p0520

See TARGETED THERAPY available online at www.studentconsult.com

CHAPTER 17

c00017

The Gastrointestinal Tract

Jerrold R. Turner

CHAPTER CONTENTS

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

p0525 The gastrointestinal (GI) tract is a hollow tube extending from the oral cavity to the anus that consists of anatomically distinct segments, including the esophagus, stomach, small intestine, colon, rectum, and anus. Each of these segments has unique, complementary, and highly integrated functions, which together serve to regulate the intake, processing, and absorption of ingested nutrients and the disposal of waste products. The regional variations in structure and function are reflected in diseases of the GI tract, which often affect one or another segment preferentially. Accordingly, following consideration of several important congenital abnormalities, the discussion is organized anatomically. Disorders affecting more than one segment of the GI tract, such as Crohn disease, are discussed with the region that is involved most frequently.

s0010 CONGENITAL ABNORMALITIES

p0530 Depending on both the nature and timing of the insult during gestation, a variety of developmental anomalies can affect the GI tract. Importantly, because many organs develop simultaneously during embryogenesis, the presence of congenital GI disorders should prompt evaluation of other organs. Some defects are commonly associated with GI lesions.

s0015 Atresia, Fistulae, and Duplications

p0535 Atresia, fistulae, and duplications may occur in any part of the GI tract. When present within the esophagus they are discovered shortly after birth, usually due to regurgitation during feeding. Without prompt surgical repair, these lesions are incompatible with life. Absence, or *agenesis*, of the esophagus is extremely rare, but *atresia*, in which development is incomplete, is more common. In esophageal atresia a thin, noncanalized cord replaces a segment of esophagus, causing a mechanical obstruction (Fig. 17-1*A*). Atresia occurs most commonly at or near the tracheal bifurcation and is usually associated with a *fistula* connecting the upper or lower esophageal pouches to a bronchus or the trachea (17-1*B*). In other cases, a fistula can be present without atresia (Fig. 17-1*B, C*). Either form of fistula can lead to aspiration, suffocation, pneumonia, and severe fluid and electrolyte imbalances. Developmental abnormalities of the esophagus are associated with congenital heart defects, genitourinary malformations, and neurologic disease. Intestinal atresia is less common than esophageal atresia but frequently involves the duodenum. *Imperforate anus*, the most common form of congenital intestinal atresia, is due to a failure of the cloacal diaphragm to involute.

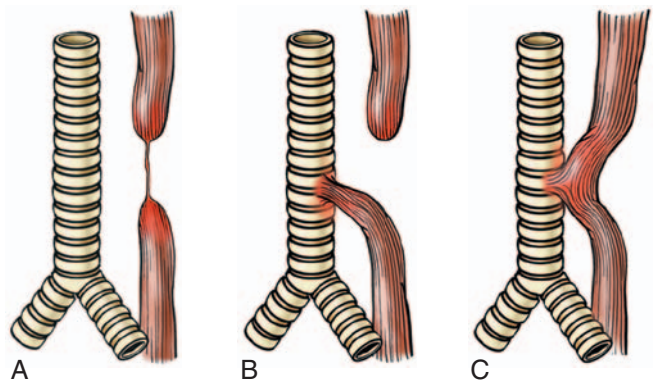
f0010 

Figure 17-1 Esophageal atresia and tracheoesophageal fistula. **A,** Blind upper and lower esophagus with thin cord of connective tissue linking the two segments. **B,** Blind upper segment with fistula between lower segment and trachea. **C,** Fistula (without atresia) between patent esophagus and trachea. The developmental anomaly shown in **B** is the most common. (Adapted from Morson BC, Dawson IMP, eds: Gastrointestinal Pathology. Oxford, Blackwell Scientific Publications, 1972, p 8.)

p0540 *Stenosis* is an incomplete form of atresia in which the lumen is markedly reduced in caliber as a result of fibrous thickening of the wall. This results in either partial or complete obstruction. In addition to congenital forms, stenosis can be acquired as a consequence of inflammatory scarring, such as that caused by chronic gastroesophageal reflux, irradiation, systemic sclerosis, or caustic injury. Stenosis can involve any part of the GI tract, but the esophagus and small intestine are affected most often.

Diaphragmatic Hernia, Omphalocele, and Gastroschisis s0020

p0550 Diaphragmatic hernia occurs when incomplete formation of the diaphragm allows the abdominal viscera to herniate into the thoracic cavity. When severe, the space-filling effect of the displaced viscera can cause pulmonary hypoplasia that is incompatible with life. *Omphalocele* occurs when closure of the abdominal musculature is incomplete and the abdominal viscera herniate into a ventral membranous sac. This may be repaired surgically, but as many as 40% of infants with an omphalocele have other birth defects. *Gastroschisis* is similar to omphalocele except that it involves all of the layers of the abdominal wall, from the peritoneum to the skin.

Ectopia s0025

p0555 Ectopic tissues (developmental rests) are common in the GI tract. The most frequent site of *ectopic gastric mucosa* is the upper third of the esophagus, where it is referred to as an *inlet patch*. While generally asymptomatic, acid released by gastric mucosa within the esophagus can result in dysphagia, esophagitis, Barrett esophagus, or, rarely, adenocarcinoma. *Ectopic pancreatic tissue* occurs less frequently and can be found in the esophagus or stomach. Like inlet patches, these nodules are most often asymptomatic but they produce damage and local inflammation in some cases. When ectopic pancreatic tissue is

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

present in the pylorus, inflammation and scarring may lead to obstruction. Because the rests may be present within any layer of the gastric wall, they can mimic invasive cancer. *Gastric heterotopia,* small patches of ectopic gastric mucosa in the small bowel or colon, may present with occult blood loss due to peptic ulceration of adjacent mucosa.

Meckel Diverticulum

s0030

p0560 A true diverticulum is a blind outpouching of the alimentary tract that communicates with the lumen and includes all three layers of the bowel wall. *The most common true diverticulum is the Meckel diverticulum, which occurs in the ileum.*

p0565 Meckel diverticulum occurs as a result of failed involution of the vitelline duct, which connects the lumen of the developing gut to the yolk sac. This solitary diverticulum extends from the antimesenteric side of the bowel (Fig. 17-2). The "rule of 2s" is often used to help remember characteristics of Meckel diverticula, which

u0520 • Occur in approximately 2% of the population
u0525 • Are generally present within 2 feet (60 cm) of the ileocecal valve
u0530 • Are approximately 2 inches (5 cm) long
u0535 • Are twice as common in males
u0540 • Are most often symptomatic by age 2 (only approximately 4% are ever symptomatic).

p0595 The mucosal lining of Meckel diverticula may resemble that of normal small intestine, but ectopic pancreatic or gastric tissue may also be present. The latter may secrete acid, cause peptic ulceration of adjacent small intestinal mucosa, and present with occult bleeding or abdominal pain resembling acute appendicitis or obstruction.

p0600 Less commonly, congenital diverticula occur in other parts of the small intestine and ascending colon. Virtually all other diverticula are acquired and either lack muscularis entirely or have an attenuated muscularis propria. The most common site of acquired diverticula is the sigmoid colon (discussed later).

f0015

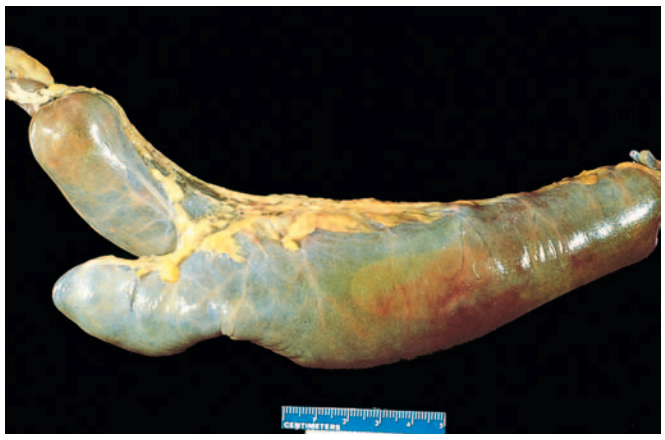


Figure 17-2 Meckel diverticulum. The blind pouch is located on the antimesenteric side of the small bowel.

Pyloric Stenosis

s0035

p0605 *Congenital hypertrophic pyloric stenosis is three to five times more common in males* and occurs once in 300 to 900 live births. Monozygotic twins have a high rate of concordance, with a 200-fold increased risk if one twin is affected. Incidence of congenital hypertrophic pyloric stenosis is also increased in dizygotic twins and siblings of affected individuals, although here the risk is only increased by 20-fold, reflecting a complex multifactorial pattern of inheritance. Consistent with a genetic basis, Turner syndrome and trisomy 18 also confer an increased risk of congenital hypertrophic pyloric stenosis. While the underlying mechanisms are not understood, erythromycin or azithromycin exposure, either orally or via mother's milk, in the first 2 weeks of life has been linked to increased disease incidence.

p0610 Congenital hypertrophic pyloric stenosis generally presents between the third and sixth weeks of life as new-onset regurgitation, projectile, nonbilious vomiting after feeding, and frequent demands for re-feeding. Physical examination reveals a firm, ovoid, 1 to 2 cm abdominal mass. In some cases abnormal left to right hyperperistalsis is evident during feeding and immediately before vomiting. This constellation of findings stems from hyperplasia of the pyloric muscularis propria, which obstructs the gastric outflow tract. Edema and inflammatory changes in the mucosa and submucosa may aggravate the narrowing. Surgical splitting of the muscularis (myotomy) is curative. Acquired pyloric stenosis occurs in adults as a consequence of antral gastritis or peptic ulcers close to the pylorus. Carcinomas of the distal stomach and pancreas may also narrow the pyloric channel due to fibrosis or malignant infiltration.

Hirschsprung Disease

s0040

p0615 Hirschsprung disease occurs in approximately 1 of 5000 live births. It may be isolated or occur in combination with other developmental abnormalities; 10% of all cases occur in children with Down syndrome and serious neurologic abnormalities are present in another 5%.

s0045 p0620 ***Pathogenesis.*** The enteric neuronal plexus develops from neural crest cells that migrate into the bowel wall during embryogenesis. Hirschsprung disease, also known as congenital aganglionic megacolon, results when the normal migration of neural crest cells from cecum to rectum is arrested prematurely or when the ganglion cells undergo premature death. This produces a distal intestinal segment that lacks both the Meissner submucosal and the Auerbach myenteric plexus ("aganglionosis"). Coordinated peristaltic contractions are absent and functional obstruction occurs, resulting in dilation proximal to the affected segment.

p0625 The mechanisms underlying defective neural crest cell migration in Hirschsprung disease are unknown, but a genetic component is present in nearly all cases, and 4% of patients' siblings are affected. Heterozygous loss-of-function mutations in the receptor tyrosine kinase *RET* account for the majority of familial cases and

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

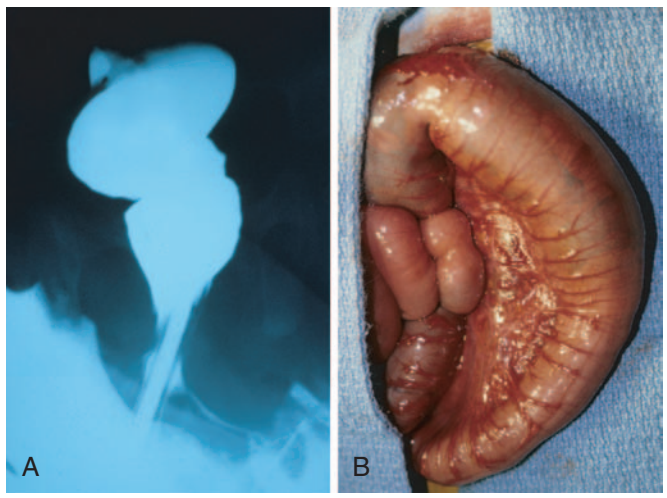
approximately 15% of sporadic cases. Mutations in at least seven other genes encoding proteins involved in enteric neurodevelopment, including the RET ligand glial-derived neurotrophic factor, endothelin, and the endothelin receptor, have also been described. However, these account for fewer than 30% of patients, suggesting that many other defects remain to be discovered. Because penetrance is incomplete, modifying genes or environmental factors must also be important. In addition, it is clear that sex-linked factors exist, since the disease is more common in males, but, when present in females, tends to involve longer aganglionic segments.

b0010

MORPHOLOGY

p0630 **Diagnosis of Hirschsprung disease requires documenting the absence of ganglion cells within the affected segment.** In addition to their characteristic morphology in hematoxylin and eosin–stained sections, ganglion cells can be identified using immunohistochemical stains for acetylcholinesterase.

p0635 The rectum is always affected, but the length of the additional involved segments varies widely, from the rectum and sigmoid colon in most cases to the entire colon in severe cases. The aganglionic region may have a grossly normal or contracted appearance. In contrast, the normally innervated proximal colon may undergo progressive dilation (Fig. 17-3) and, in time become massively distended **(megacolon)**, reaching diameters of as much as 20 cm. This may stretch and thin the colonic wall to the point of rupture, which occurs most frequently near the cecum. Mucosal inflammation or shallow ulcers may also be present in normally innervated segments, making gross identification of the extent of aganglionosis difficult. Hence, intraoperative frozen-section analysis is commonly used to confirm the presence of ganglion cells at the anastomotic margin.



f0020 **Figure 17-3** Hirschsprung disease. **A,** Preoperative barium enema study showing constricted rectum (bottom of the image) and dilated sigmoid colon. **B,** Corresponding intraoperative photograph showing constricted rectum and dilation of the sigmoid colon. (Courtesy Dr. Aliya Husain, The University of Chicago, Chicago, Ill.)

Clinical Features. Hirschsprung disease typically presents with a failure to pass meconium in the immediate postnatal period. Obstruction or constipation follows, often with visible, ineffective peristalsis, and may progress to abdominal distention and bilious vomiting. When only a few centimeters of rectum are involved occasional passage of stool may occur and obscure the diagnosis. The major threats to life are enterocolitis, fluid and electrolyte disturbances, perforation, and peritonitis. The primary mode of treatment is surgical resection of the aganglionic segment followed by anastomosis of the normal proximal colon to the rectum. Even after successful surgery, it may take years to attain normal bowel function and continence. s0065 p0640

In contrast to the congenital megacolon of Hirschsprung disease, acquired megacolon may occur at any age as a result of Chagas disease, obstruction by a neoplasm or inflammatory stricture, toxic megacolon complicating ulcerative colitis, visceral myopathy, or in association with functional psychosomatic disorders. Of these, only Chagas disease (discussed later) is associated with loss of ganglion cells. p0645

KEY CONCEPTS b0015

Congenital malformations of the GI tract s9005

- The GI tract is a common site of developmental abnormalities. In these cases, defects of other organs that develop in the same embryonic period should be sought. p0650
- **Atresia, and fistulae,** are structural developmental anomalies that disrupt normal gastrointestinal transit and typically present early in life. **Imperforate anus** is the most common form of congenital intestinal atresia, while the esophagus is the most common site of fistulization. u0550
- **Stenosis** may be developmental or acquired. Both forms are characterized by a thickened wall and partial or complete luminal obstruction. Acquired forms are often due to inflammatory scarring. u0555
- **Diaphragmatic hernia** is characterized by incomplete diaphragm development and herniation of abdominal organs into the thorax. This often results in pulmonary hypoplasia. **Omphalocele** and **gastroschisis** refer to ventral herniation of abdominal organs. u0560
- **Ectopia** refers to the presence of normally formed tissues in an abnormal site. This is common in the gastrointestinal tract, with **ectopic gastric mucosa** in the upper third of the esophagus being the most common form. u0565
- The **Meckel diverticulum** is a true diverticulum, defined by the presence of all three layers of the bowel wall, that reflects failed involution of the vitelline duct. It is common and is a frequent site of gastric ectopia, which may result in occult bleeding. u0570
- **Congenital hypertrophic pyloric stenosis** is a form of obstruction that presents between the third and sixth weeks of life. There is an ill-defined genetic component to this disease, which is most common in males. u0575
- **Hirschsprung disease** is caused by the absence of neural crest derived ganglion cells within the colon. It causes functional obstruction of the affected bowel and proximal dilation. The defect always begins at the rectum, but extends proximally for variable lengths. u0580

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

s0070

ESOPHAGUS

p0695 The esophagus develops from the cranial portion of the foregut and is recognizable by the third week of gestation. It is a hollow, highly distensible muscular tube that extends from the epiglottis in the pharynx to the gastroesophageal junction. Acquired diseases of the esophagus run the gamut from highly lethal cancers to the persistent "heartburn" of gastroesophageal reflux that may be chronic and incapacitating or merely an occasional annoyance.

s0075

Esophageal Obstruction

p0700 The esophagus is, essentially, a tube that delivers ingested solid food and fluids to the stomach. This can be impeded by structural, i.e. (mechanical) obstruction or functional obstruction. The latter results from disruption of the coordinated waves of peristaltic contractions that follow swallowing. Esophageal manometry allows separation of esophageal dysmotility into three principal forms, termed nutcracker esophagus, diffuse esophageal spasm, and hypertensive lower esophageal sphincter.

u9000 • *Nutcracker esophagus* describes patients with high-amplitude contractions of the distal esophagus that are, in part, due to loss of the normal coordination of inner circular layer and outer longitudinal layer smooth muscle contractions.

u9005 • *Diffuse esophageal spasm* is characterized by repetitive, simultaneous contractions of the distal esophageal smooth muscle.

u9010 • Lower esophageal sphincter dysfunction, such as high resting pressure or incomplete relaxation, are present in many patients with nutcracker esophagus or diffuse esophageal spasm. In the absence altered patterns of esophageal contraction, these sphincter abnormalities are termed *hypertensive lower esophageal sphincter*. As discussed below, these can be distinguished from achalasia in that the latter includes reduced esophageal peristaltic contractions.

p0705 Because wall stress is increased, esophageal dysmotility may result in development of small diverticulae, primarily the epiphrenic diverticulum located immediately above the lower esophageal sphincter. Similarly, impaired relaxation and spasm of the cricopharyngeus muscle after swallowing can result in increased pressure within the distal pharynx and development of a Zenker diverticulum (pharyngoesophageal diverticulum), which is located immediately above the upper esophageal sphincter. Zenker diverticulae are uncommon, but typically develop after age 50 and may reach several centimeters in size. When small they may be asymptomatic, but larger Zenker diverticulae may accumulate significant amounts of food, producing a mass and symptoms that include regurgitation and halitosis.

p0710 In contrast to functional obstruction, mechanical obstruction, which can be caused by strictures or cancer, presents as progressive dysphagia that begins with inability to swallow solids. With progression ingestion of liquids is also affected. Because obstruction develops slowly, patients may subconsciously modify their diet to favor soft foods and liquids and be unaware of their condition until the obstruction is nearly complete.

p0715 Benign *esophageal stenosis*, or narrowing of the lumen, is generally caused by fibrous thickening of the submucosa and is associated with atrophy of the muscularis propria as well as secondary epithelial damage. Although occasionally congenital, stenosis is most often due to inflammation and scarring that may be caused by chronic gastroesophageal reflux, irradiation, or caustic injury. In general, patients with functional obstruction or benign strictures maintain their appetite and weight, while, as discussed later, malignant strictures are often associated with weight loss.

p0720 *Esophageal mucosal webs* are idiopathic ledge-like protrusions of mucosa that may cause obstruction. These uncommon lesions typically occur in women older than age 40 and can be associated with gastroesophageal reflux, chronic graft-versus-host disease, or blistering skin diseases. In the upper esophagus, webs may be accompanied by iron-deficiency anemia, glossitis, and cheilosis as part of the *Paterson-Brown-Kelly* or *Plummer-Vinson syndrome*. In general, esophageal webs are semi-circumferential lesions that protrude less than 5 mm, have a thickness of 2 to 4 mm, and are composed of a fibrovascular connective tissue and overlying epithelium. The main symptom of webs is nonprogressive dysphagia associated with incompletely chewed food.

p0725 Esophageal rings, or *Schatzki rings*, are similar to webs, but are circumferential, thicker, and include mucosa, submucosa, and, occasionally, hypertrophic muscularis propria. When present in the distal esophagus, above the gastroesophageal junction, they are termed *A rings* and are covered by squamous mucosa; in contrast, those located at the squamocolumnar junction of the lower esophagus are designated *B rings* and may have gastric cardia-type mucosa on their undersurface.

Achalasia

s0080

p0730 Increased tone of the lower esophageal sphincter (LES), as a result of impaired smooth muscle relaxation, is an important cause of esophageal obstruction. Normally, release of nitric oxide and vasoactive intestinal polypeptide from inhibitory neurons, along with interruption of normal cholinergic signaling, allows the LES to relax during swallowing. *Achalasia is characterized by the triad of incomplete LES relaxation, increased LES tone, and aperistalsis of the esophagus.* Symptoms include dysphagia for solids and liquids, difficulty in belching, and chest pain. Although there is some increased risk for esophageal cancer, it is not considered great enough to warrant surveillance endoscopy.

p0735 *Primary achalasia is the result of distal esophageal inhibitory neuronal, that is, ganglion cell, degeneration.* This leads to increased tone, an inability to relax of the lower esophageal sphincter, and esophageal aperistalsis. Degenerative changes in the extraesophageal vagus nerve or the dorsal motor nucleus of the vagus may also occur. The cause is unknown; rare familial cases have been described.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

p0740 *Secondary achalasia may arise in Chagas disease, in which Trypanosoma cruzi infection causes destruction of the myenteric plexus, failure of peristalsis, and esophageal dilatation.* Duodenal, colonic, and ureteric myenteric plexuses can also be affected in Chagas disease. Achalasia-like disease may be caused by diabetic autonomic neuropathy; infiltrative disorders such as malignancy, amyloidosis, or sarcoidosis; lesions of dorsal motor nuclei, particularly polio or surgical ablation; in association with Down syndrome; or as part of Allgrove (triple A) syndrome, an autosomal recessive disorder characterized by achalasia, alacrima, and adrenocorticotrophic hormone-resistant adrenal insufficiency. The association of some achalasia cases with remote herpes simplex virus 1 (HSV1) infection, linkage of immunoregulatory gene polymorphisms to achalasia, and occasional coexistence of Sjögren syndrome or autoimmune thyroid disease suggest that achalasia may also be driven by immune-mediated destruction of inhibitory esophageal neurons. Treatment modalities for both primary and secondary achalasia aim to overcome the mechanical obstruction, and include laparoscopic myotomy and pneumatic balloon dilatation. Botulinum neurotoxin (Botox) injection, to inhibit LES cholinergic neurons, can also be effective.

s0085 # Esophagitis

s0090 ## Lacerations

p0745 Longitudinal mucosal tears near the gastroesophageal junction are termed *Mallory-Weiss tears,* and are most often associated with severe retching or vomiting secondary to acute alcohol intoxication. Normally, a reflex relaxation of the gastroesophageal musculature precedes the antiperistaltic contractile wave associated with vomiting. It is speculated that this relaxation fails during prolonged vomiting, with the result that refluxing gastric contents overwhelm the gastric inlet and cause the esophageal wall to stretch and tear. The roughly linear lacerations of Mallory-Weiss syndrome are longitudinally oriented and range in length from millimeters to several centimeters. These tears usually cross the gastroesophageal junction and may also be located in the proximal gastric mucosa. Up to 10% of upper GI bleeding, which often presents as hematemesis (Table 17-1), is due to superficial esophageal lacerations such as those associated with Mallory-Weiss syndrome. These do not generally require surgical intervention, and healing tends to be rapid and complete. In contrast, Boerhaave syndrome is a much less common but more serious disorder characterized by transmural tearing and rupture of the distal esophagus. This catastrophic event produces severe mediastinitis and generally requires surgical intervention. Because patients can present with severe chest pain, tachypnea, and shock, the initial differential diagnosis can include myocardial infarction.

t0010 **Table 17-1** Esophageal Causes of Hematemesis

u0585	Lacerations (Mallory-Weiss syndrome)
u0590	Esophageal perforation (cancer or Boerhaave syndrome)
u0595	Varices (cirrhosis)
u0600	Esophageal-aortic fistula (usually with cancer)
u0605	Chemical and pill esophagitis
u0610	Infectious esophagitis (*Candida*, herpes)
u0615	Benign strictures
u0620	Vasculitis (autoimmune, cytomegalovirus)
u0625	Reflux esophagitis (erosive)
u0630	Eosinophilic esophagitis
u0635	Esophageal ulcers (many etiologies)
u0640	Barrett esophagus
u0645	Adenocarcinoma
u0650	Squamous cell carcinoma
u0655	Hiatal hernia

Chemical and Infectious Esophagitis s0095

p0825 The stratified squamous mucosa of the esophagus may be damaged by a variety of irritants including alcohol, corrosive acids or alkalis, excessively hot fluids, and heavy smoking. Symptoms range from self-limited pain, particularly on swallowing, that is, *odynophagia*, to hemorrhage, stricture, or perforation in severe cases.

p0830 In children esophageal chemical injury is often secondary to accidental ingestion of household cleaning products; severe damage may follow attempted suicide in adults. Less severe chemical injury to the esophageal mucosa can occur when medicinal pills lodge and dissolve in the esophagus rather than passing into the stomach intact, a condition termed *pill-induced esophagitis.* Iatrogenic esophageal injury may be caused by cytotoxic chemotherapy, radiation therapy, or graft-versus-host disease. The esophagus may also be involved by the desquamative skin diseases bullous pemphigoid, epidermolysis bullosa and, rarely, Crohn disease.

p0835 Esophageal infections in otherwise healthy individuals are uncommon and most often due to herpes simplex virus. Infections in patients who are debilitated or immunosuppressed, as a result of disease or therapy, is more common and can be caused by herpes simplex virus, cytomegalovirus (CMV), or fungal organisms. Among fungi, candidiasis is most common, although mucormycosis and aspergillosis are also seen.

