors

<table>
<thead>
<tr>
<th>Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular</td>
</tr>
<tr>
<td>Villous</td>
</tr>
<tr>
<td>Tubulovillous</td>
</tr>
</tbody>
</table>

Intraepithelial neoplasia (dysplasia) associated with chronic inflammatory diseases

<table>
<thead>
<tr>
<th>Low-grade intraepithelial neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade intraepithelial neoplasia</td>
</tr>
</tbody>
</table>

Carcinoma

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Signet ring cell carcinoma</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
</tr>
</tbody>
</table>

Carcinoid (well-differentiated endocrine neoplasm)

<table>
<thead>
<tr>
<th>Gastrin cell tumor, functioning (gastrinoma) or nonfunctioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin cell tumor</td>
</tr>
<tr>
<td>EC-cell, serotonin-producing tumor</td>
</tr>
<tr>
<td>L-cell, glucagon-like peptide, and PP/PYY-producing tumor</td>
</tr>
</tbody>
</table>

Mixed carcinoid–adenocarcinoma

Gangliocytic paraganglioma

Others

### Nonepithelial tumors

<table>
<thead>
<tr>
<th>Lipoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
</tr>
</tbody>
</table>

Others

### Malignant lymphomas
Immunoproliferative small intestinal disease (includes α-heavy chain disease)
Western-type B-cell lymphoma of MALT
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Burkitt lymphoma
Burkitt-like/atypical Burkitt lymphoma
T-cell lymphoma
- Enteropathy associated
- Unspecified
Others

Secondary tumors
Polyps
Hyperplastic
Peutz-Jeghers
Juvenile

MALT, mucosa-associated lymphoid tissue.

Patients with small intestinal adenomas range in age from 30 to 90 years, with a peak incidence in the 7th decade. Patients with adenomas are generally younger than those with carcinomas or adenomas containing carcinoma (13). Adenomas affect both sexes equally. Many small adenomas remain asymptomatic, only to be discovered incidentally at the time of upper endoscopy for other reasons. They may also be found in those undergoing endoscopic surveillance because they have a polyposis syndrome or have a family history of a polyposis syndrome. Large lesions become symptomatic. Ampullary adenomas present as biliary colic, biliary obstruction, cholangitis, jaundice, pancreatitis, and/or pain (10). Partial or total intestinal obstruction, low-grade bleeding,
cramps, vomiting, nausea, anorexia, weight loss, intussusception, or hemorrhage may also develop depending on adenoma size and location. Villous adenomas tend to be larger and are more likely to become symptomatic than smaller tubular adenomas. Rare patients with secretory villous adenomas present with mucorrhea and electrolyte imbalances (14).

### TABLE 7.2 Conditions That Predispose Patients to Develop Small Intestinal Epithelial Neoplasms

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>α-Chain disease</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Adenomas</td>
</tr>
<tr>
<td>Familial polyposis</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
</tr>
<tr>
<td>Multiple cancer syndrome (familial cancer syndrome)</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer syndrome</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>Duplications</td>
</tr>
<tr>
<td>Heterotopic pancreas</td>
</tr>
<tr>
<td>Meckel diverticulum</td>
</tr>
<tr>
<td>Longstanding ileostomies</td>
</tr>
<tr>
<td>Ileal pouches</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>Smoking and alcohol use</td>
</tr>
<tr>
<td>Previous radiation</td>
</tr>
</tbody>
</table>
Chapter 7

FIG. 7.2. Brunner gland adenoma. A: There is a large expansion of the Brunner gland epithelium. Note that the fibrous septa are lacking in some areas. B: The lack of the septa is more obvious in this slightly higher power picture. There is no lobulation present in this area. The overlying mucosa is affected by peptic duodenitis. C: Some of the glands contain cells with an increased nuclear:cytoplasmic ratio. D: Isolated cells lose the semilunar basal shape of the nuclei.

Adenomas appear as soft, lobulated, pedunculated or sessile, single or multiple lesions (Fig. 7.3). The mucosa may have a discolored granular appearance, but without erosions or ulcers (15). Evenness of the granularity helps distinguish adenomas from cancers. Sessile adenomas are more frequent than pedunculated ones. Tubular adenomas vary in size from 0.5 to 3 cm in maximum diameter. Villous adenomas are usually larger and may attain a size of ≥8 cm. Large villous adenomas may encircle the bowel lumen (1) and appear as a cauliflower-like lobulated sessile polypoid mass. Villous adenomas may also be encountered in the jejunum. The presence of multiple small intestinal adenomas suggests that the patient has a polyposis syndrome (see Chapter 12) or an underlying disorder such as Crohn disease (16).

Adenomas are benign neoplasms that display varying degrees of dysplasia. They are tubular (Fig. 7.4), tubulovillous, or villous (Fig. 7.5) in nature, resembling their colonic counterparts. Tall, immature columnar, pseudostratified epithelial cells displaying a typical “picket fence” pattern line the neoplastic tubules (Figs. 7.5, 7.6, 7.7, and 7.8). Goblet cells that exhibit variable degrees of differentiation lie among the immature enterocytes. Sometimes the goblet cells appear to be dystrophic as evidenced by the presence of signet ring cells. Small intestinal adenomas can also contain endocrine cells (Fig. 7.6), Paneth cells (Fig. 7.7), and squamous cells.
Chapter 7

(Fig. 7.7), attesting to their origin from multipotent crypt stem cells. Paneth cells may be quite numerous, especially in patients with familial polyposis. Variable degrees of nuclear atypia affect all cell types present within adenomas, supporting the concept that each represents an inherent neoplastic component of the lesion and not entrapped normal cells. In small lesions, the adenomatous epithelium may be confined to the surface and not involve the crypts. Normal lamina propria separates the neoplastic glands (Figs. 7.4, 7.5, 7.6, 7.7, and 7.8).
FIG. 7.3. Gross appearance of small intestinal adenomas. A: A semisessile polypoid adenoma arising in the second portion of the duodenum (arrow). The red tissue to the right of the duodenal mucosa as well as above it represents gastric mucosa that was resected at the same time. It shows severe hemorrhagic gastritis. B: Jejunal adenoma presenting as a discrete polypoid mass.
FIG. 7.4. Duodenal adenoma. A: Note the focal adenomatous proliferation present in the duodenum (arrows). B: Tubular adenoma. Note the presence of pseudostratified penicillate nuclei and the paucity of goblet cells. Numerous mitoses are present. C: Junction of immature adenomatous epithelium (below arrow) with normal small intestinal surface epithelium (above arrow). The nuclei appear pseudostratified in a way that produces the characteristic “picket-fence” pattern.

FIG. 7.5. Sessile villous adenoma. A: Adenomatous epithelium extends along the duodenal villi and replaces the pre-existing normal epithelium. B: Higher magnification of a different villous lesion demonstrating a slightly higher degree of dysplasia as evidenced by the focal loss of the normal epithelial polarity. Neoplastic cells have completely replaced the normal epithelium.
A small villous component may be present on the surface, but most of the lesion should consist of tubules to classify it as a tubular adenoma (Fig. 7.4). Villous adenomas consist of fingerlike villous or papillary processes containing central thin cores of lamina propria lined by a neoplastic epithelium resembling that seen in tubular adenomas (Fig. 7.5). Occasionally one sees mixed tubulovillous adenomas.

A full spectrum of neoplasia can be seen in small intestinal adenomas, ranging from low-grade dysplasia to high-grade dysplasia to invasive carcinoma. The probability of finding areas of carcinoma depends on the size and location of the lesion (17). The larger the tumor, the more likely one is to find invasive cancer and the less likely one is to see residual adenoma. As the dysplasia becomes more severe, the nuclear:cytoplasmic ratio increases, epithelial polarity disappears, and the cells demonstrate increased mitotic activity (Figs. 7.8 and 7.9). The nuclei consistently approach the glandular lumens in high-grade dysplasia. Marked glandular budding with loss of nuclear polarization and variable loss of mucinous differentiation heralds the development of malignancy. If one sees severe dysplasia with unequivocal invasion into the lamina propria, with a back-to-back glandular configuration and glandular fusion, one can make the diagnosis of intramucosal carcinoma.
FIG. 7.7. Cell types in adenomas. **A:** Dysplastic Paneth cells (arrowheads) in this adenoma appear more eosinophilic and granular than their neighbors. The granules are larger than the smaller subnuclear eosinophilic endocrine cell granules. **B:** Lysozyme immunostain (dark brown) highlights the numerous Paneth cells within the lesion. **C:** Squamous morule (SM) in an adenoma. It abuts on the adjacent adenomatous epithelium. The squamous epithelium has a bland histologic appearance.
FIG. 7.8. High-grade dysplasia in a duodenal adenoma. **A:** The cells contain rounded nuclei rather than penicillate nuclei and some lose their polarity. **B:** Note the extreme stratification of the nuclei of the cells lining the glands. Some of the cells have begun to lose their normal polarity. Normal lamina propria separates the neoplastic glands.
FIG. 7.9. Duodenal villous adenoma. A: Low magnification showing the overall architecture of the lesion. B: Higher magnification showing the complex surface tufting and multilayering of the epithelium that covers the lamina propria core of the villous structures. High-grade dysplasia is present but there is no invasion into the underlying lamina propria.

Serrated Adenomas

We have encountered occasional examples of serrated duodenal adenomas and there is one reported case of this lesion (18). They resemble their large intestinal counterparts. These adenomas have serrated lumens lined by eosinophilic-appearing cells that contain pseudostatified nuclei with prominent nucleoli (Fig. 7.10). Goblet cells are typically not well developed in these lesions. These lesions are too uncommon in the duodenum to comment on the implications of this histologic variant. However, we have not seen any containing either high-grade dysplasia or carcinoma.

FIG. 7.10. Duodenal serrated adenoma. A: Low-power illustration of the lesion that, at this magnification, appears densely crowded but otherwise not unlike other duodenal adenomas. B: Higher magnification of the lesion discloses the characteristic eosinophilic epithelium and saw-toothed pattern of a serrated adenoma.

Interpretation of Biopsies with Areas Suspicious for Epithelial Neoplasia

Typically, the initial diagnosis of a duodenal neoplasm involves interpretation of small biopsy specimens that yield only a small sample of the superficial parts of the lesion. The deeper parts of an adenoma, where an invasive tumor is most likely to develop, are often not present in the biopsy. For this reason, it is difficult to exclude the presence of an invasive cancer, especially in larger lesions. In one study of duodenal villous adenomas, biopsies missed areas of malignancy in 56% of cases, indicating the poor sensitivity of biopsies in detecting an invasive cancer (19). Generally, the best that one can do is to recognize that the lesion is neoplastic and to provide an accurate assessment of the degree of dysplasia that is present, stating whether there is invasion into the lamina propria and whether one sees lymphovascular invasion or desmoplasia. One can also state whether submucosal tissue is present to be evaluated for the presence of invasion. If severe dysplasia or intramucosal carcinoma is present, consideration should be given to resection of the lesion, because it may harbor an invasive malignancy. The absence of identifiable lamina propria surrounding glands, the presence of large vessels near the tumor cells, a desmoplastic response, and an intravascular or intralymphatic invasion all support a diagnosis of invasive cancer. Tumors with high-grade dysplasia or a villous morphology are more likely to harbor an invasive carcinoma than adenomas lacking these features (19). Larger, ulcerated lesions that are fixed or cause obstruction usually contain invasive cancer.

Special caution must be applied to the evaluation of ampullary lesions because the anatomy of this area is quite complex and numerous small branched submucosal glands normally reside in this region (see Chapter 6). A significant diagnostic dilemma results when carcinoma in situ or intramucosal cancer involves these submucosal glands (Figs. 7.11 and 7.12). It is easy to confuse involvement of ampullary glands with invasive disease, and care needs to be taken not to overdiagnose invasive malignancy in this setting. If one sees a lobular glandular
architecture with lamina propria surrounding the glands, invasive malignancy is unlikely. Further, if the glands are round and not angulated, the lesion is more likely to be benign. The lack of desmoplasia also favors a benign lesion.

**FIG. 7.11.** Ampullary tumor. **A:** Whole mount section through the tumor demonstrates the relationship of the pancreas (P) to the muscularis propria of the duodenal wall (MP) and surrounding normal small intestinal mucosa (SI). A complex neoplasm involves the ampullary region and surface of the duodenum (arrows). **B:** This figure represents a higher magnification of the lesion illustrated in A. One can see residual normal-appearing ducts (D) as well as nonneoplastic glandular epithelium (arrows). In other areas, the ductal epithelium is replaced by changes that variously appear papillary, clear, hyperplastic, and dysplastic. Normal-appearing lamina propria and muscle fibers separate the various glandular components and there is no evidence of invasion by the neoplastic epithelium. The muscularis mucosa is indicated by MM and the muscularis by MP. **C:** The nonneoplastic glands display angular features easily misinterpreted as neoplastic.

It is important not to mistake regenerative atypia present on the eroded surface of an adenoma for high-grade dysplasia or an invasive cancer. Areas of acute inflammation containing prominent capillaries and fibrin deposits, especially when superficial, should alert the examiner to the possibility of reparative atypia in the setting of surface erosion.

Another common area of diagnostic error is the presence of the marked reactive atypia that can be present in the duodenum, especially in the area surrounding the ampulla of Vater in patients with sclerosing papillitis (see Chapter 6). Patients who have had stents or who have had cholelithiasis may exhibit very significant ampullary inflammation, often accompanied by a marked papillary hyperplasia with significant reactive atypia. The papillary hyperplasia can appear polypoid and may even obstruct the ampulla—leading to secondary alterations in the biliary tree or pancreatic ducts. These circumstances lead to the strong clinical impression that the patient has a neoplasm. We see many cases of reactive atypia that were misdiagnosed as adenoma, often as adenoma with high-grade dysplasia. One should exercise caution in making a diagnosis of dysplasia in the presence of acute inflammation. We find that Ki-67 immunostaining can be helpful in distinguishing between a reactive and a neoplastic lesion. In reactive lesions, one usually sees a proliferative
zone that extends upward from the base of the crypt. Not all cells exhibit positive staining. In contrast, neoplastic lesions often have much stronger Ki-67 staining that is localized superficially and not in the crypt base, especially if the lesion is early. If one is unable to distinguish a reactive from a neoplastic process, a diagnosis of indefinite for dysplasia is appropriate.

**FIG. 7.12.** Higher magnification of the lesion illustrated in Figure 7.11. *A:* Stratified epithelium lines the glandular spaces. The glands are separated by normal-appearing lamina propria. In some foci the epithelium appears more dysplastic than in others (arrow). These same glands also lack normal mucinous differentiation. *B:* This area of the tumor demonstrates areas of glandular hyperplasia (*H*) as well as foci of adenoma (*A*). One of the adenomatous glands contains an area of intramusosal carcinoma (arrow). Normal lamina propria separates the hyperplastic and adenomatous glands (stars). Note the absence of desmoplastic stroma. This neoplasm is of the hepatobiliary type.

**Mixed Hyperplastic and Adenomatous Polyps of Gastric Origin**

Rare polypoid lesions that contain both hyperplastic and adenomatous gastric mucosa arise in areas of heterotopic gastric mucosa. The hyperplastic foci resemble those seen in gastric hyperplastic polyps. These hyperplastic foci intermingle with adenomatous epithelium indistinguishable from small intestinal adenomas (20). The lesions are histologically identical to similar lesions arising in the stomach (see Chapter 4).

**Carcinomas**

**Epidemiology**

Relative to the length and surface area of the small intestine, adenocarcinomas are quite rare. It was estimated that in 2006 there were approximately 6,000 new cases of small intestinal cancer in the United States (21). Most carcinomas develop in the duodenum and their incidence is increasing slightly due to the increased use of upper endoscopy and enteroscopy. As a result, they are commonly detected early. Small intestinal carcinomas generally present between the ages of 50 and 70 unless the patient has an underlying inflammatory condition or polyposis syndrome. The median age at presentation is approximately 55 to 67 years. However, these tumors have been described in children as young as 12 (22). The frequency of small bowel cancer roughly parallels the frequency of colon cancer among the participating registries of the International Association of Cancer Registries (23). The U.S. registries for the years 1993–1997 showed the highest rates, followed by Canada and Western Europe, with the lowest rates in Africa and East Asia. Ethnic variations in small bowel cancer in the United States constitute an interesting example of this trend. African-American small bowel cancer rates (male, 2.4; female, 1.8) are double those of U.S. Caucasians (male, 1.2; female, 0.9) and, although the differences are not as large, their large bowel rates are also higher than those of U.S. Caucasians for both sexes. A population-based study of 13 of these registries found 10,946 small bowel cancers among over 4 million first primary cancers (24). There were 4,096 small bowel carcinomas (37.4%), compared to 3,991 carcinoids (36.5%), 1,334 sarcomas (12.2%), 442 lymphomas (4%), and 1,083 unspecified (9.9%). There was a statistically significant increase in the risk of acquiring a second primary cancer. Second primary cancers of the colorectum and the hepatobiliary tree showed the strongest associations between small bowel cancer (*p* = 0.01), followed by pancreas and ovary (*p* = 0.02) and soft part sarcoma (*p* = 0.06). There were similar associations when small bowel cancer followed cancer at another primary site. When assessed by subsite, cancers proximal to the sigmoid colon showed the
Chapter 7

The reasons for the relative rarity of small bowel carcinomas in contrast to colon carcinomas remain unknown, but several explanations exist (41,42,43,44). Secretions may predispose to tumor development (40). The constant influx of alkaline bile and/or acidic pancreatic juice may cause local cell damage. Increased mitotic activity associated with mucosal repair from injury induced by these secretions may predispose to tumor development (40).

Pathogenesis

Adenocarcinomas develop far less frequently in the small intestine than they do in the colon or rectum, despite the fact that the small bowel has a high cellular turnover rate and one of the largest epithelial surfaces in the body. More than 50% to 70% of small intestinal carcinomas arise in the duodenum in the periampullary region, even though it constitutes only 4% of the entire small intestine. The longest small intestinal segment, the ileum, is most resistant to tumor formation unless the patient has Crohn disease. Adenocarcinomas also arise in ileostomies and ileal conduits, with the time interval between the formation of the ileostomy and carcinoma development usually involving several decades (36). Many develop in patients with inflammatory bowel disease (IBD) who had either antecedent backwash ileitis or dysplasia (36). Ileal pouches fashioned as part of the treatment of adenomatous polyposis, or ulcerative colitis, may develop adenocarcinomas, although the risk is low (37). Ileal carcinomas may also develop in the setting of abetalipoproteinemia (38). Finally, ampullary carcinomas may affect siblings without a known polyposis syndrome, suggesting a possible underlying genetic disorder (39).

The luminal contents are more liquid in the small intestine than in the large intestine and potential luminal carcinogens become diluted, leading to reduced mucosal contact. Small intestinal transit time is rapid as compared to colonic transit time so that potential intraluminal carcinogens have shorter mucosal contact times. The small bowel usually lacks the anaerobic bacteria present in the large bowel that are capable of converting bile salts to potential carcinogens (42). When bacterial flora is disturbed, as in bacterial overgrowth syndromes, small intestinal carcinomas develop with a higher frequency than expected.) The antibacterial function of Paneth cells may contribute to the relative sterility of the small bowel lumen (43).

Large amounts of lymphoid tissue in the lamina propria, and especially in Peyer patches, provide potential intensive immunosurveillance against neoplastic cells as they develop. Large amounts of small intestinal mucosal enzymes, such as benzopyrene hydroxylase, detoxify luminal contents (42).