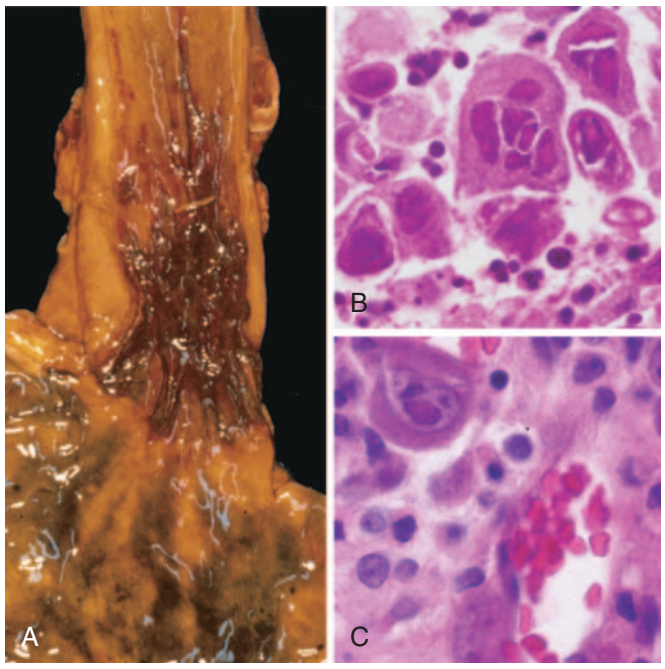
MORPHOLOGY b0020

p0840 The morphology of chemical and infectious esophagitis varies with etiology. Dense infiltrates of neutrophils are present in most cases but may be absent following injury induced by chemicals (lye, acids, or detergent), which can lead to outright necrosis of the esophageal wall. Pill-induced esophagitis frequently occurs at the site of strictures that impede passage of luminal contents. When present, ulceration is accompanied by superficial necrosis with granulation tissue and eventual fibrosis.

p0845 Esophageal irradiation causes damage similar to that seen in other tissues and includes intimal proliferation and luminal narrowing of submucosal and mural blood vessels. The mucosal damage is, in part, secondary to this radiation-induced vascular injury as discussed in Chapter 9.

p0850 Infection by fungi or bacteria can either cause injury or complicate a preexisting ulcer. Nonpathogenic oral bacteria are frequently found in ulcer beds, while pathogenic organisms, which account for about 10% of infectious esophagitis, may invade the lamina propria and cause necrosis of overlying mucosa. Candidiasis, in its most advanced form, is characterized by adherent, gray-white **pseudomembranes** composed

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0025 **Figure 17-4** Viral esophagitis. **A,** Postmortem specimen with multiple, overlapping herpetic ulcers in the distal esophagus. **B,** Multinucleate squamous cells containing herpesvirus nuclear inclusions. **C,** Cytomegalovirus-infected endothelial cells with nuclear and cytoplasmic inclusions.

of densely matted fungal hyphae and inflammatory cells covering the esophageal mucosa.

p0855 The endoscopic appearance often provides a clue as to the infectious agent in viral esophagitis. Herpes viruses typically cause punched-out ulcers (Fig. 17-4*A*). Biopsy specimens demonstrate nuclear viral inclusions within a rim of degenerating epithelial cells at the margin of the ulcer (Fig. 17-4*B*). In contrast, CMV causes shallower ulcerations and characteristic nuclear and cytoplasmic inclusions within capillary endothelium and stromal cells (Fig. 17-4*C*). Although the histologic appearance is characteristic, immunohistochemical stains for virus-specific antigens are sensitive and specific ancillary diagnostic tools.

p0860 Histologic features of esophageal **graft-versus-host disease** are similar to those in the skin and include basal epithelial cell apoptosis, mucosal atrophy, and submucosal fibrosis without significant acute inflammatory infiltrates. The microscopic appearances of esophageal involvement in bullous pemphigoid, epidermolysis bullosa, and Crohn disease are also similar to those in the skin (Chapter 25).

s0100 Reflux Esophagitis

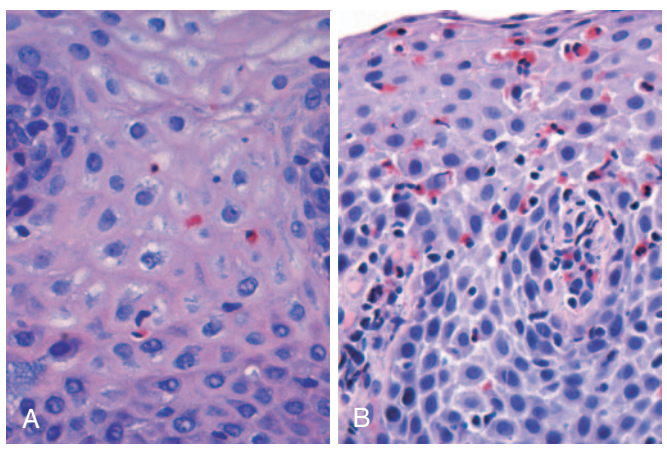
p0865 The stratified squamous epithelium of the esophagus is resistant to abrasion from foods but is sensitive to acid. Submucosal glands, which are most abundant in the proximal and distal esophagus, contribute to mucosal protection by secreting mucin and bicarbonate. More importantly, the tone of the lower esophageal sphincter prevents reflux of acidic gastric contents, which are under positive pressure and would otherwise enter the esophagus. Reflux of gastric contents into the lower esophagus is the most frequent cause of esophagitis and the most common outpatient GI diagnosis in the United States. The associated clinical condition is termed *gastroesophageal reflux disease (GERD)*.

Pathogenesis. The most common cause of gastroesophageal reflux is transient lower esophageal sphincter relaxation. This is thought to be mediated via vagal pathways, and can be triggered by gastric distention, by gas or food, mild pharyngeal stimulation that does not trigger swallowing, and stress. Gastroesophageal reflux can also occur following swallow-induced lower esophageal sphincter relaxations or due to forceful opening of a relatively hypotensive lower esophageal sphincter by an abrupt increase in intraabdominal pressure, such as that due to coughing, straining, or bending. Other conditions that decrease lower esophageal sphincter tone or increase abdominal pressure and contribute to GERD include alcohol and tobacco use, obesity, central nervous system depressants, pregnancy, hiatal hernia (discussed later), delayed gastric emptying, and increased gastric volume. In many cases, no definitive cause is identified. Reflux of gastric juices is central to the development of mucosal injury in GERD. In severe cases, reflux of bile from the duodenum may exacerbate the damage. s0105 p0870

MORPHOLOGY b0025

Simple hyperemia, evident to the endoscopist as redness, may be the only alteration. In mild GERD the mucosal histology is often unremarkable. With more significant disease, eosinophils are recruited into the squamous mucosa followed by neutrophils, which are usually associated with more severe injury (Fig. 17-5*A*). Basal zone hyperplasia exceeding 20% of the total epithelial thickness and elongation of lamina propria papillae, such that they extend into the upper third of the epithelium, may also be present. p0875

Clinical Features. GERD is most common in individuals older than age 40 but also occurs in infants and children. The most frequent clinical symptoms are heartburn, dysphagia, and regurgitation of sour-tasting gastric contents. s0120 p0880



f0030 **Figure 17-5** Esophagitis. **A,** Reflux esophagitis with scattered intraepithelial eosinophils and mild basal zone expansion. **B,** Eosinophilic esophagitis is characterized by numerous intraepithelial eosinophils. Abnormal squamous maturation is also apparent.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

Rarely, chronic GERD is punctuated by attacks of severe chest pain that may be mistaken for heart disease. Treatment with proton pump inhibitors, which have replaced H_2 histamine receptor antagonists, to reduce gastric acidity typically provides symptomatic relief. While the severity of symptoms is not closely related to the degree of histologic damage, the latter tends to increase with disease duration. Complications of reflux esophagitis include ulceration, hematemesis, melena, stricture development, and Barrett esophagus.

p0885 Hiatal hernia can give rise to symptoms, such as heartburn and regurgitation of gastric juices, that are similar to those of GERD. It is characterized by separation of the diaphragmatic crura and protrusion of the stomach into the thorax through the resulting gap. Congenital hiatal hernias are recognized in infants and children, but many are acquired in later life. Hiatal hernia is symptomatic in fewer than 10% of adults, but can be a cause of lower esophageal sphincter incompetence.

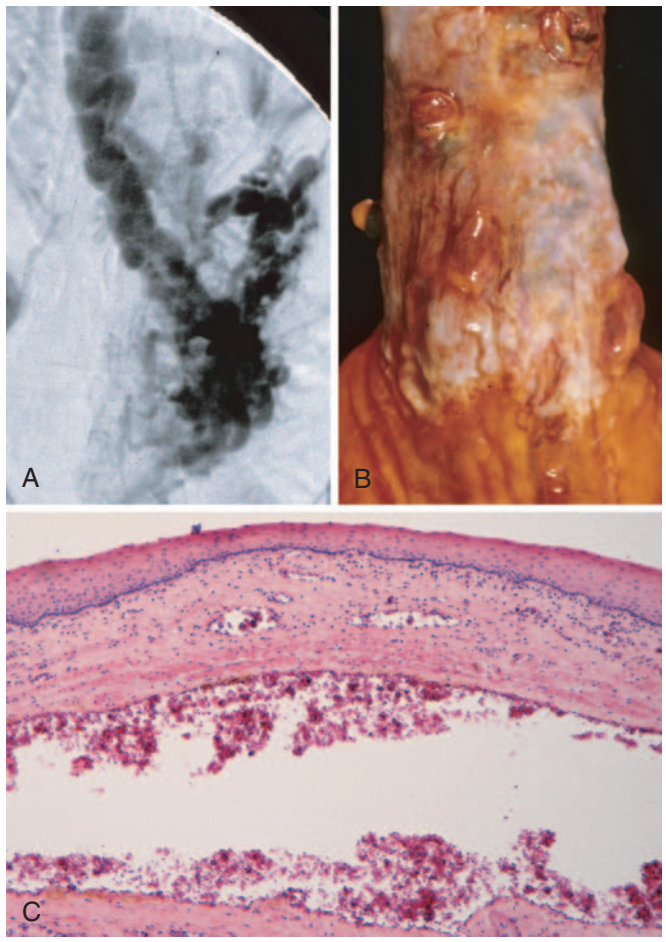
s0125 Eosinophilic Esophagitis

p0890 The incidence of eosinophilic esophagitis is increasing markedly. Symptoms include food impaction and dysphagia in adults and feeding intolerance or GERD-like symptoms in children. The cardinal histologic feature is large numbers of intraepithelial eosinophils, particularly superficially (Fig. 17-5*B*). Their abundance can help to differentiate eosinophilic esophagitis from GERD, Crohn disease, and other causes of esophagitis. In addition, unlike patients with GERD, acid reflux is not prominent and high doses of proton pump inhibitors usually do not provide relief. *The majority of individuals with eosinophilic esophagitis are atopic* and many have atopic dermatitis, allergic rhinitis, asthma, or modest peripheral eosinophilia. Treatments include dietary restrictions to prevent exposure to food allergens, such as cow's milk and soy products, and topical or systemic corticosteroids.

s0130 Esophageal Varices

p0895 Venous blood from the GI tract passes through the liver, via the portal vein, before returning to the heart. This circulatory pattern is responsible for the first-pass effect in which drugs and other materials absorbed in the intestines are processed by the liver before entering the systemic circulation. Diseases that impede this flow cause portal hypertension and can lead to the development of esophageal varices, an important cause of esophageal bleeding.

s0135 p0900 ***Pathogenesis.*** **Portal hypertension results in the development of collateral channels at sites where the portal and caval systems communicate.** These collateral veins allow some drainage to occur, but at the same time they lead to development of congested subepithelial and submucosal venous plexi within the distal esophagus and proximal stomach. These vessels, termed *varices,* develop in the vast majority of cirrhotic patients, most commonly in association with alcoholic liver disease. Worldwide, hepatic schistosomiasis is the second most common cause of varices. A more detailed consideration of portal hypertension is given in Chapter 18.



f0035

Figure 17-6 Esophageal varices. **A,** Although no longer used as a diagnostic approach, this angiogram demonstrates several tortuous esophageal varices. **B,** Collapsed varices are present in this postmortem specimen corresponding to the angiogram in **A**. The polypoid areas represent previous sites of variceal hemorrhage that have been ligated with bands. **C,** Dilated varices beneath intact squamous mucosa.

MORPHOLOGY b0030

p0905 Varices are tortuous dilated veins lying primarily within the submucosa of the distal esophagus and proximal stomach (Fig. 17-6*A*). Venous channels directly beneath the esophageal epithelium may also become massively dilated. Varices may not be grossly obvious in surgical or postmortem specimens, because they collapse in the absence of blood flow (Fig. 17-6*B*) and are obscured by the overlying mucosa (Fig. 17-6*C*). Variceal rupture results in hemorrhage into the lumen or the esophageal wall, in which case the overlying mucosa appears ulcerated and necrotic. If rupture has occurred in the past, venous thrombosis, inflammation, and evidence of prior therapy may also be present.

s0150 p0910 ***Clinical Features.*** Gastroesophageal varices are present in nearly half of the patients with cirrhosis, and 25-40% of patients with cirrhosis develop variceal bleeding. Approximately 12% of previously asymptomatic varices bleed each year. Variceal hemorrhage is an emergency that can be treated medically by inducing splanchnic vasoconstriction or endoscopically by sclerotherapy (injection of thrombotic agents), balloon tamponade, or variceal

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

ligation. Despite these interventions, 30% or more of patients with variceal hemorrhage die as a direct consequence of hemorrhage such as hypovolemic shock, hepatic coma, or other complications. Furthermore, more than 50% of patients who survive a first variceal bleed have recurrent hemorrhage within 1 year, and this carries a mortality rate similar to that of the first episode. Thus, patients with risk factors for hemorrhage, including large varices, elevated hepatic venous pressure gradient, previous bleeding, and advanced liver disease may be treated prophylactically with beta-blockers to reduce portal blood flow and with endoscopic variceal ligation. Despite the frequency and risks of variceal hemorrhage, it is important to recognize that cirrhosis patients with small varices that have never bled are at relatively low risk for bleeding and death, and that, even when varices are present, they are only one of several causes of hematemesis.

s0155 Barrett Esophagus

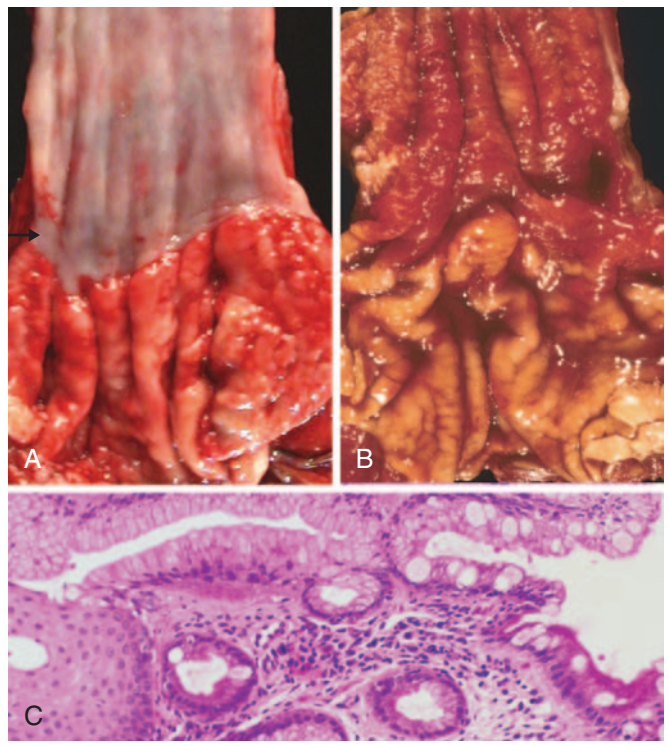
p0915 **Barrett esophagus is a complication of chronic GERD that is characterized by intestinal metaplasia within the esophageal squamous mucosa.** The incidence of Barrett esophagus is rising, and it is estimated to occur in as many as 10% of individuals with symptomatic GERD. Barrett esophagus is most common in white males and typically presents between 40 and 60 years of age. *The greatest concern in Barrett esophagus is that it confers an increased risk of esophageal adenocarcinoma.* Genomic sequencing of biopsies involved by Barrett esophagus has revealed the presence of mutations that are shared with esophageal adenocarcinoma, in keeping with the idea that Barrett esophagus is a precursor lesion to cancer. Potentially oncogenic mutations are more numerous when biopsies demonstrate dysplasia, which is detected in 0.2% to 2% of persons with Barrett esophagus each year. The presence of dysplasia, a preinvasive change, is associated with prolonged symptoms, longer segment length, increased patient age, and Caucasian race. Although the vast majority of esophageal adenocarcinomas are associated with Barrett esophagus, it is important to remember that most individuals with Barrett esophagus do not develop esophageal tumors.

b0035 MORPHOLOGY

p0920 Barrett esophagus can be recognized as one or several tongues or patches of red, velvety mucosa extending upward from the gastroesophageal junction. This metaplastic mucosa alternates with residual smooth, pale squamous (esophageal) mucosa and interfaces with light-brown columnar (gastric) mucosa distally (Fig. 17-7*A, B*). High-resolution endoscopes have increased the sensitivity of Barrett esophagus detection. This has led to subclassification of Barrett esophagus as long segment, which involves 3 cm or more, or short segment, in which less than 3 cm is involved. Available data suggest that the risk of dysplasia correlates with length of esophagus affected.

p0925 Diagnosis of Barrett esophagus requires endoscopic evidence of metaplastic columnar mucosa above the gastroesophageal junction. Microscopically, intestinal-type metaplasia is seen as replacement of the squamous esophageal epithelium with goblet cells. These are diagnostic of Barrett esophagus, and have distinct mucous vacuoles that stain pale blue by hematoxylin and eosin and impart the shape of a wine goblet to the remaining cytoplasm (Fig. 17-7*C*). Non-goblet columnar cells, such as gastric type foveolar cells, may also be present. However, whether the latter are sufficient for diagnosis is controversial.

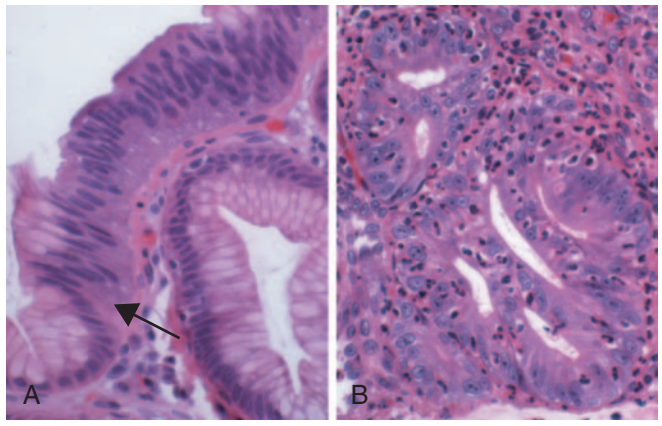
p0930 When **dysplasia** is present, it is classified as low grade or high grade. Atypical mitoses, nuclear hyperchromasia, irregularly clumped chromatin, increased nuclear-to-cytoplasmic ratio, and a failure of epithelial cells to mature as they migrate to the esophageal surface are present in both grades of dysplasia (Fig. 17-8*A*). Gland architecture is frequently abnormal and is characterized by budding, irregular shapes, and cellular crowding. High-grade dysplasia (Fig. 17-8*B*) exhibits more severe cytologic and architectural changes. With progression, epithelial cells may invade the lamina propria, a feature that defines intramucosal carcinoma.



f0040 **Figure 17-7** Barrett esophagus. **A,** Normal gastroesophageal junction. **B,** Barrett esophagus. Note the small islands of residual pale squamous mucosa within the Barrett mucosa. **C,** Histologic appearance of the gastroesophageal junction in Barrett esophagus. Note the transition between esophageal squamous mucosa (left) and Barrett metaplasia, with abundant metaplastic goblet cells (right).

s0170 p0935 ***Clinical Features.*** **Barrett esophagus can only be identified thorough endoscopy and biopsy, which are usually prompted by GERD symptoms.** Once diagnosed, the best course of management is a matter of debate. Many support periodic endoscopy with biopsy, for dysplasia surveillance. However, randomized trials have failed to demonstrate that surveillance improves patient survival. Furthermore, uncertainties regarding the potential of dysplasia, particularly low grade, to regress spontaneously and limited information on the risk of progression complicate clinical decisions.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0045 **Figure 17-8** Dysplasia in Barrett esophagus. **A,** Abrupt transition from Barrett metaplasia to low-grade dysplasia *(arrow)*. Note the nuclear stratification and hyperchromasia. **B,** Architectural irregularities, including gland-within-gland, or cribriform, profiles in high-grade dysplasia.

p0940 Intramucosal or invasive carcinoma requires therapeutic intervention. Treatment options include surgical resection, or esophagectomy, as well as newer modalities such as photodynamic therapy, laser ablation, and endoscopic mucosectomy. Multifocal high-grade dysplasia, which carries a significant risk of progression to intramucosal or invasive carcinoma, is treated as intramucosal carcinoma. Many physicians follow low-grade dysplasia or a single focus of high-grade dysplasia with endoscopy and biopsy at frequent intervals. However, management of esophageal dysplasia is evolving, and it is hoped that improved molecular understanding of neoplastic progression may allow development of chemopreventive approaches that reduce the incidence of esophageal adenocarcinoma.

s0175 Esophageal Tumors

p0945 **The vast majority of esophageal cancers fall into one of two types, adenocarcinoma and squamous cell carcinoma.** Squamous cell carcinoma is more common worldwide, but adenocarcinoma is on the rise in the United States and other Western countries. Other malignancies of the esophagus are far less common and include unusual forms of adenocarcinoma, undifferentiated carcinoma, carcinoid tumor, melanoma, lymphoma, and sarcoma; these are not discussed here. Benign tumors of the esophagus are generally mesenchymal, and arise within the esophageal wall, with leiomyomas being most common. Fibromas, lipomas, hemangiomas, neurofibromas, and lymphangiomas also occur.

s0180 Adenocarcinoma

p0950 **Most esophageal adenocarcinomas arise from Barrett esophagus.** Thus, increased rates of esophageal adenocarcinoma may be partly due to the increased incidence of obesity-related gastroesophageal reflux and Barrett esophagus. Additional risk factors include tobacco use and exposure to radiation. Conversely, risk is reduced by diets rich in fresh fruits and vegetables. Some serotypes of *Helicobacter pylori* are associated with decreased risk of esophageal adenocarcinoma, because they cause gastric atrophy, which in turn leads to reduced acid secretion and reflux, and reduced incidence of Barrett esophagus. Thus, reduced rates of *Helicobacter pylori* infection may also be a factor in the increasing incidence of esophageal adenocarcinoma.

p0955 Esophageal adenocarcinoma occurs most frequently in Caucasians and shows a strong gender bias, being sevenfold more common in men. However, the incidence varies widely worldwide, with rates being highest in countries that include the United States, the United Kingdom, Canada, Australia, the Netherlands, and Brazil, and lowest in Korea, Thailand, Japan, and Ecuador. In countries where esophageal adenocarcinoma is more common, the incidence has increased markedly since 1970, more rapidly than almost any other cancer. For unknown reasons, these increases have been restricted to white and Hispanic men and white women in the United States. As a result, esophageal adenocarcinoma, which represented less than 5% of esophageal cancers before 1970, now accounts for more than half of all esophageal cancers in the United States.

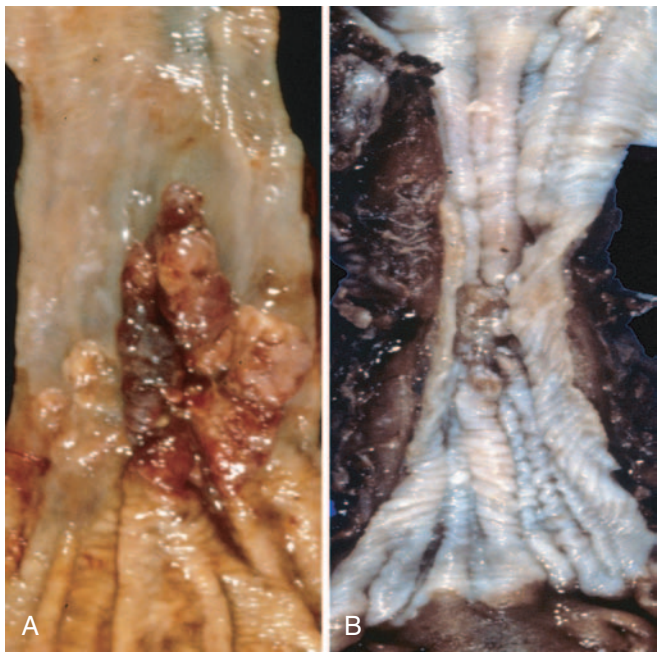
s0185 p0960 ***Pathogenesis.*** **Molecular studies suggest that the progression of Barrett esophagus to adenocarcinoma occurs over an extended period through the stepwise acquisition of genetic and epigenetic changes.** This model is supported by the observation that epithelial clones identified in nondysplastic Barrett metaplasia persist and accumulate mutations during progression to dysplasia and invasive carcinoma. Chromosomal abnormalities, mutation of *TP53*, and downregulation of the cyclin-dependent kinase inhibitor *CDKN2A,* also known as *p16/INK4a,* are detected at early stages. In the case of *CDKN2A,* both allelic loss and hypermethylation-induced epigenetic silencing have been described. Later during progression there is amplification of *EGFR, ERBB2, MET, cyclin D1*, and *cyclin E* genes.

b0040 MORPHOLOGY

p0965 Esophageal adenocarcinoma usually occurs in the distal third of the esophagus and may invade the adjacent gastric cardia (Fig. 17-9*A*). Initially appearing as flat or raised patches in otherwise intact mucosa, large masses of 5 cm or more in diameter may develop. Alternatively, tumors may infiltrate diffusely or ulcerate and invade deeply. Microscopically, Barrett esophagus is frequently present adjacent to the tumor. Tumors most commonly produce mucin and form glands (Fig. 17-10*A*), often with intestinal-type morphology; less frequently tumors are composed of diffusely infiltrative signet-ring cells (similar to those seen in diffuse gastric cancers) or, in rare cases, small poorly differentiated cells (similar to small-cell carcinoma of the lung).

s0200 p0970 ***Clinical Features.*** Although esophageal adenocarcinomas are occasionally discovered in evaluation of GERD or surveillance of Barrett esophagus, they more commonly present with pain or difficulty in swallowing, progressive weight loss, hematemesis, chest pain, or vomiting. By the time symptoms appear, the tumor has usually spread to submucosal lymphatic vessels. As a result of the advanced stage at diagnosis, overall 5-year survival is less than 25%. In contrast, 5-year survival approximates 80% in the few patients with adenocarcinoma limited to the mucosa or submucosa.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0050

Figure 17-9 Esophageal cancer. **A,** Adenocarcinoma usually occurs distally and, as in this case, often involves the gastric cardia. **B,** Squamous cell carcinoma is most frequently found in the mid-esophagus, where it commonly causes strictures.

s0205 Squamous Cell Carcinoma

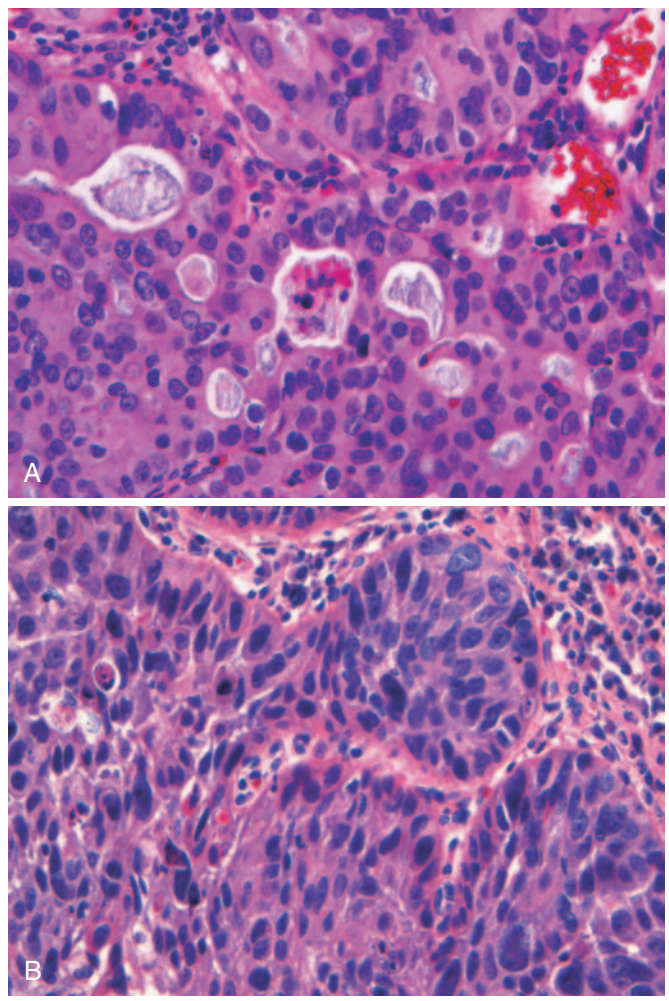
p0975 In the United States, esophageal squamous cell carcinoma occurs in adults older than age 45 and affects males four times more frequently than females. Risk factors include alcohol and tobacco use, poverty, caustic esophageal injury, achalasia, tylosis, Plummer-Vinson syndrome, diets that are deficient in fruits or vegetables, and frequent consumption of very hot beverages. Previous radiation to the mediastinum also predisposes individuals to esophageal carcinoma, with most cases occurring 5 to 10 or more years after exposure. Esophageal squamous cell carcinoma is nearly eight-fold more common in African Americans than Caucasians, a striking risk disparity that reflects differences in rates of alcohol and tobacco use as well as other poorly understood factors.

p0980 Esophageal squamous cell carcinoma incidence varies up to 180-fold between and within countries, being more common in rural and underdeveloped areas. The regions with highest incidence are Iran, central China, Hong Kong, Brazil, and South Africa. A pocket of extremely high esophageal squamous cell carcinoma incidence in western Kenya includes patients younger than 30 years of age and has been linked to consumption of a traditional fermented milk, termed mursik, which contains the carcinogen acetaldehyde (Chapter 9).

s0210 p0985 ***Pathogenesis.*** The majority of esophageal squamous cell carcinomas in Europe and the United States are linked to the use of alcohol and tobacco, which synergize to increase the risk. However, esophageal squamous cell carcinoma is also common in some regions where alcohol and tobacco use is uncommon. Thus, nutritional deficiencies, as well as polycyclic hydrocarbons, nitrosamines, and other mutagenic compounds, such as those found in fungus-contaminated foods, must also be considered. Human papillomavirus (HPV) infection has also been implicated in esophageal squamous cell carcinoma in high-risk areas but not in low-risk regions. The molecular pathogenesis of esophageal squamous cell carcinoma remains incompletely defined, but recurrent abnormalities include amplification of the transcription factor gene *SOX2* (believed to be involved in cancer stem cell self-renewal and survival); overexpression of the cell cycle regulator cyclin D1; and loss-of-function mutations in the tumor suppressors *TP53, E-cadherin,* and *NOTCH1.*

MORPHOLOGY b0045

p0990 In contrast to adenocarcinoma, half of squamous cell carcinomas occur in the middle third of the esophagus (Fig. 17-9*B*). Squamous cell carcinoma begins as an in situ lesion termed **squamous dysplasia** (this lesion is referred to as intraepithelial neoplasia or carcinoma in situ at other sites). Early lesions appear as small, gray-white, plaque-like thickenings. Over months to years they grow into tumor masses that may be



f0055

Figure 17-10 Esophageal cancer. **A,** Esophageal adenocarcinoma organized into back-to-back glands. **B,** Squamous cell carcinoma composed of nests of malignant cells that partially recapitulate the organization of squamous epithelium.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

polypoid, or exophytic, and protrude into and obstruct the lumen. Other tumors are either ulcerated or diffusely infiltrative lesions that spread within the esophageal wall and cause thickening, rigidity, and luminal narrowing. They may invade surrounding structures including the respiratory tree, causing pneumonia; the aorta, causing catastrophic exsanguination; or the mediastinum and pericardium.

p0995 Most squamous cell carcinomas are moderately to well-differentiated (Fig. 17-10*B*). Less common histologic variants include verrucous squamous cell carcinoma, spindle cell carcinoma, and basaloid squamous cell carcinoma. Regardless of histology, symptomatic tumors are generally very large at diagnosis and have already invaded the esophageal wall. The rich lymphatic network promotes circumferential and longitudinal spread, and intramural tumor nodules may be present several centimeters away from the principal mass. The sites of lymph node metastases vary with tumor location: cancers in the upper third of the esophagus favor cervical lymph nodes; those in the middle third favor mediastinal, paratracheal, and tracheobronchial nodes; and those in the lower third spread to gastric and celiac nodes.

s0225 ***Clinical Features.*** The onset of esophageal squamous cell
p1000 carcinoma is insidious and it most commonly presents with dysphagia, odynophagia (pain on swallowing), or obstruction. Patients subconsciously adjust to the progressively increasing obstruction by altering their diet from solid to liquid foods. Prominent weight loss and debilitation result from both impaired nutrition and effects of the tumor itself. Hemorrhage and sepsis may accompany tumor ulceration, and symptoms of iron deficiency are often present. Occasionally, the first symptoms are caused by aspiration of food via a tracheoesophageal fistula.

p1005 Increased prevalence of endoscopic screening has led to earlier detection of esophageal squamous cell carcinoma. This is critical, because 5-year survival rates are 75% in individuals with superficial esophageal squamous cell carcinoma but much lower in patients with more advanced tumors. Lymph node metastases, which are common, are associated with poor prognosis. The overall 5-year survival rate in the United States remains less than 20%, and varies by tumor stage and patient age, race, and gender.

KEY CONCEPTS b0050

Esophageal Diseases s9010

- Abnormalities of esophageal motility include **nutcracker esophagus** and **diffuse esophageal spasm**. p1010
- **Achalasia**, characterized by incomplete lower esophageal sphincter (LES) relaxation, increased LES tone, and esophageal aperistalsis, is a common form of functional esophageal obstruction. It can be primary or secondary, with the latter form most commonly due to *Trypanosoma cruzi* infection. u0665
- **Mallory-Weiss tears** of mucosa at the gastroesophageal junction develop as a result of severe retching or vomiting. u0670
- **Esophagitis** can result from chemical or infectious mucosal injury. Infection is most common in immunocompromised individuals. u0675
- The most prevalent cause of esophagitis is **gastroesophageal reflux disease** (GERD). u0680
- **Eosinophilic esophagitis** is strongly associated with food allergy, allergic rhinitis, asthma, or modest peripheral eosinophilia. It is a common cause of GERD-like symptoms in children living in developed countries. u0685
- **Gastroesophageal varices** are a consequence of portal hypertension and are present in nearly half of cirrhosis patients. u0690
- **Barrett esophagus** develops in patients with chronic GERD and represents columnar metaplasia of the esophageal squamous mucosa. u0695
- Barrett esophagus is a risk factor for development of **esophageal adenocarcinoma**. u0700
- **Esophageal squamous cell carcinoma** is associated with alcohol and tobacco use, poverty, caustic esophageal injury, achalasia, tylosis, and Plummer-Vinson syndrome. u0705

STOMACH s0230

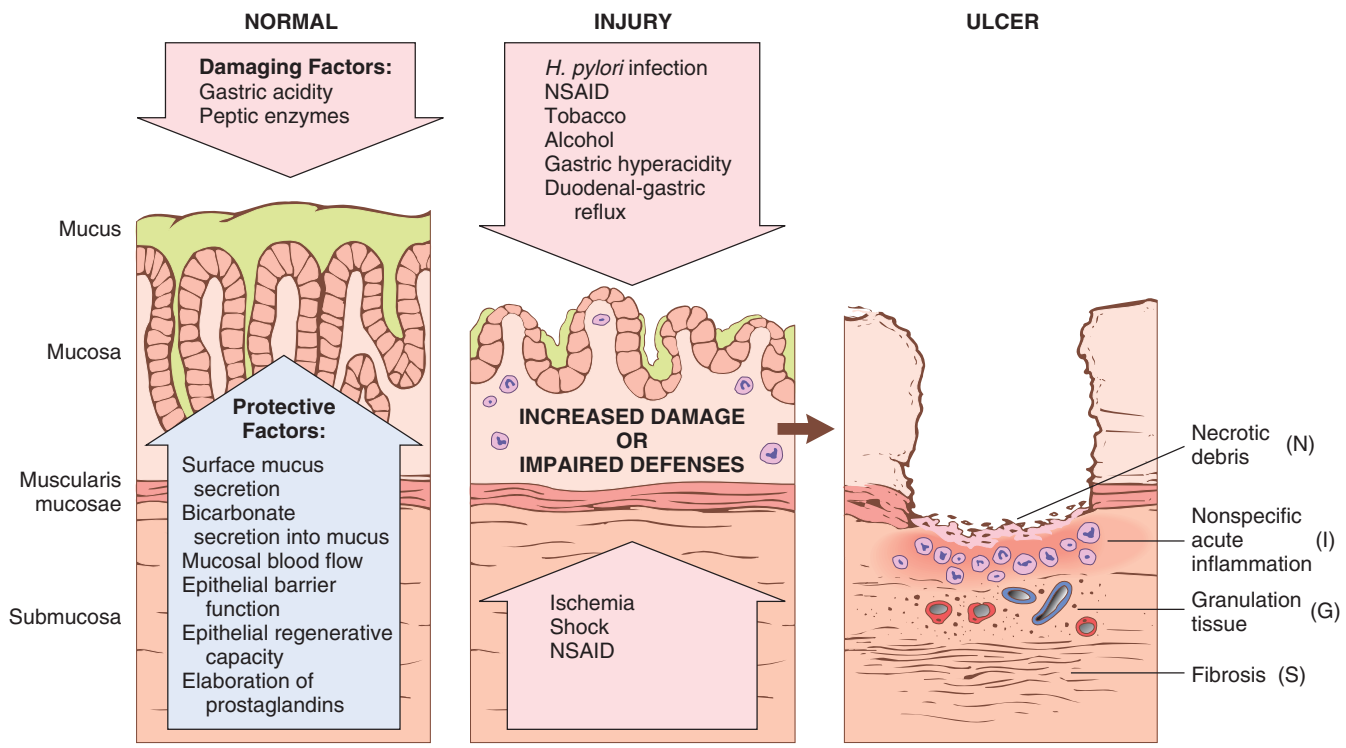
p1065 **Disorders of the stomach are a frequent cause of clinical disease, with inflammatory and neoplastic lesions being particularly common.** In the United States, diseases related to the stomach account for nearly one third of all health care spending on GI disease. In addition, despite decreasing incidence in certain locales such as the United States, gastric cancer remains a leading cause of death worldwide.

p1070 The stomach is divided into four major anatomic regions: the cardia, fundus, body, and antrum. The cardia and antrum are lined mainly with mucin-secreting foveolar cells that form small glands. The antral glands are similar but also contain endocrine cells, such as G cells, that release gastrin to stimulate luminal acid secretion by parietal cells within the gastric fundus and body. The well-developed glands of the body and fundus also contain chief cells that produce and secrete digestive enzymes such as pepsin.

Gastropathy and Acute Gastritis s0235

p1075 **Gastritis is a mucosal inflammatory process. When neutrophils are present, the lesion is referred to as acute gastritis. When inflammatory cells are rare or absent, the term *gastropathy* is applied**; it includes a diverse set of disorders marked by gastric injury or dysfunction. Agents that cause gastropathy include NSAIDs, alcohol, bile, and stress induced injury. Acute mucosal erosion or hemorrhage, such as Curling ulcers or lesions following disruption of gastric blood flow, for example, in portal hypertension, can also cause gastropathy that typically progress to gastritis. The term *hypertrophic gastropathy* is applied to a specific group of diseases exemplified by Ménétrier disease and Zollinger-Ellison Syndrome (discussed later).

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0060

Figure 17-11 Mechanisms of gastric injury and protection. This diagram illustrates the progression from more mild forms of injury to ulceration that may occur with acute or chronic gastritis. Ulcers include layers of necrosis (N), inflammation (I), and granulation tissue (G), but a fibrotic scar (S), which takes time to develop, is only present in chronic lesions.

p1080 Both gastropathy and acute gastritis may be asymptomatic or cause variable degrees of epigastric pain, nausea, and vomiting. In more severe cases there may be mucosal erosion, ulceration, hemorrhage, hematemesis, melena, or, rarely, massive blood loss.

s0240 p1085 ***Pathogenesis.*** The gastric lumen has a pH of close to 1, more than a million times more acidic than the blood. This harsh environment contributes to digestion but also has the potential to damage the gastric mucosa. Multiple mechanisms have evolved to protect the gastric mucosa (Fig. 17-11). Mucin secreted by surface foveolar cells forms a thin layer of mucus and phospholipids that prevents large food particles from directly touching the epithelium. The mucus covering also promotes formation of an "unstirred" layer of fluid over the epithelium that protects the mucosa and has a neutral pH as a result of bicarbonate ion secretion by surface epithelial cells. Beneath the mucus, a continuous layer of gastric epithelial cells forms a physical barrier that limits back diffusion of acid and leakage of other luminal materials, including pepsin, into the lamina propria. Complete replacement of the surface foveolar cells every 3 to 7 days is essential for both the maintenance of the epithelial layer and the secretion of mucus and bicarbonate from these cells. In acid-secreting parts of the stomach, a capillary "alkaline tide" is generated as parietal cells secrete hydrochloric acid into the gastric lumen and bicarbonate into the vessels. In addition to delivering bicarbonate, the rich mucosal vasculature delivers oxygen and nutrients while washing away acid that has back-diffused into the lamina propria.

p1090 Gastropathy, acute gastritis, and chronic gastritis can occur following disruption of any of these protective mechanisms.

- u9015 Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit cyclooxygenase- (COX) dependent synthesis of prostaglandins E_2 and I_2, which stimulate nearly all of the above defense mechanisms including mucus, bicarbonate, and phospholipid secretion, mucosal blood flow, and epithelial restitution while reducing acid secretion. Although COX-1 plays a larger role than COX-2, both isoenzymes contribute to mucosal protection. Thus, while the risk of NSAID-induced gastric injury is greatest with nonselective inhibitors, for example, aspirin, ibuprofen, and naproxen, selective COX-2 inhibition, for example, by celecoxib, can also result in gastropathy or gastritis.
- u9020 The gastric injury that occurs in uremic patients and those infected with urease-secreting *H. pylori* may be due to inhibition of gastric bicarbonate transporters by ammonium ions.
- u9025 Reduced mucin and bicarbonate secretion have been suggested as factors that explain the increased susceptibility of older adults to gastritis.
- u9030 Decreased oxygen delivery may account for an increased incidence of acute gastritis at high altitudes.

p1095 Ingestion of harsh chemicals, particularly acids or bases, either accidentally or as a suicide attempt, also results in severe gastric injury, predominantly as a result of direct injury to mucosal epithelial and stromal cells. Direct cellular damage also contributes to gastritis induced by excessive alcohol consumption, NSAIDs, radiation therapy, and

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

chemotherapy. Agents that inhibit DNA synthesis or the mitotic apparatus, including those used in cancer chemotherapy, may cause generalized mucosal damage due to insufficient epithelial renewal.

b0055 MORPHOLOGY

p1105 Histologically, gastropathy and mild acute gastritis may be difficult to recognize, since the lamina propria shows only moderate edema and slight vascular congestion. The surface epithelium is intact, but foveolar cell hyperplasia, with characteristic corkscrew profiles and epithelial proliferation are typically present. Neutrophils are not abundant, but a few may be found among the epithelial cells or within mucosal glands in gastritis. There are few lymphocytes and plasma cells.

p1110 The presence of neutrophils above the basement membrane in direct contact with epithelial cells is abnormal in all parts of the GI tract and signifies active inflammation, or, in this case, gastritis (rather than gastropathy). The term active inflammation is preferred over acute inflammation, since active inflammation may be present in both acute and chronic disease states. With more severe mucosal damage, erosions and hemorrhage develop. Erosion denotes loss of the epithelium, resulting in a superficial mucosal defect. It is accompanied by a pronounced mucosal neutrophilic infiltrate and a fibrin-containing purulent exudate in the lumen. Hemorrhage may occur and cause dark punctae in hyperemic mucosa. Concurrent erosion and hemorrhage is termed **acute erosive hemorrhagic gastritis.** Large areas of the gastric surface may be denuded, although the involvement is typically superficial. When erosions extend deeply, they may progress to ulcers, as described later.

s0260 p1115 ***Clinical Features.*** The presentation of gastropathy and acute gastritis varies according to etiology, and the two cannot be distinguished on clinical grounds. Patients with NSAID-induced gastropathy may be asymptomatic or have persistent epigastric pain that responds to antacids or proton pump inhibitors. In contrast, pain associated with bile reflux is typically refractory to such therapies and may be accompanied by occasional bilious vomiting.

s0265 Stress-Related Mucosal Disease

p1120 Stress-related mucosal disease occurs in patients with severe trauma, extensive burns, intracranial disease, major surgery, serious medical disease, and other forms of severe physiologic stress. More than 75% of critically ill patients develop endoscopically visible gastric lesions during the first 3 days of their illness. In some cases, the associated ulcers are given specific names based on location and clinical associations. For example:

u0710 • *Stress ulcers* are most common in individuals with shock, sepsis, or severe trauma.

u0715 • Ulcers occurring in the proximal duodenum and associated with severe burns or trauma are called *Curling ulcers.*

u0720 • Gastric, duodenal, and esophageal ulcers arising in persons with intracranial disease are termed *Cushing ulcers* and carry a high incidence of perforation.

s0270 p1140 ***Pathogenesis.*** The pathogenesis of stress-related gastric mucosal injury is most often related to local ischemia. This may be due to systemic hypotension or reduced blood flow caused by stress-induced splanchnic vasoconstriction. Upregulation of inducible NO synthase and increased release of the vasoconstrictor endothelin-1 also contribute to ischemic gastric mucosal injury, while increased COX-2 expression appears to be protective.

p1145 Lesions associated with intracranial injury are thought to be caused by direct stimulation of vagal nuclei, which causes hypersecretion of gastric acid. Systemic acidosis, a frequent finding in these settings, may also contribute to mucosal injury by lowering the intracellular pH of mucosal cells.

b0060 MORPHOLOGY

p1150 Stress-related gastric mucosal injury ranges from shallow erosions caused by superficial epithelial damage to deeper lesions that penetrate the depth of the mucosa. Acute ulcers are rounded and less than 1 cm in diameter. The ulcer base is frequently stained brown to black by acid digestion of extravasated blood and may be associated with transmural inflammation and local serositis. Unlike peptic ulcers, which arise in the setting of chronic injury, acute stress ulcers are found anywhere in the stomach and are most often multiple. Microscopically, acute stress ulcers are sharply demarcated, with essentially normal adjacent mucosa. There may be a suffusion of blood into the mucosa and submucosa and an associated inflammatory reaction. Conspicuously absent are the scarring and blood vessel thickenings that characterize chronic peptic ulcers. Healing with complete re-epithelialization occurs within days to several weeks after removal of the injurious factors.

s0290 p1155 ***Clinical Features.*** **Most critically ill patients admitted to hospital intensive care units have histologic evidence of gastric mucosal damage.** Bleeding from superficial gastric erosions or ulcers that may require transfusion develops in 1% to 4% of these patients. Other complications, including perforation, can also occur. Prophylactic proton pump inhibitors may blunt the impact of stress ulceration, but the most important determinant of clinical outcome is the ability to correct the underlying condition. The gastric mucosa can recover completely if the patient does not succumb to the primary disease.

p9055 Other, non-stress-related causes of gastric bleeding include the *Dieulafoy lesion* and *gastric antral vascular ectasia* (GAVE).

u9035 • Dieulafoy lesion is caused by a submucosal artery that does not branch properly within the wall of the stomach. This results in a mucosal artery with a diameter of up to 3 mm, or 10 times the size of mucosal capillaries. Dieulafoy lesions are most commonly found along the lesser curvature, near the gastroesophageal junction. Erosion of the overlying epithelium can cause gastric bleeding that, while usually self-limited, can be copious. Bleeding is often associated with NSAID use and may be recurrent.

u9040 • GAVE is responsible for 4% of non-variceal upper gastrointestinal bleeding. It can be recognized endoscopically as longitudinal stripes of edematous erythematous mucosa that alternate with less severely injured, paler mucosa, and is sometimes referred to as watermelon

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

stomach. The erythematous stripes are created by ectatic mucosal vessels. Histologically, the antral mucosa shows reactive gastropathy with dilated capillaries containing fibrin thrombi. While most often idiopathic, GAVE can also be associated with cirrhosis and systemic sclerosis. Patients may present with occult fecal blood or iron deficiency anemia.

Chronic Gastritis

p1235 **The most common cause of chronic gastritis is infection with the bacillus *H. pylori*. Autoimmune gastritis, the most common cause of diffuse atrophic gastritis, represents less than 10% of cases of chronic gastritis, but is the most common form of chronic gastritis in patients without *H. pylori* infection.** However, it is important to recognize that longstanding *H. pylori* infection can also result in atrophic gastritis, typically in a multifocal rather than diffuse pattern. Less common causes of chronic gastritis include radiation injury, chronic bile reflux, mechanical injury (e.g. an indwelling nasogastric tube), and involvement by systemic diseases, such as Crohn disease, amyloidosis, or graft-versus-host disease.

p9070 In contrast to acute gastritis, the symptoms associated with chronic gastritis are typically less severe but more persistent. Nausea and upper abdominal pain are typical, sometimes with vomiting, but hematemesis is uncommon.

Helicobacter pylori Gastritis

p1240 *H. pylori* are spiral-shaped or curved bacilli present in gastric biopsy specimens of almost all patients with duodenal ulcers as well as most individuals with gastric ulcers or chronic gastritis. Acute *H. pylori* infection does not produce sufficient symptoms to come to medical attention in most cases; it is the chronic gastritis that ultimately causes the individual to seek treatment. *H. pylori* organisms are present in 90% of individuals with chronic gastritis affecting the antrum.

Epidemiology. In the United States, *H. pylori* infection p1245 is associated with poverty, household crowding, limited education, African American or Mexican American ethnicity, residence in rural areas, and birth outside of the United States. Humans are the primary carriers, suggesting that transmission is primarily by the fecal-oral route. Infection is typically acquired in childhood and persists for life without treatment. Improved sanitation in the United States likely explains the marked reduction in *H. pylori* infection rates among younger people that has resulted in a cohort effect. For example, the prevalence of *H. pylori* infection in those younger than 12 years old is less than 15% relative to the 50% to 60% prevalence in those older than 60 years of age. Accordingly, colonization rates vary from less than 10% to more than 80% worldwide, as a function of age and geography.

Pathogenesis. ***H. pylori* infection most often presents as** p1250 **a predominantly antral gastritis with normal or increased acid production.** Local gastrin production may be increased, but hypergastrinemia (increased serum gastrin) is uncommon. When inflammation remains limited to the antrum, increased acid production results in greater risk of duodenal peptic ulcer (see later). In other patients gastritis may progress to involve the gastric body and fundus. This *multifocal atrophic gastritis* is associated with patchy mucosal atrophy, reduced parietal cell mass and acid secretion, intestinal metaplasia, and increased risk of gastric adenocarcinoma. Thus, there is an inverse relationship between duodenal ulcer and gastric adenocarcinoma that correlates with the pattern of gastritis. The bacterial and host factors that determine which pattern develops in an individual patient are discussed later.

H. pylori organisms have adapted to the ecologic p1255 niche provided by gastric mucus. Its virulence is linked to the following factors:

- *Flagella*, which allow the bacteria to be motile in viscous u0800 mucus
- *Urease*, which generates ammonia from endogenous u0805 urea and thereby elevates local gastric pH and enhances bacterial survival
- *Adhesins* that enhance bacterial adherence to surface u0810 foveolar cells
- *Toxins*, such as cytotoxin-associated gene A *(CagA)*, that u0815 may be involved in disease progression

Variation in these and other bacterial factors are strongly p1280 linked to outcome. For example, *CagA* gene and the associated 20 gene pathogenicity islands are present in 50% of *H. pylori* isolates overall but in 90% of *H. pylori* isolates found in populations with elevated gastric cancer risk. This may, in part, be because CagA expressing strains can effectively colonize the gastric body and cause multifocal atrophic gastritis.

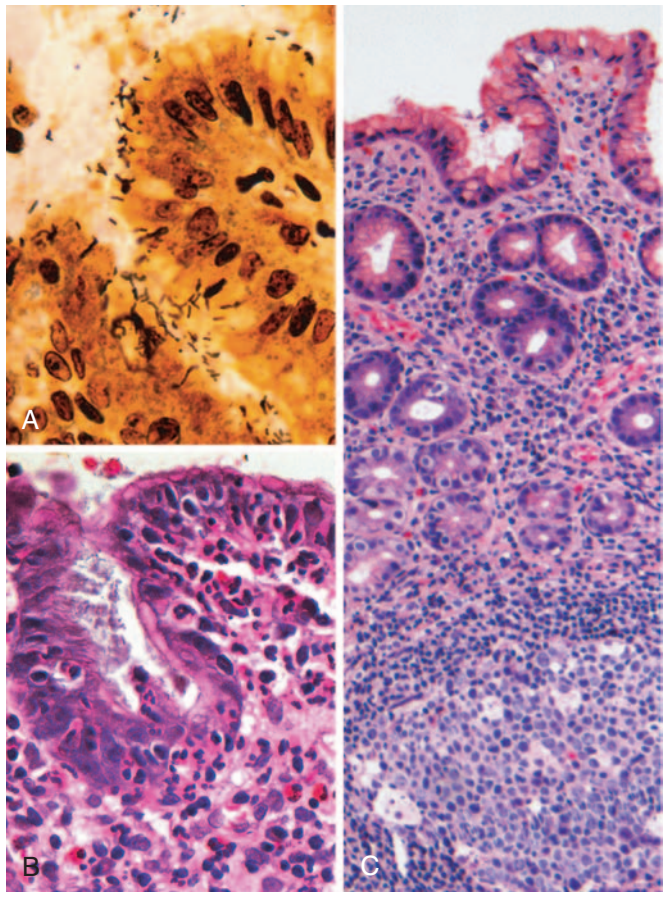
Host factors also play an important role in the outcome p1285 of *H. pylori* infection. Genetic polymorphisms that lead to increased expression of the proinflammatory cytokines tumor necrosis factor (TNF) and interleukin-1β (IL-1β) or decreased expression of the antiinflammatory cytokine interleukin-10 (IL-10) are associated with development of pangastritis, atrophy, and gastric cancer. Iron deficiency may also be a risk factor for *H. pylori*–associated gastric cancer. The course of *H. pylori* gastritis is, therefore, the result of interplay between gastroduodenal mucosal defenses, inflammatory responses, and bacterial virulence factors.

MORPHOLOGY b0065

Gastric biopsy specimens generally demonstrate *H. pylori* in p1290 infected individuals. The organism is concentrated within the superficial mucus overlying epithelial cells in the surface and neck regions. The distribution can be irregular, with areas of heavy colonization adjacent to those with few organisms. In extreme cases, the organisms carpet the luminal surfaces of foveolar and mucous neck cells, and can even extend into the gastric pits. Organisms are most easily demonstrated with special stains (Fig. 17-12A). *H. pylori* display tropism for gastric epithelia and are generally not found in association with intestinal metaplasia or duodenal epithelium.

Within the stomach, *H. pylori* are most often found in the p1295 antrum (Table 17-2). Although there is often concordance between colonization of the antrum and cardia, infection of the

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0065

Figure 17-12 *Helicobacter pylori* gastritis. **A,** Spiral-shaped *H. pylori* are highlighted in this Warthin-Starry silver stain. Organisms are abundant within surface mucus. **B,** Intraepithelial and lamina propria neutrophils are prominent. **C,** Lymphoid aggregates with germinal centers and abundant subepithelial plasma cells within the superficial lamina propria are characteristic of *H. pylori* gastritis.

cardia occurs at somewhat lower rates. *H. pylori* are less common in oxyntic (acid-producing) mucosa of the fundus and body. Thus, an antral biopsy is preferred for evaluation of *H. pylori* gastritis. When viewed endoscopically, *H. pylori*-infected antral mucosa is usually erythematous and has a coarse or even nodular appearance. The inflammatory infiltrate generally includes variable numbers of neutrophils within the lamina propria, including some that cross the basement membrane to assume an intraepithelial location (Fig. 17-12*B*) and accumulate in the lumen of gastric pits to create pit abscesses. In addition, the superficial lamina propria contains large numbers of plasma cells, often in clusters or sheets, and increased numbers of lymphocytes and macrophages. Intraepithelial neutrophils and subepithelial plasma cells are characteristic of *H. pylori* gastritis. When intense, inflammatory infiltrates may create thickened rugal folds, mimicking the appearance of early cancers. Lymphoid aggregates, some with germinal centers, are frequently present (Fig. 17-12*C*) and represent an induced form of mucosa-associated lymphoid tissue, or MALT, that has the potential to transform into lymphoma.

p1300 Long-standing *H. pylori* gastritis may extend to involve the body and fundus, and the mucosa can become atrophic, with loss of parietal and chief cells. As a result, the oxyntic mucosa can take on the appearance of antral mucosa. In contrast to autoimmune gastritis, this is typically a patchy process, and biopsies of the gastric body can show intact oxyntic glands adjacent to antral-type glands. The development of atrophy is typically associated with the presence of intestinal metaplasia and increased risk of gastric adenocarcinoma.