The liquefied chyme induces less mechanical trauma than the harder, better formed stool in the colon. Stem cells located at the crypt base lie deeper in the small intestinal mucosa than in the large intestine because of the presence of both crypts and villi in the former and therefore the stem cells do not come in as close contact with potential luminal carcinogens as do colonic crypt cells. The apoptosis-suppressing protein bcl2 is not expressed in the normal small intestinal mucosa (44) so that cells affected by genotoxic damage can be eliminated by unrestrained apoptosis.
Molecular Biology of Small Intestinal Carcinomas

There is good evidence for the accumulation of molecular abnormalities during the adenoma–carcinoma progression of small intestinal tumors. These alterations involve activating mutations in oncogenes and inactivating mutations in tumor suppressor genes and share many similarities with the alterations found in colon cancers. In addition, there are a series of epigenetic changes that occur, but these are not as well characterized in small bowel tumors as they are in colon cancers. The alterations begin even before the appearance of an adenoma and increase in frequency and number as carcinomas develop and then metastasize.

The molecular features differ depending on whether the tumors arise as part of familial adenomatous polyposis, HNPCC, Peutz-Jeghers syndrome, or juvenile polyposis. Germline mutations in patients with inherited syndromes that predispose to small intestinal malignancy involve the following genes: APC, hMSH2, hMLH1, LKB1, and SMAD 4 (see Chapters 12 and 14).

APC alterations (mutations and deletions) occur in patients with familial adenomatous polyposis (FAP) and sporadic tumors and in Crohn-associated tumors. APC and b-catenin alterations are common in ampullary and duodenal lesions, whereas microsatellite instability (MSI) is uncommon. APC mutations are present in 67% of adenomas and 50% of carcinomas of FAP patients (45); their incidence is much lower in sporadic lesions.

The mutation rate in mismatch repair genes in patients with HNPCC is 81% (46). The tumors show an MSI-high phenotype. They show a decreasing gradient from the duodenum to the ileum, reflecting the distribution of sporadic small bowel cancers (46). The MSI phenotype characteristic of HNPCC patients occurs in approximately 20% of ampullary carcinomas. This finding associates with a lower incidence of p53 mutations and lymph node metastases and a better survival (47).

The sensitivity of each microsatellite marker is similar to that for colorectal cancer and thus, the recommended marker panel for colon cancer is also suitable for evaluation of high MSI in small bowel cancers (see Chapter 14) (46). The majority of the tumors lose immunohistochemical expression of at least one of the mismatch repair proteins (MLH1, MSH6, or MSH2).

K-ras mutations occur in sporadic, FAP-associated (50), and Crohn-associated (48,49,51) tumors. These occur early and do not significantly increase in the transition from adenoma to carcinoma. The incidence of K-ras mutations differs in ampullary tumors, depending on whether they are of the intestinal phenotype or the pancreaticobiliary phenotype. They are more common in the pancreaticobiliary type (52). Mutations also occur in the p53 gene (53). p53 proteins are expressed in 30% of adenomas and about 50% of sporadic and Crohn-associated adenocarcinomas (49).

Data on the prognostic significance of p53 immunostaining are conflicting (49). p16 protein is overexpressed in 92% of adenomas and 91% of adenocarcinomas. The increased expression of p16 is paradoxic, since it is a tumor suppressor gene, and this finding remains to be further evaluated. There is also an increased expression of cyclin D, cyclin E, and p21 in both adenomas and carcinomas (49,54). Cyclin D1 overexpression associates with decreased survival (49). It also associates with aberrant b-catenin expression and K-ras mutation (55). Loss of the p27 protein occurs in 17% of adenomas and 23% of carcinomas.

Increased expression of Her2/neu affects 60% of small bowel tumors, a finding associated with a poorer prognosis (56). DCC alterations, which are common in colon carcinomas, are uncommon in small intestinal carcinomas (48).

Epigenetic changes also occur in small intestinal tumors. These mainly involve methylation changes in a number of genes. Some methylation changes associate with ras mutations and others with high MSI (57). Thus, the MSI phenotype results from mutations in mismatch repair genes (predominantly MLH1 or MLH2) or via epigenetic silencing by hypermethylation of the MLH1 promoter. The latter tends to occur in sporadic tumors, whereas gene mutations occur in HNPCC patients. Inactivation of the gene by either mutation or hypermethylation results in loss of protein expression.

Clinical Features

The clinical features of small intestinal adenocarcinomas differ depending on the size of the lesion and its location and growth pattern. Most malignant small bowel tumors present in a nonspecific way, often resulting in a therapeutic delay. Early symptoms of ileal and jejunal tumors include vague, nonspecific abdominal pain. Later, crampy abdominal pain, nausea, vomiting, and weight loss occur. Gastrointestinal bleeding or anemia can develop. Polypoid lesions, especially those arising in the jejunum or ileum, can cause chronic, intermittent, or acute obstruction by intussusception. (Intussusception does not occur in the duodenum because its retroperitoneal location does not allow free mobility.) Intestinal obstruction resulting from mural infiltration by tumor cells or blockage of the lumen by a bulky tumor (Figs. 7.13 and 7.14) are common presentations in advanced tumors. The bowel proximal to the tumor dilates. Carcinomas may also perforate (58,59).

Duodenal tumors produce nausea, vomiting, anemia, and postprandial distress. Ampullary tumors generally are smaller than nonampullary lesions because they tend to become symptomatic early. They may also be detected earlier than more distal tumors due to the frequent use of upper gastrointestinal endoscopy. Patients with primary small intestinal cancers have a high incidence of other cancers involving both
Chapter 7

Gastrointestinal and extraintestinal sites. Most of the other primaries are colonic adenocarcinomas, but other primary sites include the prostate, female genital tract, lung, urinary tract, skin, and breast (61,62). Some of these patients will have HNPCC or FAP. The presence of multiple tumors may also suggest the presence of metastatic cancer.

FIG. 7.13. Gross photograph of a polypoid neoplasm protruding into the duodenal lumen. The resection specimen came from a 52-year-old woman who presented with jaundice, abdominal pain, nausea, and vomiting. It shows a carcinoma of the duodenum obstructing the ductal system at the ampulla of Vater. The ducts draining into the ampulla are massively dilated. Note the dilation of the common bile duct.

**Gross Features**

Small bowel adenocarcinomas most commonly arise in the duodenum (55.2%) followed by the jejunum (17.6%), ileum (13%), and the remainder of the small bowel (1). The location of the tumor often reflects the nature of the associated conditions. Familial adenomatous polyposis, HNPCC (46), and neurofibromatosis (63) predispose to ampullary carcinomas, whereas celiac disease and Crohn disease predispose to more distal tumors.

The gross features of the tumors reflect the site of origin, the presence of an underlying condition, and the stage of the lesion. Duodenal carcinomas are typically polypoid rather than ulcerating or infiltrative in their gross appearance. If the tumor arises within the ampulla itself and is small, the duodenal mucosa may appear normal but stretched over what appears to be a submucosal mass. Jejunal and ileal tumors are typically advanced lesions that appear flat, stenosing, ulcerative, infiltrating (Fig. 7.15), or polypoid in their growth patterns. The tumors measure from 1.2 to 15 cm in greatest diameter, with the largest lesions tending to occur distally because they fail to become symptomatic early. The tumors tend to develop in areas of strictures in patients with Crohn disease, making it difficult to detect them, either at the time of the surgery or in pathology specimens, since the gross features of strictures and infiltrating carcinomas may resemble one another. This is further complicated by the fact that the development of enteritis cystica profunda may mimic a neoplasm. Patients with Crohn disease may have multiple tumors. Tumors that develop in ileal pouches and ileostomies show the features of the surgical intervention as well as the tumor.
FIG. 7.14. A carcinoma occludes the ileal lumen. Bile stains the mucosa proximal to the obstructing lesion and is absent distally.

**Histologic Features**

Small intestinal carcinomas develop along the same adenoma (dysplasia)–carcinoma sequence as seen in the colon. Therefore, the lesions begin as adenomas (or as areas of dysplasia in Crohn disease) that progressively increase in size and eventually develop into metastasizing carcinomas. As the tumors enlarge, the cytologic features become increasingly abnormal and the architecture becomes increasingly complex. The tumor is considered to be a carcinoma once the neoplastic cells invade into the lamina propria or through the muscularis mucosae into the underlying submucosa (6). This contrasts with colon carcinomas that require invasion into the submucosa to be diagnosed as invasive. The basis for the difference relates to the lymphatic distribution in the small bowel versus the colon. The colon lacks lymphatics in the mucosa except in the area of the muscularis mucosae (64). In contrast, the central lacteal, which is the most superficial part of the small intestinal lymphatic system, lies immediately beneath the luminal epithelium and the lymphatics richly supply the mucosa facilitating absorption of many nutrients.

**Ampullary Tumors**

Small intestinal carcinomas are divided into ampullary tumors and tumors arising in the remainder of the small bowel. Ampullary tumors include those arising in the duodenal mucosa, the ampulla itself, the common bile ducts, or the pancreatic ducts. In contrast, periampullary carcinomas present as tumors that show a circumferential growth pattern around the ampulla of Vater. The most difficult practical issue is deciding whether a tumor involving the ampulla is primarily ampullary or duodenal or whether it is periampullary extending into the ampulla. Occasionally, it is difficult to determine the exact site of origin of a cancer arising in this general area. Nonetheless, it is important to try to differentiate among these various lesions, since a significant difference exists between the 5-year survival rates of patients with ampullary carcinomas (20% to 50%) and those with pancreas cancers (15%) and bile duct cancers (17%) (1,65,66). It is also important to try to distinguish among these lesions because stage affects outcome and the staging systems are site dependent (67). Finding residual adenomatous epithelium in the duodenal mucosa allows one to diagnose a primary duodenal carcinoma with certainty. Similarly, finding residual adenomatous epithelium in the bile duct helps identify invasive biliary cancer. Pancreatic intraepithelial neoplasia accompanies both pancreatic and ampullary tumors (68).
FIG. 7.15. Gross features of small intestinal cancers. A: Opened bowel demonstrating a napkin ring–like lesion (arrows). Focal ischemia is present proximally as evidenced by the reddened mucosa. B: The unopened specimen with evidence of extension to the serosal surface as noted by the area of indentation and prominent engorgement of the vasculature surrounding the bowel (arrows).

Ampullary carcinomas differ from those arising elsewhere in the small bowel in that the ampullary epithelium shows features of the duodenal epithelium as well as that of the associated ducts. Ampullary tumors are divided into several histologic types: an intestinal type arising from the covering intestinal mucosa of the papillae (intestinal-type adenocarcinoma of duodenal origin) (Figs. 7.16 and 7.17), a pancreaticobiliary type deriving from biliary or pancreatic ductal epithelium that penetrates the duodenal muscularis propria (ampullary carcinoma of pancreaticobiliary origin) (Fig. 7.18), a mixed type containing both types of epithelium, and an undifferentiated type (69). Intestinal-type tumors outnumber pancreaticobiliary-type tumors. The age distribution and size of the two types of tumors are similar but the intestinal type has a better prognosis than the pancreaticobiliary type (69). Small adenocarcinomas of the intestinal type tend to be much less invasive than tumors of the pancreaticobiliary type. As a result, nodal metastases are much more common in pancreaticobiliary-type tumors. The intestinal type histologically resembles intestinal carcinomas elsewhere, containing a mixture of Paneth and endocrine cells; often residual adenomatous epithelium is present. Intestinal-type adenocarcinomas often develop in large bulky papillary adenomas (1). Ampullary tumors may appear poorly differentiated as they infiltrate the bowel wall but they frequently have a superficial papillary component. The pancreaticobiliary type is characterized by papillary growth with scant fibrous cores. The pancreaticobiliary type lacks Paneth cells and endocrine cells. When the tumors are small, one may be able to distinguish between these two types of tumors on histologic grounds, but when they are large it may be impossible to distinguish between a duodenal, pancreatic, or biliary neoplasm purely on histologic grounds. However, immunostaining may be helpful (see below). Of interest, ampullary adenomas and adenocarcinomas commonly associate with concurrent pancreatic intraductal neoplasia. The latter is frequently high grade in nature (68). This is true whether the tumors arise in the ampulla itself or in the duodenal mucosa.
FIG. 7.16. Ampullary carcinoma. A: The neoplasm arises from the duodenal surface of the ampulla of Vater. Microscopically residual adenomatous epithelium is present in the heaped-up margins surrounding the ulcer crater. B: Cross section through the tumor showing the relationship with the underlying pancreas and pancreatic duct. C: Opened common bile duct showing relationship of tumor to other ampullary structures. D: Cross section of the common bile duct (star) surrounded by a signet ring cell carcinoma.

Extra-ampullary Carcinomas

Small intestinal tumors arising away from the ampulla resemble large intestinal carcinomas. Extra-ampullary tumors tend to be larger than ampullary ones and therefore the cancer more commonly overgrows the benign component so that no residual adenoma is present by the time the tumors are detected. The adenocarcinomas usually invade lymphatics and nerves and extend through the muscularis propria, often metastasizing to regional lymph nodes (70) by the time they are initially diagnosed.

Features Common to Both Intestinal Ampullary and Extra-Ampullary Tumors

Small intestinal carcinomas usually have a tubular architecture, although some tumors are papillary in nature. The glands are lined by cells with significant cellular and nuclear pleomorphism and loss of epithelial polarity. The tumors show a variable back-to-back, gland-in-gland architecture with invasion into the submucosa and adjacent normal tissues. Most small intestinal adenocarcinomas are moderately well-differentiated tumors with variable mucin production. Neoplastic endocrine cells (Fig. 7.19) and Paneth cells can be present. The tumors may also contain benign or malignant squamous cells (Fig. 7.20). The presence of squamous, endocrine, or Paneth cells has no prognostic significance.

Duodenal carcinomas may also contain areas of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma admixed with one another and attesting to the origin of these various cell types from a common stem cell (71). About 20% of tumors are poorly differentiated, sometimes containing signet ring cells (Fig. 7.21). The use of immunohistochemical stains in these poorly differentiated tumors may help establish the histologic type of tumor that is present.
FIG. 7.17. Duodenal adenocarcinoma. **A:** Moderately differentiated carcinoma invades the underlying tissues in the area of the ampulla of Vater. Parts of the tumor lie superficial to the Brunner glands (BG). **B:** Higher magnification of the tumor at its junction with the normal mucosa (M). The normal ducts in the ampulla are indicated by the star. **C:** The area represents a higher magnification of the area outlined by the box in B. The tumor appears moderately differentiated. Well-defined glands are present. In other areas the tumor is poorly differentiated and grows in more solid nests (lower left).

**Immunohistochemical Features**

Small intestinal adenocarcinomas usually produce carcinoembryonic antigen (CEA) (72), CDX2 (73), and villin. They are also commonly positive for cyclooxygenase-2 (COX-2), SPLA-2, and cPLA2 (74). COX-2 expression may associate with a poor outcome in resected ampullary carcinomas (75). The endocrine components of the adenocarcinomas will be positive for neuroendocrine cell markers and Paneth cells stain with antibodies to lysozyme.

CDX2 helps identify tumors of duodenal origin since this marker is specific for intestinal differentiation (73) and it is absent in the vast majority of pancreatic and hepatobiliary tumors. Villin is also helpful in this regard, although it is sometimes produced by hepatobiliary tumors. We prefer to use CDX2 and villin to show the intestinal differentiation. However, it must be kept in mind that tumors arising in the small bowel or colon as well as those arising from areas of intestinal metaplasia in the stomach or esophagus will also be positive for these markers. However, tumors arising in the pancreas, hepatobiliary tract, lung, ovaries, and other nonintestinalized sites are generally negative when stained with these antibodies.
FIG. 7.18. Ampullary carcinoma of the hepatobiliary type. There is a small invasive carcinoma (arrows) arising from the epithelium of the ampulla.

Adenocarcinomas in the Setting of Genetically Defined Diseases

The relative risk of developing a duodenal carcinoma in patients with FAP is >300 times that of the normal population (76) and is a major cause of death in these patients. The tumors arising in this setting usually have residual adenoma and they are frequently accompanied by additional adenomas in the second and third parts of the duodenum. These lesions are discussed further in Chapter 11.

Carcinomas also arise in the setting of HNPCC and these tumors may be the first manifestation of the disease. The median age at diagnosis is 39 years (46). The tumors range from well-differentiated to poorly differentiated lesions. The tumors may have expansile rather than infiltrating margins and a high number of peritumoral lymphocytes may be seen creating the pattern of a medullary carcinoma (46). The tumors may also have a prominent mucinous component.

Patients are generally diagnosed with localized disease and this is reflected in the excellent overall survival (46).
Carcinomas Arising in Meckel Diverticulum

Meckel diverticulum develops numerous complications (see Chapter 6), including tumor development (77). Patients with carcinomas arising in Meckel diverticulum range in age from 13 to 52. Intermittent colicky abdominal pain represents the most common presenting symptom. Other patients experience milder, nonspecific GI complaints such as anorexia, nausea, vomiting, and constipation. Sometimes a mass is palpable in the right lower quadrant. The tumors vary in size from 1 to >10 cm. The tumors have been described as medullary, mucinous, papillary, and anaplastic carcinomas. Sometimes they resemble gastric or pancreatic cancers because they arise in heterotopic gastric or pancreatic tissues within the diverticulum (78,79). The tumors metastasize to mesenteric and aortic lymph nodes as well as to the liver. They may also spread diffusely throughout the abdomen. Long-term survival is generally poor.
Carcinomas Arising in Heterotopic Pancreas

Pancreatic heterotopia is a common congenital small intestinal abnormality. It may exist alone or lie within a congenital abnormality such as a duplication or, more commonly, Meckel diverticulum. The full spectrum of pancreatic neoplasms may develop in this heterotopic tissue. Adenocarcinomas usually arise from the ducts and they may metastasize to regional lymph nodes. Intraductal papillary mucinous adenomas may also develop (80), as may islet cell tumors or acinar tumors, although these are very uncommon.

Unusual Histologic Variants

Adenosquamous carcinomas are uncommon small intestinal tumors. They contain both malignant glandular as well as squamous components and they resemble their large intestinal counterparts. Many patients present with metastatic disease at the time of initial diagnosis (81).
Pure squamous cell carcinomas involving the small intestine are rare (82) and usually develop in congenital anomalies such as duplications and Meckel diverticula. They may also develop in ileoanal pouches in patients with ulcerative colitis (83). Most small bowel squamous cell carcinomas represent metastases from other sites such as the cervix or lung.

Mucinous (colloid) adenocarcinomas and signet ring cell carcinomas are adenocarcinoma variants characterized by prominent mucus secretion. These tumors may appear gelatinous grossly. Abundant mucus forms pools in the connective tissue. The amount of mucus required to qualify a tumor as mucinous is 50% or more. In mucinous (colloid) tumors the mucin is primarily extracellular in location; in signet ring cell carcinoma the mucin accumulation is intracellular. These tumor types, especially colloid-type tumors, are more common in patients with HNPCC and Crohn disease. Signet ring cell tumors tend to affect younger patients and are aggressive tumors.

Small intestinal carcinomas with hepatoid differentiation are rare and they produce unusual tumor markers such as a-fetoprotein (AFP). These tumors are usually moderately to poorly differentiated adenocarcinomas that resemble AFP-producing tumors arising in the stomach (see Chapter 5) (84,85). Histologically, the tumors consist of solid, papillary, and/or tubular proliferations. Clear cell areas can be seen. The glandular areas produce mucin and are strongly CEA-positive (84,85). Most tumor cells react with antibodies to antichymotrypsin, prealbumin, transferrin, and AFP (85). The serum of these patients contains elevated AFP levels. Occasionally, variably sized intracellular, eosinophilic, α1-antitrypsin immunoreactive hyaline droplets are present. Bile production also occurs. Small bowel metastases from primary liver cell carcinoma or hepatoid gastric cancer should be ruled out before making a diagnosis of this extremely uncommon lesion.