Clinical Features. In addition to histologic identification of the organism, several diagnostic tests have been developed including a noninvasive serologic test for antibodies to *H. pylori*, fecal bacterial detection, and the urea breath test based on the generation of ammonia by the bacterial urease. Gastric biopsy specimens can also be analyzed by the rapid urease test, bacterial culture, or bacterial DNA detection by PCR. s0325 p1305

Effective treatments for *H. pylori* infection include combinations of antibiotics and proton pump inhibitors. Individuals with *H. pylori* gastritis usually improve after treatment, although relapses can occur after incomplete eradication or reinfection, which is common in regions with high endemic colonization rates. Prophylactic and therapeutic vaccines are still at an early stage of development. p1310

Autoimmune Gastritis s0330

Autoimmune gastritis accounts for less than 10% of cases of chronic gastritis. In contrast to *H. pylori*–associated gastritis, autoimmune gastritis typically spares the antrum and is associated with hypergastrinemia (Table 17-2). Autoimmune gastritis is characterized by: p1315

- Antibodies to parietal cells and intrinsic factor that can be detected in serum and gastric secretions u0820
- Reduced serum pepsinogen I concentration u0825
- Endocrine cell hyperplasia u0830
- Vitamin B_{12} deficiency u0835
- Defective gastric acid secretion (achlorhydria) u0840

Table 17-2 Characteristics of *Helicobacter pylori*–Associated and Autoimmune Gastritis t0020

	H. pylori–Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to decreased	Increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+,K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, MALToma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease; thyroiditis, diabetes mellitus, Graves disease

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

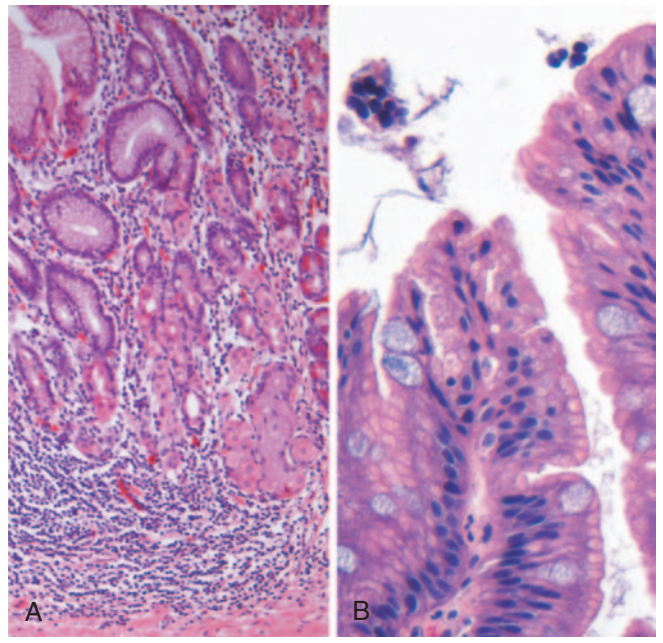
s0335 ***Pathogenesis.*** **Autoimmune gastritis is associated with**
p1345 **loss of parietal cells, which are responsible for secretion of gastric acid and intrinsic factor.** The absence of acid production stimulates gastrin release, resulting in hypergastrinemia and hyperplasia of antral gastrin-producing G cells. Lack of intrinsic factor disables ileal vitamin B_{12} absorption, which ultimately leads to vitamin B_{12} deficiency and a slow-onset megaloblastic anemia *(pernicious anemia)*. Reduced serum pepsinogen I concentration results from chief cell destruction. Although *H. pylori* infection can cause gastric atrophy and hypochlorhydria, it is not associated with achlorhydria or pernicious anemia. This is because, in contrast to the diffuse atrophy of autoimmune gastritis, the damage in *H. pylori* gastritis is multifocal and leaves patches of residual parietal and chief cells.

p9075 **CD4+ T cells directed against parietal cell components, including the H+,K+–ATPase, are considered to be the principal agents of injury in autoimmune gastritis.** This is supported by the observation that transfer of H+,K+-ATPase-reactive CD4+ T cells into naïve mice results in gastritis and production of H+,K+-ATPase autoantibodies. There is no evidence of an autoimmune reaction to chief cells, suggesting that these may be lost through gastric gland destruction during autoimmune attack on parietal cells. If autoimmune destruction is controlled by immunosuppression, the glands can repopulate, demonstrating that gastric stem cells survive and are able to differentiate into parietal and chief cells.

p1350 **Autoantibodies to parietal cell components, most prominently the H+,K+-ATPase, or proton pump, and intrinsic factor are present in up to 80% of patients with autoimmune gastritis.** However, these antibodies are not thought to be pathogenic because neither secreted intrinsic factor nor the luminally oriented proton pump are accessible to circulating antibodies, and passive transfer of these antibodies does not produce gastritis in experimental animals. Nevertheless, the presence of these autoantibodies is a useful diagnostic tool.

b0070 MORPHOLOGY

p1360 **Autoimmune gastritis is characterized by diffuse mucosal damage of the oxyntic (acid-producing) mucosa within the body and fundus.** Damage to the antrum and cardia is typically absent or mild. With diffuse atrophy, the oxyntic mucosa of the body and fundus appears markedly thinned, and rugal folds are lost. If vitamin B_{12} deficiency is severe, nuclear enlargement (megaloblastic change) occurs within epithelial cells. Neutrophils may be present, but the inflammatory infiltrate is typically composed of lymphocytes, macrophages, and plasma cells, often in association with lymphoid aggregates and follicles. The superficial lamina propria plasma cells typical of *H. pylori* gastritis are absent, and the inflammatory reaction is deeper and centered on the gastric glands (Fig. 17-13*A*). Loss of parietal and chief cells can be extensive. When atrophy is incomplete, residual islands of oxyntic mucosa may give the appearance of multiple small polyps or nodules. In other areas, small surface elevations may represent sites of intestinal metaplasia, characterized by the presence of goblet cells and columnar absorptive cells (Fig. 17-13B). Although present in most patients, endocrine cell hyperplasia can be difficult to appreciate on hematoxylin and eosin-stained sections. This hyperplasia, which can be clearly demonstrated with immunostains for proteins such as chromogrannin A, parallels the degree of mucosal atrophy and is a physiologic response to decreased acid production. Over time, hypergastrinemia can stimulate endocrine cell hyperplasia in the fundus and body. Rarely, this may progress to form small, multicentric, low-grade neuroendocrine (carcinoid) tumors.



f0070

Figure 17-13 Autoimmune gastritis. **A,** Low-magnification image of gastric body demonstrating deep inflammatory infiltrates, primarily composed of lymphocytes, and glandular atrophy. **B,** Intestinal metaplasia, recognizable as the presence of goblet cells admixed with gastric foveolar epithelium.

s0350 ***Clinical Features.*** Antibodies to parietal cells and to
p1365 intrinsic factor are present early in the disease course. Progression to gastric atrophy probably occurs over 2 to 3 decades, and anemia is seen in only a few patients. Because of the slow onset and variable progression, patients are generally diagnosed only after being affected for many years; the median age at diagnosis is 60. Slightly more women than men are affected. Pernicious anemia and autoimmune gastritis are often associated with other autoimmune diseases including Hashimoto thyroiditis, insulin-dependent (type I) diabetes mellitus, Addison disease, primary ovarian failure, primary hypoparathyroidism, Graves disease, vitiligo, myasthenia gravis, and Lambert-Eaton syndrome. These associations, along with concordance in some monozygotic twins and clustering of disease in families, support a genetic predisposition. In general, about 20% of relatives of individuals with pernicious anemia also have autoimmune gastritis, although they may be asymptomatic. Despite this strong genetic influence, autoimmune gastritis stands apart from many other autoimmune diseases in that there is little evidence of linkage to specific HLA alleles.

p1370 Clinical presentation may be linked to symptoms of anemia (Chapter 14). Vitamin B_{12} deficiency may also cause atrophic glossitis, in which the tongue becomes smooth and beefy red, epithelial megaloblastosis, malabsorptive

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

diarrhea, peripheral neuropathy, spinal cord lesions, and cerebral dysfunction. Neuropathic changes include demyelination, axonal degeneration, and neuronal death. The most frequent manifestations of peripheral neuropathy are paresthesias and numbness. The spinal lesions result from demyelination of the dorsal and lateral spinal tracts, giving rise to a clinical picture that is often referred to as *subacute combined degeneration of the cord.* It is associated with a mixture of loss of vibration and position sense, sensory ataxia with positive Romberg sign, limb weakness, spasticity, and extensor plantar responses. Cerebral manifestations range from mild personality changes and memory loss to psychosis. In contrast to anemia, neurologic changes are not reversed by vitamin B_{12} replacement therapy.

Uncommon Forms of Gastritis

Eosinophilic Gastritis. This form of gastritis is characterized by tissue damage associated with dense infiltrates of eosinophils in the mucosa and muscularis, usually in the antral or pyloric region. The lesion may also be present at other sites within the GI tract and is associated with peripheral eosinophilia and increased serum IgE levels. Allergic reactions are one cause of eosinophilic gastritis, with cow's milk and soy protein being the most common allergens in children. Eosinophilic gastritis can also occur in association with immune disorders such as systemic sclerosis and polymyositis, parasitic infections, and even *H. pylori* infection.

Lymphocytic Gastritis. This disease preferentially affects women and produces nonspecific abdominal symptoms. It is idiopathic, but approximately 40% of cases are associated with celiac disease, suggesting an immune-mediated pathogenesis. Lymphocytic gastritis typically affects the entire stomach and is often referred to as *varioliform gastritis* based on the distinctive endoscopic appearance (thickened folds covered by small nodules with central aphthous ulceration). Histologically there is a marked increase in the number of intraepithelial T lymphocytes.

Granulomatous Gastritis. This descriptive term is applied to any gastritis that contains well-formed granulomas or aggregates of epithelioid macrophages. It encompasses a diverse group of diseases with widely varying clinical and pathologic features. Many cases are idiopathic. In Western populations, gastric involvement by Crohn disease is the most common specific cause of granulomatous gastritis, followed by sarcoidosis and infections (including mycobacteria, fungi, CMV, and *H. pylori*). In addition to the presence of histologically evident granulomas, narrowing and rigidity of the gastric antrum may occur secondary to transmural granulomatous inflammation.

Complications of Chronic Gastritis

Peptic Ulcer Disease

Peptic ulcer disease (PUD) refers to chronic mucosal ulceration affecting the duodenum or stomach. Nearly all peptic ulcers are associated with *H. pylori* infection,

Table 17-3 Risk factors for Peptic Ulcer Disease

- *H. pylori* infection
- Cigarette use (synergizes with *H. pylori* for gastric PUD)
- Chronic obstructive pulmonary disease
- Illicit drugs, e.g. cocaine, that reduce mucosal blood flow
- NSAIDs (potentiated by corticosteroids)
- Alcoholic cirrhosis (primarily duodenal PUD)
- Psychological stress (can increase gastric acid secretion)
- Endocrine cell hyperplasia (can stimulate parietal cell growth and gastric acid secretion)
- Zollinger-Ellison Syndrome (PUD of stomach, duodenum, and jejunum)
- Viral infection (CMV, herpes simplex virus)

NSAIDs, or cigarette smoking. The most common form of peptic ulcer disease (PUD) occurs within the gastric antrum or duodenum as a result of chronic, *H. pylori*-induced antral gastritis, which is associated with increased gastric acid secretion, and decreased duodenal bicarbonate secretion. In contrast, PUD within the gastric fundus or body is usually accompanied by lesser acid secretion as a result of mucosal atrophy (associated with some cases of *H. pylori*-induced or autoimmune chronic gastritis, as discussed earlier). While these patients still secrete more acid than normal individuals, they are incapable of secreting the much larger amounts needed to overcome the defense mechanisms that "protect" the antral and duodenal mucosa. Thus, individuals with gastric mucosal atrophy are generally protected from antral and duodenal ulcers. PUD may also be caused by acid secreted by ectopic gastric mucosa within the duodenum or an ileal Meckel diverticulum. PUD may also occur in the esophagus as a result of GERD or acid secretion by esophageal ectopic gastric mucosa (an inlet patch).

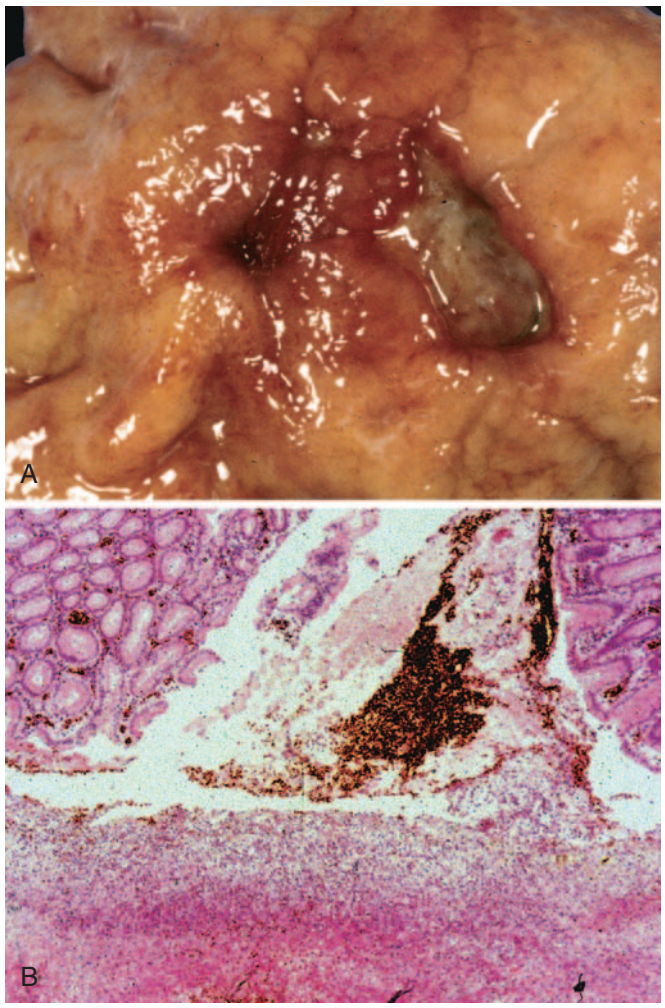
Epidemiology. The incidence of PUD is falling in developed countries along with reduced prevalence of *H. pylori*, infection. However, a new group of duodenal PUD patients older than 60 years of age has emerged as a result of increased NSAID use. This is particularly true when low-dose aspirin (for cardiovascular benefits) is combined with other NSAIDs. This is facilitated if concurrent *H. pylori* infection is also present. PUD has been associated with cigarette use and cardiovascular disease, likely due to reduced mucosal blood flow, oxygenation, and healing. Other risk factors for PUD are listed in Table 17-3.

Pathogenesis. **PUD results from imbalances between mucosal defense mechanisms and damaging factors that cause chronic gastritis** (discussed earlier). Thus, PUD generally develops on a background of chronic gastritis. The reasons why some people develop only chronic gastritis while others develop PUD are poorly understood. However, as with *H. pylori* gastritis, it is likely that host factors as well as variation between bacterial strains are involved.

MORPHOLOGY

Peptic ulcers occur in the context of chronic gastritis, but are most common in the proximal duodenum, where they occur within a few centimeters of the pyloric valve and involve the anterior duodenal wall. Gastric peptic ulcers are predominantly located along the lesser curvature near the interface of the body and antrum.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0075 **Figure 17-14** Acute gastric perforation in a patient presenting with free air under the diaphragm. **A,** Mucosal defect with clean edges. **B,** The necrotic ulcer base is composed of granulation tissue.

p1415 Peptic ulcers are solitary in more than 80% of patients. Lesions less than 0.3 cm in diameter tend to be shallow while those greater than 0.6 cm are likely to be deeper. The classic peptic ulcer is a round to oval, **sharply punched-out defect** (Fig. 17-14*A*). The mucosal margin may overhang the base slightly, particularly on the upstream side, but is usually level with the surrounding mucosa. In contrast, **heaped-up margins are more characteristic of cancers**. The depth of ulcers may be limited by the thick gastric muscularis propria or by adherent pancreas, omental fat, or the liver. Hemorrhage and fibrin deposition are often present on the gastric serosa. **Perforation** into the peritoneal cavity is a surgical emergency that may be identified by detection of free air under the diaphragm on upright radiographs of the abdomen.

p1420 The base of peptic ulcers is smooth and clean as a result of peptic digestion of exudate. Active ulcers may be lined by a thin layer of fibrinoid debris underlaid by a predominantly neutrophilic inflammatory infiltrate. Beneath this, granulation tissue infiltrated with mononuclear leukocytes and a fibrous or collagenous scar forms the ulcer base (Fig. 17-14*B*). Vessel walls within the scarred area are typically thickened and are occasionally thrombosed. Bleeding from damaged vessels within the ulcer base may cause life-threatening **hemorrhage.** Scarring may involve the entire thickness of the wall and pucker the surrounding mucosa into folds that radiate outward.

p1425 Size and location do not differentiate between benign and malignant ulcers. However, the gross appearance of chronic peptic ulcers is virtually diagnostic. **Malignant transformation of peptic ulcers occurs rarely**, if ever, and reports of transformation probably represent cases in which a lesion thought to be a chronic peptic ulcer was actually an ulcerated carcinoma from the start.

s0415 ***Clinical Features.*** Peptic ulcers can be chronic, recurring lesions with significant morbidity. The majority of peptic p1430 ulcers come to clinical attention because of *epigastric burning or aching pain*, although a significant fraction present with complications such as *iron deficiency anemia*, *hemorrhage*, or *perforation* (Table 17-4). The pain tends to occur 1 to 3 hours after meals during the day, is worse at night (usually between 11 PM and 2 AM), and is relieved by alkali or food. Nausea, vomiting, bloating, belching, and significant weight loss are additional manifestations. With penetrating ulcers the pain is occasionally referred to the back, the left upper quadrant, or the chest, where it may be misinterpreted as cardiac in origin.

p1435 Current therapies for PUD are aimed at *H. pylori* eradication and neutralization of gastric acid, primarily with proton pump inhibitors. It is also important to withdraw other offending agents, such as NSAIDs, including selective COX-2 inhibitors, that may interfere with mucosal healing. While peptic ulcers were previously notorious for their recurrence, the recurrence rate is now less than 20% following successful clearance of *H. pylori*.

p1440 A variety of surgical approaches were formerly used to treat PUD, including antrectomy to remove gastrin-producing cells and vagotomy to prevent the acid-stimulatory effects mediated by the vagus nerve. However, the success of proton pump inhibitors and *H. pylori* eradication has relegated surgical intervention to treatment of bleeding or perforated peptic ulcers.

Table 17-4 Complications of Peptic Ulcer Disease t0015

Bleeding	
Occurs in 15% to 20% of patients	u0725
Most frequent complication	u0730
May be life-threatening	u0735
Accounts for 25% of ulcer deaths	u0740
May be the first indication of an ulcer	u0745
Perforation	
Occurs in up to 5% of patients	u0750
Accounts for two thirds of ulcer deaths	u0755
Is rarely first indication of an ulcer	u0760
Obstruction	
Mostly in chronic ulcers	u0765
Secondary to edema or scarring	u0770
Occurs in about 2% of patients	u0775
Most often associated with pyloric channel ulcers	u0780
May occur with duodenal ulcers	u0785
Causes incapacitating, crampy abdominal pain	u0790
Can rarely cause total obstruction and intractable vomiting	u0795

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

b0080 **KEY CONCEPTS**

s9015 **Gastritis**

p1445 ■ **Gastritis** is a mucosal inflammatory process. When inflammatory cells are absent or rare, the term **gastropathy** can be applied.

u0850 ■ The spectrum of **acute gastritis** ranges from asymptomatic disease to mild epigastric pain, nausea, and vomiting. Causative factors include any agent or disease that interferes with gastric mucosal protective mechanisms.

u0855 ■ Severe acute gastritis can result in **acute gastric ulceration**.

u0860 ■ The most common cause of chronic gastritis is ***H. pylori* infection**. Other agents include NSAIDs and alcohol.

u0865 ■ ***H. pylori* gastritis** typically affects the antrum and is associated with increased gastric acid production. In later disease, the body can be involved and the resulting glandular atrophy can lead to mildly reduced acid production. Host immune responses and bacterial characteristics determine whether the infection remains antral or progresses to **pangastritis**.

u0870 ■ ***H. pylori* gastritis induces mucosa-associated lymphoid tissue (MALT)** that can give rise to B cell lymphomas (MALTomas).

u0875 ■ **Autoimmune gastritis** is the most frequent etiology of noninfectious chronic gastritis. It results in atrophy of the gastric body oxyntic glands, which leads to decreased gastric acid production, antral G cell hyperplasia, achlorhydria, and vitamin B_{12} deficiency. Anti-parietal cell and anti-intrinsic factor antibodies are typically present.

u0885 ■ **Intestinal metaplasia** develops in both forms of chronic gastritis and is a risk factor for gastric adenocarcinoma.

u0890 ■ **Peptic ulcer disease** is usually secondary to *H. pylori* chronic gastritis and the resulting hyperchlorhydria. Ulcers can develop in the stomach or duodenum, and usually heal after suppression of gastric acid production and eradication of *H. pylori*.

s0420 Mucosal Atrophy and Intestinal Metaplasia

p1500 Long-standing chronic gastritis that involves the body and fundus may ultimately lead to significant loss of parietal cell mass. This oxyntic atrophy may be associated with intestinal metaplasia, recognized by the presence of goblet cells, and is strongly associated with increased risk of gastric adenocarcinoma. The risk of adenocarcinoma is greatest in autoimmune gastritis. This may be because achlorhydria of gastric mucosal atrophy permits overgrowth of bacteria that produce carcinogenic nitrosamines. Intestinal metaplasia also occurs in chronic *H. pylori* gastritis and may regress after clearance of the organism.

s0425 Dysplasia

p1505 Chronic gastritis exposes the epithelium to inflammation-related free radical damage and proliferative stimuli. Over time this combination of stressors can lead to the accumulation of genetic alterations that result in carcinoma. Preinvasive in situ lesions can be recognized histologically as dysplasia. The morphologic hallmarks of dysplasia are variations in epithelial size, shape, and orientation along with coarse chromatin texture, hyperchromasia, and nuclear enlargement. The distinction between dysplasia and regenerative epithelial changes induced by active inflammation can be a challenge for the pathologist, since increased epithelial proliferation and mitotic figures may be prominent in both. However, reactive epithelial cells mature as they reach the mucosal surface, while dysplastic lesions remain cytologically immature.

Gastritis Cystica s0430

p1510 Gastritis cystica is an exuberant reactive epithelial proliferation associated with entrapment of epithelial-lined cysts. These may be found within the submucosa (gastritis cystica polyposa) or deeper layers of the gastric wall (gastritis cystica profunda). Because of the association with chronic gastritis and partial gastrectomy, it is presumed that gastritis cystica is trauma-induced, but the reasons for the development of epithelial cysts within deeper portions of the gastric wall are not clear. Regenerative epithelial changes can be prominent in the entrapped epithelium, and gastritis cystica can therefore mimic invasive adenocarcinoma.

Hypertrophic Gastropathies s0435

p1515 **Hypertrophic gastropathies are uncommon diseases characterized by giant "cerebriform" enlargement of the rugal folds due to epithelial hyperplasia without inflammation.** As might be expected, the hypertrophic gastropathies are linked to excessive growth factor release. Two well-defined examples are Ménétrier disease and Zollinger-Ellison syndrome, the morphologic features of which are compared with other gastric proliferations in Table 17-5.

Ménétrier Disease s0440

p1520 **Ménétrier disease** is a rare disorder associated with excessive secretion of transforming growth factor α (TGF-α). It is characterized by diffuse hyperplasia of the foveolar epithelium of the body and fundus and hypoproteinemia due to protein-losing enteropathy. Secondary symptoms, such as weight loss, diarrhea, and peripheral edema, are commonly present. Symptoms and pathologic features of Ménétrier disease in children are similar to those in adults, but pediatric disease is usually self-limited and often follows a respiratory infection. Risk of gastric adenocarcinoma is increased in adults with Ménétrier disease.

MORPHOLOGY b0085

p1525 Ménétrier disease is characterized by irregular enlargement of the gastric rugae. Some areas may appear polypoid. Enlarged rugae are present in the body and fundus (Fig. 17-15*A*), but the antrum is generally spared. Histologically, the most characteristic feature is hyperplasia of foveolar mucous cells. The glands are elongated with a corkscrew-like appearance and cystic dilation is common (Fig. 17-15*B*). Inflammation is usually modest, although some cases show marked intraepithelial lymphocytosis. Diffuse or patchy glandular atrophy, evident as hypoplasia of parietal and chief cells, is typical.

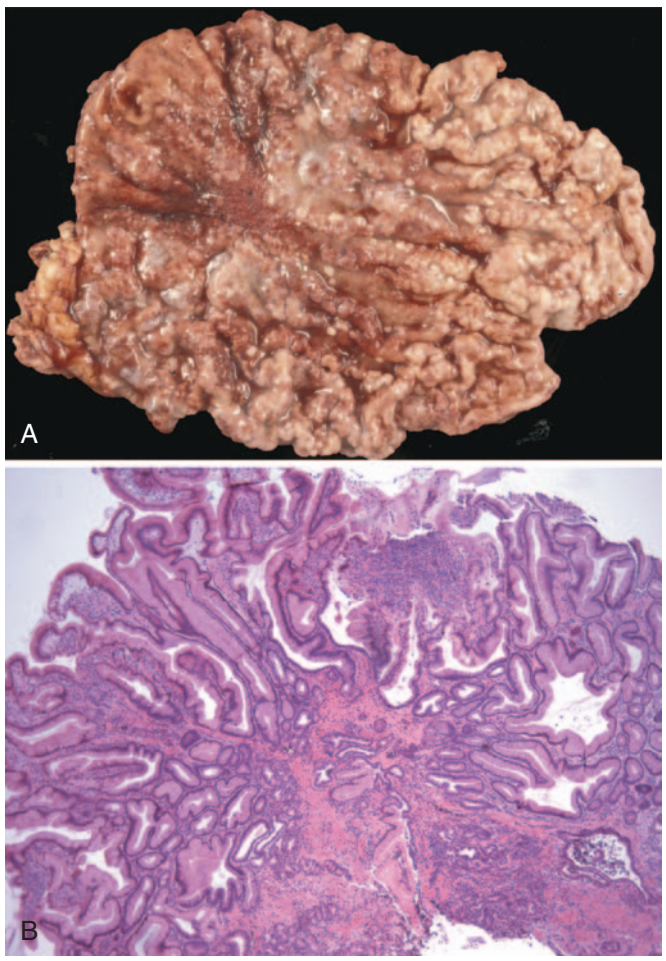
ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

t0025 **Table 17-5** Hypertrophic Gastropathies and Gastric Polyps

Parameter	Ménétrier Disease (adult)	Zollinger-Ellison Syndrome	Inflammatory and Hyperplastic Polyps	Gastritis Cystica	Fundic Gland Polyps	Gastric Adenomas
Mean patient age (yr)	30-60	50	50-60	Variable	50	50-60
Location	Body and fundus	Fundus	Antrum > body	Body	Body and fundus	Antrum > body
Predominant cell type	Mucous	Parietal > mucous, endocrine	Mucous	Mucous, cyst-lining	Parietal and chief	Dysplastic, intestinal
Inflammatory infiltrate	Limited, lymphocytes	Neutrophils	Neutrophils and lymphocytes	Neutrophils and lymphocytes	None	Variable
Symptoms	Hypoproteinemia, weight loss, diarrhea	Peptic ulcers	Similar to chronic gastritis	Similar to chronic gastritis	None, nausea	Similar to chronic gastritis
Risk factors	None	Multiple endocrine neoplasia	Chronic gastritis, *H. pylori*	Trauma, prior surgery	PPIs, FAP	Chronic gastritis, atrophy, intestinal metaplasia
Association with adenocarcinoma	Yes	No	Occasional	No	Syndromic (FAP) only	Frequent

FAP, Familial adenomatous polyposis; PPIs, proton pump inhibitors.

p1530 Treatment of Ménétrier disease is supportive, with intravenous albumin and parenteral nutritional supplementation. In severe cases gastrectomy may be needed. More recently, agents that block TGF-α-mediated activation of the epidermal growth factor receptor have shown promise.



f0080 **Figure 17-15** Ménétrier disease. **A,** Marked hypertrophy of rugal folds. **B,** Foveolar hyperplasia with elongated and focally dilated glands. (Courtesy Dr. M. Kay Washington, Vanderbilt University, Nashville, Tenn.)

Zollinger-Ellison Syndrome s0445

p1535 **Zollinger-Ellison syndrome is caused by gastrin-secreting tumors.** These gastrinomas are most commonly found in the small intestine or pancreas. Patients often present with duodenal ulcers or chronic diarrhea. Within the stomach, the most remarkable feature is a doubling of oxyntic mucosal thickness due to a five-fold increase in the number of parietal cells. Gastrin also induces hyperplasia of mucous neck cells, mucin hyperproduction, and proliferation of endocrine cells within oxyntic mucosa. In some cases these endocrine cells can form small dysplastic nodules or, rarely, true carcinoid tumors.

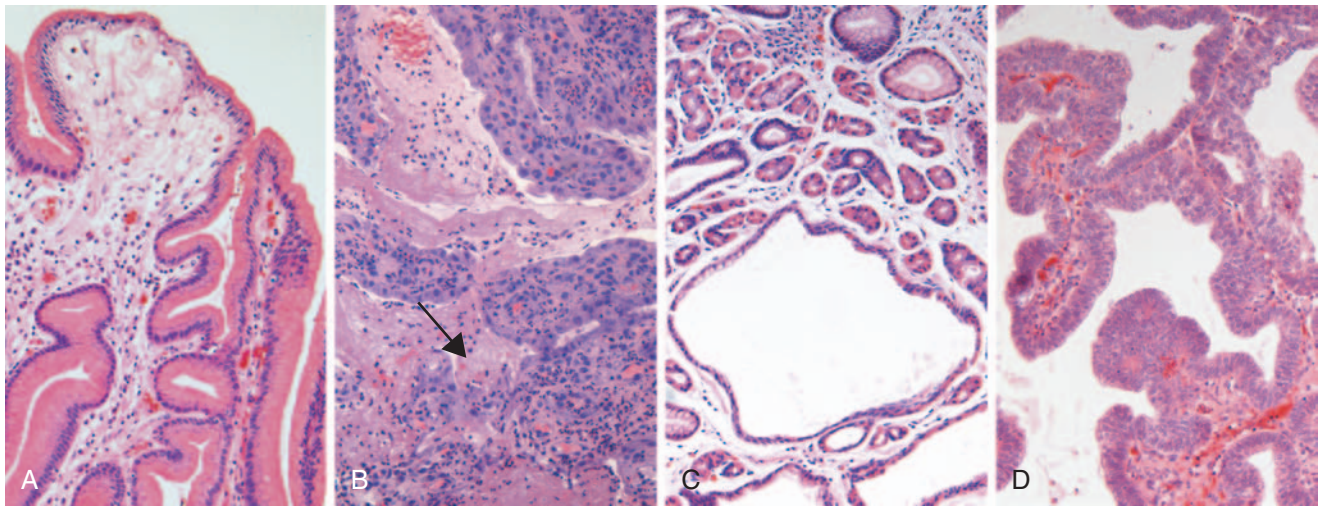
p1540 Treatment of individuals with Zollinger-Ellison syndrome includes blockade of acid hypersecretion. This can be accomplished in almost all patients with proton pump inhibitors. Acid suppression allows peptic ulcers to heal and prevents gastric perforation, allowing treatment to focus on the gastrinoma, which becomes the main determinant of long-term survival.

p1545 Although they grow slowly, 60% to 90% of gastrinomas are malignant. Tumors are sporadic in 75% of patients. These tend to be solitary and can be surgically resected. The remaining 25% of patients with gastrinomas have multiple endocrine neoplasia type I (MEN I). These individuals often have multiple tumors or metastatic disease and may benefit from treatment with somatostatin analogues. Detection of tumors may be enhanced by using somatostatin receptor scintigraphy or endoscopic ultrasonography.

Gastric Polyps and Tumors s0450

p1550 Polyps, nodules or masses that project above the level of the surrounding mucosa, are identified in up to 5% of upper GI endoscopies. Polyps may develop as a result of epithelial or stromal cell hyperplasia, inflammation, ectopia, or neoplasia. Only the most common types of polyps will be discussed here (Peutz-Jeghers and juvenile polyps are discussed with intestinal polyps). This is followed by a presentation of gastric tumors, including adenocarcinomas, lymphomas, carcinoid tumors, and stromal tumors.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0085

Figure 17-16 Gastric polyps. **A,** Hyperplastic polyp containing corkscrew-shaped foveolar glands. **B,** Hyperplastic polyp with ulceration *(arrow)*. **C,** Fundic gland polyp composed of cystically dilated glands lined by parietal, chief, and foveolar cells. **D,** Gastric adenoma recognized by the presence of epithelial dysplasia.

s0455

Inflammatory and Hyperplastic Polyps

p1555 **Up to 75% of all gastric polyps are inflammatory or hyperplastic polyps.** Since chronic inflammation drives the development of such polyps, the incidence depends partly on the regional prevalence of *H. pylori* infection. These polyps are most common in individuals between 50 and 60 years of age, and usually develop in association with chronic gastritis, which initiates the injury that leads to reactive hyperplasia and polyp growth. Among individuals with *H. pylori* gastritis, polyps may regress after bacterial eradication. Because the risk of dysplasia correlates with size, polyps larger than 1.5 cm should be resected and examined histologically.

b0090

MORPHOLOGY

p1560 The majority of inflammatory or hyperplastic polyps are smaller than 1 cm in diameter and are frequently multiple, particularly in individuals with atrophic gastritis. These polyps are ovoid in shape and have a smooth surface, though superficial erosions are common. Microscopically, polyps have irregular, cystically dilated, and elongated foveolar glands (Fig. 17-16*A*). The lamina propria is typically edematous with variable degrees of acute and chronic inflammation, and surface ulceration may be present (Fig. 17-16*B*).

s0460

Fundic Gland Polyps

p1565 Fundic gland polyps occur sporadically and in individuals with familial adenomatous polyposis (FAP). The prevalence of fundic gland polyps has increased markedly in recent years as a result of increasing use of proton pump inhibitor therapy. These drugs inhibit acid production, which leads to increased gastrin secretion and, in turn, oxyntic gland growth. Fundic gland polyps may be asymptomatic or associated with nausea, vomiting, or epigastric pain.

b0095

MORPHOLOGY

p1570 Fundic gland polyps occur in the gastric body and fundus and are well-circumscribed lesions with a smooth surface. They may be single or multiple and are composed of cystically dilated, irregular glands lined by flattened parietal and chief cells. Inflammation is typically absent or minimal (Fig. 17-16*C*). Dysplasia and even cancer may occur in FAP-associated fundic gland polyps, but sporadic fundic gland polyps carry no cancer risk.

s0465

Gastric Adenoma

p1575 Gastric adenomas represent up to 10% of all gastric polyps (Table 17-5). Their frequency increases progressively with age, and there is a marked variation in prevalence among different populations that parallels the incidence of gastric adenocarcinoma. Patients are usually between 50 and 60 years of age, and males are affected three times more often than females. Like fundic gland polyps, the incidence of adenomas is increased in individuals with FAP. *Similar to other forms of gastric dysplasia, adenomas almost always occur on a background of chronic gastritis with atrophy and intestinal metaplasia.* The risk of adenocarcinoma in gastric adenomas is related to the size of the lesion and is particularly increased in lesions greater than 2 cm in diameter. Overall, carcinoma may be present in up to 30% of gastric adenomas.

b0100

MORPHOLOGY

p1580 Gastric adenomas are usually solitary lesions less than 2 cm in diameter, most commonly located in the antrum. The majority of adenomas are composed of intestinal-type columnar epithelium that exhibits varying degrees of dysplasia (Fig. 17-16*D*). Dysplasia can be classified as low or high grade, and both grades may include enlargement, elongation, pseudostratification, and hyperchromasia of epithelial cell nuclei, and epithelial

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

crowding. High-grade dysplasia is characterized by more severe cytologic atypia and irregular architecture, including glandular budding and gland-within-gland, or cribriform, structures. Like intestinal adenomas, gastric adenomas are premalignant neoplastic lesions. However, the risk of transformation to invasive cancer is much higher in gastric adenomas.

s0470 Gastric Adenocarcinoma

p1585 **Adenocarcinoma is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers.** As discussed in more detail later, gastric adenocarcinoma is often separated morphologically into intestinal type, which tends to form bulky masses, and a diffuse type, which infiltrates the wall diffusely, thickens it, and is typically composed of signet ring cells. Early symptoms of both types of gastric adenocarcinoma resemble those of chronic gastritis and peptic ulcer disease, including dyspepsia, dysphagia, and nausea. As a result, these tumors are often discovered at advanced stages, when symptoms such as weight loss, anorexia, early satiety (primarily in diffuse cancers), anemia, and hemorrhage trigger further diagnostic evaluation.

s0475 p1590 ***Epidemiology.*** Gastric cancer incidence varies markedly with geography. In Japan, Chile, Costa Rica, and Eastern Europe, the incidence is up to 20-fold higher than in North America, northern Europe, Africa, and Southeast Asia. Mass endoscopic screening programs have been successful in regions where the incidence is high, such as Japan, where 35% of newly detected cases are early gastric cancers, limited to the mucosa and submucosa. Unfortunately, mass screening programs are not cost-effective in regions where the incidence is low, and fewer than 20% of cases are detected at an early stage in North America and northern Europe. Metastases are often detected at time of diagnosis. Sites most commonly involved include the supraclavicular sentinel lymph node (Virchow node), periumbilical lymph nodes (Sister Mary Joseph nodule), the left axillary lymph node (Irish node), the ovary (Krukenberg tumor), or the pouch of Douglas (Blumer shelf).

p1595 Gastric cancer is more common in lower socioeconomic groups and in individuals with multifocal mucosal atrophy and intestinal metaplasia. *Gastric dysplasia and adenomas are recognizable precursor lesions associated with gastric adenocarcinoma.* PUD does not impart an increased risk of gastric cancer, but patients who have had partial gastrectomies for PUD have a slightly higher risk of developing cancer in the residual gastric stump, possibly due to hypochlorhydria, bile reflux, and chronic gastritis.

p1600 *In the United States, gastric cancer rates dropped by more than 85% during the twentieth century.* Adenocarcinoma of the stomach was the most common cause of cancer death in the United States in 1930 and remains a leading cause of cancer death worldwide, but now accounts for fewer than 2.5% of cancer deaths in the United States. Similar declines have been reported in many other Western countries, suggesting that environmental and dietary factors contribute to the development of gastric cancers. Consistent with this conclusion, studies of migrants from high-risk to low-risk regions have shown that gastric cancer rates in second-generation immigrants are similar to those in their new country of residence.

p1605 *The cause of the overall reduction in gastric cancer is most closely linked to decreases in H. pylori prevalence.* Another possible contributor is the decreased consumption of dietary carcinogens, such as N-nitroso compounds and benzo[*a*]pyrene, because of the reduced use of salt and smoking for food preservation and the widespread availability of food refrigeration.

p1610 Although overall incidence of gastric adenocarcinoma is falling, cancer of the gastric cardia is on the rise. This is probably related to Barrett esophagus and may reflect the increasing incidence of chronic GERD and obesity. Consistent with this presumed common pathogenesis, distal esophageal adenocarcinomas and gastric cardia adenocarcinomas are similar in morphology, clinical behavior, and therapeutic response.

s0490 p1615 ***Pathogenesis.*** While the majority of gastric cancers are not hereditary, the mutations identified in familial gastric cancer have provided important insights into mechanisms of carcinogenesis in sporadic cases. Familial gastric cancer is strongly associated with germline loss-of-function mutations in the tumor suppressor gene *CDH1*, which encodes the cell adhesion protein E-cadherin (discussed in Chapter 7). Loss-of-function mutations in *CDH1* are also present in about 50% of sporadic diffuse gastric tumors, while E-cadherin expression is drastically decreased in the rest, often by hyper methylation and silencing of the *CDH1* promoter. *Thus, the loss of E-cadherin is a key step in the development of diffuse gastric cancer. CDH1* mutations are also common in sporadic and familial lobular carcinoma of the breast, which, like diffuse gastric cancer (see later), tends to infiltrate as single cells, and individuals with *BRCA2* mutations are at increased risk of developing diffuse gastric cancer. Mutation of *TP53* is also found in the majority of sporadic gastric cancers of both diffuse and intestinal types.

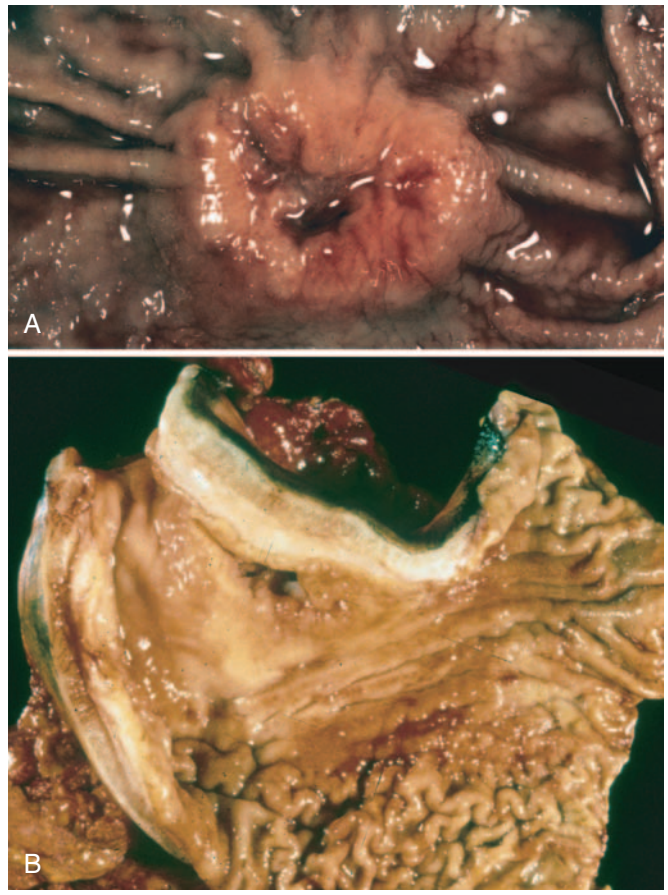
p1620 *In contrast to diffuse gastric cancers, sporadic intestinal-type gastric cancers are strongly associated with mutations that result in increased signaling via the Wnt pathway. These include loss-of-function mutations in the adenomatous polyposis coli (APC) tumor suppressor gene and gain-of-function mutations in the gene encoding β-catenin. Loss-of-function mutations or silencing of a number of other tumor suppressor genes have also been identified, including those involved in TGFβ signaling (TGFβRII), regulation of apoptosis (BAX), and cell cycle control (CDKN2A), all of which are discussed in more detail in* Chapter 7. As expected, FAP patients, who carry germline *APC* mutations, have an increased risk of intestinal-type gastric cancer. This is particularly true in Japan and other high-risk areas, as compared to individuals with FAP residing in areas of low gastric cancer incidence. Thus, both host genetic background and environmental factors affect risk. As discussed in the context of *H. pylori* gastritis, genetic variants of proinflammatory and immune response genes, including those that encode IL-1β, TNF, IL-10, IL-8, and Toll-like receptor 4 (TLR4), are associated with elevated risk of gastric cancer when accompanied by *H. pylori* infection. Thus, it is clear that chronic inflammation promotes gastric neoplasia. Other associations between chronic inflammation and cancer are discussed in Chapter 7.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

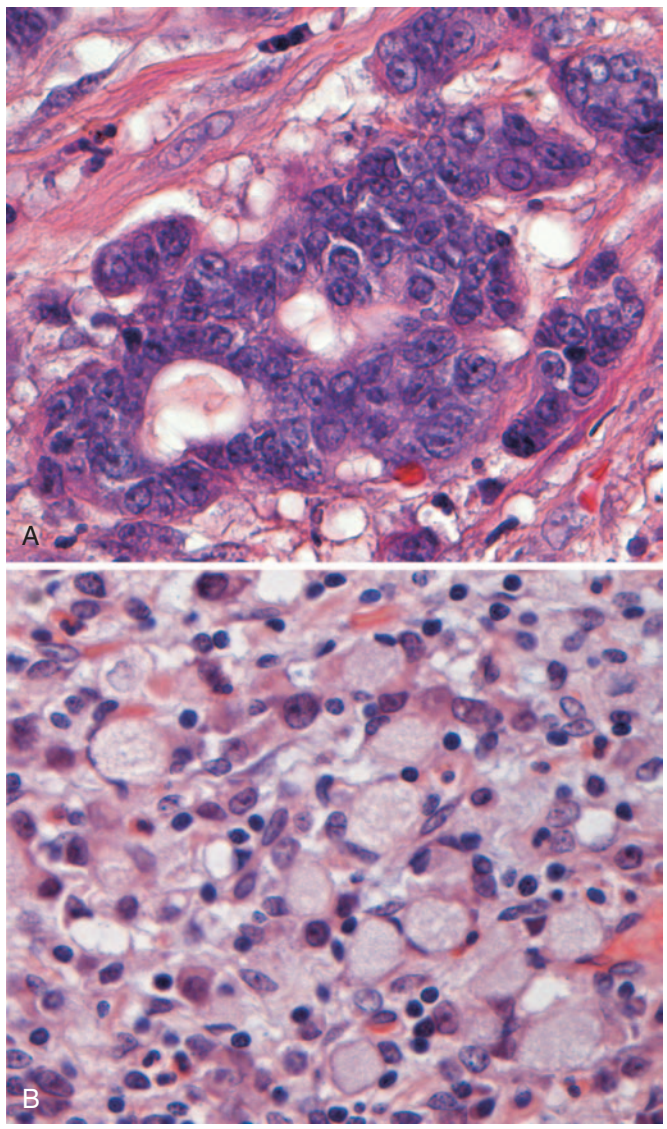
b0105

MORPHOLOGY

p1625 Gastric adenocarcinomas are classified according to their location and gross and histologic morphology. Most gastric adenocarcinomas involve the gastric antrum; the lesser curvature is involved more often than the greater curvature. **Gastric tumors with an intestinal morphology,** which tend to form bulky tumors (Fig. 17-17*A*), are composed of glandular structures (Fig. 17-18*A*), while cancers with a **diffuse infiltrative growth pattern** (Fig. 17-17*B*) are more often composed of signet-ring cells (Fig. 17-18*B*). Although intestinal-type adenocarcinomas may penetrate the gastric wall, they more frequently grow along broad cohesive fronts to form either an exophytic mass or an ulcerated tumor. The neoplastic cells often contain apical mucin vacuoles, and abundant mucin may be present in gland lumina. In contrast, diffuse gastric cancer is generally composed of discohesive cells, likely as a result of E-cadherin loss. These cells do not form glands but instead have large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery, creating a signet-ring cell morphology. They permeate the mucosa and stomach wall individually or in small clusters, and may be mistaken for inflammatory cells, such as macrophages, at low magnification. Release of extracellular mucin in either type of gastric cancer can result in formation of large mucin lakes that dissect tissue planes.



f0090 **Figure 17-17** Gastric adenocarcinoma. **A,** Intestinal-type adenocarcinoma consisting of an elevated mass with heaped-up borders and central ulceration. Compare to the peptic ulcer in Figure 17-14*A*. **B,** Linitis plastica. The gastric wall is markedly thickened and rugal folds are partially lost.



f0095 **Figure 17-18** Gastric adenocarcinoma. **A,** Intestinal-type adenocarcinoma composed of columnar, gland-forming cells infiltrating through desmoplastic stroma. **B,** Signet-ring cells can be recognized by their large cytoplasmic mucin vacuoles and peripherally displaced, crescent-shaped nuclei.

p1630 A mass may be difficult to appreciate in diffuse gastric cancer, but these infiltrative tumors often evoke a **desmoplastic** reaction that stiffens the gastric wall and may provide a valuable diagnostic clue. When there are large areas of infiltration, diffuse rugal flattening and a rigid, thickened wall may impart a **leather bottle** appearance termed **linitis plastica** (Fig. 17-17*B*).

s0495 p1635 *Clinical Features.* **Intestinal-type gastric cancer predominates in high-risk areas and develops from precursor lesions, including flat dysplasia and adenomas.** The mean age of presentation is 55 years, and the male-to-female ratio is 2:1. In contrast, the incidence of diffuse gastric cancer is relatively uniform across countries, there are no identified precursor lesions, and the disease occurs at similar frequencies in males and females. Notably, the remarkable decrease in gastric cancer incidence applies only to the intestinal type, which is most closely associated with

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

atrophic gastritis and intestinal metaplasia. As a result, the incidence of diffuse type gastric cancer, which was previously low, is now similar to intestinal type gastric cancer.

p1640 **The depth of invasion and the extent of nodal and distant metastases at the time of diagnosis remain the most powerful prognostic indicators in gastric cancer.** Local invasion into the duodenum, pancreas, and retroperitoneum is common. In such cases efforts are usually focused on chemotherapy or radiation therapy and palliative care. However, when possible, surgical resection remains the preferred treatment for gastric adenocarcinoma. With surgical resection, the 5-year survival rate of early gastric cancer can exceed 90%, even if lymph node metastases are present. In contrast, the 5-year survival rate for advanced gastric cancer remains less than 20%. Because of the advanced stage at which most gastric cancers are discovered in the United States, the overall 5-year survival is less than 30%.

s0500 Lymphoma

p1645 **Although extranodal lymphomas can arise in virtually any tissue, they do so most commonly in the GI tract, particularly the stomach.** In allogeneic hematopoietic stem cell and organ transplant recipients, the bowel is also the most frequent site for Epstein-Barr virus-positive B-cell lymphoproliferations. This preferential location is most likely because the deficits in T-cell function caused by oral immunosuppressive agents (e.g., cyclosporine) are greatest at intestinal sites of drug absorption. Nearly 5% of all gastric malignancies are primary lymphomas, the most common of which are indolent extranodal marginal zone B-cell lymphomas. *In the gut these tumors are often referred to as lymphomas of mucosa-associated lymphoid tissue (MALT), or MALTomas*. This and other lymphomas of the gut are discussed in Chapter 13.

s0505 ***Pathogenesis.*** Extranodal marginal zone B-cell lymphop1650 mas usually arise at sites of chronic inflammation. They can originate in the GI tract at sites of preexisting MALT, such as the Peyer patches of the small intestine, but more commonly arise within tissues that are normally devoid of organized lymphoid tissue. *In the stomach, MALT is induced, typically as a result of chronic gastritis. H. pylori* infection is the most common inducer in the stomach and, therefore, is found in association with most cases of gastric MALToma. Remarkably, *H. pylori* eradication results in durable remissions with low rates of recurrence in most MALToma patients.

p1655 Three translocations are associated with gastric MALToma, the t(11;18)(q21;q21) and the less common t(1;14)(p22;q32) and t(14;18)(q32;q21). The t(11;18)(q21;q21) translocation brings together the apoptosis inhibitor 2 *(API2)* gene on chromosome 11 with the "mutated in MALT lymphoma," or *MLT*, gene on chromosome 18. This creates a chimeric *API2-MLT* fusion gene that encodes an API2-MLT fusion protein. The t(14;18)(q32;q21) and t(1;14)(p22;q32) translocations cause increased expression of intact MALT1 and BCL-10 proteins, respectively.

p1660 Each of the three translocations has the same net effect, the constitutive activation of NF-κB, a transcription factor that promotes B-cell growth and survival. Antigen-dependent activation of NF-κB in normal B and T cells requires both BCL-10 and MLT, which work together in a pathway downstream of the B- and T-cell antigen receptors. Thus, *H. pylori*–induced inflammation may trigger NF-κB activation through the MLT/BCL-10 pathway in MALTomas that lack these translocations. Removal of this stimulus may explain why these tumors tend to respond to *H. pylori* eradication. In contrast, NF-κB is constitutively active in tumors bearing translocations involving *MLT* or *BCL10*, and *H. pylori* treatment is ineffective. Other tumor characteristics, including invasion to the muscularis propria or beyond and lymph node involvement, also correlate with failure of *H. pylori* eradication to induce remission.

p1665 As with other low-grade lymphomas, MALTomas can transform into more aggressive tumors that are histologically identical to diffuse large B-cell lymphomas. This is often associated with additional genetic changes, such as inactivation of the tumor suppressor genes that encode p53 and p16. As one might guess, MALTomas that have undergone such transformation are not responsive to *H. pylori* eradication.

MORPHOLOGY b0110

p1670 Histologically, gastric MALToma takes the form of a dense lymphocytic infiltrate in the lamina propria (Fig. 17-19*A*). Characteristically, the neoplastic lymphocytes infiltrate the gastric glands focally to create **diagnostic lymphoepithelial lesions** (Fig. 17-19*A*, inset). Reactive-appearing B-cell follicles may be present, and, in about 40% of tumors, plasmacytic differentiation is observed. At other sites GI lymphomas may disseminate as discrete small nodules (Fig. 17-19*B*) or infiltrate the wall diffusely (Fig. 17-19*C*).

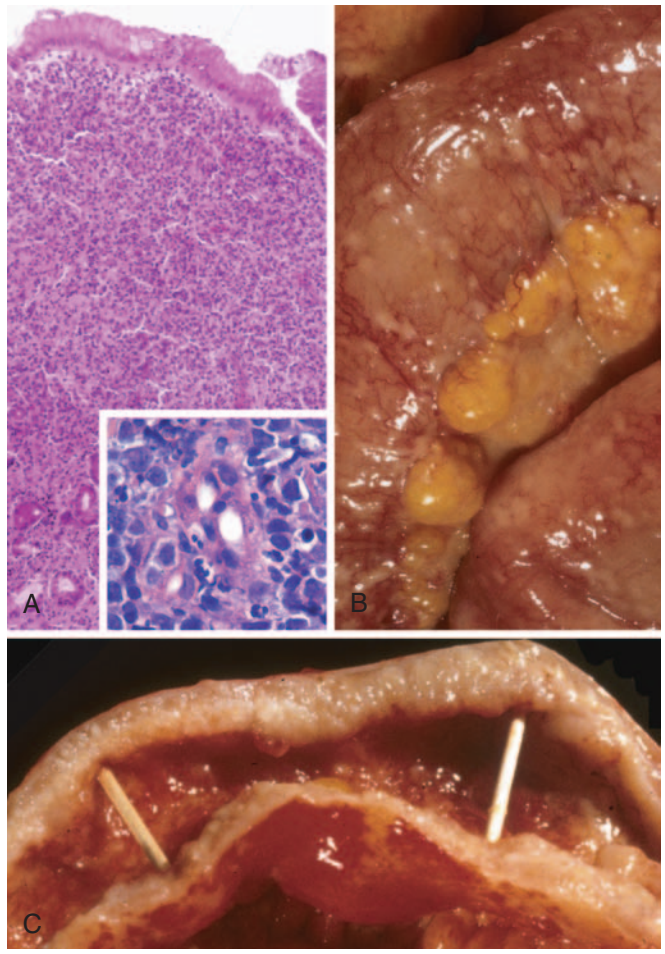
p1675 Like other tumors of mature B cells, MALTomas express the B-cell markers CD19 and CD20. They do not express CD5 or CD10, but are positive for CD43 in about 25% of cases, an unusual feature that can be diagnostically helpful. In cases lacking lymphoepithelial lesions, monoclonality may be demonstrated by restricted expression of either κ or λ immunoglobulin light chains or by molecular detection of clonal IgH rearrangements. Molecular analysis is being used increasingly to identify tumors with translocations that predict resistance to therapy.

s0520 ***Clinical Features.*** The most common presenting symp-p1680 toms are dyspepsia and epigastric pain. Hematemesis, melena, and constitutional symptoms such as weight loss can also be present. Because gastric MALTomas and *H. pylori* gastritis often coexist and have overlapping clinical symptoms and endoscopic appearances, diagnostic difficulties may arise, particularly in small biopsy specimens.

Carcinoid Tumor s0525

p1685 Carcinoid tumors arise from the diffuse components of the endocrine system and are now properly referred to as *well-differentiated neuroendocrine tumors.* The term carcinoid, or "carcinoma-like," was applied because these tumors tend to have a more indolent clinical course than GI carcinomas. Most are found in the GI tract, and more than 40% occur in the small intestine (Table 17-6). The tracheobronchial tree and lungs are the next most

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0100 **Figure 17-19** Lymphoma. **A,** Gastric MALT lymphoma replacing much of the gastric epithelium. Inset shows lymphoepithelial lesions with neoplastic lymphocytes surrounding and infiltrating gastric glands. **B,** Disseminated lymphoma within the small intestine with numerous small serosal nodules. **C,** Large B-cell lymphoma infiltrating the small intestinal wall and producing diffuse thickening.

commonly involved sites. Gastric carcinoid tumors may be associated with endocrine cell hyperplasia, autoimmune chronic atrophic gastritis, MEN-I, and Zollinger-Ellison syndrome. In addition to autoimmune chronic atrophic gastritis, as already discussed, gastric endocrine cell hyperplasia has been linked to proton pump inhibitor therapy, but the risk of progression to a neuroendocrine neoplasm in this circumstance is extremely low.

MORPHOLOGY b0115

p1695

Grossly, carcinoids are intramural or submucosal masses that create small polypoid lesions (Fig. 17-20*A*). In the stomach they typically arise within oxyntic mucosa. At all GI sites, the overlying mucosa may be intact or ulcerated, and in the intestines the tumors may invade deeply to involve the mesentery. Carcinoids tend to be yellow or tan in color and are very firm as a consequence of an intense desmoplastic reaction, which may cause kinking and obstruction of the bowel. Histologically, carcinoids are composed of islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and a round to oval stippled nucleus (Fig. 17-20). In most tumors there is minimal pleomorphism, but anaplasia, mitotic activity, and necrosis may be present in rare cases. Immunohistochemical stains are typically positive for endocrine granule markers, such as synaptophysin and chromogranin A.