Primary small intestinal choriocarcinomas are rare. Grossly, they appear extensively hemorrhagic and necrotic. The tumors consist of standard adenocarcinoma admixed with aggregates of uniform eosinophilic cells containing basophilic vesicular nuclei. Multinucleated syncytial cells with bizarre anaplastic nuclei and irregular cytoplasmic margins cap the more uniform smaller cytotoxophoblastic cells. Cytotoxophoblastic cells also intermingle with knots of multinucleated syncytial cells. Vascular invasion is common. The tumor produces both human chorionic gonadotropin (hCG) and human placental lactogen (hPL). hCG immunoreactivity is restricted to syncytiotrophoblasts and hPL positivity localizes to syncytial cells and to focal collections of cytotoxophoblasts (86). This tumor is distinguished from giant cell variants of adenocarcinoma by the presence of the dual-cell population (syncyto- and cytotoxophoblasts) and by its positivity for hPL. A metastasis from a primary intrauterine, ovarian, or testicular choriocarcinoma should be excluded (Fig. 7.22). The presence of adjacent adenocarcinoma or anaplastic large cell carcinoma and the absence of other germ cell elements suggest that the tumors arise from multipotential stem cells.

Sarcomatoid small intestinal carcinomas are biphasic with evidence of a spindle cell or sarcomatoid morphology admixed with areas of more conventional adenocarcinoma. The sarcomatoid areas are usually positive for both cytokeratin and vimentin and may produce mucin. These lesions may have a herringbone or storiform pattern and they may resemble unusual GI stromal tumors. The tumors may also show rhabdoid (87) or osteoclastic (88) differentiation. The prognosis of these lesions is poor. The few tumors that the authors have seen have behaved in a very aggressive fashion with prominent lymphatic involvement and metastases present at the time of diagnosis. The differential diagnosis of the lesion includes GI stromal tumors, pleomorphic carcinoma, sarcoma, and amelanotic malignant melanoma. Some tumors exhibit neuroendocrine differentiation. These are discussed in Chapter 17.
FIG. 7.22. Metastatic choriocarcinoma from the testis. A: Hematoxylin and eosin–stained section showing both syncytiotrophoblast and cytotrophoblast. B: Tumor stained with an antibody to CK7. The metastatic tumor is positive, whereas the surrounding small intestine is negative.

### Staging Small Intestinal Carcinomas

The spread of small intestinal carcinomas resembles that of colonic carcinomas. Direct invasion occurs into other loops of the small bowel, stomach, colon, pancreas, omentum, mesentery, and retroperitoneum. Because lymphatic invasion is common, regional nodal metastases are frequently present. The regional lymph nodes for the duodenum are the pancreaticoduodenal, pyloric, hepatic (pericholedochal), cystic duct, hilar, and superior mesenteric nodes. The regional lymph nodes for the jejunum and ileum are the mesenteric nodes including the superior mesenteric nodes. Lesions arising in the distal ileum may also metastasize to the ileocolic nodes including the posterior cecal nodes. Hematogenous and intraperitoneal spread also commonly occurs. The staging of small intestinal tumors only applies to carcinomas and not other tumor types. The staging classifications are shown in Tables 7.3 and Table 7.4.

### Prognosis

The overall prognosis of small intestinal carcinomas relates to a number of factors, including patient age, tumor location, tumor size, stage, resectability, histologic type and grade, and the presence or absence of lymphovascular invasion (22). With the exception of ampullary tumors, the prognosis of patients with small intestinal carcinoma remains uniformly poor due to the fact that patients often present late in the course of their disease and metastases are commonly present at the time of diagnosis. An exception to the generally poor prognosis of small intestinal tumors may be the cancers that arise in the setting of HNPCC because these tumors tend to be diploid and display less aggressive growth characteristics. Early carcinomas arising at the area of the ampulla of Vater have an excellent prognosis when the growth is confined to the wall of the ampulla or the common duct, or immediately surrounding tissues, and does not infiltrate either the lymph nodes or the pancreas (89). Patients with node-negative ampullary cancers enjoy a 5-year survival of up to 50% following radical resection (89). One of the reasons for the good prognosis of ampullary carcinomas is their more expansive rather than infiltrative growth pattern. These are less likely to show lymphatic or venous invasion than are bile duct or pancreatic carcinomas of the same stage (90,91). Today, these lesions also tend to be detected early due to the widespread use of upper endoscopy.

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T—Primary tumor</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades the muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum with extension 2 cm or less)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor perforates visceral peritoneum or directly invades other organs or structures (includes loops of small intestine, mesentery, or retroperitoneum more than 2 cm and abdominal by way of serosa; for duodenum only, invasion of the pancreas)</td>
</tr>
<tr>
<td><strong>N—Regional nodes</strong></td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Regional node metastases</td>
</tr>
</tbody>
</table>
### TABLE 7.4 TNM Classification: Ampulla of Vater

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>T—Primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Primary tumor</td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the ampulla of Vater or sphincter of Oddi</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades the duodenal wall</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades pancreas</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades peripancreatic tissues or other adjacent organs or structures</td>
</tr>
<tr>
<td>NX</td>
<td>Regional nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Regional node metastases</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

### Stage grouping

<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Chapter 7

Stage 0  Tis  N0  M0
Stage I A  T1  N0  M0
Stage IB  T2  N0  M0
Stage IIA  T3  N0  M0
Stage IIB  T1, T2, T3  N1  M0
Stage III  T4  Any N  M0
Stage IV  Any T  Any N  M1

However, ampullary carcinomas extending beyond the sphincter of Oddi have as poor a prognosis as tumors arising in other parts of the small bowel (92). The prognosis may actually be even worse since the patients require a Whipple procedure rather than a mere intestinal resection (22). Ampullary tumors arising in the pancreas or distal bile ducts have a worse prognosis than those arising in the duodenum (93,94).

Polypoid tumors tend to have a better prognosis than infiltrative ones. Patients with well-differentiated carcinomas (90,95) or papillary lesions (92) enjoy a better prognosis than patients with moderately or poorly differentiated tumors. Tumor proliferative rate may also serve as a useful prognostic indicator. Independent adverse prognostic factors include involvement of resection margins, presence of metastases, small blood vessel invasion, and perineural infiltration by tumor cells (90,92,94,95,96). Tumors that invade into the pancreas or those with nodal metastases display a particularly poor prognosis. The median overall survival time is 20 months. The overall 5-year survival rate is 22% to 28% for adenocarcinoma (22). The prognosis is particularly poor when the mesenteric lymph nodes are involved. In a recent study, 4% of patients had stage I, 20% had stage II, 39% had stage III, and 35% had stage IV disease (22). The liver is the most common site of metastasis.

Small intestinal carcinomas recur both locally and at distant sites. The most common sites of tumor recurrence include the tumor bed, regional lymph nodes, and liver. Most recurrences become evident within 2 years of curative resection, but one also sees relapses 5 years or more following the initial surgery (97,98). Peritoneal carcinomatosis is a common recurrence pattern and associates with a very poor prognosis (99).

**Treatment**

Surgery remains the mainstay of treatment, but there is a significant increase in the use of adjuvant therapy in the last 5 or 6 years (99,100). Overall, only approximately 50% to 60% of patients can undergo curative resections and 50% of patients die within a year of diagnosis. Patients with peritoneal carcinomatosis are very resistant to standard chemoradiation (100). Treatment is usually palliative. However, more recently, cytoreductive surgery and intraperitoneal hyperthermic chemotherapy have become treatment options (101), and can significantly improve patient prognosis (102). Thus, the surgical pathologist may encounter multiple specimens from the cytoreductive surgical procedure. In this setting it may be impossible to recognize that the tumor arose in the small bowel rather than the appendix or colon.

**Secondary Tumors**

Metastatic tumors and tumors extending into the duodenum from adjacent organs are the most common tumors to involve the small intestine (1). These may closely mimic primary small intestinal carcinomas both grossly and microscopically. No specific histologic features distinguish a small intestinal adenocarcinoma from other gastrointestinal carcinomas unless one sees residual adenoma. Clues for distinguishing primary from secondary tumors are listed in Table 7.5.

Secondary tumors extending into the duodenum from adjacent organs are the most common tumors to involve the small intestine (1). These may closely mimic primary small intestinal carcinomas both grossly and microscopically. No specific histologic features distinguish a small intestinal adenocarcinoma from other gastrointestinal carcinomas unless one sees residual adenoma. Clues for distinguishing primary from secondary tumors are listed in Table 7.5.

Tumors arising in the mesentery, pancreas, stomach, or colon spread contiguously into the small bowel. Well-differentiated pancreatic cancer grows in irregular tubular and glandular patterns. The glands are lined by cylindric to cuboidal cells that produce variable amounts of mucin. As the tumor becomes more undifferentiated, the glandular pattern becomes more bizarre, epithelial anaplasia increases, and mucin production decreases. The tumors induce a marked desmoplastic response (103) and are often associated with multiple areas of pancreatic intraepithelial neoplasia.

| TABLE 7.5 Clues for Distinguishing Primary from Secondary Small Intestinal Carcinomas |

file:///F|/Gastro/Chapter%207%20epithelial%20tumors%20of%20small%20intestine.htm (28 of 36)2/4/2009 2:05:48 PM
### Primary Cancer | Secondary Cancer
--- | ---
Association with adenomatous epithelium | No evidence of premalignancy
Small lesion confined to the mucosa or upper submucosa | Large lesion appearing to come from the external surface of the bowel
Radiologic evidence that the lesion is solitary | Evidence of cancer histologically identical elsewhere
Primarily intramural mass | Primarily intramural mass
Multiple lesions | Multiple lesions
Radiologic evidence of extension from another site | Radiologic evidence of extension from another site
Presence of extensive lymphatic involvement | Presence of extensive lymphatic involvement

We have seen secondary cancers, especially pancreatic cancer (Fig. 7.23), induce a hyperplastic epithelial response in the duodenal mucosa that resembles premalignant changes adjacent to primary small intestinal carcinomas. Very atypical cells line the villi. The cells demonstrate cytologic features suggestive of malignancy. The cells often appear more disorderly than does adenomatous epithelium and the characteristic pseudostratified nuclei of adenomatous epithelium are absent. It is unclear whether the atypia represents an unusual hyperplastic response, transformation of the native intestinal mucosa, or pagetoid spread of the tumor.
FIG. 7.23. Carcinoma of the pancreas extending into the small intestine. This case was published in the first edition of this book as primary adenocarcinoma. Subsequently, it became apparent that the patient had a pancreatic primary. A: The mucosa demonstrates hyperplastic features that somewhat resemble adenomatous epithelium. B: Carcinoma is seen dropping off the bottom of the mucosa.

Some types of tumors (such as ovarian carcinomas or pseudomyxoma peritonei) characteristically seed the serosal surfaces of the small bowel (Fig. 7.24). Metastases may also present as intramural masses forming submucosal nodules or plaques. These eventually bulge into the intestinal lumen producing polypoid structures or sessile lesions that can present as an acute obstruction, intussusception, or perforation. They may also ulcerate. Napkin ring–like circumferential stenotic lesions also develop, leading to localized serosal retraction and intestinal kinking. When a limitis plastica–type of infiltration of the bowel wall occurs, the metastatic malignancy simulates Crohn disease or an ischemic stricture.

Metastases from melanoma (Fig. 7.25) and carcinomas of the lung, testes, adrenal, ovary, stomach, breast, large intestine, uterus, cervix, liver (104), and kidney to the small intestine have all been reported. Of these, melanomas and ovarian tumors are the most common. Melanoma, perhaps the most common tumor to metastasize to the small intestine, accounts for approximately one third of all small intestinal metastases (105). Metastatic malignant melanomas may mimic primary GI malignancies. They may be carcinomalike, carcinoidlike, or sarcomalike. The lesion may also resemble a pleomorphic neuroendocrine cell carcinoma but special stains allow one to diagnose the lesions correctly. Multiple metastatic melanotic or amelanotic lesions involve the serosal surfaces of the bowel wall. The diagnosis is generally straightforward if one has a previous history of melanoma or if the tumor cells contain melanin pigment. In amelanotic melanoma, the diagnosis may be more difficult. Tumor color and consistency rarely indicate the primary site of the metastases, except in the case of malignant melanoma when the lesion may appear jet black (Fig. 7.25). If the metastases demonstrate a fish flesh consistency, then a lymphoma may be suspected.

FIG. 7.24. Metastatic carcinoma to the small bowel. A: The metastases are clustered at the mesenteric border as well as in the mesentery itself. B: Multiple metastases are present throughout the mesentery as well as on the serosal surfaces of the bowel. Both patients had primary gynecologic malignancies.
FIG. 7.25. Metastatic melanoma. A: Large submucosal metastases that acted as the lead point of an intussusception. B: Low-power examination shows the submucosal tumor. C: Higher magnification showing the pleomorphic pigmented cells accounting for the black gross appearance seen in A. D: Numerous nodules of metastatic melanoma involving mesentery and bowel wall. E: Single-contrast examination of the small bowel shows numerous target lesions representing ulcerated metastases from malignant melanoma. F: A low-power photograph demonstrating extensive replacement of the small intestinal mucosa by tumor cells. G: One sees diffuse involvement of the mucosa by highly pleomorphic cells, both within the lamina propria of the villous and within the lymphatic channels. H: A higher magnification of the tumor demonstrating the highly anaplastic appearance of the individual cells along with the prominent amphophilic cytoplasm. This tumor was positive for HMB45, negative for cytokeratin, and negative for neuroendocrine markers.

Approximately 5% of testicular tumors, usually embryonal carcinomas and choriocarcinomas, involve the GI tract. These patients usually also have extensive retroperitoneal node involvement (106). GI metastases occur via direct tumor infiltration from affected lymph nodes or via lymphatic (Fig. 7.26) or hematogenous spread. If the site is in the small intestine, the duodenum is most commonly affected.
Chapter 7

FIG. 7.26. Metastatic gastric carcinoma involving small intestinal lymphatics. A: Biopsy that was removed in a patient with epigastric distress. Highly atypical cells lie at the base of the mucosa in the area where the muscularis mucosae has been stripped off by the biopsy procedure. B: In a deeper level that was used to perform immunostains, one can see the presence of cytokeratin-positive cells within the lymphatics. The immunostain was ordered because of the atypia of the cells at the base of the mucosa seen in A. The patient subsequently was shown to have a gastric cancer.

Retrograde lymphatic metastases cause another pattern of metastasis. This occurs most often with gastric, pancreatic, or colon cancers. Subserosal lymphangitic spread appears as small nodules associated with a delicate grayish network of lymphatic channels. Colon cancers may also preferentially metastasize to the duodenum since the lymphatics from the right colon drain into the paraduodenal lymph nodes. When this occurs, the duodenal loop enlarges, ulcerates, and becomes distorted with eventual mucosal erosion.

Hematogenous spread to the small intestine occurs more commonly in tumors originating outside of the digestive tract, such as melanomas. Occasionally one sees intravenous tumor associated with areas of thrombosis, suggesting either secondary venous involvement by an intraintestinal metastasis or retrograde dissemination due to venous invasion and thrombosis of a large mesenteric vein.

Metastatic lung tumors, particularly of the spindle cell squamous cell variant, may grossly and histologically simulate a sarcoma, requiring the use of special stains to arrive at the appropriate diagnosis. Lung cancers, particularly squamous cell carcinoma, appear to preferentially localize to the proximal jejunum (1). Finally, sarcomas rarely metastasize to the small bowel (1).

Use of antibodies to CDX2, villin, CK7, CK20, CEA, HAM56, HMB45, MELAN-A, and TTF-1 help separate primary small intestinal tumors from metastatic nongastrointestinal carcinomas.

Handling the Specimens from Patients with Small Bowel Carcinomas

Pancreaticoduodenectomy (Whipple)

Patients with invasive duodenal adenocarcinomas are often treated with a pancreaticoduodenectomy (i.e., Whipple resection: A resection of the distal stomach, duodenum, distal biliary tree, and head of pancreas). The stomach and duodenum should first be placed in a fixative, preferably formalin, to allow for deep fixation. Inserting a probe from the cut surface of the common bile duct through the biliary tree and into the duodenal lumen is not recommended. Metal probes damage and distort the lining cells of these ducts and subsequent
sections will often show complete loss of the epithelial lining. Neoplasms involving the ampulla and distal bile ducts should be blocked in their entirety. Sections should be taken parallel to the long axis of the bile duct and pancreatic ducts as they enter the ampillary area. In this manner, the entire distal duct system can be followed and reconstructed, as the ducts will appear on more than one slide. In addition, the entire mucosal surface surrounding the ampulla should be examined. In many cases, residual adenomatous epithelium can be found involving the adjacent duodenal mucosa, the ampulla, or the biliary and/or pancreatic ducts.

If, on gross examination, a tumor grossly involves the serosal surface or the adjacent pancreas, sections should be taken in these areas to document the extent of local invasion. Sections should be taken of the pancreas, including the surgical line of resection, to examine the pancreatic ductal system. Carcinomas arising in the duodenum and ampulla will infrequently be associated with atypical changes within pancreatic ducts away from the ampulla, and usually not at the line of resection. In contrast, carcinomas arising in the head of the pancreas are often associated areas of pancreatic intraepithelial neoplasia. Similarly, one should examine the resected end of the common bile duct to look for atypia of the lining cells. Again, as for the pancreatic ducts, one usually will not find dysplastic or neoplastic changes in the lining cells of the common bile duct at the line of resection when the tumor originates in the duodenum. However, an invasive carcinoma that has extended from a primary site may be found in the wall of the bile duct. The connective tissue between the duodenum and pancreas should be examined carefully for lymph nodes. Adenocarcinomas arising in the duodenum or ampulla metastasize first to these pancreaticoduodenal nodes and then more distantly (1). The College of American Pathologists' suggested protocol for examining and reporting these specimens is found in reference 107.

**Other Small Intestinal Resections**

Carcinomas arising in the distal duodenum, jejunum, or ileum are often treated by segmental resection. The resected segment of bowel should be opened and fixed, preferably in formalin. Sections should show the relationship of the tumor to the adjacent mucosa and to the underlying serosa. If the resection margins are closer than 5 cm to the tumor, they should be examined. The mesentery should be examined for lymph nodes.

Invasive carcinomas arising in Crohn disease may also produce grossly apparent lesions that resemble other small bowel carcinomas. However, the carcinomas may also produce stenotic areas or diffuse thickening of the bowel wall, mimicking the gross appearance of the underlying Crohn disease. In this setting, the carcinomas may not be recognized at the time of surgery or even when the pathologist examines the gross specimen. In many cases, the diagnosis of carcinoma is made at the time of histologic examination. Because carcinomas arising in intestines affected by inflammatory bowel disease may be difficult to identify by gross examination, we recommend that many sections be obtained of the resection specimens from patients with longstanding Crohn disease. Ideally, sections should be taken along the entire length of the grossly abnormal bowel, but this may not be practical, especially when long segments of bowel are involved. At least one section should be taken for every 5 cm of inflamed bowel, but in the relatively short resection specimens often obtained in Crohn disease cases, the entire length of the grossly diseased bowel should be sectioned.

**References**

Chapter 7


64. Fenoglio CM, Kaye GI, Lane N: Distribution of human colonic lymphatics in normal, hyperplastic and adenomatous tissue. Its relationship to metastasis from small carcinomas in pedunculated adenomas with two case reports. *Gastroenterology* 1973;64:926.


Chapter 8
Nonneoplastic Diseases of the Appendix

Normal Embryonic Development

The cecum appears during the fifth fetal week, arising as a diverticulum from the distal primitive intestinal loop before it differentiates into the small and large intestine. The appendix develops from the cecum and matures in the second trimester (1). As the appendix lengthens, the junction between the appendix and the cecum becomes increasingly more distinct. Longitudinal folds and ridges form, producing a segmented appearance; villi form (Fig. 8.1) that eventually involute. The epithelium appears clear due to large amounts of intracytoplasmic glycogen. Endocrine cells develop in the subepithelial connective tissue around the ninth fetal week when the epithelial basement membrane is not fully formed and the muscularis mucosae has not yet developed.