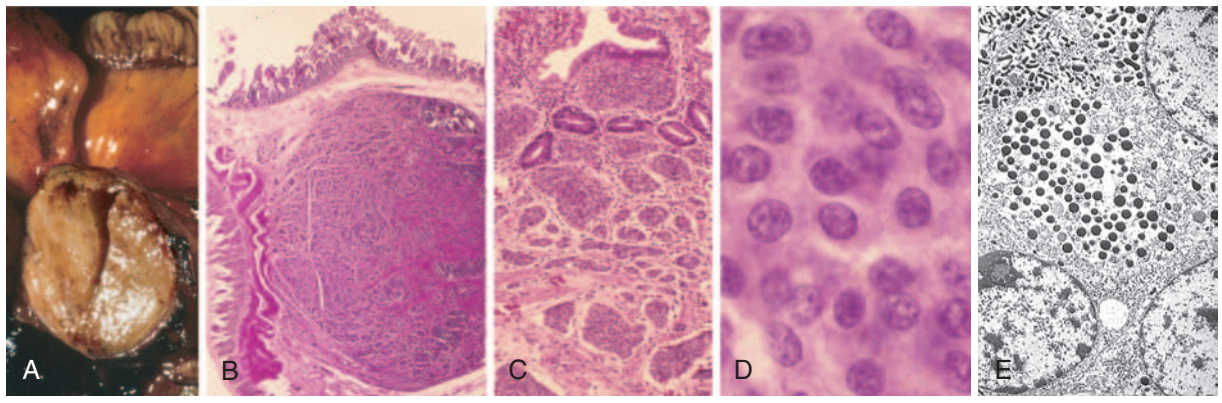
Clinical Features. The peak incidence of carcinoid tumors is in the sixth decade, but they may appear at any age. Symptoms are determined by the hormones produced. For example, *tumors that produce gastrin may cause Zollinger-Ellison syndrome, while ileal tumors may cause carcinoid syndrome,* which is characterized by cutaneous flushing, sweating, bronchospasm, colicky abdominal pain, diarrhea, and right-sided cardiac valvular fibrosis. Carcinoid syndrome occurs in fewer than 10% of patients and is caused by vasoactive substances secreted by the tumor into the systemic circulation. When tumors are confined to the s0530 p1700

t0030 **Table 17-6** Features of Gastrointestinal Carcinoid Tumors

Feature	Esophagus	Stomach	Proximal Duodenum	Jejunum and Ileum	Appendix	Colorectum
Fraction of GI carcinoids	<1%	<10%	<10%	>40%	<25%	<25%
Mean patient age (yr)	Rare	55	50	65	All ages	60
Location	Distal	Body and fundus	Proximal third, peri-ampullary	Throughout	Tip	Rectum > cecum
Size	Limited data	1-2 cm, multiple; >2 cm, solitary	0.5-2 cm	<3.5 cm	0.2-1 cm	>5 cm (cecum); <1 cm (rectum)
Secretory product(s)	Limited data	Histamine, somatostatin, serotonin	Gastrin, somatostatin, cholecystokinin	Serotonin, substance P, polypeptide YY	Serotonin, polypeptide YY	Serotonin, polypeptide YY
Symptoms	Dysphagia, weight loss, reflux	Gastritis, ulcer, incidental	Peptic ulcer, biliary obstruction, abdominal pain	Asymptomatic, obstruction, metastatic disease	Asymptomatic, incidental	Abdominal pain, weight loss, incidental
Behavior	Limited data	Variable	Variable	Aggressive	Benign	Variable
Disease associations	None	Atrophic gastritis, MEN-I	Zollinger-Ellison syndrome, NF-1, sporadic	None	None	None

MEN-I, Multiple endocrine neoplasia type I; NF-1, neurofibromatosis type I.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0105 **Figure 17-20** GI carcinoid tumor (neuroendocrine carcinoma). **A,** Gross cross-section of a submucosal tumor nodule. **B,** Microscopically the nodule is composed of tumor cells embedded in dense fibrous tissue. **C,** In other areas, the tumor has spread extensively within mucosal lymphatic channels. **D,** High magnification shows the bland cytology of carcinoid tumors. The chromatin texture, with fine and coarse clumps, is frequently described as a "salt and pepper" pattern. Despite their innocuous appearance, carcinoids can be clinically aggressive. **E,** Electron microscopy reveals cytoplasmic dense core neurosecretory granules.

intestine, the vasoactive substances released are metabolized to inactive forms by the liver, a "first-pass" effect similar to that exerted on oral drugs. This can be overcome by a large tumor burden or, more commonly, when tumors secrete hormones into a nonportal venous circulation. The carcinoid syndrome is therefore strongly associated with metastatic disease in the liver since the bioactive products can be released directly into systemic circulation.

p1705 The most important prognostic factor for GI carcinoid tumors is location.

u0895 • *Foregut carcinoid tumors*, those found within the stomach, duodenum proximal to the ligament of Treitz, and esophagus, rarely metastasize and are generally cured by resection. This is particularly true for gastric carcinoid tumors that arise in association with atrophic gastritis, while gastric carcinoid tumors without predisposing factors are often more aggressive.

u0900 • *Midgut carcinoid tumors* that arise in the jejunum and ileum are often multiple and tend to be aggressive. In these tumors, greater depth of local invasion, increased size, and the presence of necrosis and mitoses are associated with a worse outcome.

u0905 • *Hindgut carcinoids* arising in the appendix and colorectum are typically discovered incidentally. Those in the appendix occur at any age and are generally located at the tip. These tumors are rarely more than 2 cm in diameter and are almost always benign. Rectal carcinoid tumors tend to produce polypeptide hormones and, when symptomatic, present with abdominal pain and weight loss. Because they are usually discovered when small, metastasis of rectal carcinoid tumors is uncommon.

s0545 Gastrointestinal Stromal Tumor

p1725 A wide variety of mesenchymal neoplasms may arise in the stomach. Many are named according to the cell type they most resemble; for example, smooth muscle tumors are called *leiomyomas* or *leiomyosarcomas,* nerve sheath tumors are termed *schwannomas,* and those resembling glomus bodies in the nail beds and at other sites are termed *glomus tumors.* These are all rare and are discussed in greater detail in Chapter 26. ***GI stromal tumor (GIST)* is the most common mesenchymal tumor of the abdomen,** with annual incidences between 11 and 20 per million people. More than half of these tumors occur in the stomach. The term stromal reflects historical confusion about the origin of this tumor, which is now recognized to arise from the interstitial cells of Cajal, or pacemaker cells, of the gastrointestinal muscularis propria.

Epidemiology. Clinically silent, microscopic proliferations s0550 that may represent precursors to GIST are present in 10% p1730 to 30% of resected stomachs. These have a low mitotic index and lack pleomorphism and other features suggesting malignancy. The risk of of these benign proliferations becoming a GIST is estimated to be 1 in 2000.

The peak age at which clinically evident GISTs are rec- p1735 ognized is approximately 60 years, with fewer than 10% occurring in individuals younger than 40 years of age. Of the uncommon GISTs in children, some are related to the *Carney triad*, a nonhereditary syndrome of unknown etiology seen primarily in young females that includes gastric GIST, paraganglioma, and pulmonary chondroma. There is also an increased incidence of GIST in individuals with neurofibromatosis type 1.

Pathogenesis. **Approximately 75% to 80% of all GISTs** s0565 **have oncogenic, gain-of-function mutations in the recep-** p1740 **tor tyrosine kinase KIT.** Approximately 8% of GISTs have mutations that activate a closely related receptor tyrosine kinase, platelet-derived growth factor receptor α (PDGFRA). For unknown reasons, GISTs bearing PDGFRA mutations are overrepresented in the stomach. *KIT* and *PDGFRA* gene mutations are mutually exclusive, reflecting their activities within the same signal transduction pathway. Germline mutations in these same genes are present in rare familial GISTs, in which patients develop multiple GISTs and may also have diffuse hyperplasia of Cajal cells. Both sporadic and germline mutations result in constitutively active KIT or PDGFRA receptor tyrosine kinases and produce intracellular signals that promote tumor cell proliferation and survival (Chapter 7). Some GISTs without mutated *KIT* or *PDGFRA* have mutations in

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

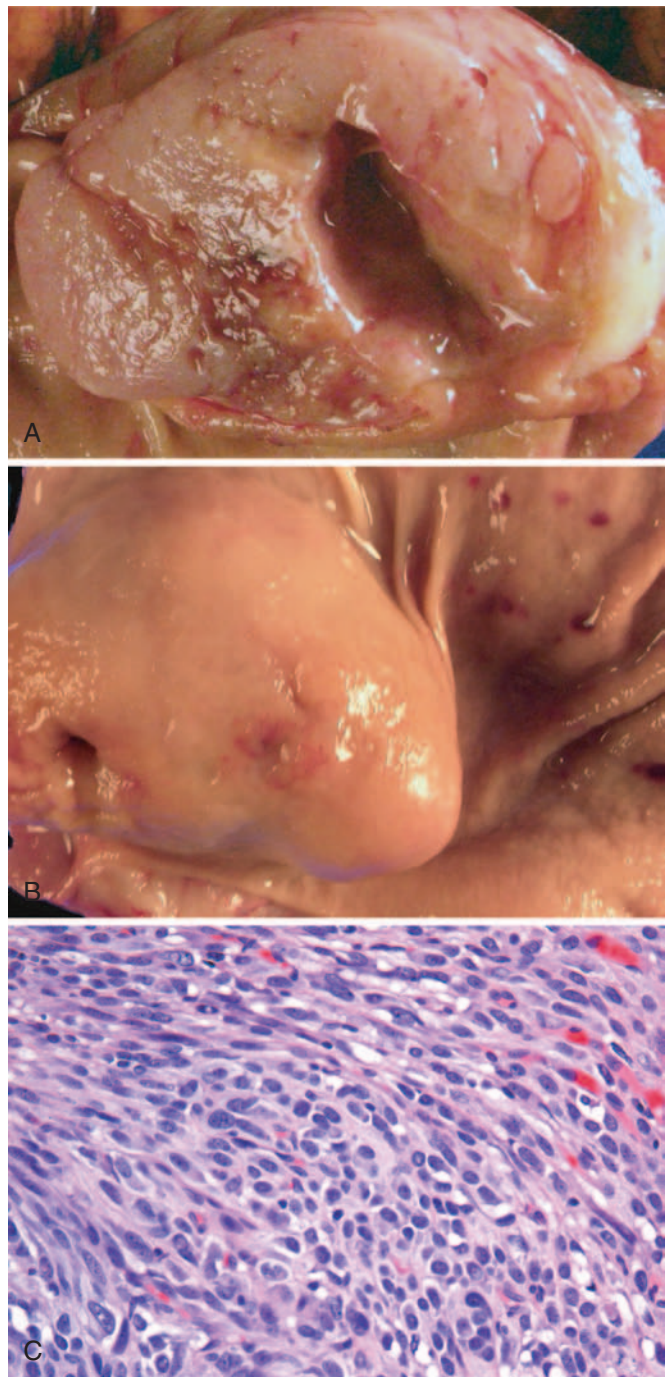
other genes that function in these pathways (*NF1*, *BRAF, HRAS,* or *NRAS*). However, more common are mutations in genes encoding components of the mitochondrial succinate dehydrogenase complex (*SDHA, SDHB, SDHC, SDHD*). These mutations, which cause loss of SDH function, are often inherited in the germline and confer an increased risk for GIST and paraganglioma (*Carney-Stratakis syndrome*, not to be confused with Carney triad); with the second copy of the affected gene being either mutated or lost in the tumor. The mechanisms by which SDH mutations lead to GIST are unclear; one hypothesis is that the accumulation of succinate leads to dysregulation of hypoxia inducible factor-1α (HIF-1α), which results in increased transcription of the vascular endothelial growth factor (*VEGF*) and insulin-like growth factor-1 (*IGF1R*) genes.

p1745 *Mutation of KIT or PDGFRA is an early event in sporadic GISTs and is detectable in lesions as small as 3 mm.* Therefore, *KIT* or *PDGFRA* mutations alone are insufficient for tumorigenesis. Changes associated with progression to overt GIST are not well-defined, but loss or partial deletion of chromosomes 14 and 22 is common and losses and gains at other chromosomes also occur. In particular, deletion of 9p results in loss of the cell cycle regulator *CDKN2A*, a tumor suppressor that is involved in many cancers. In addition to potentially being related to progression, increased numbers of chromosomal alterations correlate with poor prognosis.

b0120 MORPHOLOGY

p1750 Primary gastric GISTs can be quite large, as much as 30 cm in diameter. They usually form a solitary, well-circumscribed, fleshy mass (Fig. 17-21*A*) covered by ulcerated or intact mucosa (Fig. 17-21*B*), but can also project outward toward the serosa. The cut surface shows a whorled appearance. Metastases may take the form of multiple serosal nodules throughout the peritoneal cavity or as one or more nodules in the liver; spread outside of the abdomen is uncommon, but can occur. GISTs composed of thin elongated cells are classified as **spindle cell type** (Fig. 17-21*C*), whereas tumors dominated by epithelial-appearing cells are termed **epithelioid type**; mixtures of the two patterns also occur. The most useful diagnostic marker is KIT, which is detectable in Cajal cells and 95% of gastric GISTs by immunohistochemical stains.

s0570 ***Clinical Features.*** Symptoms of GISTs at presentation may
p1755 be related to mass effects. Mucosal ulceration can cause blood loss, and approximately half of individuals with GIST present with anemia or related symptoms. GISTs may also be discovered as an incidental finding during radiologic imaging, endoscopy, or abdominal surgery performed for other reasons. Complete surgical resection is the primary treatment for localized gastric GIST. The prognosis correlates with tumor size, mitotic index, and location, with gastric GISTs being less aggressive than those arising in the small intestine. Recurrence or metastasis is rare for gastric GISTs smaller than 5 cm but common for mitotically active tumors larger than 10 cm. Many tumors fall into an intermediate category where the malignant potential of the lesion cannot be predicted with certainty on the basis of histology alone.



f0110 **Figure 17-21** GI stromal tumor. **A,** On cross-section a whorled texture is evident within the white, fleshy tumor. **B,** The mass is covered by intact mucosa. **C,** Histologically the tumor is primarily composed of bundles, or fascicles, of spindle-shaped tumor cells. (Courtesy Dr. Christopher Weber, The University of Chicago, Chicago, Ill.)

p1760 The molecular phenotype is an important consideration in the treatment of patients with unresectable, recurrent, or metastatic GISTs. Those with mutations in *KIT* or *PDGFRA* often respond to the tyrosine kinase inhibitor imatinib. In contrast, tumors without these mutations are generally resistant. Further, specific *KIT* or *PDGFRA* mutations are associated with different drug sensitivities. In treated patients, development of imatinib-resistance is common.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

This is due to secondary *KIT* or *PDGFRA* mutations. Tumors with secondary mutations may respond to other tyrosine kinase inhibitors as well as experimental therapies that target other pathways.

b0125 **KEY CONCEPTS**

s9020 **Neoplastic and Non neoplastic proliferations of the stomach**

p1765 ■ **Ménétrier disease** is a rare disorder caused by excessive secretion of transforming growth factor α (TGF-α) and characterized by diffuse foveolar hyperplasia and protein-losing enteropathy.

u0915 ■ **Zollinger-Ellison syndrome** is caused by gastrin-secreting tumors that cause parietal cell hyperplasia and acid hyper secretion; 60% to 90% of gastrinomas are malignant.

u0920 ■ The majority of gastric polyps are **inflammatory or hyperplastic polyps,** reactive lesions that are associated with chronic gastritis.

u0925 ■ **Fundic gland polyps** occur sporadically, most often as a consequence of proton pump inhibitor therapy, and in familial adenomatous polyposis (FAP) patients.

u0930 ■ **Gastric adenomas** develop in a background of chronic gastritis and are particularly associated with intestinal metaplasia and mucosal (glandular) atrophy. Adenocarcinoma is frequent in gastric adenomas, which therefore require more aggressive therapy than adenomas of the colon.

u0935 ■ **Gastric adenocarcinoma** incidence varies markedly with geography. Individual tumors are classified according to location, gross, and histologic morphology. Gastric tumors with an **intestinal histology tend to form bulky tumors** and may be ulcerated, while those composed of **signet-ring cells typically display a diffuse infiltrative growth pattern** that may thicken the gastric wall without forming a discrete mass. Gastric adenocarcinomas are linked to *H. pylori* induced chronic gastritis.

u0945 ■ **Primary gastric lymphomas** are most often derived from mucosa-associated lymphoid tissue (MALT), whose development is induced by chronic gastritis that is most often induced by *H. pylori*.

u0950 ■ **Carcinoid tumors** (well-differentiated neuroendocrine tumors) arise from diffuse components of the endocrine system and are most common in the GI tract, particularly the small intestine. Prognosis is based on location; tumors of the small intestine tend to be most aggressive, while those of the appendix are typically benign.

u0955 ■ **Gastrointestinal stromal tumor (GIST)** is the most common mesenchymal tumor of the abdomen, occurs most often in the stomach, and is related to benign pacemaker cells, or interstitial cells of Cajal. Tumors generally have activating mutations in either KIT or PDGFRA tyrosine kinases and respond to specific kinase inhibitors.

s0575 SMALL INTESTINE AND COLON

p1820 The small intestine and colon make up the majority of the GI tract and are the sites of a broad array of diseases. Some of these relate to nutrient and water transport. Perturbation of these processes can cause malabsorption and diarrhea. The intestines are also the principal site where the immune system interfaces with a diverse array of antigens present in food and gut microbes. Indeed, intestinal bacteria outnumber eukaryotic cells in our bodies by tenfold. Thus, it is not surprising that the small intestine and colon are frequently affected by infectious and inflammatory disorders. Finally, the colon is the most common site of GI neoplasia in Western populations.

s0580 Intestinal Obstruction

p1825 Obstruction of the GI tract may occur at any level, but the small intestine is most often involved because of its relatively narrow lumen. Collectively, *hernias, intestinal adhesions, intussusception, and volvulus* account for 80% of mechanical obstructions (Fig. 17-22), while tumors, infarction, and other causes of strictures, for example, Crohn disease, account for an additional 10% to 15%. **The clinical manifestations of intestinal obstruction include abdominal pain and distention, vomiting, and constipation.** Surgical intervention is usually required in cases where the obstruction has a mechanical basis or is associated with bowel infarction.

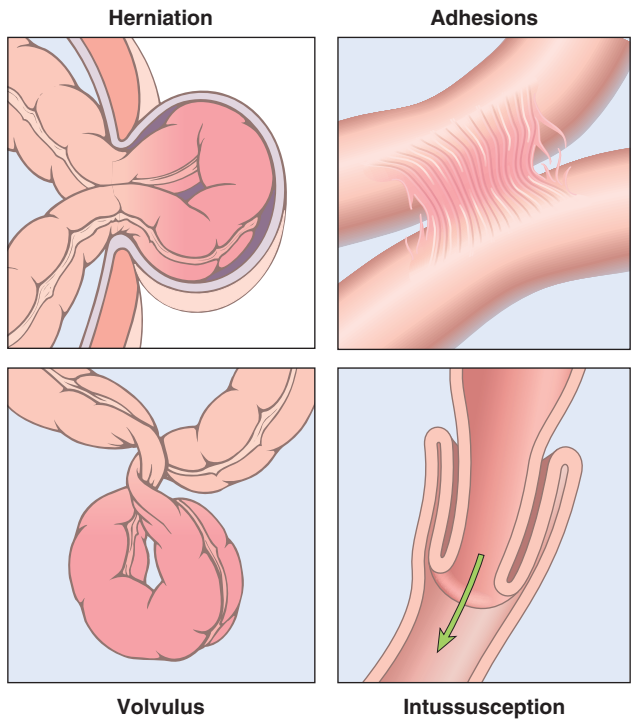
Hernias s0585

p1830 Any weakness or defect in the abdominal wall may permit protrusion of a serosa-lined pouch of peritoneum called a hernia sac. Acquired hernias typically occur anteriorly, via the inguinal and femoral canals, umbilicus, or at sites of surgical scars, and are common, occurring in up to 5% of the population. *Hernias are the most frequent cause of intestinal obstruction worldwide* and the third most common cause of obstruction in the U.S. Obstruction usually occurs because of visceral protrusion (external herniation) and is most frequently-associated with inguinal hernias, which tend to have narrow orifices and large sacs. Small bowel loops are typically involved, but omentum or large bowel may also protrude, and any of these may become entrapped. Pressure at the neck of the pouch may impair venous drainage of the entrapped viscus. The resultant stasis and edema increase the bulk of the herniated loop, leading to permanent entrapment (incarceration) and, over time, arterial and venous compromise (strangulation), and infarction (Fig. 17-23*A*).

Adhesions s0590

p1835 Surgical procedures, infection, or other causes of peritoneal inflammation, such as endometriosis, may result in development of adhesions between bowel segments, the abdominal wall, or operative sites. These fibrous bridges can

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0115

Figure 17-22 Intestinal obstruction. The four major causes of intestinal obstruction are (1) herniation of a segment in the umbilical or inguinal regions, (2) adhesion between loops of intestine, (3) volvulus, and (4) intussusception.

create closed loops through which other viscera may slide and become entrapped, resulting in internal herniation. Sequelae, including obstruction and strangulation, are much the same as with external hernias; *adhesions are the most common cause of intestinal obstruction in the United States.* Fibrous adhesions are most often acquired, but can be congenital in rare cases. Therefore, internal herniation must be considered even in the absence of a history of peritonitis or surgery.

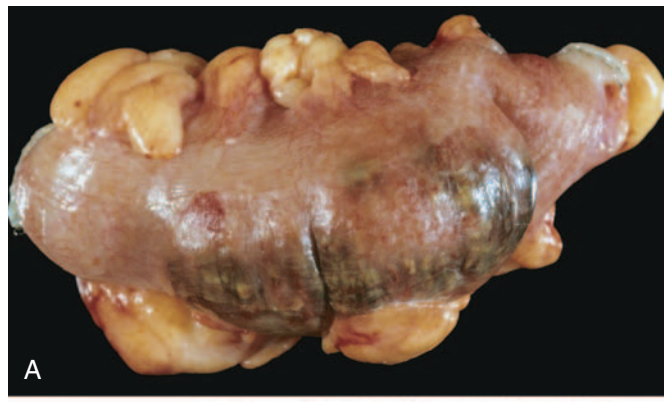
s0595 ## Volvulus

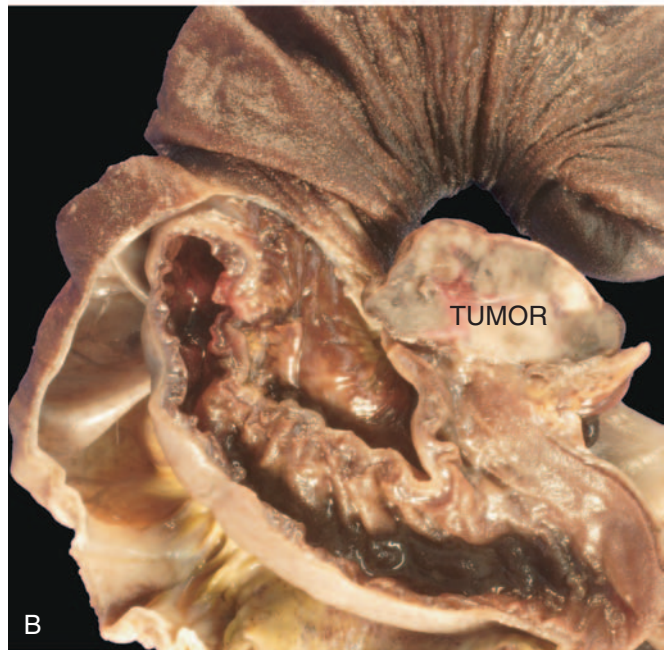
p1840 Twisting of a loop of bowel about its mesenteric point of attachment is termed volvulus; it results in both luminal and vascular compromise. Thus, volvulus presents with features of both obstruction and infarction. It occurs most often in large redundant loops of sigmoid colon, followed in frequency by the cecum, small bowel, stomach, or, rarely, transverse colon. Because it is rare, volvulus can be overlooked clinically.

s0600 ## Intussusception

p1845 Intussusception occurs when a segment of the intestine, constricted by a wave of peristalsis, telescopes into the immediately distal segment. Once trapped, the invaginated segment is propelled by peristalsis and pulls the mesentery along. Untreated intussusception may progress to intestinal obstruction, compression of mesenteric vessels, and infarction.

p1850 *Intussusception is the most common cause of intestinal obstruction in children younger than 2 years of age.* In these idiopathic cases there is usually no underlying anatomic defect and the patient is otherwise healthy. Other cases have been associated with viral infection and rotavirus vaccines, perhaps due to reactive hyperplasia of Peyer patches and other mucosa-associated lymphoid tissue which can act as the leading edge of the intussusception. Intussusception is rare in older children and adults, and is generally caused by an intraluminal mass or tumor that serves as the initiating point of traction (Fig. 17-23*B*). Contrast enemas can be used both diagnostically and therapeutically for idiopathic intussusception in infants and young children, in whom air enemas may also effectively reduce the intussusception. However, surgical intervention is necessary when a mass is present, as is generally the case in older children and adults.





f0120

Figure 17-23 Intestinal obstruction. **A,** Portion of bowel incarcerated within an inguinal hernia. Note dusky serosa and hemorrhage that indicate ischemic damage. **B,** Intussusception caused by a tumor. The outermost layer of intestine with external serosa has been removed, leaving the mucosa of the second layer exposed. The serosa of the second layer is apposed to the serosa of the intussuscepted intestine. A tumor mass (right, labeled tumor) is present at the leading edge of the intussusception. Compare to Figure 17-22. (**B,** Courtesy Dr. Christopher Weber, The University of Chicago, Chicago, Ill.)

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

s0605

Ischemic Bowel Disease

p1855 The majority of the GI tract is supplied by the celiac, superior mesenteric, and inferior mesenteric arteries. As they approach the intestinal wall the superior and inferior mesenteric arteries ramify into the mesenteric arcades. Interconnections between arcades, as well as collateral supplies from the proximal celiac and distal pudendal and iliac circulations, make it possible for the small intestine and colon to tolerate slowly progressive loss of blood supply from one artery.

In contrast to chronic, progressive hypoperfusion, acute compromise of any major vessel can lead to infarction of several meters of intestine. Damage can range from mucosal infarction, extending no deeper than the muscularis mucosae; to mural infarction of mucosa and submucosa; to transmural infarction involving all three wall layers. While mucosal or mural infarctions can follow acute or chronic hypoperfusion, transmural infarction is typically caused by acute vascular obstruction. Important causes of acute arterial obstruction include severe atherosclerosis (which is often prominent at the origin of mesenteric vessels), aortic aneurysm, hypercoagulable states, oral contraceptive use, and embolization of cardiac vegetations or aortic atheromas. Intestinal hypoperfusion can be associated with cardiac failure, shock, dehydration, or use of vasoconstrictive drugs. Systemic vasculitides, such as polyarteritis nodosa, Henoch-Schönlein purpura, or granulomatosis with polyangiitis (Wegener granulomatosis), may also damage intestinal arteries. Mesenteric venous thrombosis, which can also lead to ischemic disease, is uncommon but can result from inherited or acquired hypercoagulable states, invasive neoplasms, cirrhosis, trauma, or abdominal masses that compress the portal drainage.

s0610 p1860 ***Pathogenesis.*** Intestinal responses to ischemia occur in two phases. The initial *hypoxic injury* occurs at the onset of vascular compromise. While some damage occurs during this phase, the epithelial cells lining the intestine are relatively resistant to transient hypoxia. The second phase, *reperfusion injury*, is initiated by restoration of the blood supply and it is at this time that the greatest damage occurs. In severe cases this may trigger multiorgan failure. While the underlying mechanisms of reperfusion injury are incompletely understood, they include leakage of gut lumen bacterial products, e.g. lipopolysaccharide, into the systemic circulation, free radical production, neutrophil infiltration, and release of additional inflammatory mediators (Chapter 2).

p1865 The severity of vascular compromise, the time frame during which it develops, and the vessels affected are the major variables in ischemic bowel disease. Two aspects of intestinal vascular anatomy also contribute to the distribution of ischemic damage and are worthy of note:

u9075
- Intestinal segments at the end of their respective arterial supplies are particularly susceptible to ischemia. These *watershed zones* include the splenic flexure, where the superior and inferior mesenteric arterial circulations terminate, and, to a lesser extent, the sigmoid colon and rectum where inferior mesenteric, pudendal, and iliac arterial circulations end. Generalized hypotension or hypoxemia can therefore cause localized injury, and ischemic disease should be considered in the differential diagnosis of focal colitis of the splenic flexure or rectosigmoid colon.
- Intestinal capillaries run alongside the glands, from crypt to surface, before making a hairpin turn to empty into the post-capillary venules. This arrangement makes the surface epithelium particularly vulnerable to ischemic injury, relative to the crypts. Organization of the blood supply in this patterns has advantages, as it protects the epithelial stem cells, which are located within the crypts and are necessary for recovery from epithelial injury. This pattern of surface epithelial atrophy, or even necrosis and sloughing, with normal or hyperproliferative crypts is a morphologic signature of ischemic intestinal disease. u9080

MORPHOLOGY b0130

p1880 Although the colon is the most common site of gastrointestinal ischemia, mucosal and mural infarction may involve any level of the gut from stomach to anus. The lesions can be continuous but are most often segmental and patchy (Fig. 17-24*A*). The mucosa is hemorrhagic and may be ulcerated (Fig. 17-24*B*). The bowel wall is also thickened by edema that may involve the mucosa or extend into the submucosa and muscularis propria.

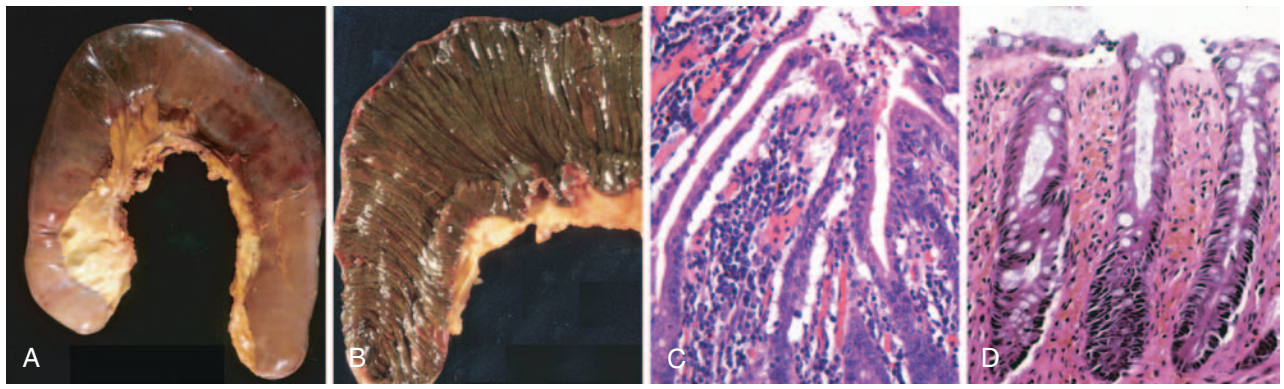
p1885 Substantial portions of the bowel are generally involved in **transmural infarction** due to acute arterial obstruction. The demarcation between normal and ischemic bowel is sharply defined and the infarcted bowel is initially intensely congested and dusky to purple-red. Later, blood-tinged mucus or frank blood accumulates in the lumen and the wall becomes edematous, thickened, and rubbery. There is coagulative necrosis of the muscularis propria within 1 to 4 days, and perforation may occur. Serositis, with purulent exudates and fibrin deposition, may be prominent.

p1890 In mesenteric venous thrombosis, arterial blood continues to flow for a time, resulting in a less abrupt transition from affected to normal bowel. However, propagation of the thrombus may lead to secondary involvement of the splanchnic bed. The ultimate result is similar to that produced by acute arterial obstruction because impaired venous drainage eventually prevents oxygenated arterial blood from entering the capillaries.

p1895 Microscopic examination of ischemic intestine demonstrates the characteristic atrophy or sloughing of surface epithelium (Fig. 17-24*C*). In contrast, crypts may be hyperproliferative. Inflammatory infiltrates are initially absent in acute ischemia, but neutrophils are recruited within hours of reperfusion. Chronic ischemia is accompanied by fibrous scarring of the lamina propria (Fig. 17-24*D*) and, uncommonly, stricture formation. In both acute and chronic ischemia, bacterial superinfection and enterotoxin release may induce **pseudomembrane formation** that resembles *Clostridium difficile*–associated pseudomembranous colitis (discussed later).

s0630 p1900 ***Clinical Features.*** Ischemic disease of the colon is most common in patients older than 70 years of age, and occurs slightly more often in women. While frequently associated with coexisting cardiac or vascular disease ischemia can also be precipitated by therapeutic vasoconstrictors, some illicit drugs, for example, cocaine, endothelial damage and small vessel occlusion after cytomegalovirus or *Escherichia*

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0125

Figure 17-24 Ischemic bowel disease. **A,** Jejunal resection with dusky serosa of acute ischemia (mesenteric thrombosis). **B,** Mucosa is stained with blood after hemorrhage. **C,** Characteristic attenuated villous epithelium in this case of acute mesenteric thrombosis. **D,** Chronic colonic ischemia with atrophic surface epithelium and fibrotic lamina propria.

coli O157:H7 infection, strangulated hernia, or vascular compromise due to prior surgery.

p1905 *Acute colonic ischemia typically presents with sudden onset of cramping, left lower abdominal pain, a desire to defecate, and passage of blood or bloody diarrhea*. The blood loss is usually insufficient to require transfusion, but patients may progress to shock and vascular collapse within hours in severe cases. Surgical intervention, which is necessary in approximately 10% of cases, should be considered if peristaltic sounds diminish or disappear, that is, paralytic ileus, or other features of infarction, such as guarding and rebound tenderness develop. Because these physical signs overlap with those of other abdominal emergencies, including acute appendicitis, perforated ulcer, and acute cholecystitis, the diagnosis of intestinal necrosis may be delayed or missed, with disastrous consequences.

p1910 With appropriate management, mortality in the first 30 days is approximately 10%. Mortality is doubled in patients with right sided colonic disease, who have a more severe course in general. This may be because the right side of the colon is supplied by the superior mesenteric artery, which also supplies much of the small intestine. Thus, right sided colonic ischemia may be the initial presentation of more severe disease, including that caused by acute occlusion of the superior mesenteric artery (Fig. 17-24). Other poor prognostic indicators include co-existing chronic obstructive pulmonary disease (COPD) and persistence of symptoms for more than 2 weeks. Happily, most patients recover fully and colonic ischemia does not recur in the majority of cases. Listed below are some additional forms of bowel ischemia, their antecedents and outcomes.

u0960 • *Mucosal and mural infarctions* by themselves may not be fatal. However, these often progress to more extensive infarction if the vascular supply is not restored by correction of the insult or, in chronic disease, by development of in adequate collateral supplies. The diagnosis of nonocclusive ischemic enteritis and colitis can be particularly difficult because there may be a confusing array of nonspecific abdominal symptoms, including intermittent bloody diarrhea and intestinal obstruction.

u0965 • *Chronic ischemia* may masquerade as inflammatory bowel disease, with episodes of bloody diarrhea interspersed with periods of healing.

u0970 • *CMV infection* causes ischemic GI disease due to viral tropism for endothelial cells. CMV infection, which can be a complication of immunosuppressive therapy, is discussed further in Chapter 8.

u0975 • *Radiation enterocolitis* occurs when the GI tract is irradiated. In addition to epithelial damage, radiation-induced vascular injury may be significant and produce changes that are similar to ischemic disease. Beyond clinical history, the presence of highly atypical "radiation fibroblasts" within the stroma may provide an important clue to the etiology. Acute radiation enteritis manifests as anorexia, abdominal cramps, and malabsorptive diarrhea, while chronic radiation enteritis or colitis is often more indolent and may present as an inflammatory entero colitis.

u0980 • *Necrotizing enterocolitis* (NEC) is an acute disorder of the small and large intestines that can result in transmural necrosis. It is the most common acquired GI emergency of neonates, particularly those who are premature or of low birth weight, and frequently presents when oral feeding is initiated. NEC is discussed in more detail in Chapter 10, but is noted here because ischemic injury is thought to contribute to the pathogenesis.

Angiodysplasia s0635

p1940 Angiodysplasia, a lesion characterized by malformed submucosal and mucosal blood vessels, occurs most often in the cecum or right colon and usually presents after the sixth decade of life. Although the prevalence of angiodysplasia is less than 1% in the adult population, it accounts for 20% of major episodes of lower intestinal bleeding; intestinal hemorrhage may be chronic and intermittent or acute and massive.

p1945 The pathogenesis of angiodysplasia remains undefined but has been attributed to mechanical and congenital factors. Normal distention and contraction may intermittently occlude the submucosal veins that penetrate through the muscularis propria and can lead to focal dilation and tortuosity of overlying submucosal and mucosal vessels. Because the cecum has the largest diameter of

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

any colonic segment, it develops the greatest wall tension. This may explain the preferential distribution of angiodysplastic lesions in the cecum and right colon. Finally, some data link angiodysplasia with Meckel diverticulum, suggesting the possibility of a developmental component.

p1950 Morphologically, angiodysplastic lesions are characterized by ectatic nests of tortuous veins, venules, and capillaries. The vascular channels may be separated from the intestinal lumen by only the vascular wall and a layer of attenuated epithelial cells; limited injury may therefore result in significant bleeding.

s0640 Malabsorption and Diarrhea

p1955 **Malabsorption, which presents most commonly as chronic diarrhea, is characterized by defective absorption of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes and minerals, and water.** Chronic malabsorption can be accompanied by weight loss, anorexia, abdominal distention, borborygmi, and muscle wasting. A hallmark of malabsorption is *steatorrhea*, characterized by excessive fecal fat and bulky, frothy, greasy, yellow or clay-colored stools. The chronic malabsorptive disorders most commonly encountered in the United States are pancreatic insufficiency, celiac disease, and Crohn disease (Table 17-7). Intestinal graft-versus-host disease is an important cause of malabsorption and diarrhea after allogeneic hematopoietic stem cell transplantation.

p1960 *Malabsorption results from disturbance in at least one of the four phases of nutrient absorption:*

u9085 • *Intraluminal digestion,* in which proteins, carbohydrates, and fats are broken down into forms suitable for absorption;

u9090 • *Terminal digestion,* which involves the hydrolysis of carbohydrates and peptides by disaccharidases and peptidases in the brush border of the small intestinal mucosa;

u9095 • *Transepithelial transport,* in which nutrients, fluid, and electrolytes are transported across and processed within the small intestinal epithelium; and

u9170 • *Lymphatic transport of absorbed lipids.*

p1965 In many malabsorptive disorders a defect in one of these processes predominates, but more than one usually contributes. As a result, malabsorption syndromes resemble each other more than they differ. General symptoms include diarrhea (from nutrient malabsorption and excessive intestinal secretion), flatus, abdominal pain, and weight loss. Inadequate absorption of vitamins and minerals can result in anemia and mucositis due to pyridoxine, folate, or vitamin B_{12} deficiency; bleeding, due to vitamin K deficiency; osteopenia and tetany due to calcium, magnesium, or vitamin D deficiencies; or peripheral neuropathy due to vitamin A or B_{12} deficiencies. A variety of endocrine and skin disturbances may also occur.

p1970 *Diarrhea is defined as an increase in stool mass, frequency, or fluidity, typically greater than 200 gm per day*. In severe cases stool volume can exceed 14 L per day and, without fluid resuscitation, result in death. Painful, bloody, small-volume diarrhea is known as *dysentery*. Diarrhea can be classified into four major categories:

u0985 • *Secretory diarrhea* is characterized by isotonic stool and persists during fasting.

u0990 • *Osmotic diarrhea*, such as that which occurs with lactase deficiency, is due to the excessive osmotic forces exerted by unabsorbed luminal solutes. The diarrhea fluid is more than 50 mOsm more concentrated than plasma and abates with fasting.

u0995 • *Malabsorptive diarrhea* follows generalized failure of nutrient absorption, is associated with steatorrhea, and is relieved by fasting.

u1000 • *Exudative diarrhea* due to inflammatory disease is characterized by purulent, bloody stools that continue during fasting.

t0035 **Table 17-7** Defects in Malabsorptive and Diarrheal Disease

Disease	Intraluminal Digestion	Terminal Digestion	Transepithelial Transport	Lymphatic Transport
Celiac disease		+	+	
Environmental enteropathy		+	+	
Chronic pancreatitis	+			
Cystic fibrosis	+			
Primary bile acid malabsorption	+		+	
Carcinoid syndrome			+	
Autoimmune enteropathy		+	+	
Disaccharidase deficiency		+		
Whipple disease				+
Abetalipoproteinemia			+	
Viral gastroenteritis		+	+	
Bacterial gastroenteritis		+	+	
Parasitic gastroenteritis		+	+	
Inflammatory bowel disease	+	+	+	

+ indicates that the process is abnormal in the disease indicated. Other processes are not affected.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

s0645 Cystic Fibrosis

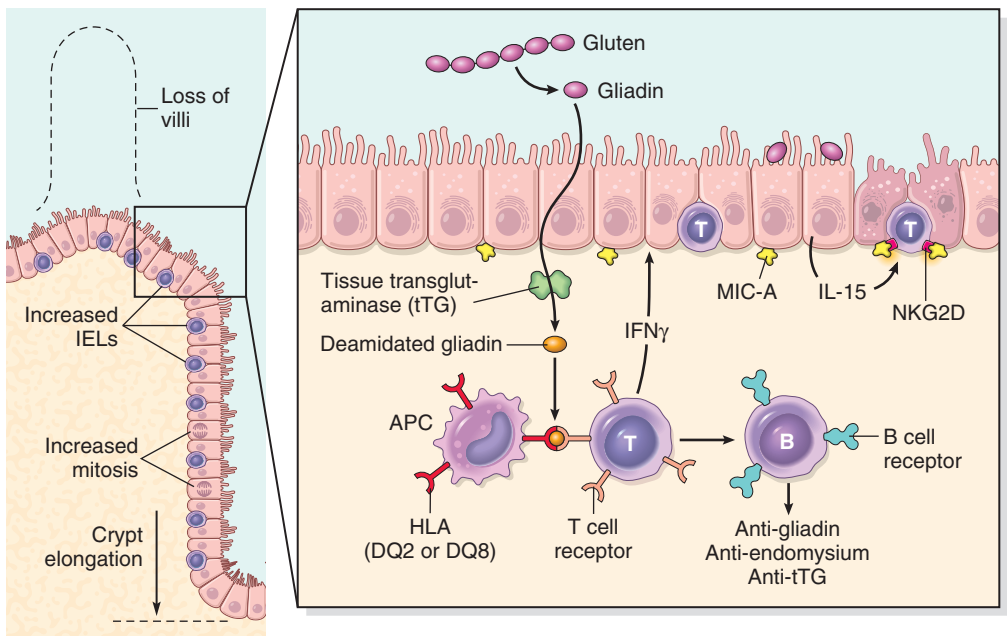
p1995 Cystic fibrosis affects many organ systems, primarily the lungs, and is discussed in greater detail elsewhere (Chapter 10). Only the malabsorption associated with cystic fibrosis is considered here. Due to the absence of the epithelial cystic fibrosis transmembrane conductance regulator (CFTR), individuals with cystic fibrosis have defects in chloride and, in certain tissues, bicarbonate ion secretion. This interferes with bicarbonate, sodium, and water secretion, ultimately resulting in defective luminal hydration. Reduced hydration can occasionally lead to intestinal obstruction, but commonly results in formation of pancreatic intraductal concretions. The latter can begin in utero, and result in duct obstruction, low-grade chronic autodigestion of the pancreas, and eventual exocrine pancreatic insufficiency in more than 80% of patients. The result is failure of the intraluminal phase of nutrient absorption, which can be effectively treated in most patients with oral enzyme supplementation.

s0650 Celiac Disease

p2000 **Celiac disease is also known as celiac sprue or gluten-sensitive enteropathy. It is an immune-mediated enteropathy triggered by the ingestion of gluten-containing foods, such as wheat, rye, or barley, in genetically predisposed individuals.** Celiac disease has an overall worldwide incidence of 0.6% to 1%, but its prevalence varies widely between countries and regions. Some of these differences correlate with variation in wheat consumption, but the reasons for other disparities are not defined. While previously uncommon, the incidence of celiac disease in developing countries is growing, possibly as a result of adoption of Western diets.

Pathogenesis. Celiac disease is triggered by ingestion of gluten, which is the major storage protein of wheat and similar grains. The alcohol-soluble fraction of gluten, *gliadin*, contains most of the disease-producing components. Gluten is digested by luminal and brush-border enzymes into amino acids and peptides, including a 33-amino acid α-gliadin peptide that is resistant to degradation by gastric, pancreatic, and small intestinal proteases (Fig. 17-25). Some gliadin peptides may induce epithelial cells to express IL-15, which in turn triggers activation and proliferation of CD8+ intraepithelial lymphocytes. These lymphocytes express NKG2D, a natural killer cell marker and receptor for MIC-A. Enterocytes that have been induced to express surface MIC-A, in response to stress, are then attacked by NKG2D-expressing intraepithelial lymphocytes. The resulting epithelial damage may enhance passage of other gliadin peptides into the lamina propria where they are deamidated by tissue transglutaminase. These gliadin peptides interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and, in turn, can stimulate CD4+ T cells to produce cytokines that contribute to tissue damage. s0655 p2005

While nearly all people eat grain and are exposed to gluten and gliadin, most do not develop celiac disease. Thus, host factors determine whether disease develops. Among these, HLA proteins seem to be critical, since almost all people with celiac disease carry the class II HLA-DQ2 or HLA-DQ8 allele. However, the HLA locus accounts for less than half of the genetic component of celiac disease. Remaining genetic factors may include polymorphisms of genes involved in immune regulation and epithelial function. These genetic variables may also contribute to associations between celiac disease and other immune diseases, including type 1 diabetes, thyroiditis, and Sjögren syndrome, IgA nephropathy, as well as neu- p2010



f0130

Figure 17-25 The left panel illustrates the morphologic alterations that may be present celiac disease, including villous atrophy, increased numbers of intraepithelial lymphocytes (IELs), and epithelial proliferation with crypt elongation (compare to Fig. 17-26). The right panel depicts a model for the pathogenesis of celiac disease. Note that both innate (CD8+ intraepithelial T cells, activated by IL 15) and adaptive (CD4+ T cells, and B cells sensitization to gliadin) immune mechanisms are involved in the tissue responses to gliadin.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

rologic disorders, such as ataxia, autism, depression, epilepsy, Down syndrome, and Turner syndrome.

b0135 ## MORPHOLOGY

p2015 Biopsy specimens from the second portion of the duodenum or proximal jejunum, which are exposed to the highest concentrations of dietary gluten, are generally diagnostic in celiac disease. The histopathology is characterized by increased numbers of intraepithelial CD8+ T lymphocytes (intraepithelial lymphocytosis), crypt hyperplasia, and villous atrophy (Fig. 17-26). This loss of mucosal and brush-border surface area probably accounts for the malabsorption. In addition, increased rates of epithelial turnover, reflected in increased crypt mitotic activity, may limit the ability of absorptive enterocytes to fully differentiate and express proteins necessary for terminal digestion and transepithelial transport. Other features of fully developed celiac disease include increased numbers of plasma cells, mast cells, and eosinophils, especially within the upper part of the lamina propria. With increased frequency of serologic screening and early detection of disease-associated antibodies, it is now appreciated that an increase in the number of intraepithelial lymphocytes, particularly within the villus, is a sensitive marker of celiac disease, even in the absence of epithelial damage and villous atrophy. However, intraepithelial lymphocytosis and villous atrophy are not specific for celiac disease and can be present in other diseases, including viral enteritis. The combination of histology and serology, therefore, is most specific for diagnosis of celiac disease.

p2020 Adherence to a gluten-free diet typically results in resolution of symptoms, decreasing titers of anti-tissue transglutaminase or other celiac disease-associated antibodies, and restoration of normal or near normal mucosal histology within 6 to 24 months.

s0670 p2025 ***Clinical Features.*** In adults, celiac disease presents most commonly between the ages of 30 and 60. Many cases of celiac disease escape clinical attention for extended periods because of atypical presentations. Other patients may have silent celiac disease, defined as positive serology and villous atrophy without symptoms, or latent celiac disease, in which positive serology is not accompanied by villous atrophy. Celiac disease may be associated with chronic diarrhea, bloating, or chronic fatigue, but is often asymptomatic. These cases may present with anemia due to chronic iron and vitamin malabsorption. In adults, celiac disease is detected twice as frequently in women, perhaps because monthly menstrual bleeding accentuates the effects of impaired absorption.

p2030 Pediatric celiac disease, which affects males and females equally, may present with malabsorption or atypical symptoms affecting almost any organ. In those with classic symptoms, disease typically begins after introduction of gluten to the diet, between ages of 6 and 24 months, and manifests as irritability, abdominal distention, anorexia, chronic diarrhea, failure to thrive, weight loss, or muscle wasting. Children with nonclassic symptoms tend to present at older ages with complaints of abdominal pain, nausea, vomiting, bloating, or constipation. Common extraintestinal complaints include arthritis or joint pain, aphthous stomatitis, iron deficiency anemia, delayed puberty, and short stature.

p2035 A characteristic itchy, blistering skin lesion, dermatitis herpetiformis (Chapter 25), can be present in as many as 10% of patients. Unfortunately, the only treatment currently available for celiac disease is a gluten-free diet. While adhering to this diet can be challenging, it does result in symptomatic improvement for most patients. A gluten-free diet may also reduce the risk of long-term complications including anemia, female infertility, osteoporosis, and cancer (discussed bellow).

p2040 Noninvasive serologic tests are generally performed prior to biopsy. The most sensitive tests are the measurement of IgA antibodies against tissue transglutaminase. IgA anti-endomysial antibodies can also be present. IgG anti-tissue transglutaminase antibodies may be detected in patients with IgA deficiency. The absence of HLA-DQ2 and HLA-DQ8 is useful for its high negative predictive value, but the presence of these alleles is not helpful in confirming the diagnosis.

p2045 *Individuals with celiac disease have a higher than normal rate of malignancy.* The most common celiac disease-associated cancer is enteropathy-associated T-cell lymphoma, an aggressive lymphoma of intraepithelial T lymphocytes. Small intestinal adenocarcinoma is also more frequent in individuals with celiac disease. Thus, when symptoms such as abdominal pain, diarrhea, and weight loss develop despite a strict gluten-free diet, cancer or refractory sprue, in which the response to a gluten-free diet is lost, must be considered.

f0135

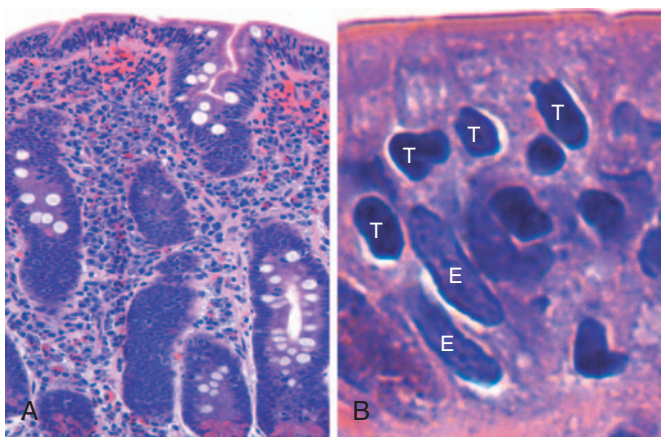


Figure 17-26 Celiac disease. **A,** Advanced cases of celiac disease show complete loss of villi, or total villous atrophy. Note the dense plasma cell infiltrates in the lamina propria. **B,** Infiltration of the surface epithelium by T lymphocytes, which can be recognized by their densely stained nuclei (labelled **T**). Compare to elongated, pale-staining epithelial nuclei (labeled **E**).

Environmental Enteropathy s0675

p2055 *Environmental enteropathy*, which has also been referred to as *tropical enteropathy* or *tropical sprue*, is a disorder prevalent in areas and populations with poor sanitation and hygiene, such as those in developing countries, including many parts of sub-Saharan Africa, such as Gambia; aboriginal populations within northern Australia; and some groups within South America and Asia, such as residents of impoverished communities within Brazil, Guatemala, India, and Pakistan. Affected individuals often suffer from malabsorption and malnutrition, stunted growth, and

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

defective intestinal mucosal immune function. The relatively high oral vaccine failure rates in regions where environmental enteropathy is endemic has been proposed to be due to defective mucosal immune function.

p9260 There are presently no accepted clinical, laboratory, or histopathologic criteria that allow diagnosis of environmental enteropathy. Intestinal biopsy specimens have been examined in a small number of cases, and reported histologic features are more similar to severe celiac disease than infectious enteritis.

p2060 The underlying causes of environmental enteropathy are unknown, but defective intestinal barrier function, chronic exposure to fecal pathogens and other microbial contaminants, and repeated bouts of diarrhea within the first 2 or 3 years of life are likely involved. Many pathogens are endemic in these communities, but no single infectious agent has been linked to environmental enteropathy. Neither oral antibiotics nor nutritional supplementation, with calorie-dense foods, vitamins, or minerals, are able to correct these deficits. Moreover, recent data suggest that irreversible losses in physical development may be accompanied by uncorrectable cognitive deficits. Thus, the global impact of environmental enteropathy, which is estimated to affect more than 150 million children worldwide and may contribute to a very large number of childhood deaths, is difficult to overstate.

s0680 Autoimmune Enteropathy

p2065 **Autoimmune enteropathy is an X-linked disorder characterized by severe persistent diarrhea and autoimmune disease that occurs most often in young children.** A particularly severe familial form, termed *IPEX*, an acronym denoting immune dysregulation, polyendocrinopathy, enteropathy, and X-linkage, is due to a germline mutation in the *FOXP3* gene, which is located on the X chromosome. FOXP3 is a transcription factor expressed in CD4+ regulatory T cells, and individuals with IPEX and *FOXP3* mutations have defective function of these cells. Other defects in regulatory T cell function have also been linked to less severe forms of autoimmune enteropathy. Autoantibodies to enterocytes and goblet cells are common, and some patients may have antibodies to parietal or islet cells. Within the small intestine, intraepithelial lymphocytes may be increased, but not to the extent seen in celiac disease, and neutrophils are often present. Therapy includes immunosuppressive drugs such as cyclosporine and, in rare cases, hematopoietic stem cell transplantation.

s0685 Lactase (Disaccharidase) Deficiency

p2070 The disaccharidases, including lactase, are located in the apical brush-border membrane of the villus absorptive epithelial cells. Because the defect is biochemical, biopsy histology is generally unremarkable. Lactase deficiency is of two types:

u1005 • *Congenital lactase deficiency*, caused by a mutation in the gene encoding lactase, is an autosomal recessive disorder. The disease is rare and presents as explosive diarrhea with watery, frothy stools and abdominal distention upon milk ingestion. Symptoms abate when exposure to milk and milk products is terminated, thus removing the osmotically active but unabsorbable lactose from the lumen. As a result, congenital lactase deficiency was often fatal prior to the availability of soy-based infant formula.

u1010 • *Acquired lactase deficiency* is caused by down-regulation of lactase gene expression and is particularly common among Native American, African American, and Chinese populations. Acquired lactase deficiency can develop following enteric viral or bacterial infections and may resolve over time. Symptoms of acquired lactase deficiency, including abdominal fullness, diarrhea, and flatulence, due to fermentation of the unabsorbed sugars by colonic bacteria, are triggered by ingestion of lactose-containing dairy products.

Abetalipoproteinemia s0690

p2085 **Abetalipoproteinemia is a rare autosomal recessive disease characterized by an inability to secrete triglyceride-rich lipoproteins.** It is caused by a mutation in the microsomal triglyceride transfer protein (MTP) that catalyzes transfer of lipids to specialized domains of the nascent apolipoprotein B polypeptide within the rough endoplasmic reticulum. MTP also promotes production of triglyceride droplets within the smooth endoplasmic reticulum. Without MTP, enterocytes cannot assemble or export lipoproteins. This results in intracellular lipid accumulation. The malabsorption of abetalipoproteinemia is therefore a failure of intraepithelial processing and transport. Because of the triglyceride accumulation, vacuolization of small intestinal epithelial cells is evident and can be highlighted by special stains, such as oil red-O, particularly after a fatty meal.

p2090 Abetalipoproteinemia presents in infancy and the clinical picture is dominated by failure to thrive, diarrhea, and steatorrhea. Patients also have a complete absence of all plasma lipoproteins containing apolipoprotein B, although the gene that encodes apolipoprotein B itself is not affected. Failure to absorb essential fatty acids leads to deficiencies of fat-soluble vitamins as well as lipid membrane defects that can be recognized by the presence of *acanthocytic red cells (burr cells)* in peripheral blood smears.