Lymphoid stem cells migrate into the appendiceal mesenchyme. Mature lymphocytes appear when the fetus measures approximately 100 mm in length (2); lymphoid aggregates appear by the 17th week. The apical poles of incipient lymphoid follicles impinge on the surface epithelium by the time the fetus reaches 150 mm in length and lymphoid cells invade the epithelium. Germinal centers develop between the third and sixth postnatal weeks after the introduction of foreign protein (by eating) into the gut. Macrophages appear shortly after the lymphocytes (3). Primitive neural structures develop in the first trimester.

Normal Gross Anatomy

The appendix usually arises from the posteromedial cecal wall, 2.5 to 3 cm below the ileocecal valve at the convergence of the taeniae coli (Fig. 8.2). The adult appendix averages 7 cm in length; lengths up to 20 cm have been reported. The appendix is longer in adults than in children. Its external diameter ranges from 0.3 to 0.8 cm. The appendiceal lumen measures from 1 to 2 mm in diameter appearing round, oval, irregular, or slitlike. The distal tip obliterates in adults. The appendix is suspended from the mesoappendix, and attaches to the cecum in several ways (4). In 65% of adults, the appendix lies behind the cecum with its orifice opening into the cecum near the ileocecal valve. It may also lie to the side of the ascending colon, in front of, or behind, the ileum, lying on the psoas muscle or hanging over the pelvic brim (4). The appendix receives its blood supply from a branch of the posterior cecal artery; its venous drainage is to the portal system, explaining the coexistence of hepatic inflammation in the setting of appendicitis. The lymphatics first drain into the nodes of the mesoappendix and then to the right pericolic lymph nodes as well as to the ileocecal lymph nodes.

Histology of the Appendix

The appendiceal mucosa resembles that of the large intestine, except for the prominent circumferential arrangement of lymphoid follicles known as Peyer patches. Peyer patches (Fig 8.3) are most prominent in children, decreasing in size with age. They are markedly diminished or absent in the elderly. The appendiceal epithelium is modified over the dome of each lymphoid follicle to form M cells with a structure similar to that seen in the small intestine (see Chapter 6). Nonbranching crypts are lined by tall mucus-secreting goblet cells that extend from the luminal surface to the crypt bases. The crypts also contain endocrine cells, Paneth cells, and small numbers of intraepithelial lymphocytes. The muscularis mucosae is often absent; it is sometimes difficult to determine the mucosal–submucosal boundary.

The regularly arranged Peyer patches lie at the mucosal–submucosal junction (Fig. 8.3), and a well-defined lymphatic sinus surrounds both the lateral and basal parts of the follicle. These lymphatic sinuses empty into the submucosal-collecting lymphatics. Lymphocytes that proliferate in the gut-associated lymphoid tissues migrate into the surrounding lymphatic sinus or capillaries and enter the systemic circulation to be redistributed to other lymphoid tissues and organs. The endocrine cell population is discussed in Chapter 17.

Congenital Abnormalities of the Appendix

Congenital appendiceal anomalies are rare (5). They include appendiceal agenesis (6), hypoplasia, duplications, horseshoe shape (7), heterotopia, and diverticula. These
occur in the presence of either a normal cecum or with cecal dysgenesis.

**FIG. 8.1.** Fetal appendix. **A:** Differentiation of the ileum, cecum, and appendix is not easy at this time since villi are present in all three areas. **B:** Higher magnification of the fetal villi showing a glycogenated epithelium, proliferating crypts, and villi. The section comes from the blind distal end of the specimen shown in A.

**FIG. 8.2.** The normal appendix arises at the junction of the three taenia coli.
FIG. 8.3. Appendix from a 1-year-old boy. A: Low-power magnification showing the regular arrangement of the lymphoid follicles and the straight tubular crypts. B: Higher magnification showing a single follicle.

FIG. 8.4. Hypoplastic appendix. A: The lamina propria blends into the underlying submucosa and muscularis propria. No muscularis mucosae is present. Numerous cystically dilated glands are present in the submucosa. B: Higher magnification showing the lack of a distinction between the lamina propria and the underlying submucosa.
Appendiceal Agenesis

Appendiceal agenesis (or absence) differs from appendiceal hypoplasia in that in the latter condition, the appendix is present but underdeveloped with a simplified structure and with mucosal cysts (Fig. 8.4). There are five types of appendiceal agenesis (Fig. 8.5) (6). All result from failure of the primitive cecal diverticulum to differentiate into the appendix, except for the fourth type. The fourth type results from intrauterine atrophy of a previously well-formed appendix. Appendiceal agenesis sometimes accompanies ileal atresia (8), thalidomide ingestion (9), or trisomy 18. Patients with trisomy 18 usually have multiple gastrointestinal and extragastrointestinal congenital abnormalities (6).

Positional Abnormalities

The appendix may lie in unusual locations, usually because of the cecal mobility, excessive appendiceal length, situs inversus, or intestinal malrotation. This may cause an otherwise typical appendicitis to present in atypical ways.

Duplications

Three patterns of appendiceal duplication exist: Double barreled, paired, and accessory (10). In “double-barrel” appendix, two separate tubes, each lined by a mucosa and separated by a submucosa, lie within a single muscular coat. Two symmetrically placed appendices lie on either side of the ileocecal valve in the paired form of duplication. This only occurs in infants with multiple congenital anomalies. A normal-appearing appendix lying in its usual position and a second rudimentary appendix arising from the cecum represents the accessory type of duplication. Triplication of the appendix can also occur (11).

Heterotopias

Heterotopic tissues rarely affect the appendix. However, heterotopic gastric, esophageal, ileal, and pancreatic tissues can all occur in this location.


Diverticulosis

Diverticula affect 0.004% to 2.8% of histologically examined appendices (5,12). They can be congenital or acquired; both
types may be single or multiple. Congenital diverticula present as antimesenteric outpouchings with complete muscular walls, contrasting with acquired diverticula that lack the muscularis propria (Fig. 8.6). Some congenital diverticula are attached to the umbilicus by a fibrous band, resembling Meckel diverticulum.

Acquired diverticula are ten times more frequent than their congenital counterparts (5). They affect both sexes equally and develop along the area of the penetrating arteries, often secondary to inflammation or tumors. Associated neoplasms, particularly low-grade mucinous neoplasms, are present in many patients (Fig. 8.6) (13). Diverticula develop due to the increased pressure of the accumulated intraluminal mucin. A similar mechanism may be responsible for the relatively high incidence (14%) of appendiceal diverticula in patients with cystic fibrosis.

Acquired diverticula are commonly multiple (Fig. 8.6), lying along the mesenteric and antimesenteric borders. They usually involve the distal appendix, giving the appendix a beaded appearance. Their size varies from 2 to 5 mm. Like colonic diverticula, they are subject to inflammation or perforation. Inflammation may distort, obliterate, or disrupt a diverticulum. When the inflammatory process spreads into the periappendiceal tissues, an abscess results.

**Appendiceal Intussusception, Autoamputation, and Inverted Appendiceal Stump**

Appendiceal intussusception is rare, usually affecting young boys (14). Patients range in age from 8 months to 75 years. Predispositions to intussusception include the presence of a fetal cone-shaped appendix, an unusually thin mesoappendix, or the presence of mass lesions, most typically endometriosis, adenomas, carcinoid tumors, or the lymphoid hyperplasia associated with viral infections. The presenting signs and symptoms resemble those of acute appendicitis. The lesions may also remain asymptomatic only to be discovered incidentally.

![FIG. 8.6. Appendiceal diverticulosis associated with an appendiceal adenoma. There are multiple diverticula extending through the appendiceal wall. They lack the muscularis propria as is typical of acquired diverticula.](image)

| TABLE 8.1 Types of Appendiceal Intussusception |
There are four types of appendiceal intussusceptions (Table 8.1). In some cases, the distal appendix intussuscepts into the proximal appendix; in other cases, the proximal appendix intussuscepts into the cecoappendicular opening or the whole appendix intussuscepts into the cecum (Fig. 8.7), presenting as an edematous or infarcted cecal “polyp.” Intussusception can also appear as an umbilicated area at the junction of the taeniae coli on the cecal serosal surface. The mucosa may appear normal, hyperplastic, inflamed, eroded, or ischemic. The latter occurs if the vascular supply has been compromised. If there have been recurrent intussusceptions, the mucosa and muscular layers may become hyperplastic. In intussusception, the histology may also appear to be reversed from normal, with the epithelium lying on the external surface of tissue and the submucosa and muscularis propria lying inside the mucosa (Fig. 8.8). The submucosa becomes edematous and the muscularis propria may appear hyperplastic, fibrotic, or splayed (Fig. 8.9). The muscular layers maintain a normal relationship with one another and with the submucosa and mucosa. Sometimes the bowel wall appears to have two muscularis propriae. It is important that the appendix be examined carefully in this setting to exclude the presence of an underlying neoplasm or other lesion such as endometriosis that may have been the lead point for the intussusception. Treatment of the intussusception is surgical resection.
FIG. 8.7. Appendiceal intussusception. Double-contrast barium examination demonstrating inverted appendiceal stump.
**Fig. 8.8.** Diagram of appendiceal intussusception. **A:** The tip of the appendix begins to move toward the junction of the appendix with the cecum. A section taken through the appendix (indicated by the *black line*) demonstrates essentially normal histologic features. **B:** Once the appendix intussuscepts into the cecum, it may produce a small polyp. A cross section through the lesion taken at the level of the black line shows the inverted histology.

**Fig. 8.9.** Appendiceal intussusception. **A:** The lesion presented as a cecal polyp. One can see the cautery margin (*arrows*) of the “polypectomy” specimen. The center of the “polyp” consists of hyperplastic muscularis propria. External to this is an edematous submucosa. The surface of the polyp is covered by appendiceal-type mucosa with prominent lymphoid follicles. **B:** Higher magnification showing the presence of the submucosal edema and marked lymphatic dilation.

Occasionally, the appendix autoamputates following intussusception or volvulus. The presence of cecal scarring and hemosiderin in the absence of other cecal abnormalities provides clues that the appendix was present at birth. Inverted appendiceal stump follows appendiceal autoamputation, and may appear as a cecal polyp grossly or endoscopically. One of the complications of an appendiceal stump is a vascular malformation. Patients may present with massive bleeding from cecal ulcerations. Histologically, massively dilated vessels are present.

**Torsion**

Appendiceal torsion is rare, and when it occurs it causes ischemic appendicitis (Fig. 8.10). Histologically, one sees distal inflammation with areas of hemorrhage and necrosis. As with intussusceptions, a careful examination for the presence of an underlying neoplasm, as well as the assessment of the adequacy of the resection of the appendix if a neoplasm is present, is important.

P.502
FIG 8.10. Appendices that undergo torsion usually show some evidence of ischemia.
FIG. 8.11. Septated appendix. A: Several cross sections through areas showing incomplete septa. The lumen contains projections of tissue covered by atrophic appendiceal mucosa. Extensions of the submucosa form the core of the septum. B: Higher magnification of the septum.

**Septated Appendix**

Single or multiple, complete or incomplete septa consisting of mucosa and submucosa may divide in the appendiceal lumen into compartments (Fig. 8.11), predisposing the appendix to develop appendicitis. The inflammation usually remains confined to one compartment of the septated lumen. These lesions present most often in the 15- to 19-year age group with a clear-cut male predominance. They represent residual fetal septations.

**“Absent Appendix”**

The appendix may appear to be absent for several reasons: (a) agenesis; (b) previous resection; (c) obliteration from previous episodes of acute appendicitis, intussusception, or torsion; or (d) its presence in unusual locations. Retrocecal, retrocolic, and retroileal appendices are uncommon but can cause clinical confusion, especially in the individual who presents with acute abdominal pain. Acute appendicitis can resolve, leaving only a thin fibrous cord. Resection of the appendix should be suspected in individuals who have undergone previous surgical procedures. The confluence of the three cecal taeniae is the only consistent landmark for the appendiceal origin.

**Appendicitis**

**Demographic Features**

Appendicitis develops at any age, with a peak incidence in the 2nd and 3rd decades. However, it also affects neonates and the very elderly. Between 7% and 12% of the U.S. population develop appendicitis. Appendicitis occurs more commonly in
Western cultures than in Eastern cultures, likely due to dietary differences between these populations (15). Heredity may also play a role in the pathogenesis of appendicitis (16). Appendicitis affects males more commonly than females, particularly during early childhood (17).

Acute appendicitis may also develop in neonates. Although this is rare, it associates with high morbidity and mortality rates (18,19). Neonatal appendicitis usually results from the presence of neonatal necrotizing enterocolitis, cystic fibrosis, Hirschsprung disease, or the bacteremia associated with maternal chorioamnionitis (18).

Despite the proclivity of appendicitis to involve younger individuals, it also affects the elderly and other age groups. The incidence of appendicitis in the elderly may be increasing due to their longer life expectancies. Appendicitis in the elderly also has a high mortality and complication rate (20), perhaps due to concomitant nonsteroidal anti-inflammatory drug (NSAID) use. NSAIDs may impair the inflammatory processes and suppress white cell responses increasing the risk of developing appendicitis (20). Additionally, NSAIDs mask the symptoms so that patients present with late-stage disease.

**Pathophysiology**

The etiology of appendicitis is multifactorial. It may involve obstruction, ischemia, infections, and hereditary factors. A common scenario in the pathogenesis of the disease involves a sequential series of events that begins with luminal obstruction due to any of the factors listed in Table 8.2. The obstruction is followed by loss of mucosal integrity, ischemia, and bacterial invasion. Secretions accumulate under pressure behind the obstruction. The mucosa can also be primarily involved by infections, as in the rest of the intestines without antecedent obstruction, or it may be affected by inflammatory bowel disease (IBD). Bacterial, viral, fungal, and parasitic diseases may all cause specific forms of acute appendicitis. However, microbiologic studies generally show that no single organ is identified; rather, a mixed aerobic and anaerobic bacterial population is present in most cases. The most commonly isolated bacteria are *Bacteroides fragilis* and *Escherichia coli* (21). *Streptococcus milleri* can also be detected (22). *S. milleri* may be more important than some of the other bacterial species, since these have a sevenfold increased risk for abscess formation (22). *Campylobacter jejuni* is also an important cause of acute appendicitis (23).

**TABLE 8.2 Causes of Appendiceal Obstruction Leading to Appendicitis**

<table>
<thead>
<tr>
<th>Stones (fecaliths)</th>
<th>Food</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucus—most often in cystic fibrosis</td>
<td>Kinks (angulated appendix)</td>
</tr>
<tr>
<td>Parasites</td>
<td>Tumors in the appendix or cecum</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Foreign objects</td>
</tr>
<tr>
<td>Lymphoid hyperplasia—usually secondary to viral infection</td>
<td></td>
</tr>
</tbody>
</table>

Once an infection becomes established, pressure from inflammation and edema predisposes to the rapid development of gangrene, perforation, and peritonitis. Infections may also cause fibrin thrombi, which can block the small appendiceal vessels, causing secondary ischemia. The appendix is particularly prone to ischemia, since the appendiceal artery is an end artery. The enteric nervous system may also play a role in the pathogenesis of acute appendicitis. Increased numbers of nerve fibers, Schwann cells, and enlarged ganglia have all been found in patients with acute appendicitis (24).

**Clinical Features**

The diagnosis of appendicitis is straightforward when it presents classically with right lower quadrant abdominal pain of short duration, abdominal rigidity, and anorexia. Appendicitis also causes acute periumbilical, colicky pain or vomiting. Fever and
leukocytosis develop early. However, there are many examples of appendices that are removed for suspected acute appendicitis in which histologic evidence of an acute appendicitis is lacking.

**Pathologic Features**

Normally, the appendiceal mucosa appears smooth, light yellow-tan; the serosa appears pink-tan, smooth, and glistening. When the inflammation is restricted to the mucosa, the exterior of the appendix may grossly appear normal. Dilation and congestion of serosal vessels produce localized or generalized hyperemia and constitute the earliest visible external changes (Figs. 8.12, 8.13, and 8.14). Well-developed acute appendicitis shows marked congestion with a dull (rather than glistening) serosal surface or there may be a serosal granular, fibrinous, or purulent coating and vascular engorgement reflecting severe necrosis and inflammation. The mesoappendix appears edematous and contiguous structures may become inflamed. The appendix often exudes purulent material from the cut surface; one may sometimes identify an impacted intraluminal fecalith. Mucosal necrosis and ulceration are usually present. The acute inflammation can localize to one segment of the organ or the entire appendix may be affected. There may be the appearance of a mucocele. If so, the appendix should be well sampled to exclude the presence of a coexisting mucinous neoplasm.

*Fig. 8.12. Fecalith and acute appendicitis. A: Gross photograph. The proximal bulge is due to the presence of an intraluminal fecalith. Marked vascular engorgement is seen and a fibropurulent exudate covers the appendix (curved arrows). B: Specimen radiograph showing a radiopaque fecalith.*

By the time full-blown gangrenous appendicitis develops, the organ appears soft, purplish, and hemorrhagic or even greenish black, sometimes with visible thrombi in the mesoappendix. These may spread along the ileocecal and upper mesenteric veins. Perforation may be present. In complicated cases, abscesses may form around a site of perforation and inflammation may extend into the mesoappendix (Fig. 8.15).

Histologic changes associated with appendicitis reflect disease duration and severity, and some changes may not reflect clinical disease at all. The term *acute intraluminal appendicitis* has been used when there are neutrophils in the appendiceal lumen but they have not yet infiltrated the mucosa (25). This may not be of any significance since this finding can be seen in incidental appendectomy specimens. Other minimal changes may consist of focal neutrophilic collections in the lumen and lamina propria. This is sometimes referred to as *mucosal or early* appendicitis. The term *mucosal appendicitis* has been used both in the presence and the absence of ulcers if the inflammation is restricted to the mucosa (26,27,28). The clinical significance of pure mucosal inflammation in the absence of ulcers is uncertain. Since these changes may reflect sampling error, more sections should be taken of the appendix to be certain that there is not more extensive inflammation elsewhere in the appendix.
In better-developed disease, focal erosions, cryptitis, and crypt abscesses develop. The inflammation then extends to the submucosa. After the inflammatory process reaches the submucosa, it spreads quickly to involve the remaining appendix. Eventually, the mucosa erodes, the wall becomes necrotic, and the vessels may thrombose. Submucosal abscesses, edema, and congestion follow. Some appendices contain prominent eosinophilic infiltrates. Extravasated mucin in the bowel wall may induce a foreign body reaction or even small mucin granulomas.

Gangrenous appendicitis shows extensive suppuration, often extending deep into or through the appendiceal wall with complete mural destruction (Figs. 8.16 and 8.17) with or without rupture. If perforation occurs, an intense nonspecific inflammatory process ensues. Perforation may be suspected clinically, but it is sometimes difficult to see in the resected specimen due to the extensive inflammation. Resolving appendicitis is characterized by the presence of a predominantly lymphocytic infiltrate involving the subserosa and muscularis propria or the subserosa. When appendicitis heals, it assumes one of two basic patterns: The “usual” pattern, sometimes with an intraluminal cord of granulation tissue, and a xanthogranulomatous pattern (29). Fibrosis may develop.
FIG. 8.14. Gangrenous appendicitis. The external surface of the appendix is hemorrhagic and reddened with a well-developed fibropurulent membrane.

Although full-blown appendicitis is histologically easily identified by mucosal ulceration and neutrophilic infiltrates extending through the appendix wall to the peritoneal serosa, occasionally minimal inflammation can be difficult to diagnose due to inconspicuous pathologies. Staining with E-selectin, the first inducible cell adhesion molecule, expressed in early appendicitis, may help detect minimal or less obvious disease (30), although correlation between clinical findings and pathologic abnormalities may be speculative at best.

Complications

The most common complication of appendicitis is perforation, which can lead to generalized peritonitis, subdiaphragmatic and periappendiceal abscesses, serosal pneumatosis, and suppurative pylephlebitis (Fig. 8.15). Infected thrombi may involve the serosal and mesoappendiceal small vessels and may extend or embolize to distant sites such as the liver, where they can establish secondary bacterial infections, cholangitis, and hepatic abscesses (31). Fistulae may form between the appendix and the rest of the gastrointestinal tract, vagina, or bladder.

If a perforation occurs slowly, the inflammation often walls itself off, producing a periappendiceal abscess that typically localizes in the right iliac fossa lateral to the cecum. One may find little in the way of residual appendix and only a mass of granulation or xanthomatous tissue surrounding the abscess. This can progress to larger masses of chronic fibrous tissue containing granulomas. Extensive granulomatous reactions may raise the clinical suspicion of a cecal carcinoma. These
granulomas often contain foreign material including feces. In some cases, the inflammatory reaction results in mesothelial entrapment that eventually becomes cystic, simulating a benign cystic mesothelioma, particularly if the mesothelial lining appears reactive and atypical.

**Specific Forms of Infectious Appendicitis**

Any infection affecting the large or small intestine may also affect the appendix. The features of specific bacterial infections resemble those seen in the rest of the intestines (see Chapters 6 and 13). Some of the more common appendiceal infections are discussed briefly here.

*Actinomyces israelii* is part of the normal oral flora. Yet, the same organism can become pathogenic. When it survives passage through gastric acid and reaches the appendix, it usually lodges there without causing disease or inflammation. Sometimes, however, one sees inflammation surrounding organisms in the appendix and one assumes that the *Actinomyces* caused the appendicitis. Actinomycotic appendicitis is rare, but it is important to diagnosis, since it can cause a chronic suppurative appendicitis, periappendicitis, or periappendicular mass. The infection can lead to a granulomatous mass with multiple sinus tracts draining to the overlying skin, or leading to pelvic abscesses. The infection can also spread to the liver via the portal system, creating hepatic abscesses. Fluid draining from the sinuses usually contains characteristic “sulfur granules” (Fig. 8.18). Examination of hematoxylin and eosin (H&E)-stained sections reveals collections of long dark blue filamentous organisms, often associated with characteristic sulphur granules. Acute inflammation is often present. A dense fibrous connective tissue mass may surround the actinomycotic mycelia. The diagnosis should be suspected in any patient who develops sinus tracts and/or fistulas following appendectomy. *Actinomyces turicensis* can also be found in patients with appendicitis (32).

*Tubercular* appendicitis may complicate tubercular infections in other parts of the gastrointestinal tract or may develop as an isolated disorder. The appendix is frequently involved in this setting due to the abundant lymphoid tissues that are present in this location. The disease is more progressive in children than in adults. Individuals who perforate are likely to develop generalized peritonitis (33). The histologic features resemble those described in the intestines (see Chapter 13).
FIG. 8.16. Acute appendicitis. A: Cross section through the appendix showing the transmural inflammation. B: High magnification of the surface exudate that contains necrotic debris and bacteria. C: Below the surface of the debris shown in B there is acute and chronic inflammation. D: Acute and chronic inflammation with small thrombi within the dilated and congested veins. E: Cross section through a larger vessel containing an organizing thrombus at the base of the vessel (arrow). Overlying the vessel is necrotic and inflammatory debris. Under the vessel is a zone of acute and chronic inflammation. F: Cross section through a small vessel demonstrating with fibrinoid necrosis and acute and chronic inflammation. G: The serosa shows marked vascular engorgement and small thrombi in the dilated vessels (arrow). H: Lower magnification showing the extension of fibrosing stands of tissue extending into the mesoappendiceal fat. The vessels on the serosal surface are markedly engorged. The lumen of the appendix at this level is completely necrotic (star).

FIG. 8.17. Appendicitis (A and B, acute appendicitis; C and D, chronic appendicitis). A: At this stage, one sees acute inflammation involving the appendiceal epithelium. The epithelium lining the crypt becomes flattened and cuboidal in shape. An intense inflammatory process is present in the luminal side of the crypt (star). Cryptitis appears. The inflammatory cells present on the opposite side of the epithelium represent the normal lamina propria. B: Necrosis. The entire epithelium has become denuded and replaced by hemorrhage and exudate. C: Higher power magnification of the inflammatory process showing chronic inflammation and giant cells. D: Higher power magnification of the giant cells.
Yersinia infections may localize to the appendix producing a granulomatous appendicitis. The infections affect both children and adults. Both Yersinia enterocolitica (YE) and Yersinia pseudotuberculosis (YP) cause gastrointestinal disease. These two forms of Yersinia infection can coexist in the same patient. The granulomas are predominantly epithelioid and noncaseating in nature with striking lymphoid cuffing. Prominent microabscesses in the center of the granulomas may be seen in YP infections. The granulomas may be located in all layers of the appendiceal wall, or they may be restricted to the mucosa and submucosa. The number of granulomas varies from 1 to >15/× objective field (Fig. 8.19). There is usually an accompanying transmural mixed inflammatory infiltrate associated with the prominent lymphoid aggregates.

This inflammation may extend into the mesoappendix. Other features that may be present include marked lymphoid hyperplasia, giant cells, mucosal ulceration, focal architectural distortion, and crypt abscesses (34).
FIG. 8.19. *Yersinia* appendicitis. A: Cross section through the appendix in *Yersinia* appendicitis demonstrates the presence of a thickened wall and small nonconfluent granulomas. B: Low-power magnification photograph showing the prominent lymphoid follicles within the Peyer patches and inflammation extending from the lumen to the submucosa. Areas of ulceration overlying the lymphoid tissue are evident. In addition, granulomas are present. C, D: Progressively higher power magnifications of the granulomatous process.

The appendix is seldom removed in patients with viral appendicitis since the disease remains self-limited and the appendicitis resolves once the viral infection resolves. Viral infections frequently localize to the lymphoid tissue of Peyer patches, inducing lymphoid hyperplasia. The enlarged follicles may temporarily block the egress of luminal secretions, producing the characteristic symptoms of acute appendicitis.

Viral infections commonly associated with transient appendicitis include *measles* and *adenovirus* infections. Finding huge, multinucleated giant lymphoreticular cells known as Warthin-Finkeldey cells in the lymphoid tissues of Peyer patches suggests the diagnosis of measles (Fig. 8.20). However, similar cells may also occur in other viral infections as well. Furthermore, Warthin-Finkeldey cells may not be specific for viral infections, since they have been seen in patients with systemic lupus erythematosus. Thus, they may merely indicate reactive lymphocytic lesions (35).

The appendix of patients with *adenovirus* infections appears normal or demonstrates marked lymphoid hyperplasia, unless an intussusception has occurred. The most common site of the intussusception is at the ileocecal valve with focal lymphoid hyperplasia acting as the lead point (see Chapter 6). The epithelium overlying the lymphoid hyperplasia appears tattered and necrotic when an intussusception develops. Clues to the presence of the virus include focally necrotic-appearing epithelium showing loss of nuclear polarity. Affected cells may have an eosinophilic appearance due to mucin depletion. The intranuclear inclusions of adenovirus are typically Cowdry type B, consisting of nuclear smudging (Fig. 8.20). Cowdry A inclusions featuring sharply demarcated globules surrounded by a clear zone can also be found. Histologically, the intranuclear inclusions appear...
as reddish globules surrounded by halos or a poorly demarcated purple smudge in otherwise well-preserved cells. If one wishes to confirm that a specific virus is present, one can use antibodies to the virus or perform in situ hybridization with an appropriate genetic probe.

P.509

FIG. 8.20. Viral infections. A: Warthin-Finkeldey cell in the lymphoid tissue in a patient with a known measles infection. The figure demonstrates the characteristic multinucleated giant cells seen in this disorder. B: Adenovirus infection. The cells are fused together in a syncytium and contain characteristic intranuclear inclusions. (B courtesy of Dr. Renate Reif, “Assaf Harofe” Medical Center, Tel Aviv Medical School, Zrifin, Israel.)

Cytomegalovirus (CMV) infections also represent a possible etiologic agent for appendicitis, particularly in immunocompromised individuals. The changes resemble those seen in the large and small intestines.

Acute abdominal pain from abdominal lymphadenopathy, hepatitis, splenic involvement, or involvement of the gut-associated lymphoid tissues in the intestine and appendix may be the presenting feature of infectious mononucleosis (36). One sees intense lymphoid hyperplasia with marked expansion of the interfollicular lamina propria by a mixed diffuse proliferation of immunoblasts including Reed-Sternberg–like cells admixed with large and small lymphocytes. Mitoses are absent and the glands appear to be reduced in number because of the extensive lymphoid hyperplasia. The lymphoid infiltrate extends deep into the underlying submucosa. The predominant cell type is an atypical lymphocyte, many of which lie around vessels, producing a vasculitislike pattern. In fatal forms of the disease, the mucosa becomes ulcerated.

Appendiceal fungal infections resemble similar infections in the intestines. They include mucormycoses (Fig. 8.21), histoplasmosis, South American blastomycosis, aspergillosis, and candidiasis. Enterobius vermicularis (pinworm) is one of the most common parasites seen in the appendiceal lumen with the incidence varying from 0.2% to 75% worldwide (37,38). The organism occurs more frequently in temperate and cold climates than in the tropics and the disease is common in developed countries of the northern hemisphere. In the United States about 3% of appendix specimens contain E. vermicularis (39). Children are especially susceptible to the infection, with the most common method of transmission being the anus–finger–mouth route (Fig. 8.22). Ingested ova hatch in the duodenum where the larvae molt twice and become sexually mature. Infrequent bathing, use of soiled underwear, crowded habitation, and lack of exposure to sunshine all favor disease transmission. Autoinfection results in repeated infections and a heavy worm burden. Symptoms include perineal or perianal pain and itching. E. vermicularis may also represent an incidental finding in an asymptomatic patient (40).
Chapter 8

FIG. 8.22. Diagram of the life cycle of *Enterobius vermicularis*.

Adult female worms measure 6 to 12 mm and males 2 to 5 mm in length. Because of their gross appearance, they are commonly called pinworms or thread worms (Fig. 8.23). There are three labia in adult females and a lateral pair of cephalic winglike alae; the muscular esophagus terminates in a bulb and the posterior tip is attenuated. The reproductive system is T-shaped in cross section and characteristic eggs are present within the uteri. Adult males possess a ventrally curved tail with caudal alae and a single large copulatory spicule. Adult worms live in the colon and appendix, where they mate. The males die soon after copulation; females migrate to the perianal and perineal regions to lay eggs and die after oviposition. About 11,000 ovoid, asymmetrically flattened, and almost colorless eggs are produced by a gravid female. The asymmetric eggs measure 50 to 60 microns and contain fully developed larvae when they are detected in stools. The eggs of *Enterobius* species are highly contagious because they are infectious at body temperature about 6 hours after deposition and require no intermediate host. The ova are also highly resistant to commonly used disinfectants and can survive as long as 2 weeks in the environment. Identification of adult worms in the tissue depends on demonstrating a pair of cuticular crests (Fig. 8.24), typical eggs in the parasitic uterus, or the characteristic narrow meromyarian type of musculature, which consists of two or three muscle layers per quarter section divided by four cords.
FIG. 8.23. Enterobius. Cross section of an appendix of a 9-year-old girl who presented with acute appendicitis. The appendix contains several worms attached to the wall. (Picture courtesy of Dr. Lida Crooks, Laboratory Services, Albuquerque VA Medical Center, Albuquerque, NM.)

FIG. 8.24. *Enterobius vermicularis*. Cross section of the worm in the appendiceal lumen. Note the characteristic cuticular crests (arrow).

FIG. 8.25. *Enterobius vermicularis*. Cross section through the appendix showing worms in the lumen. Note that the underlying mucosa appears essentially normal except for a mild increase in the number of eosinophils.

Often worms lying in the appendiceal lumen fail to elicit an inflammatory response, except for mild mucosal eosinophilia (Fig. 8.25).
8.25). However, when the worms obstruct the appendiceal lumen, acute appendicitis develops. Severe infestations cause lesions in the colon, cecum, appendix, and lower ileum. The usual manifestations include superficial ulceration, petechial hemorrhages, and sometimes mucosal or submucosal abscesses. When mucosal inflammation is present, it usually surrounds parasitic ova and not the organism itself. The parasite only rarely invades the mucosa, but when it does, granulomas known as Oxyuris nodules form. Severe mucosal eosinophilia occurs in approximately 2% of infections. A rim of granulation tissue enclosed by a fibrous capsule surrounds an eosinophilic center. In addition, one can see eosinophils, lymphocytes, giant cells, and Charcot-Leyden crystals in the nodules. The nodules eventually fibrose and hyalinize, forming obstructive masses that lead to secondary obstruction followed by acute appendicitis. In some cases, the adult worms migrate into the peritoneum and omentum, where they induce a foreign body inflammatory reaction.

Schistosomiasis, a water-borne trematode infection, represents one of the most widespread parasitic diseases; an estimated 300 million people are affected worldwide (41). In endemic areas, schistosomes are found in 1% to 15% of appendiceal resections (42). Not all infected individuals become symptomatic. Granulomatous appendicitis develops in younger patients in the early phase of egg laying in the appendix when an acute granulomatous inflammation surrounds viable ova. Concomitant tissue necrosis, tissue eosinophilia, and neutrophil exudation ensue. Obstructive appendicitis may develop as a result of fibrosis of the appendiceal wall, secondary to a longstanding inflammatory reaction to the schistosomal eggs, which may appear calcified in tissue sections. Ova can also be impacted within vascular lumens, sometimes causing hemorrhagic ischemic necrosis (43).

Ascaris (Fig. 8.26), fascioliasis, sparganosis, various types of amoebae, Balantidium coli (44), Toxocara species, Trichuris trichiura, Trichuris vulpis (45), Reticularis (46), Strongyloides, and Capillaria hepatica all can infect the appendix, either alone or in conjunction with infestation of other parts of the intestine. The histologic features of these infections are described in Chapters 6 and 13.

**FIG. 8.26.** Ascaris adult worm present within the appendiceal lumen.

Consumption of food contaminated with bovine spongiform encephalopathy is believed to cause variant Creutzfeldt-Jakob disease.
disease (vCJD) (47). The infection requires normal numbers of Peyer patches to be present in the small intestine and appendix (48). Immunoreactivity for prion proteins, particularly in the germinal centers of the lymphoid follicles in the appendix, can be seen before the clinical onset of the vCJD. The appendix does not show evidence of acute appendicitis. The presence of the prion proteins in the appendix during the incubation period of vCJD potentially offers the opportunity for screening for the disease in patients undergoing appendectomy (49). However, it should be noted that the abnormal prion protein is not present in all cases of vCJD (50).

“Idiopathic” Granulomatous Appendicitis

Idiopathic appendicitis is a poorly understood disease that is seen in 0.1% to 2% of appendectomy specimens (51,52). It may represent an early manifestation of other granuloma-associated diseases, such as Crohn disease, sarcoidosis, or parasitic or bacterial infections (53). In this setting, appendiceal involvement occurs before other disease manifestations become evident, and therefore the etiology of the granuloma is unclear. In other cases, idiopathic granulomatous appendicitis may in fact be just that. However, the histologic features alone may have very low sensitivity in differentiating among these various etiologies. It has been suggested that, when up to 20 granulomas per tissue section of the appendix are found, this most likely represents isolated idiopathic granulomatous appendicitis (54). However, others have found that patients with 21 granulomas per cross section later developed Crohn disease elsewhere in their gastrointestinal tract, suggesting that the number of granulomas present is not a reliable criterion for separate Crohn disease and idiopathic granulomatous appendicitis (55,56). When neural hyperplasia is present in addition to the granulomas, this may represent early Crohn disease.

Lamps et al confirmed that Yersinia infections are an important cause of granulomatous appendicitis by using a combination of histologic evaluation and molecular techniques to demonstrate Yersinia DNA sequences in tissues. There were no reliable histologic features (described in an earlier section) that distinguished between Yersinia-negative and Yersinia-positive cases. Yersinia infections could only be reliably diagnosed using the polymerase chain reaction (PCR) analysis (53).

When granulomas are found, an effort should be made to determine their etiology by correlation with other findings. In cases suspicious for Yersinia, an attempt should be made to rule in (or rule out) this as the etiology of the granulomas, either by serologic tests or PCR analysis on the tissues in order to facilitate appropriate treatment. If no etiology can be established, the diagnosis of idiopathic granulomatous appendicitis can be made until some other etiology (such as Crohn disease) becomes clear. The provisional nature of the diagnosis can be reflected in a comment.

Appendiceal Changes in Immunocompromised Patients

Immunocompromised individuals develop the usual form of appendicitis as well as involvement by the same infections seen in the remainder of the gastrointestinal tract. In addition, the appendix may be involved by neutropenic enterocolitis. The clue to the diagnosis is the absence of acute inflammation in the presence of ulcers as would be expected in nonneutropenic patients. The histologic features of this entity are described in detail in Chapter 13. One may also see the side effects of drugs used in the transplant setting (see Chapter 13) or increased apoptotic activity in AIDS patients. Lymphoid hyperplasia is also very common in the setting of AIDS.

Inflammatory Bowel Disease

Both ulcerative colitis (UC) and Crohn disease (CD) affect the appendix, although appendiceal involvement occurs more commonly in CD than in UC. The diagnosis of appendiceal UC and CD relies on a combination of clinical, radiologic, and morphologic findings. Examination of an appendectomy specimen may provide the first clue to the presence of IBD, especially when the disease remains confined to the appendix. The histologic changes resemble those seen in the remainder of the intestines. The histologic features of appendiceal involvement by IBD are discussed in Chapter 11.
Drug Effects

The appendix is affected by drugs in much the same way as the small intestine and large intestine (see Chapters 6 and 13); however, there are some unique features that affect the appendix. *Chemotherapy* severely depletes the normal lymphoid tissues, producing a hypocellular lamina propria and loss of Peyer patches (Fig. 8.27). The epithelial cells may appear necrotic or megaloblastic. There is an increased incidence of appendicitis during locoregional chemoradiation for patients treated for rectal and cervical cancers. *Thalidomide* has been connected with appendiceal agenesis.

The introduction of *highly active antiretroviral therapy* (HAART) has revolutionized the management of HIV-infected individuals and its use is usually followed by immune restoration and clinical improvement. While this therapy has changed the profile of HIV-related morbidity, there have been several reports linking HAART with acute inflammatory or infective conditions, including possibly acute appendicitis (57). This may result from the so-called immune restoration inflammatory syndrome. Appendicitis may be precipitated by local lymphatic hyperplasia or by an infectious process in the appendix during the restoration. Another possibility is that the antiretroviral therapy itself may cause appendicitis.

Periappendicitis

Periappendicitis is defined as appendiceal serosal inflammation without mucosal involvement (Fig. 8.28). Periappendicitis most commonly affects boys below the age of 12 years and females between the ages of 17 and 21. Periappendicitis can be classified into two types, juvenile and secondary. In the juvenile form, the inflammation reaches the submucosa but there is a gradient in the severity of the process. It is slight in the submucosa and increases as the serosa is approached. This form is believed to result from previous episodes of appendicitis with resolution of the mucosal inflammation. Secondary periappendicitis complicates concurrent intra-abdominal infections or other inflammatory conditions. Common causes of periappendicitis are listed in Table 8.3. Salpingitis caused by *Chlamydia trachomatis* is especially prone to produce periappendicitis (58). Serious complications develop in a large percentage of patients with periappendicitis, suggesting that establishing a diagnosis of periappendicitis has clinical significance (59).

**TABLE 8.3 Causes of Inflammation in Periappendicitis**
Abdominal aortic aneurysm
Appendicitis in another appendiceal segment
Colitis
Diverticulitis
Inflammation associated with colonic neoplasms
Inflammatory bowel disease
Pelvic inflammatory disease
Urologic diseases
Unknown causes
Intestinal infections

The histologic findings reflect the duration of the inflammatory process. Most commonly one sees acute inflammation and edema limited to the serosa and muscularis propria. There may be accompanying mesothelial hyperplasia. (If one only sees scattered neutrophils on the serosal surface of the appendix with actively marginating neutrophils, it is likely that these changes reflect surgical handling of the appendix and not true periappendicitis.) In some cases there is a prominent fibrinous exudate without much in the way of inflammation. As the process resolves, fibrous tissue and chronic inflammatory cells replace the acute inflammation and edema and fibrosing strands penetrate the mesoappendix (Fig. 8.28).

**Progressive Fibrous Occlusion**

Fibrous occlusion (fibrous obliteration) of the distal tip of the appendix occurs as part of the natural aging process. The fibrosing process starts distally and progresses proximally (Fig. 8.29), eventually resulting in the loss of the normal appendiceal mucosa and Peyer patches. During the initial stages of fibrosis, the mast cell density in the lamina propria increases, accompanied by neural hyperplasia.

P.514
FIG. 8.28. Periappendicitis. A: Acute periappendicitis. The appendiceal lumen is indicated by the *star*. The majority of the inflammation surrounds the appendix. This patient had diverticulitis with a ruptured diverticulum. B: Higher power magnification of the inflammatory process involving the periappendiceal fat. C: The end result of periappendiceal inflammation is the formation of adhesions between the appendix and adjacent structures. A periappendiceal adhesion is indicated by the *arrow*. D: Periappendicitis at a later stage in its evolution demonstrating the presence of proliferating fibroblasts and chronic inflammatory cells.
FIG. 8.29. Appendiceal atrophy with fibrous obliteration demonstrating the loss of the epithelium as well as its surrounding lamina propria and lymphoid follicles. Fatty infiltration and ingrowth of fibrous tissue has occurred. The muscularis propria appears atrophic.

Neural Hyperplasia

As noted above, distal fibrous occlusion may be accompanied by neural hyperplasia. The incidence of neural hyperplasia varies geographically, occurring more commonly in countries with a high incidence of appendicitis. The finding of increased numbers of nerve fibers, Schwann cells, and enlarged ganglia in patients with acute appendicitis suggests that not all neural hyperplasias seen in appendices represent a physiologic aging phenomenon as has been postulated. Rather, it may result from previous episodes of inflammation followed by neural remodeling. The neural proliferation may be augmented by mast cells that produce nerve growth factors.

Three types of neural proliferations are seen: One accompanying distal fibrous occlusions, one arising from the plexuses, and one involving the lamina propria. In the form associated with distal fibrous occlusion, one sees small nodules of Schwann cells with spindled comma-shaped nuclei and scant indistinct cytoplasm aggregated in onionskinlike lamellae in a myxoid stroma, producing a vaguely whorled pattern (Fig. 8.30). These features may be best appreciated using immunostains for neural markers such as S100, PGP 9.5, or Leu-7. In the mucosal form, one sees focal collections of pale spindle cells in the lamina propria or in an obliterated appendix (60). S100, PGP 9.5, Leu-7, or synaptophysin highlights the neuronal or the perineuronal Schwann cells. Neural hyperplasia arising from the mucosal nerve plexuses tends to involve Meissner and Auerbach plexuses, and can extend into the periappendiceal fat.
FIG. 8.30. Neural hyperplasia. Hyperplastic Schwann cells are present involving the lamina propria between the crypts of Lieberkühn (star).

Retention Mucocele

Retention mucoceles (simple mucoceles, retention cysts) result from luminal obstruction with distention of part or all of the appendiceal lumen by mucus accumulations (Fig. 8.31). We recommend that the term mucocele be reserved solely for appendices that are dilated and contain inspissated mucin in which there are no mucin-secreting neoplasms. Mucoceles have an equal sex distribution and most typically affect the middle-aged. They usually follow acute appendicitis with postinflammatory fibrosis, obstruction, and progressive mucin accumulations. Usually mucoceles are small and symptomless, but they may enlarge and contain a thick, gelatinous mucin that can result in abdominal pain, with or without a palpable mass.

FIG. 8.31. Mucocele. A: The appendix is opened lengthwise to show the presence of gelatinous material within the appendix. The proximal portion of the appendix is more dilated than the distal portion. B: Cross section through the appendix of a patient with a mucocele. The appendiceal lumen is completely filled with gelatinous mucoid material. No neoplasms were present.

Retention mucoceles are usually unilocular, thin walled, and lined by flattened, atrophic epithelium. The lining may also
contain normal-appearing goblet cells. The appendiceal wall may appear focally fibrotic and chronically inflamed. Rupture of a retention mucocele produces localized periappendiceal mucin accumulations that are easily resectable and the mucin does not reaccumulate. However, a careful search should be made for neoplastic epithelium to rule out the presence of an underlying neoplasm. A granulomatous response may develop (Fig. 8.32).

**Myxoglobulosis**

Myxoglobulosis, a variant of appendiceal mucocele, is characterized by the presence of mucinous, occasionally calcified pearl- or caviarlike globules in a usually dilated appendiceal lumen. The distinctive features of the globules give rise to terms such as “fish-egg” or “caviar” appendix (Fig. 8.33). Myxoglobulosis constitutes 0.35% to 8.0% of mucoceles (61,62). The lesions can present clinically as an acute abdomen or may represent an incidental finding at the time of laparotomy or autopsy. Grossly, the characteristic finding is that of a group of opaque white globules consisting of calcified amorphous material (Fig. 8.33) without an underlying architecture. Perforation represents an infrequent complication, with the usual consequence being peritonitis. In the case of perforation, the white globules may become walled off by fibrous adhesions in a pericecal collection. An occlusive membrane in the proximal appendix may lead to the development of this lesion (63).

![FIG. 8.32. Mucocele. The lumen contains mucus and collections of giant cells and inflammatory cells. This form of granulomatous reaction is often seen in mucoceles of various etiologies.](image)

Histologically, the “pearls” or “caviar” consist of concentrically layered mucous and cell debris. Factors that lead to the transformation of mucin into globular masses are unknown. Hypotheses include the formation of a tissue core that acts as a nidus for concentric mucin deposition. The core may represent an organizing mass of mucin and granulation tissue that originates in the appendiceal wall, breaks off, and undergoes necrosis.

**Benign Nonneoplastic Polyps**

Small, localized hyperplastic polyps resembling those in the colorectum develop in the appendix (Fig. 8.34). The glands have serrated lumens lined by benign epithelium demonstrating an orderly progression of cellular maturation. The collagen table appears thickened and cytologic atypia is absent. Peutz-Jeghers and juvenile polyps also affect the appendix as part of a more generalized syndrome. They resemble Peutz-Jeghers and juvenile polyps arising elsewhere (see Chapter 12). These lesions should be distinguished from serrated adenomas and sessile serrated polyps (see Chapter 14).

**Lymphoid Hyperplasia**
Lymphoid hyperplasia usually affects younger individuals (Fig. 8.35), producing obstruction and secondary appendicitis. Viral infections often induce the lymphoid hyperplasia. Appendices with virally induced lymphoid hyperplasias are seldom removed unless a secondary acute appendicitis ensues, since the process remains self-limited and the lymphoid hyperplasia eventually regresses. The process is characterized by the presence of enlarged lymphoid follicles containing prominent germinal centers and a mantle of surrounding benign-appearing lymphocytes. The germinal centers may contain numerous tingible body macrophages.

**Graft Versus Host Disease**

*Graft versus host disease* (GVHD) affects the appendix as part of a more generalized gastrointestinal involvement. In GVHD, the lamina propria appears extremely acellular with loss of Peyer patches due to the pretransplant conditioning. The characteristic apoptotic lesions develop as elsewhere in the gut (Fig. 8.36). Because of the setting in which this lesion occurs, concomitant CMV infections may be present.

**Vascular Diseases**

Vascular disorders that affect the appendix include varices, vascular malformations, vascular neoplasms, angiodysplasia, and vasculitis (Fig. 8.37). Appendiceal necrotizing arteritis varies in incidence from 0.89% to 1.9% of patients (64,65). It results in mucosal ulceration or infarction. Often the vasculitis exists in the absence of appendicitis. The disorder represents part of the clinicopathologic spectrum of systemic polyarteritis nodosa. It may be diagnosed first in the appendix due to the frequency of appendectomies that are performed annually. The features of these vascular lesions are discussed elsewhere in this book.

**Gynecologic Abnormalities Seen in the Appendix**

**Endometriosis**

Endometriosis affects 1% to 8% of examined appendices (66,67). Most patients are between the ages of 20 and 40. Endometriosis usually involves the serosal surface or the muscular layers (Fig. 8.38). Only rarely does it involve the mucosa. It can present as appendicitis, especially when bleeding occurs in the endometriotic tissue, or as an intussusception. Grossly, endometriosis may appear as discrete brownish foci, although more often it is an incidental histologic finding, not having been appreciated grossly. Both endometrial glands and stroma associate with variable amounts of fibrosis and hemosiderin deposits.

Appendiceal endometriosis occurs alone or coexists with other conditions such as appendiceal inversion. The latter results from muscular hyperplasia, which stimulates appendiceal peristalsis, causing complete inversion and intussusception of the appendix into the cecum. There is a rare case of mucinous metaplasia with epithelial dysplasia occurring in the endometriotic epithelium of the appendix (66). The endometrial glands display extensive areas of mucinous epithelium and Paneth cells. Focally, the mucinous epithelium demonstrate low-grade epithelial dysplasia. Both the intestinal and endometrial epithelium are surrounded by typical endometrial stroma, showing strong positivity for estrogen receptor proteins. Support for a metaplastic origin of the mucinous epithelium was the presence of glands containing mixtures of mucinous cells, goblet cells, Paneth cells, ciliated cells and nonciliated endometrial cells, and ciliated and nonciliated mucinous cells, all showing estrogen receptor positivity (67).
**FIG. 8.33.** “Caviar” appendix. **A:** Opened ileocolectomy specimen. The appendix is in the lower right-hand part of the picture. It contains masses of round whitish globules (*arrows*). The white mass in the cecum/ascending colon (*star*) is a lipoma that has been cut through. **B:** Cross section through eight of the globules demonstrating their amorphous character. **C:** Higher magnification showing the presence of mucinous debris concentrically layered upon itself.

**FIG. 8.34.** Hyperplastic polyp of the appendix. The *arrow* indicates an area where the mucosa is focally thicker than the surrounding areas. The lesion is histologically identical to similar lesions that more commonly arise in the colon.

**Endosalpingiosis**

Endosalpingiosis, the ectopic location of benign epithelium resembling that lining the normal fallopian tube, often involves the peritoneal and gastrointestinal serosal surfaces. It likely results from metaplasia of the peritoneal surface (68). The lesion consists of papillary, multiglandular structures that may be complex in nature but do not demonstrate cytologic atypia. Psammoma bodies may be present.
FIG. 8.35. Lymphoid hyperplasia. Cross section of an adult appendix demonstrating confluent hyperplastic lymphoid follicles.

The distinction of this lesion from endometriosis is relatively straightforward since endometrial epithelium and stroma, areas of periglandular hemorrhage, and hemosiderin-laden macrophages are absent in endosalpingiosis. The identification of müllerian-type cells differentiates this lesion from mesonephric remnants and mesothelial inclusion cysts. The absence of goblet cells also precludes a gastrointestinal origin. Furthermore, the lesion is positive for CA-125 and estrogen receptors (ER) (Fig. 8.39), further confirming its müllerian origin (69).

Endosalpingiosis causes diagnostic difficulty since it may be difficult to distinguish from serosal implants of low-grade (borderline) ovarian cancer. The diagnosis of endosalpingiosis is favored when the following factors are absent: (a) past or present ovarian surface borderline peritoneal masses; (b) stromal desmoplasia, a destructive infiltrative pattern with disrupted or interrupted glandular basement membranes; and (c) nuclear atypia and mitoses (68). A mesothelial lesion is also in the differential diagnosis but immunostains with antibodies to calretinin and ER, progesterone receptors (PR), and CA-125 can
easily distinguish between these two entities.

**Decidual Islands**

Decidual islands may stud the appendiceal serosa (Fig. 8.40) in the appendices of pregnant women. They can also be found in the mucosa or muscularis propria. These islands contain sheets of large polyhedral decidual cells. Unlike endometriosis, glands are absent. This change may be mistaken for some form of neoplasm, but immunostains for keratin, S100, carcinoembryonic antigen (CEA), and EMA are usually negative. The decidual cells may express vimentin, desmin, and/or smooth muscle actin.

![Vasculitis](image)

**FIG. 8.37.** Vasculitis. A: Submucosal blood vessel surrounded by inflammatory cells. B: Higher power magnification of the mixed inflammatory infiltrates. C: Serosal vessel showing necrosis and acute inflammation.

**Mesothelial Cysts**

*Mesothelial cysts* frequently involve the tip of the appendix (Fig. 8.41) or they develop in association with periappendiceal inflammatory pseudotumors. They are often multiple and lined by cuboidal or flattened mesothelium, depending on how much pressure atrophy of the epithelium has occurred. Mesothelial cells contain abundant cytoplasm and a small centrally placed nucleus. They lie above a submesothelial mesenchyme. Mesothelial cells can appear quite reactive, normal, or flattened in the cysts. These cells are periodic acid–Schiff (PAS), CEA, and EMA negative and are cytokeratin and calretinin positive.
FIG. 8.38. Endometriosis. A: Cross section through the appendix demonstrating the lumen (star). Endometrial glands and stroma are present in the wall (arrow). B: Higher power magnification of two endometrial glands surrounded by endometrial stroma in muscularis propria.
Cystic Fibrosis

Cystic fibrosis (CF) represents the most common hereditary disease in Caucasians. The common denominator for the gastrointestinal abnormalities seen in the setting of CF is abnormal mucus production. Mucus viscosity depends on the structure of the glycogen protein, the concentration of hydrogen and calcium ions, and water content. These are abnormal in CF. CF may be diagnosed based on the presence of appendiceal changes (Fig. 8.42). Increased numbers of hyperdistended
goblet cells line the entire length of the crypts. These goblet cells release their abnormal mucin content and the appendix swells and becomes hyperdistended with inspissated eosinophilic secretions. Appendicitis results when the lumen is obstructed by the thick secretions. Diverticula may develop due to accumulations of thick mucin and increased intraluminal presence. Patients may develop appendicocutaneous fistula (69).

**FIG. 8.42.** Appendix from a child with cystic fibrosis showing enlarged goblet cells and the regenerated mucous membrane.

**Melanosis**

Melanosis is defined as the accumulation of lipofuscin granules within mucosal macrophages. These granules are composed of membrane-bound intracytoplasmic bodies with electron-dense lipid material (70). These cells are seen predominantly in the mucosa, although submucosal collections can also be seen. Melanosis is present in 7.4% to 46% of appendices (71,72). Melanosis is also present in a large percentage of pediatric patients, suggesting that it is a common nonspecific alteration (72). It is currently thought that it results from increased apoptosis (72) due to many different causes, including infections (71) and laxative ingestion.

The intensity of the change varies significantly from scanty solitary histiocytic cells to large aggregates of heavily pigmented macrophages (Fig. 8.43). The latter are particularly prominent in patients with an associated melanosis coli. The melanosis is most prominent in the proximal portion of the appendix with minimal or no involvement of the distal tip.
**Miscellaneous Changes**

Patients who have undergone appendectomies may have residual alterations that are identifiable endoscopically as well as microscopically. The most common change is *appendiceal stump inversion*, which may present as a cecal polyp. Patients who have had previous gynecologic surgeries may show ovarian tissue adherent to the appendiceal mesoappendix.

*Gastrointestinal sarcoid* is rare (73) and is best diagnosed in the presence of a positive Kveim test or clinical and histologic evidence of a disseminated disease. Appendiceal sarcoid may present as an acute appendicitis. Infiltrative diseases such as *eosinophilic granuloma, amyloidosis, malacoplakia* (74), *Whipple disease* (75), and *inflammatory pseudotumor* can all involve the appendix. The pathologic features of these entities resemble those described elsewhere in the text.

**Foreign Bodies**

Foreign bodies are present in 5.5% of the appendectomy specimens (12). They lodge there and may cause localized appendicitis, with fecaliths representing the most common foreign body. Other common foreign materials include barium and parasites. However, almost every other type of conceivable foreign body may be present, such as pins, nails, bubble gum, teeth, and seeds. Foreign bodies may cause mucosal atrophy and foreign body granulomas.

**References**


66. Mai KT, Burns BF: Development of dysplastic mucinous epithelium from endometriosis of the appendix. *Histopathology*
Chapter 9
The Neoplastic Appendix

Appendiceal tumors constitute <0.4% of all intestinal neoplasms. They pathologically resemble their small and large intestinal counterparts. The most significant difference between appendiceal and intestinal neoplasms is in the frequency of specific tumor types arising in these sites, with the appendix giving rise to a higher incidence of carcinoid tumors than carcinomas (1). Small appendiceal tumors may obstruct the appendiceal lumen, often causing appendicitis. Nevertheless, because many tumors remain asymptomatic, a diagnosis of neoplasia is seldom made prior to pathologic examination of the resected specimen. The World Health Organization (WHO) classification of appendiceal tumors is shown in Table 9.1 (2). Table 9.2 lists mucinous lesions that may be encountered with appendiceal lesions.

Adenomas
Several types of adenomas develop in the appendix. By far, the most common involve the appendiceal mucosa in a circumferential fashion creating a mucinous cystadenoma (Fig. 9.1); less commonly they grow as a localized lesion resembling their more common colonic counterparts (Fig. 9.2). Both types of adenomas may exhibit tubular, tubulovillous, or villous architectures and the degree of dysplasia can be low grade or high grade. Invasive carcinomas can develop in both. Appendiceal adenomas commonly associate with synchronous colorectal neoplasia (3,4). The molecular features of appendiceal neoplasia are similar to those found in colorectal neoplasms (5).

Mucinous Cystadenomas
Mucinous cystadenomas (also sometimes referred to as low-grade appendiceal mucinous neoplasms) (6) arise in both males and females, with many series reporting a higher incidence in females. Patients range in age from 27 to 77 years, with an average age of 53 years and a median age of 64 years (7). Approximately 20% of patients have a metachronous or synchronous colonic adenocarcinoma (8). The tumors are usually sporadic lesions but they may complicate longstanding ulcerative colitis. Some patients develop acute appendicitis because the mucin accumulation obstructs the appendiceal lumen (Fig. 9.3). Patients also develop abdominal pain, nausea and vomiting, and, sometimes, a palpable right lower quadrant mass, perforation, or intussusception (Fig. 9.4). Other patients present with pseudomyxoma peritonei or with what appears to be an ovarian tumor.

Mucinous cystadenomas can produce large amounts of mucus converting the appendix into a sausage-shaped, cystic or spherical, mucus-filled mass (Fig. 9.3); the average diameter is 2.2 cm with a range of 0.3 to 9 cm (6). Diverticula are often present and there may be areas of rupture. There may also be grossly visible mucus on the serosal surface of the appendix. Mural calcification may produce the gross pattern of a “porcelain appendix” or the obstruction can produce myxoglobulosis, a lesion discussed in Chapter 8.

A circumferential proliferation of neoplastic mucinous epithelium replaces the normal epithelium. This neoplastic epithelium may exhibit a full range of neoplasia including low-grade dysplasia, high-grade dysplasia, and invasive carcinoma. Usually a single layer of tall crowded columnar adenomatous epithelium with basally located hyperchromatic, pseudostratified nuclei and clear to eosinophilic cytoplasm lines the neoplastic glands (Fig. 9.5). The elongated nuclei lack nucleoli. Mitotic activity is usually low and usually limited to the base of the glands (7). The glands may be tubular, although a villous architecture may be present. More often the epithelial proliferation produces an undulating pattern. Most mucinous cystadenomas show minimal cytologic atypia, qualifying for a diagnosis of low-grade dysplasia. However, some cases contain moderate to marked atypia and abundant mitotic activity. Areas of high-grade dysplasia (including carcinoma in situ) appear as a disorderly proliferation of cells that lose their polarity (Fig. 9.6) and may exhibit a back-to-back glandular pattern that obliterates the intervening lamina propria. As in the colon, these changes remain confined to the area above the muscularis mucosae. Since the likelihood of an invasive carcinoma increases with the degree of dysplasia, these areas should be well sampled to rule out an invasive process.

The nonneoplastic mucosa often appears atrophic and the usually prominent Peyer patches are often absent. Mucosal denudation is common (Fig. 9.7), either from compression by the intraluminal mucin or by ulceration due to a
The mucosal ulcers may produce a granulomatous reaction with subsequent mural fibrosis. The intraluminal mucin may compress the lining epithelium in such a way that the flattened epithelium may not be easily recognizable as being neoplastic. A feature that should increase one's suspicion that an underlying neoplasm is present is the diameter of the appendix. Benign mucoceles seldom measure more than a centimeter in diameter; larger lesions almost always result from an underlying neoplasm. Therefore, these larger mucoceles should be well sampled to rule out the presence of a tumor, if one was not identified in the original sections.

**TABLE 9.1 World Health Organization Classification of Epithelial Nonendocrine Appendiceal Tumors**

<table>
<thead>
<tr>
<th>Adenoma</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular</td>
<td></td>
</tr>
<tr>
<td>Villous</td>
<td></td>
</tr>
<tr>
<td>Tubulovillous</td>
<td></td>
</tr>
<tr>
<td>Serrated</td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Signet ring cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 9.2 Mucinous Lesions of the Appendix and Peritoneum**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocele</td>
<td>Gross term for a dilated appendix filled with mucus secondary to a either a neoplastic or nonneoplastic obstruction</td>
</tr>
<tr>
<td>Mucinous cystadenoma (low-grade mucinous tumor)</td>
<td>Benign tumor that often circumferentially surrounds the appendiceal lumen. It may produce the gross appearance of a mucocele. The lesion may contain either low-grade or high-grade dysplasia</td>
</tr>
<tr>
<td>Mucinous tumor of uncertain malignant potential</td>
<td>Mucinous tumor with areas of questionable invasive carcinoma</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>Mucin-producing carcinoma that typically arises in a mucinous cystadenoma and invades through the muscularis mucosae into the submucosa. The invasive foci are surrounded by a desmoplastic response and the cells are cytologically malignant</td>
</tr>
<tr>
<td>Mucinous cystadenoma with mucus dissection</td>
<td>Low-grade or high-grade cystadenoma with mucin dissection into but not through the appendiceal wall</td>
</tr>
<tr>
<td>Pseudomyxoma peritonei</td>
<td>The presence of mucin collections in the abdomen and/or pelvis. Histologically it may show mucinosis, low-grade mucinous tumor, or a mucinous adenocarcinoma</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mucinosis</td>
<td>Presence of mucin in the peritoneal cavity, including on the surface of the appendix. No cells are present in the mucin. This lesion usually complicates a mucinous cystadenoma</td>
</tr>
<tr>
<td>Low-grade peritoneal mucinous tumor</td>
<td>These lesions also complicate mucinous cystadenoma. The peritoneal mucinous deposits contain neoplastic cells with the cytologic features of a low-grade or high-grade adenoma</td>
</tr>
<tr>
<td>Mucinous peritoneal adenocarcinoma</td>
<td>The mucin accumulations contain cytologically malignant cells. The cells often invade the underlying tissues</td>
</tr>
</tbody>
</table>

Epithelial or mucinous displacement is common in mucinous cystadenomas due to the pressure from the intraluminal mucin or from a coexisting appendicitis. Increased intraluminal pressure from the mucin can also cause diverticula, ruptures, or fistulae. The wall of the appendix may be fibrotic and significantly attenuated at the rupture site. Mucin with or without epithelial cells may be present in the perforation site and extend to the serosal surface (Fig. 9.8). The serosa itself may show an acute or chronic serositis with inflammation and mesothelial hyperplasia. It is important to search these areas carefully for the presence of both mucin and epithelial cells and to report their presence if they are seen. The histologic features of mucinous cystadenomas with and without extra-appendiceal spread are identical (with the exception of the identification of a breach in the appendiceal wall in the former) (6). The mucus extravasation can be limited to the periappendiceal area or it can spread over large areas of the peritoneal surface (see below). Noninvasive lesions that exhibit marked cytologic atypia or complex intraepithelial proliferations tend to have a higher proliferative rate than low-grade tumors, and if these lesions gain access to the peritoneal cavity, they tend to behave more aggressively than low-grade lesions. We have found that the proliferative rate of the primary tumor as well as its extra-appendiceal extensions is an important prognostic factor. Neoplastic epithelium can also extend into diverticula (Fig. 9.9), but this does not constitute an invasive carcinoma as evidenced by the presence of lamina propria surrounding the neoplastic glands. It does not carry the same prognostic significance as serosal mucin extension by dissection or rupture, provided the diverticulum has not ruptured.
FIG. 9.1. Circumferential adenoma. A: Gross appearance of a cross section of a circumferential appendiceal villous adenoma. Note the long fingerlike villiform structures in the center of the photograph. B: Low-power histologic features of the lesion demonstrated in A showing the villous architecture. The lesion is confined to the mucosa and no evidence of invasive malignancy was seen in this lesion.
FIG. 9.2. Adenoma. A: Polyp within the lumen of the appendix (arrow). A piece of paper has been slipped under the polyp to distinguish it from the surrounding normal mucosa. B: Small whitish adenomatous polyp (arrow) in the appendix of a patient who underwent an ileocolectomy for a carcinoma of the cecum.
Mucinous cystadenomas are often not appreciated when the appendix is grossed in, especially if there is a coexisting acute appendicitis. Therefore, if a tumor is found, the pathologist should carefully re-examine the appendix for areas of perforation, serosal mucin accumulations, and invasive carcinoma, since these modify the patient's prognosis and treatment if identified. Perforation sites and serosal mucin deposits should be sampled; the entire tumor should be submitted to rule out invasion. The proximal margin of resection should be identified and submitted for histologic examination. It has also become our practice to obtain a Ki-67 immunostain on the tumor and to report the proliferative rate in the most mitotically active part of the tumor.
FIG. 9.4. Ileocolectomy specimen from a patient with a large sessile nonmucinous adenoma of the distal appendix. The appendix has intussuscepted into the cecum. The *arrows* delineate the areas of the appendiceal adenoma. Normal-appearing appendix (*NA*) is present proximally.

The pathology report should indicate the degree of dysplasia in the cystadenoma and whether there is invasive cancer or perforation, whether tumor or mucin is seen outside of the appendix, and the status of the proximal margin. These factors are important because even benign neoplasms that escape the appendix may give rise to subsequent pseudomyxoma peritonei. The prognosis of patients with peritoneal spread is guarded, with just over half of the patients dying after 10 years. Because of the differences in the prognosis, some have proposed the term *mucinous borderline tumor of the appendix* to reflect the uncertain biology of the lesions (9). These lesions may also be diagnosed as *mucinous cystadenoma with mucinosis* or *cystadenoma with low-grade peritoneal mucinous tumor* depending on whether epithelial cells are identified in the mucin deposits (see below). We, unlike others (3,10), do not believe that cystadenomas with extra-appendiceal extension should be called appendiceal adenocarcinomas, since these patients have a better prognosis than patients with peritoneal carcinomatosis (6,11). Some tumors without evidence of extra-appendiceal extension may also go on to develop pseudomyxoma peritonei. In these cases failure to adequately sample the appendix to detect the tumor extension is the likely explanation.
FIG. 9.5. Mucinous cystadenoma of the appendix. A: Gross photograph showing the presence of whitish papillary excrescences within the lumen of the appendix. Abundant mucoid material is present. B: A microscopic section through this lesion. The appendix is lined circumferentially by papillary proliferations of appendiceal cells resembling a hypersecretory papillary adenoma of the large bowel. C: A cystadenoma of the appendix. The prominent pencil-shaped nuclei characteristic of adenomatous epithelium are evident. Some of the cells contain abundant mucus, whereas others do not.
Mucinous Cystadenoma Coexisting with Carcinoid Tumor

Occasionally one sees an appendiceal mucinous cystadenoma coexisting with an appendiceal carcinoid tumor. The carcinoid and the epithelial components may lie side by side or may arise in different parts of the appendix. Carr et al used the term *dual carcinoid epithelial neoplasia* to describe this phenomenon (12). One usually does not see intermediate histologies between the epithelial and neuroendocrine tumors. The carcinoid tumor may have the histologic features of any appendiceal carcinoid (see Chapter 17). Therefore, they may be trabecular, tubular, or goblet cell in type. The prognosis is determined by the histologic features of each of the components.

Localized Adenomas

Isolated sessile or pedunculated adenomas resembling their colonic counterparts occur, but it is difficult to assess their incidence because these lesions tend to remain asymptomatic and most pathologists do not open the appendix along its long axis.

The adenomas affect patients of all ages, including children (13); median patient age is the mid-50s (14). Adenomas occur in younger individuals in patients with familial polyposis. It is important to remember that patients with appendiceal adenomas often have additional primary tumors at other sites including the colon, breast, kidney, ovary, and gallbladder (14,15,16).
FIG. 9.7. Wall of a ruptured mucinous cystadenoma. A: Mucinous lakes dissect into the periappendiceal tissues. A prominent inflammatory infiltrate surrounds the edge of the mucinous lakes in the appendiceal fat. B: Higher magnification of the edge of the lesion showing fibrous tissue; benign, flattened epithelium; and inflammatory cells. Finding an area such as this in an appendix should prompt a search for a mucinous tumor in the remainder of the appendix.
FIG. 9.8. Mucinous cystadenoma with rupture. Low-power magnification demonstrating a cross section of the appendix distal to the tumor. The appendix shows central fibrous obliteration of the lumen. External to the appendiceal wall is a collection of mucin.
FIG. 9.9. Appendiceal mucinous cystadenoma with secondary diverticulum formation. A villiform mucin-secreting epithelium lines the appendiceal lumen as well as the diverticulum. The wall of the appendix on the left-hand side of the picture has become markedly thinned due to dilation.
Chapter 9

FIG. 9.10. Adenoma of the appendix. A: The epithelium resembles that seen in colonic adenomas. The adenomatous epithelium demonstrates the typical picket fence–arranged nuclei and the presence of immature goblet cells as evidenced by the small goblet cell collections. B: Another area of the tumor demonstrating marked goblet cell dystrophy.

Isolated adenomas are generally discovered incidentally in appendices removed for other reasons. They may also be detected at the time of colonoscopy if they prolapse through the appendiceal orifice into the cecum. Larger sessile adenomas produce appendicitis by obstructing the appendiceal lumen. They may also produce diverticula (Fig. 8.6). These adenomas histologically resemble colorectal adenomas (see Chapter 14); the evolution of an adenoma into a carcinoma follows the same sequence. Sporadic adenomas may be tubular, tubulovillous, or villous in architecture and contain varying degrees of dysplasia (Fig. 9.10). Grossly invisible tubular adenomas occur in patients with familial polyposis. As in the colon, a tumor must invade through the muscularis mucosae into the underlying submucosa in order to diagnose an invasive cancer. Simple appendectomy represents adequate treatment for patients with adenomas that do not contain an invasive cancer.

Mixed Hyperplastic–Adenomatous Polyps, Serrated Adenomas, and Sessile Serrated Polyps

Mixed hyperplastic–adenomatous polyps, serrated adenomas, and sessile serrated polyps can develop in the appendix. As with traditional adenomas, the histologic features of these lesions resemble their colonic counterparts, and the features of the mixed lesions are discussed in Chapter 14. Serrated adenomas represent a distinctive form of adenomatous polyp with a tendency to develop in the appendix and right colon (17). The polyp architecture reminds one of a hyperplastic polyp because of the presence of serrated lumens (Fig. 9.11), but the cytologic features differ from those seen in hyperplastic polyps in that the often eosinophilic cells appear immature and the hyperdistended goblet cells and thickened collagen table typically present in hyperplastic polyps are absent. The epithelium usually contains more mucin than seen in typical adenomas but less than one sees in mucinous cystadenomas. The nuclei appear pseudostratified and elongated in comparison to the basally located, rounder nuclei typical of hyperplastic
polyps. Mitotic activity is increased over that seen in hyperplastic polyps and mitoses can be identified at the free surface in serrated adenomas (17). The lesion may exhibit a high level of microsatellite instability (18).

**Sessile serrated polyps** also develop in the appendix, although they are seldom reported as such, especially in the older literature. The lesions described by Younes et al are an example of this lesion (19). Sessile serrated polyps superficially resemble hyperplastic polyps but they tend to be larger than the usual hyperplastic polyp, sometimes covering extensive areas of the mucosa. Typically, the glands appear serrated and the serrations extend deeper into the crypt than the usual hyperplastic polyp. The base of the glands tends to extend sideways above the muscularis mucosae and the proliferative zone is asymmetric in appearance. The cells lining the glands do not appear to be obviously adenomatous, but they are crowded and contain variable amounts of mucin. These appendiceal lesions have a high association with right-sided colonic carcinomas (19). These three lesions are discussed in greater detail in Chapter 14.

**FIG. 9.11.** Serrated adenoma. A: Low-power magnification demonstrating the presence of an almost completely circumferential serrated adenoma. B: Higher magnification demonstrating the presence of glands with a serrated architecture. Closer examination of the lesion shows the presence of serrated glandular lumens lined by cells that have histologic features between those of a classic adenoma or hyperplastic polyp.

**Adenocarcinomas**

Appendiceal adenocarcinomas occur far less commonly than carcinoid tumors or mucinous cystadenomas. They are found in only 0.1% to 1.35% of appendectomy specimens (1,8) and represent only 0.5% of all gastrointestinal neoplasms (19,20). Patients with these cancers have an average age of 51.4 to 60 years and show a male:female ratio of 3:1 (8,10,14). However,
incidence rates reported by Surveillance, Epidemiology, and End Results (SEER) registries suggest that the tumors affect both sexes equally (21). The age of presentation is significantly older than that of patients with appendiceal carcinoid tumors (22). Patients with familial polyposis may develop appendiceal carcinomas at a young age. Appendiceal carcinomas also develop in patients with underlying inflammatory bowel disease (23). A minority of appendiceal mucinous carcinomas may arise via a defective mismatch repair pathway (24) in a manner analogous to a subset of colorectal carcinomas that frequently have a mucinous histology (see Chapter 14).

Clinical presentations include acute appendicitis, the presence of an abdominal mass, or obstruction. Carcinomas that masquerade as acute appendicitis often have clinical clues suggesting that a more serious condition is present, including a prolonged history, weight loss, anemia, or the presence of a palpable mass. Some patients have widespread abdominal carcinomatosis at the time of diagnosis. Mucinous tumors tend to present with pseudomyxoma peritonei, whereas nonmucinous carcinomas present with appendicitis. The tumors may also cause appendiceal intussusception. The tumors develop in mucinous cystadenomas, in localized adenomas, and exceptionally from goblet cell carcinoids (see Chapter 17) (12). The TNM classification of appendiceal tumors is shown in Table 9.3.

Grossly, most appendiceal carcinomas appear as a polypoid, ulcerating, or infiltrative mass at the base of the appendix (Fig. 9.12), contrasting with carcinoid tumors that usually develop in the tip (11). They often produce abundant mucin (Fig. 9.13). The presence of diffuse appendiceal induration may suggest the diagnosis. Mean tumor diameter is larger than that of mucinous cystadenomas (2.9 cm) (6). Perforation or diverticula may be present. Perforations of appendiceal adenocarcinomas develop in 50% to 62% of tumors (20,25), allowing the tumor to disseminate into the peritoneum. Advanced lesions may appear as a mass enveloping or obliterating the appendix. Cecal extension may make it difficult to determine the exact site of the origin. If the major part of the mass lies in the appendix, or if one finds areas of residual adenoma in the appendix, one can be confident that the tumor is a primary appendiceal lesion.

<table>
<thead>
<tr>
<th>T—Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N—Regional Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M—Distant Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
</tr>
<tr>
<td>M0</td>
</tr>
</tbody>
</table>
M1 Distant metastases

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis/T1 or T2/T3 or T4</th>
<th>N0/N1 or N2</th>
<th>M0/M</th>
</tr>
</thead>
</table>

Stage 0 Tis N0 M0
Stage I T1 or T2 N0 M0
Stage II T3 or T4 N0 M0
Stage III Any T N1 or N2 M0
Stage IV Any T Any N M

FIG. 9.12. Carcinoma of the appendix. The appendix shows obliteration of the appendiceal wall by an infiltrating white process. At the tip of the appendix one notices the gelatinous appearance of the tumor.

There are three major histologic patterns of appendiceal carcinoma: Those resembling ordinary colorectal carcinoma (Fig. 9.14), mucinous (colloid) carcinomas (Fig. 9.15), and signet ring carcinomas (Fig. 9.16). Mucinous adenocarcinomas account for approximately 85% of appendiceal carcinomas. By definition, at least 50% of the tumor is mucinous in nature (2). The tumors arise from mucinous cystadenomas and they produce copious amounts of mucin, leading to the presence of a mucocele as well as mucinous cysts within the appendiceal...
wall (Fig. 9.15). Depending on when the lesion is detected, one may identify an underlying cystadenoma with areas of invasion. In more advanced tumors the precursor lesion is absent, replaced by tumor or eroded away by the accompanying appendicitis. Mucinous tumors tend to be well differentiated and to produce pseudomyxoma peritonei. Papillary projections of adenocarcinoma may line the appendiceal lumen. The epithelium appears cuboidal to columnar in shape and contains enlarged nuclei with prominent nucleoli. The wall of the appendix contains irregular infiltrating glands associated with desmoplasia and extracellular mucin pools lined by very atypical mucinous epithelium. Small infiltrating glands and even single cells may be present. Carcinomatous glands differ from their benign counterparts in that they have features of malignancy, including a large nuclear:cytoplasmic ratio; submucosal, vascular, or lymphatic invasion; desmoplasia; and the absence of lamina propria around the invading glands. Their destructive invasion leads to extra-appendiceal spread of the tumor. However, it should be kept in mind that well-differentiated tumors that invade in a broad front may lack a desmoplastic response. If one is uncertain whether a tumor is invasive or not, the tumor may be diagnosed as a mucinous tumor of uncertain malignant potential.

**FIG. 9.13.** Mucinous cystadenocarcinoma. *A:* Mucus is seen within the opened appendiceal lumen. *B:* Cytologically malignant cells (arrow) are present floating within the lumen and were present in other parts of the lining epithelium of this appendix.
FIG. 9.14. Carcinoma infiltrating the appendiceal wall. Carcinoma shown in the upper portion of the photograph demonstrates the histologic features of a typical colorectal carcinoma. Prominent mucin differentiation is not seen.
FIG. 9.15. Colloid carcinoma. Cross section of the appendix demonstrating the presence of mucinous cysts lined by malignant glands. Large mucus collections extend through the appendix wall.
FIG. 9.16. Signet ring cell carcinoma arising in the appendix. This tumor obliterated the appendix and became widely metastatic throughout the peritoneal cavity. A: There's back-to-back arrangement of the signet ring cells. B: Prominent perivascular lymphatic invasion is evident.

Non–mucin-producing appendiceal adenocarcinomas occur less frequently than mucinous tumors (see Fig. 9.14). These lesions arise in pre-existing adenomas, and because they resemble their large intestinal counterparts, they are referred to as colonic-type adenocarcinomas. These lesions tend not to produce pseudomyxoma peritonei. They exhibit the full range of histologies that can be seen in tumors arising in the colon and rectum, including tumors that may contain areas of small cell carcinoma (see Chapters 14 and 17).

Appendiceal signet ring cell carcinomas are rare and often develop in young people in their 30s. The tumors are frequently detected at an advanced stage; as a result, many patients die of their disease within a year or two of their original diagnosis. At least 50% of the tumor should consist of signet ring cells to classify the tumor as such. The tumors consist of proliferations of signet ring cells diffusely invading the bowel wall, usually in the absence of an associated adenoma. The signet ring cells form solid tumor sheets, or they insinuate themselves through the bowel wall. Focal larger colloid lakes may coexist with the sheets of signet ring cells. The latter tend to involve lymphatics early (Fig. 9.16) and they tend to spread beyond the appendix by the time they are detected (22). The presence of signet ring cells raises the possibility of an adenocarcinoid tumor (see Chapter 17), but the latter contains large numbers of endocrine cells and the cells are not as malignant appearing as in signet ring cell carcinomas.

The biology of well-differentiated mucinous tumors differs significantly from that of appendiceal colonic-type carcinomas in that nearly all of the patients have peritoneal dissemination at the time of diagnosis (26) and disease progression mainly affects the peritoneum. Only 2% of patients have lymph node or liver metastases at the time of diagnosis (27,28). In contrast, colonic-type carcinomas behave like ordinary colorectal tumors, metastasizing to the regional lymph nodes, including the ileocolic,
Chapter 9

infraduodenal, and para-aortic chains, or to the liver rather than presenting with peritoneal-based disease. Nodal metastases are present in approximately 25% of resection specimens and the patients experience an overall 5-year survival rate of 46% to 60% (29,30).

It is unclear whether the colonic and mucinous types differ with respect to survival. Some reports show better survival for patients with mucinous adenocarcinoma, while others have found better survival for the colonic type (29,31,32); a more recent study found that the survival was the same in both types (22). The overall 5-year survival rate in ones series of tumors was 60% (30). Patients with signet ring cell carcinoma have a significantly worse prognosis than patients with either mucinous or colonic-type tumors. Fifty-four percent of patients with signet ring cell tumors have lymph node involvement (22), contrasting with approximately 25% of tumors without a signet ring cell morphology (30).

The extent of disease at the time of diagnosis is one of the most important predictors of survival. Patients with stage IV lesions usually succumb to their disease within 5 years. Hemicolectomy is recommended for patients diagnosed with stage II or higher stage appendiceal cancers that have been initially treated with appendectomy. The value of hemicolectomy in patients with T1 lesions is less clear. Significantly better 5-year survivals follow a successful right hemicolectomy and lymph node dissection (73%) when compared with patients undergoing only appendectomy (34%) (25,29,30).

Pseudomyxoma Peritonei

The term pseudomyxoma peritonei (PMP) refers to any condition in which the peritoneal cavity becomes filled with extracellular mucin. PMP complicates both benign and malignant appendiceal neoplasms, as well as carcinomas of other sites, including the ovary, colon, or gallbladder and pancreas (33,34). Additionally, it is possible that the peritoneal lesions arise from a mucinous metaplasia of the peritoneal lining (35). Since the term PMP is nonspecific, one cannot determine whether the lesions are benign or malignant. Some have suggested that the definition of PMP be restricted to histologically benign peritoneal tumors arising from appendiceal adenomas. These authors favor the term disseminated peritoneal adenomucinosis to distinguish less aggressive lesions from overtly malignant peritoneal carcinomatosis arising from true carcinomas (27,34). As will be seen below, we utilize a different terminology to diagnose these lesions.

Patients range in age from 23 to 83, with an average age of 49 years. The condition affects both males and females.

Patients with PMP present with increasing abdominal girth, mucinous ascites, appendicitis, appendiceal abscess, obstruction, an inguinal hernia, or an ovarian tumor. Intestinal obstruction is caused by extensive tumor accumulation within the pelvis, causing pelvic outlet obstruction surrounding the gastric antrum, causing gastric outlet obstruction, or occluding the ileocecal valve region. As intestinal obstruction develops, fistulas become more common.

PMP is usually a locally persistent cancer that is nonmetastasizing and is characterized by a redistribution mechanism in which large volumes of tenacious, semisolid, mucinous tumor deposits are present in the undersurface of the right and left hemidiaphragm, abdominal gutters, and pelvis, but are relatively absent from the peritoneal surfaces of the gastrointestinal tract. The primary tumor constitutes only a minor part of the abdominopelvic cancer. Despite the low-grade biology of most of the lesions and the absence of metastases, progressive disease may cause death by a mass effect in the abdominal and pelvic cavities.

The gross appearance of the tumor is characteristic and depends in part on whether the primary lesion is benign or malignant. The hallmark of the disease is an omental cake. The tumor implants appear as glistening, mucinous globules attached to the peritoneal surfaces, the intestinal serosa, and other abdominal organs, including the spleen. In advanced disease, a mucinous mass admixed with fibrous tissue surrounds and obstructs all of the intra-abdominal organs, filling the entire abdominal cavity, giving rise to the term "jelly belly." All intestinal surfaces are relatively spared; they are not as extensively involved as the rest of the peritoneum unless there have been multiple prior surgical procedures or unless the disease is very advanced with debilitating impacted mucinous ascites throughout the abdominal cavity. Invasion into the peritoneum and abdominal viscera does not occur unless the tumor is malignant.

Pedunculated surface PMP polyps develop in patients with benign tumors, usually on the small bowel, the small bowel mesentery, and occasionally the anterior surface of the stomach. Most patients have multiple polyps that measure up to 20
mm in diameter (35). It is believed that the polyps result from the motion of the bowel so that eventually, an elongated stalk is created. This bowel motion not only creates the polyps, but also repeatedly clears the mucinous tumors from the small bowel surfaces (35).

The histologic features of PMP vary (Table 9.2). Some authors divide PMPs into adnomucinosis, adnomucinosis hybrid, and mucinous adenocarcinoma. Adnomucinosis includes mainly aggressive peritoneal tumors that produce large volumes of mucous ascites. The lesions typically arise from benign appendicetal cystadenomas (34). Hybrid malignancies show adnomucinosis combined with mucinous adenocarcinomas. Mucinous adenocarcinomas show obvious cytologic features of malignancy and the cells may even have a signet ring morphology. The features can be recognized in both histologic and cytologic preparations. The cytologic features accurately reflect the histology (36). Cytologic preparations often contain abundant mucin, reactive mesothelial cells, variable numbers of epithelial cells and fibroblasts, and chronic inflammation. The epithelium may be completely absent in mucinosis. In low-grade mucinous tumors, one may see strips of epithelial cells with basal located nuclei, single cells, or tight three-dimensional cell clusters (37). We prefer to use a different terminology that we believe more specifically describes the histologic features of the lesions that are present. It is described below.

**Peritoneal Mucinosis (Adnomucinosis)**

This lesion is characterized by the presence of acellular mucin collections that coat the surfaces of the peritoneum and the abdominal contents. No neoplastic epithelial cells are found after a diligent examination of multiple sections. The lack of cells reflects a sampling problem in a paucicellular lesion and does not indicate that the tumors lack the ability to grow. Mesothelial hyperplasia may be present. The lesion typically complicates appendicetal mucinous cystadenomas. These lesions have a much better prognosis than mucin accumulations that contain neoplastic cells.

**Low-Grade Peritoneal Mucinous Neoplasm**

The defining features of this diagnosis are the presence of neoplastic cells (unlike the situation in mucinosis) and benign cytologic features (Fig. 9.17) (in contrast to mucinous adenocarcinomas). The diagnosis is made whether the epithelial cells are very sparse in number or are quite numerous. Usually, the cells lie at the periphery of the mucin deposits on various tissue surfaces. In classic cases, more than 90% of the globular masses are composed of mucin rather than cells. These lesions consist of uniform, scant to moderately cellular low-grade adenomatous mucinous epithelium within abundant extracellular mucin accumulations. The epithelium appears as epithelial strips or undulating glands. These are lined by a single layer of cytologically bland adenomatous epithelium and they cover the surfaces of various sites. The epithelium may appear flattened in some areas and focal tufting may be present. Areas of calcification may develop. The cells display minimal cytologic atypia and mitotic activity. There is no evidence of invasion into the underlying tissues. Hyalinization, fibrosis, vascularization, mesothelial hyperplasia (Fig. 9.18), and chronic inflammation may all accompany the tumor. The fibroblastic and vascular proliferation associated with the mucin may impart a myxomatous appearance to the lesion. PMP is a disease of MUC2-expressing goblet cells (38) and the extracellular mucin accumulates because the number of MUC2-secreting cells increases and the mucin has no place to drain. These low-grade lesions may progress to frank mucinous adenocarcinoma in patients who fail reductive surgery and intraperitoneal chemotherapy (39). Appendicetal lesions are nearly always confined to the peritoneal surfaces and only rarely are the lesions identified within lymph nodes or invading the parenchyma of abdominal or pelvic organs.
FIG. 9.17. Low-grade mucinous neoplasm. A: Note the implantation of neoplastic epithelium on the peritoneal surfaces. Neoplastic epithelium lines the large colloid-filled space at the lower portion of the picture. B: Mucicarmine stain demonstrating the presence of prominent apical mucin within the neoplastic cells.

Pedunculated PMP polyps contain a head, stalk, and base resembling the pattern seen in adenomas. Histologically, the head contains pools of acellular mucin associated with blunt fibrous trabeculae. A few adenomatous epithelial cells may be identified by repeated searching. Their presence can be appreciated by immunostaining surfaces devoid of an epithelial layer. Mesothelial cells often cover these lesions (35).
FIG. 9.18. Low-grade mucinous neoplasm associated with mesothelial hyperplasia. The specimen is stained with Alcian blue (blue) highlighting the mucin, cytokeratin immunostain highlighting the mucinous neoplasm (red), and calretinin immunostain (brown) highlighting the mesothelial hyperplasia.

Peritoneal Mucinous Adenocarcinoma

In peritoneal mucinous adenocarcinoma, the mucin deposits frequently contain abundant proliferative epithelium that may be arranged in nests, irregularly shaped glands, or even single cells, all demonstrating significant cytologic atypia (Fig. 9.19). Multiple layers of neoplastic cells may be present. The cells line the surfaces of the mucin deposits, float in the middle of the mucin, or invade into the parenchyma of the organs and surfaces that the tumor coats. These surfaces include the mesentery, peritoneum, spleen, liver, and stomach. The glandular architectural complexity is greater than that seen in low-grade mucinous tumors. The tumors often demonstrate atypical mitoses, marked nuclear hyperchromasia, and loss of polarity (Fig. 9.19). Occasional signet ring cells may be seen. These lesions associate with an identifiable primary mucinous adenocarcinoma of the appendix or colon. In general, appendiceal carcinomas show lower proliferative rates as measured by Ki-67, lower M30 counts, and lower CD44 expression than their colonic counterparts. This may relate to their more indolent behavior compared to adenocarcinomas of the colon and rectum (40). The tumors strongly express epithelial growth factor receptor (EGFR), making the use of anti-EGFR targeted therapy an attractive option.

P.538

It should be kept in mind that the appearance of the epithelium in the mucus can be deceptively benign, even when the lesion in the appendix is an obvious carcinoma. Therefore, one should try to examine the appendix if it is available, and if a carcinoma is present, the peritoneal lesion should be diagnosed as a well-differentiated carcinoma.

Patients with peritoneal carcinomatosis are sometimes treated with intraperitoneal chemotherapy, and the therapy may alter the histologic features. Intraperitoneal chemotherapy with 5-fluorouracil and mitomycin C induces a marked reduction in the number of foci of atypical epithelium lining the mucin globules and in atrophy and degeneration of atypical neoplastic lining epithelium (41).

Secondary involvement of the ovaries by mucinous carcinomas of gastrointestinal origin (Fig. 9.20) simulates primary ovarian tumors clinically and histologically. In this situation, the question arises as to whether the patient has two primary lesions or whether the findings represent spread of the disease from the appendix to the ovary or vice versa. Table 9.4 compares primary and secondary ovarian mucinous tumors. The synchronous presence or history of an appendiceal tumor always suggests that the ovarian involvement is secondary in nature. In this setting, the histologic features of the tumors usually resemble one another. Today, most people believe that ovarian involvement represents secondary spread from an appendiceal lesion (9,34,38,42).

Some patients have an excellent survival, despite the presence of massive peritoneal and omental mucin accumulations (28,43). The long-term survival relates to the slowly progressive nature of the neoplastic process, which rarely metastasizes to the liver or lymph nodes. Patient survival differs depending on whether the patient has mucinosis, a low-grade peritoneal mucinous tumor, or a peritoneal mucinous adenocarcinoma (11,44). Extension, metastasis, or death usually does not follow
PMP localized to the right lower quadrant, as may occur in some patients with low-grade mucinous cystadenoma that has escaped into the peritoneal cavity. In contrast, if the underlying lesion is malignant, diffuse progressive peritoneal involvement results, with obliteration of the entire abdominal cavity and recurrent bouts of intestinal obstruction, infection, or invasion of contiguous structures. The 3-year survival rates are 77% for patients with mucinosis and low-grade tumors versus 35% for mucinous adenocarcinomas (44). It also relates to patient age at presentation, the time between the diagnosis and the treatment, the extent of the peritoneal disease, the resection status, and the length of the chemoperfusion (44). Patients with tissue invasion have a significantly worse survival than those without invasion (47% vs. 80% at 3 years).

**FIG. 9.20.** Pseudomyxoma peritonei. Patient with ovarian cystadenoma (O) and an appendiceal mucinous cystadenoma (A).

**TABLE 9.4 Comparison of Appendiceal and Ovarian Mucinous Tumors**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Appendiceal Origin</th>
<th>Ovarian Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian involvement</td>
<td>Surface involvement with or without superficial stromal involvement; frequently bilateral</td>
<td>Predominantly stromal involvement May be bilateral</td>
</tr>
<tr>
<td></td>
<td>When the ovarian tumor is unilateral, it is usually right sided</td>
<td></td>
</tr>
<tr>
<td>Signet ring cells</td>
<td>May be present</td>
<td>Usually not present</td>
</tr>
<tr>
<td>Tumor present in the appendix</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mucin:cell ratio</td>
<td>10:1</td>
<td>1:1</td>
</tr>
<tr>
<td>CDX-2</td>
<td>Usually positive</td>
<td>Often negative</td>
</tr>
<tr>
<td>CK20</td>
<td>Usually positive</td>
<td>Positive in approximately 50%</td>
</tr>
<tr>
<td>CK7</td>
<td>Positive in approximately one third of cases</td>
<td>Usually positive</td>
</tr>
<tr>
<td>MUC2</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Currently these lesions are treated with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy (11). Peritonectomy can be used to clear mucinous tumor from parietal and visceral peritoneal surfaces. The peritonectomy
procedures include greater omentectomy and splenectomy, stripping of the left hemidiaphragm, stripping of the right hemidiaphragm, lesser omentectomy/polycystectomy, antrectomy, and pelvic peritonectomy with or without sigmoid colon resection. Not all of the procedures are performed in all patients, only if deemed necessary. Typically the pathologist receives specimens from all of these sites and more. We average about 20 specimens per initial procedure. Each of these should be diagnosed separately. Patients with mucinosis fare better than those with high-grade adenocarcinomas, and minimal peritoneal surface residual disease is treated more successfully than large volume residual disease in the abdomen (11,44). Medical treatment failure results from a generalized recurrence due to resistance to the chemotherapy and/or from nonuniform chemotherapy distribution. Surgical treatment failure results from the inability to surgically clear the abdomen of tumor.

Neuromas

Appendiceal neuromas occur relatively commonly; their frequency increases with age. Some develop in patients with neurofibromatosis. Controversy exists as to whether they are true neoplasms or merely a nonneoplastic proliferation, possibly induced by previous episodes of appendicitis (see Chapter 8) (45,46). Some neuromas coexist with carcinoids, particularly microcarcinoidosis, suggesting that some neuromas give rise to some carcinoid tumors. Ganglioneuromas have also been reported in this location (47). The tumors may be single or multiple. Grossly, neuromas may be invisible. Alternatively, the appendix may appear firm, light tan or gray, frequently with a glistening fibrous myxoid appearance. Microscopically, appendiceal neuromas show three architectural patterns. The most common pattern is a central obliterative neuroma (Fig. 9.21) that consists of loosely arranged spindle cell aggregates on a background network of fine eosinophilic cell processes. The muscularis mucosae between the mucosa and the adjacent appendiceal neuroma varies, being normal or completely absent. Intramucosal appendiceal neuromas represent another microscopic pattern (Fig. 9.21). Pale-staining, ill-defined, lamina propria expansions of neural tissue separate the crypts from one another. S100-stained sections show intensely positive focal areas in the lamina propria. The third histologic pattern consists of a localized but nonencapsulated nodular accentuation of the central obliterative process. The spindled Schwann cells form rounded laminated swirls that are uniformly S100 and neuron-specific enolase (NSE) positive. Occasionally, serotonin-positive cells intermingle with the spindle cell proliferation. The presence of neuroendocrine cells in appendiceal neuromas suggests that they represent an integral part of the neuronal proliferation (45).

Other Tumors

The appendix may also become involved by direct extension of tumors arising in adjacent organs such as the cecum, and in advanced cancer one may not be able to determine the exact site of origin of a given tumor. Metastases also affect the appendix. Tumors that metastasize to the appendix include ovary (Fig. 9.22), breast, stomach, cervix, and lung cancer (48,49). Leukemic infiltrates can also secondarily involve the appendix and may even present as appendicitis (50).
FIG. 9.21. Intramucosal neural proliferation demonstrating the presence of a focal neuromatous growth. A: Low-power cross section demonstrating the relationship of this lesion to the remainder of the appendix. B: Higher magnification demonstrating the typical Schwann cell histology of the proliferation surrounded by normal-appearing lamina propria and covered by an intact appendiceal epithelium.

Mesenchymal tumors and lymphomas can originate in the appendix. They resemble similar tumors occurring elsewhere and are discussed in Chapters 18 and 19. Appendiceal mesenchymal tumors include leiomyosarcomas, leiomyomatosis peritonealis disseminata, Kaposi sarcoma, and granular cell tumors.
FIG. 9.22. Papillary serous tumor of ovarian origin metastatic to the appendix. A: The tumor lies on the serosal surface of the appendix. B: Higher power showing the psammoma bodies.

References

22. McCusker ME, Cote TR, Clegg LX, Sobin LH: Primary malignant neoplasms of the appendix: a population-based study


Tufting Enteropathy

Tufting enteropathy is a chronic watery diarrhea syndrome presenting in the first few months of life. Rarely, the disease develops in older patients. Its etiology is unknown. The disease is thought to have a genetic basis since it tends to cluster in certain families (550). Alterations suggestive of abnormal cell–cell and cell–matrix interactions are present. These include an abnormal distribution of $\alpha_2\beta_1$ integrin along the crypt–villus axis, increased immunohistochemical expression of desmoglein, and ultrastructural alterations in the desmosomes (551,552). Jejunal biopsies demonstrate partial or total villous atrophy and crypt hyperplasia. There is no increase in inflammatory cells within the lamina propria. Intraepithelial lymphocytes are normal in number. The characteristic feature of the disease is the presence of focal epithelial “tufts” composed of clusters of closely packed enterocytes with rounded, tear-drop–shaped projections of their apical cytoplasm. Patients with tufting enteropathy have a variable prognosis. Most patients require total parenteral nutrition in order to remain adequately nourished for normal growth and development.