KEY CONCEPTS b9000

Congenital and acquired (non infectious) disorders of the intestines s9025

- **Abdominal hernias** may occur through any weakness or defect in the wall of the peritoneal cavity, including inguinal and femoral canals, the umbilicus, and sites of surgical scars. p9245
- **Intussusception** occurs when a segment of intestine telescopes into the immediately distal segment. It is the most common cause of intestinal obstruction in children younger than 2 years of age. u9105
- **Ischemic bowel disease** of the colon is most common at the splenic flexure, sigmoid colon, and rectum; these u9110

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

are watershed zones where two arterial circulations terminate.

u9115 ■ **Angiodysplasia** is a malformation of submucosal and mucosal blood vessels and a common cause of lower intestinal bleeding in those older than 60 years of age.

u9120 ■ **Diarrhea** can be characterized as secretory, osmotic, malabsorptive, or exudative.

u9125 ■ The malabsorption associated with **cystic fibrosis** is the result of pancreatic insufficiency, leading to inadequate pancreatic digestive enzymes, and deficient luminal breakdown of nutrients.

u9130 ■ **Celiac disease** is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains. The malabsorptive diarrhea in celiac disease is due to loss of brush border surface area, including villous atrophy, and, possibly, deficient enterocyte maturation as a result of immune-mediated epithelial damage.

u9135 ■ **Environmental enteropathy** is prevalent in areas with poor sanitation. It is estimated to affect more than 150 million children worldwide and may contribute to a very large number of childhood deaths.

u9140 ■ **Lactase deficiency** causes an osmotic diarrhea due to the inability to break down or absorb lactose. The autosomal recessive form is rare and severe; the acquired form usually presents in adulthood and is common.

u9175 ■ **Autoimmune enteropathy** is an X-linked disorder characterized by severe persistent diarrhea and autoimmune disease that is caused by mutation in *FOXP3* gene, resulting in defective function of regulatory T cells.

u9145 ■ **Abetalipoproteinemia** is a rare autosomal recessive disease due to a mutation in microsomal triglyceride transfer protein that is required for enterocytes to process and secrete triglyceride-rich lipoproteins.

s0695 Infectious Enterocolitis

p2095 *Enterocolitis can present with a broad range of symptoms including diarrhea, abdominal pain, urgency, perianal discomfort, incontinence, and hemorrhage* (Table 17-8). This global problem is responsible for more than 2000 deaths each day among children in developing countries and greater than 10% of all deaths before age 5 worldwide. Bacterial infections, such as enterotoxigenic *Escherichia coli*, are frequently responsible, but the etiology varies with age, nutrition, and host immune status as well as environmental influences (Table 17-8). For example, epidemics of cholera are common in areas with poor sanitation, as a result of inadequate public health measures, natural disasters, such as floods and earthquakes, or war. Pediatric infectious diarrhea, which may result in severe dehydration and metabolic acidosis, is commonly caused by enteric viruses.

s0700 Cholera

p2100 ***Vibrio cholerae* are comma-shaped, gram-negative bacteria that cause cholera, a disease that has been endemic in the Ganges Valley of India and Bangladesh** for almost all of recorded history. Since 1817, seven great pandemics have spread along trade routes to large parts of Europe, Australia, and the Americas, but, for unknown reasons these pandemics resolved and cholera retreated back to the Ganges Valley. Cholera also persists within the Gulf of Mexico but causes only rare cases of seafood-associated disease; this occurs because shellfish and plankton can be reservoirs of *Vibrio* bacteria.

p2105 There is a marked seasonal variation in the incidence of cholera in most climates due to rapid growth of *Vibrio* bacteria at warm temperatures. While the bacteria can be present in food, the infection is primarily transmitted by contaminated drinking water. Thus, cholera can become rampant in areas devastated by natural or man-made disasters, such as earthquakes or war, that threaten sewage systems and drinking water supplies. For example, the January 2010 Haitian earthquake led to a cholera epidemic that began in October 2010. At the end of the first year, more than 5% of the population was affected. More than half of the cases required hospitalization and approximately 1% were fatal. In all, the cholera epidemic in Haiti accounted for more than half of worldwide cholera cases and deaths reported to the World Health Organization in 2010 and 2011.

s0705 p2110 ***Pathogenesis.*** *Despite the severe diarrhea, Vibrio organisms are noninvasive and remain within the intestinal lumen.* While cholera toxin, encoded by a virulence phage and released by the *Vibrio* organism, causes disease, the flagellar proteins, which are involved in motility and attachment, are necessary for efficient bacterial colonization. Hemagglutinin, a metalloproteinase, is important for bacterial detachment and shedding in the stool. The mechanism by which cholera toxin induces diarrhea is well understood (Fig. 17-27). Cholera toxin is composed of five B subunits and a single A subunit. The B subunit binds GM1 ganglioside on the surface of intestinal epithelial cells, and is carried by endocytosis to the endoplasmic reticulum, a process called retrograde transport. Here, the A subunit is reduced by protein disulfide isomerase, and a fragment of the A subunit is unfolded and released. This peptide fragment is then transported into the cytosol using host cell machinery that moves misfolded proteins from the endoplasmic reticulum to the cytosol. Such unfolded proteins are normally disposed of via the proteasome, but the A subunit refolds to avoid degradation. The refolded A subunit peptide then interacts with cytosolic ADP ribosylation factors (ARFs) to ribosylate and activate the stimulatory G protein $G_s\alpha$. This stimulates adenylate cyclase and the resulting increase in intracellular cAMP opens the cystic fibrosis transmembrane conductance regulator, CFTR, which releases chloride ions into the lumen. Chloride and sodium absorption are also inhibited by cAMP. The resulting accumulation of chloride, bicarbonate, and sodium within the intestinal lumen creates an osmotic driving force that draws water into the lumen and causes massive diarrhea. Remarkably, mucosal biopsies show only minimal histologic alterations.

s0720 p2115 ***Clinical Features.*** Most individuals exposed to *V. cholerae* are asymptomatic or develop only mild diarrhea. In those with severe disease there is an abrupt onset of watery diarrhea and vomiting following an incubation period of 1 to 5 days. The voluminous stools resemble rice water and are sometimes described as having a fishy odor. The rate of diarrhea may reach 1 liter per hour, leading to

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

t0040 **Table 17-8** Features of Bacterial Enterocolitides

Infection Type	Geography	Reservoir	Transmission	Epidemiology	Affected GI Sites	Symptoms	Complications
Cholera	India, Africa	Shellfish	Fecal-oral, water	Sporadic, endemic, epidemic	Small intestine	Severe watery diarrhea	Dehydration, electrolyte imbalances
Campylobacter spp.	Developed countries	Chickens, sheep, pigs, cattle	Poultry, milk, other foods	Sporadic; children, travelers	Colon	Watery or bloody diarrhea	Arthritis, Guillain-Barré syndrome
Shigellosis	Worldwide, endemic in developing countries	Humans	Fecal-oral, food, water	Children, migrant workers, travelers,nursing homes	Left colon, ileum	Bloody diarrhea	Reactive arthritis, urethritis, conjunctivitis, hemolytic-uremic syndrome
Salmonellosis	Worldwide	Poultry, farm animals, reptiles	Meat, poultry, eggs, milk	Children, older adults	Colon and small intestine	Watery or bloody diarrhea	Sepsis, abscess
Enteric (typhoid) fever	India, Mexico, Philippines	Humans	Fecal-oral, water	Children. adolescents, travelers	Small intestine	Bloody diarrhea, fever	Chronic infection, carrier state, encephalopathy, myocarditis, intestinal perforation
Yersinia spp.	Northern and central Europe	Pigs, cows, puppies, cats	Pork, milk, water	Clustered cases	Ileum, appendix, right colon	Abdominal pain, fever, diarrhea	Reactive arthritis, erythema nodosum
Escherichia coli							
Enterotoxigenic (ETEC)	Developing countries	Unknown	Food or fecal-oral	Infants, adolescents, travelers	Small intestine	Severe watery diarrhea	Dehydration, electrolyte imbalances
Enteropathogenic (EPEC)	Worldwide	Humans	Fecal-oral	Infants	Small intestine	Watery diarrhea	Dehydration, electrolyte imbalances
Enterohemorrhagic (EHEC)	Worldwide	Widespread, includes cattle	Beef, milk, produce	Sporadic and epidemic	Colon	Bloody diarrhea	Hemolytic-uremic syndrome
Enteroinvasive (EIEC)	Developing countries	Unknown	Cheese, other foods, water	Young children	Colon	Bloody diarrhea	Unknown
Enteroaggregative (EAEC)	Worldwide	Unknown	Unknown	Children, adults, travelers	Colon	Nonbloody diarrhea, afebrile	Poorly defined
Pseudomembranous colitis (*C. difficile*)	Worldwide	Humans, hospitals	Antibiotics allow emergence	Immunosuppressed, antibiotic-treated	Colon	Watery diarrhea, fever	Relapse, toxic megacolon
Whipple disease	Rural > urban	Unknown	Unknown	Rare	Small intestine	Malabsorption	Arthritis, CNS disease
Mycobacterial infection	Worldwide	Unknown	Unknown	Immunosuppressed, endemic	Small intestine	Malabsorption	Pneumonia, infection at other sites

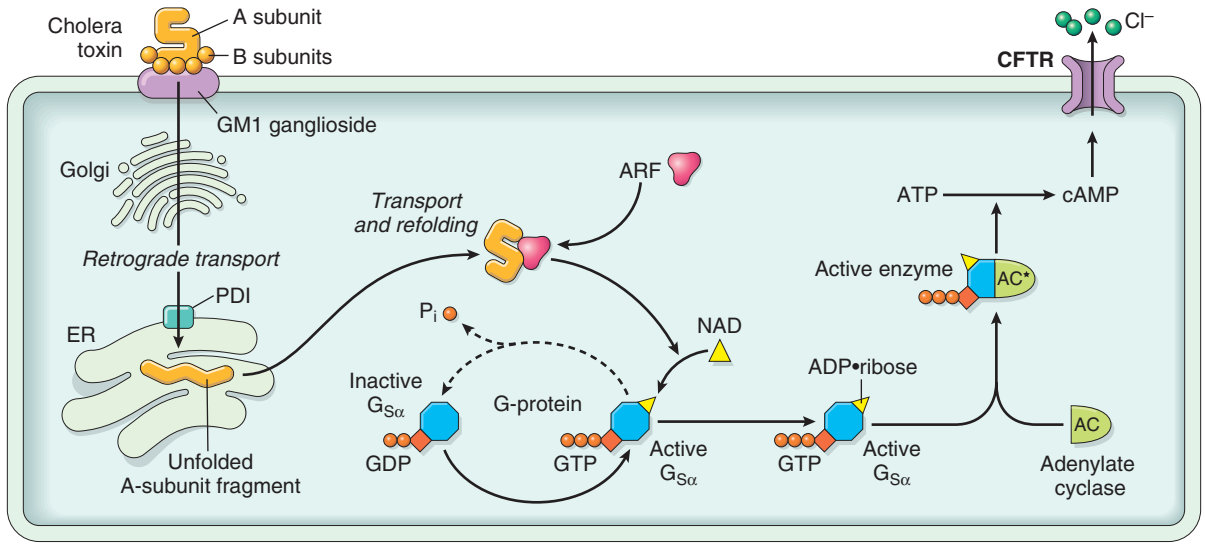
CNS, Central nervous system; GI, gastrointestinal.

dehydration, hypotension, muscular cramping, anuria, shock, loss of consciousness, and death. Most deaths occur within the first 24 hours after presentation. Although the mortality for severe cholera is about 50% without treatment, timely fluid replacement can save more than 99% of patients. Oral rehydration is often sufficient. Because of an improved understanding of the host and *Vibrio* proteins involved, new therapies are being developed, including CFTR inhibitors that block chloride secretion and prevent diarrhea. Prophylactic vaccination is a long-term goal, and data from trials of new cholera vaccines have prompted the WHO to recommend vaccination with other prevention and control strategies in endemic regions and during outbreaks. However, it should be noted that variant strains that cause more severe clinical disease may be displacing earlier strains as the major cause of disease. Thus, vaccines may need to be modified to keep pace with changes in pathogenic cholera strains.

Campylobacter Enterocolitis s0725

***Campylobacter jejuni* is the most common bacterial enteric pathogen in developed countries and is an important cause of traveler's diarrhea.** Most infections are associated with ingestion of improperly cooked chicken, but outbreaks can also be caused by unpasteurized milk or contaminated water. It is an important bacterial cause of food poisoning. p2120

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0140

Figure 17-27 Cholera toxin transport and signaling. After retrograde toxin transport to the endoplasmic reticulum (ER), the A subunit is released by the action of protein disulfide isomerase (PDI) and is then able to access the epithelial cell cytoplasm. In concert with an ADP-ribosylation factor (ARF), the A subunit then ADP-ribosylates $G_s\alpha$, which locks it in the active, GTP-bound state. This leads to adenylate cyclase (AC) activation, and the cAMP produced opens CFTR to drive chloride secretion and diarrhea.

s0730 ***Pathogenesis.*** The pathogenesis of *Campylobacter* infection p2125 remains poorly defined, but the four major properties that contribute to virulence are: motility, adherence, toxin production, and invasion. Flagella allow *Campylobacter* to be motile. This facilitates adherence and colonization, which are necessary for mucosal invasion. Cytotoxins that cause epithelial damage and a cholera toxin-like enterotoxin are also released by some *C. jejuni* isolates. Dysentery, i.e. bloody diarrhea, is generally associated with invasion and only occurs with a small minority of *Campylobacter* strains. Enteric fever occurs when bacteria proliferate within the lamina propria and mesenteric lymph nodes.

p2130 *Campylobacter infection can result in reactive arthritis, primarily in patients with HLA-B27.* Other extraintestinal complications, including erythema nodosum and Guillain-Barré syndrome, a flaccid paralysis caused by immunologically mediated inflammation of peripheral nerves, are not HLA-linked (Chapter 27). Molecular mimicry has been implicated in the pathogenesis of Guillain-Barré syndrome, as serum antibodies to *C. jejuni* lipopolysaccharide cross-react with peripheral and central nervous system gangliosides. Up to 40% of Guillain-Barré syndrome cases are associated with *Campylobacter* infection in the preceding 1 to 2 weeks and up to 50% have positive stool cultures or circulating antibodies to *Campylobacter*. Guillain-Barré syndrome develops in 0.1% or less of those infected with *Campylobacter*.

b0140 ## MORPHOLOGY

p2135 *Campylobacter* are comma-shaped, flagellated, gram-negative organisms. Diagnosis is primarily by stool culture, since biopsy findings are nonspecific, and reveal acute self-limited colitis with features common to many forms of infectious colitis. Mucosal and intraepithelial neutrophil infiltrates are prominent, particularly within the superficial mucosa (Fig. 17-28*A*); cryptitis (neutrophil infiltration of the crypts) and crypt abscesses (crypts with accumulations of luminal neutrophils) may also be present. Importantly, crypt architecture is preserved (Fig. 17-28*D*), although this can be difficult to assess in cases with severe mucosal damage.

s0745 ***Clinical Features.*** Ingestion of as few as 500 *C. jejuni* p2140 organisms can cause disease after an incubation period of up to 8 days. Watery diarrhea, either acute or following an influenza-like prodrome, is the primary symptom, but dysentery develops in 15% of adults and more than 50% of children. Patients may shed bacteria for 1 month or more after clinical resolution. Antibiotic therapy is generally not required.

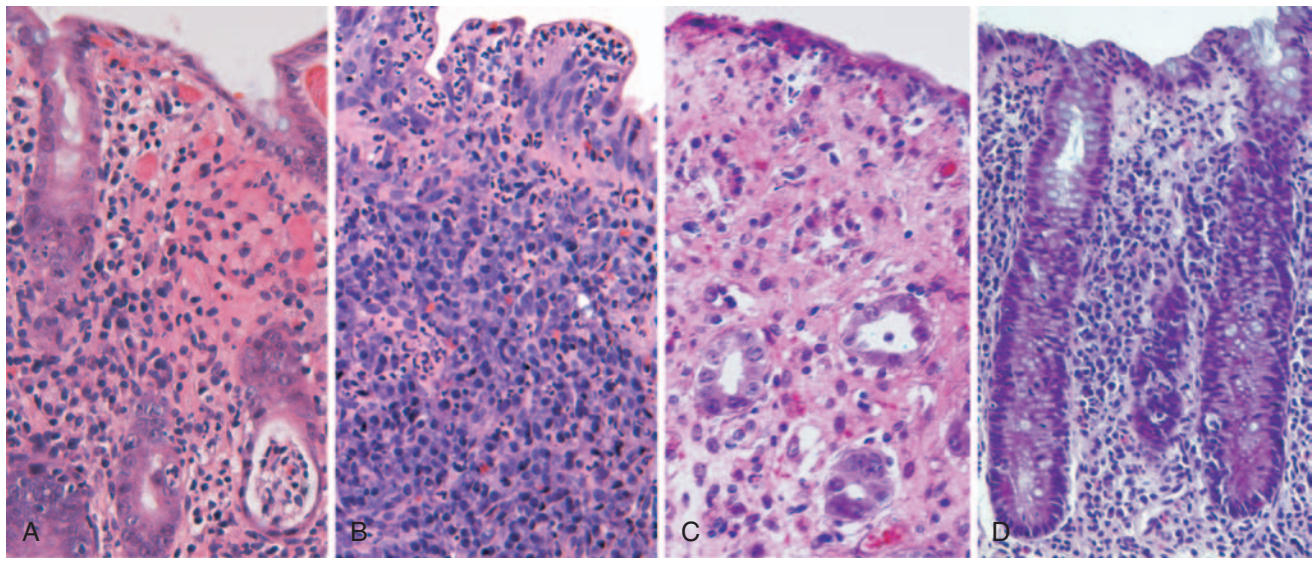
Shigellosis

s0750

p2145 *Shigella are gram-negative unencapsulated, nonmotile, facultative anaerobes that belong to the Enterobacteriaceae family and are closely related to enteroinvasive E. coli.* Although humans are the only known reservoir, *Shigella* spp. remain one of the most common causes of bloody diarrhea. It is estimated that 165 million cases occur worldwide each year. Given the infective dose of fewer than several hundred organisms and the presence of as many as 10^9 organisms in each gram of stool during acute disease, *Shigella* are highly transmissible by the fecal-oral route or via contaminated water and food.

p2150 In the United States and Europe, children in daycare centers, migrant workers, travelers to developing countries, and those in nursing homes are most commonly affected. Most *Shigella* infections and deaths occur in children younger than 5 years of age. In countries where *Shigella* is endemic it is responsible for approximately 10% of pediatric diarrheal disease and as many as 75% of diarrheal deaths.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0145

Figure 17-28 Bacterial enterocolitis. **A,** *Campylobacter jejuni* infection produces acute, self-limited colitis. Neutrophils can be seen within the surface and crypt epithelia and a crypt abscess is present at the lower right. **B,** In *Yersinia* infection the surface epithelium can be eroded by neutrophils and the lamina propria is densely infiltrated by sheets of plasma cells admixed with lymphocytes and neutrophils. **C,** Enterohemorrhagic *E. coli* O157:H7 results in an ischemia-like morphology with surface atrophy and erosion. **D,** Enteroinvasive *E. coli* infection is similar to other acute, self-limited colitides such as those caused by *Campylobacter jejuni*. Note the maintenance of normal crypt architecture and spacing, despite abundant intraepithelial neutrophils.

s0755 p2155 ***Pathogenesis.*** *Shigella are resistant to the harsh acidic environment of the stomach, thereby explaining the extremely low infective dose.* Once in the intestine, organisms are taken up by M, or microfold cells. These are epithelial cells, which are specialized for sampling and presentation of luminal antigens. *Shigella* proliferate intracellularly, escape into the lamina propria, and are phagocytosed by macrophages, in which they induce apoptosis. The ensuing inflammatory response damages surface epithelia and allows *Shigella* within the intestinal lumen to gain access to the basolateral membranes of colonic epithelial cells, which is the preferred domain for invasion. All *Shigella* spp. carry virulence plasmids, some of which encode a type III secretion system capable of directly injecting bacterial proteins into the host cytoplasm. *S. dysenteriae* serotype 1 also release the Shiga toxin Stx, which inhibits eukaryotic protein synthesis, resulting in host cell damage and death.

b0145 **MORPHOLOGY**

p2160 *Shigella* infections are most prominent in the left colon, but the ileum may also be involved, perhaps reflecting the abundance of M cells in the dome epithelium over the Peyer patches. The mucosa is hemorrhagic and ulcerated, and pseudomembranes may be present. The histology of early cases is similar to other acute self-limited colitides, such as *Campylobacter* colitis, but because of the tropism for M cells, aphthous-appearing ulcers similar to those seen in Crohn disease may occur. The potential for confusion with chronic inflammatory bowel disease is significant, particularly if there is distortion of crypt architecture.

s0770 p2165 ***Clinical Features.*** After an incubation period of up to 1 week, *Shigella* causes self-limited disease characterized by about 1 week of diarrhea, fever, and abdominal pain. The initially watery diarrhea progresses to a dysenteric phase in approximately 50% of patients, and constitutional symptoms can persist for as long as 1 month. The subacute presentation that develops in a minority of adults is characterized by several weeks of waxing and waning diarrhea that can mimic new-onset ulcerative colitis. While duration is typically shorter in children, severity is often much greater. Confirmation of *Shigella* infection requires stool culture.

Complications of *Shigella* infection are uncommon and include a triad of sterile reactive arthritis, urethritis, and conjunctivitis that preferentially affects HLA-B27-positive men between 20 and 40 years of age. Hemolytic-uremic syndrome, which is typically associated with *enterohemorrhagic E. coli* (EHEC), may also occur after infection with *S. dysenteriae* serotype 1 that secrete Shiga toxin (Chapter 20). Toxic megacolon and intestinal obstruction are uncommon complications. Antibiotic treatment shortens the clinical course and reduces the duration of organism shedding in stools, but antidiarrheal medications are contraindicated because they can prolong symptoms and delay *Shigella* clearance. p2170

Salmonella s0775

Salmonella, which are classified within the Enterobacteriaceae family of gram-negative bacilli, are divided into *Salmonella typhi*, the causative agent of typhoid fever (discussed in the next section) and nontyphoid *Salmonella*. The latter are the causative agent of salmonellosis, which is usually due to *S. enteritidis*; more than 1 million cases occur each year in the United States, and the prevalence is even greater in developing countries. Infection is most common in young children and older adults, with peak incidence in the summer and fall. Salmonella may also cause food poisoning by ingestion of contaminated food, particularly raw or undercooked meat, poultry, eggs, and milk. Centralized food processing can lead to large p2175

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

outbreaks. Vaccines are available for both humans and farm animals, e.g. egg-laying hens.

s0780 p2180 ***Pathogenesis.*** Very few viable *Salmonella* are necessary to cause infection, and the absence of gastric acid, in individuals with atrophic gastritis or those on acid-suppressive therapy, further reduces the required inoculum. *Salmonella* possess virulence genes that encode a type III secretion system capable of transferring bacterial proteins into M cells and enterocytes. The transferred proteins activate host Rho GTPases, thereby triggering actin rearrangement and bacterial endocytosis which, in turn, allows bacterial growth within endosomes. In addition, flagellin, the core protein of bacterial flagellae, activates TLR5 on host cells and increases the local inflammatory response. Similarly, bacterial lipopolysaccharide activates TLR4, although some *Salmonella* strains express a virulence factor that prevents TLR4 activation. *Salmonella* also secrete a molecule that induces epithelial cell release of the eicosanoid hepoxilin A3, thereby drawing neutrophils into the intestinal lumen and potentiating mucosal damage. Both T_H1 and T_H17 immune responses limit infection and explain why those with genetic defects in T_H17 immunity are at risk for disseminated salmonellosis.

p2185 The gross and microscopic features of *Salmonella* enteritis are nonspecific and are similar to the acute self-limited colitis of *Campylobacter* and *Shigella*. Stool cultures are essential for diagnosis.

s0795 p2190 ***Clinical Features.*** Salmonella infections are clinically indistinguishable from those caused by other enteric pathogens, and symptoms range from loose stools to cholera-like profuse diarrhea to dysentery. Fever often resolves within 2 days, but diarrhea can persist for a week and organisms can be shed in the stool for several weeks after resolution. Antibiotic therapy is not recommended in uncomplicated cases because it can prolong the carrier state or even cause relapse and does not typically shorten the duration of diarrhea. Most *Salmonella* infections are self-limited, but deaths do occur. The risk of severe illness and complications is increased in patients with malignancies, immunosuppression, alcoholism, cardiovascular dysfunction, sickle cell disease, and hemolytic anemia.

s0800 Typhoid Fever

p2195 Typhoid fever, also referred to as enteric fever, affects up to 30 million individuals worldwide each year. The disease is caused by *Salmonella enterica,* and its two subtypes, *typhi* and *paratyphi*. *The majority of cases in endemic countries are due to S. typhi, while infection by S. paratyphi is more common among travelers, perhaps because travelers tend to be vaccinated against S. typhi.* In endemic areas, children and adolescents are affected most often, but there is no age preference in developed countries. Infection is strongly associated with travel to India, Mexico, the Philippines, Pakistan, El Salvador, and Haiti. Humans are the sole reservoir for *S. typhi* and *S. paratyphi* and transmission occurs from person to person or via food or contaminated water. Gallbladder colonization with *S. typhi* or *S. paratyphi* may be associated with gallstones and the chronic carrier state.

s0805 p2200 ***Pathogenesis.*** *S. typhi* are able to survive in gastric acid and, once in the small intestine, they are taken up by and invade M cells. Bacteria are then engulfed by mononuclear cells in the underlying lymphoid tissue. Unlike *S. enteritidis*, *S. typhi* can then disseminate via lymphatic and blood vessels. This causes reactive hyperplasia of phagocytes and lymphoid tissues throughout the body.

MORPHOLOGY b0155

Infection causes **Peyer patches in the terminal ileum** to enlarge into sharply delineated, plateau-like elevations up to 8 cm in diameter. Draining mesenteric lymph nodes are also enlarged. Neutrophils accumulate within the superficial lamina propria, and macrophages containing bacteria, red cells, and nuclear debris mix with lymphocytes and plasma cells in the lamina propria. Mucosal damage creates oval ulcers, oriented along the axis of the ileum, that may perforate. The draining lymph nodes also harbor organisms and are enlarged due to phagocyte accumulation. p2205

The spleen is enlarged and soft, with uniformly pale red pulp, obliterated follicular markings, and prominent phagocyte hyperplasia. The liver shows small, randomly scattered foci of parenchymal necrosis in which hepatocytes are replaced by macrophage aggregates, called **typhoid nodules**; such nodules may also develop in the bone marrow and lymph nodes. p2210

s0820 p2215 ***Clinical Features.*** Patients experience anorexia, abdominal pain, bloating, nausea, vomiting, and bloody diarrhea followed by a short asymptomatic phase that gives way to bacteremia and fever with flulike symptoms. *Blood cultures are positive in more than 90% of affected individuals during the febrile phase. Antibiotic treatment can prevent further disease progression.* In patients who do not receive antibiotics, the initial febrile phase continues for up to 2 weeks; patients have sustained high fevers and abdominal tenderness that may mimic appendicitis. *Rose spots*, small erythematous maculopapular lesions, are seen on the chest and abdomen. Symptoms abate after several weeks in those who survive, although relapse can occur. Systemic dissemination may cause *extraintestinal complications* including encephalopathy, meningitis, seizures, endocarditis, myocarditis, pneumonia, and cholecystitis. Patients with sickle cell disease are particularly susceptible to *Salmonella* osteomyelitis.

Yersinia s0825

Three *Yersinia* species are human pathogens. *Y. enterocolitica* and *Y. pseudotuberculosis* cause GI disease and are discussed here; *Y. pestis*, the agent of pulmonic and bubonic plague, is discussed in Chapter 8. *Yersinia* infections of the GI system are more common in Europe than North America and are most frequently linked to ingestion of pork, raw milk, and contaminated water. *Y. enterocolitica* is far more common than *Y. pseudotuberculosis*, and infections tend to cluster in the winter, possibly related to inadequately cooked foods. p2220

s0830 p2225 ***Pathogenesis.*** *Yersinia* invade M cells and use specialized bacterial proteins, called adhesins, to bind to host cell β_1

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

integrins. A pathogenicity island encodes an iron uptake system that mediates iron capture and transport; similar iron transport systems are also present in *E. coli*, *Klebsiella*, *Salmonella*, and enterobacteria. In *Yersinia*, iron enhances virulence and stimulates systemic dissemination, explaining why individuals with increased non-heme iron, such as those with certain chronic forms of anemia or hemochromatosis, are more likely to develop sepsis and are at greater risk for death.

b0160 ### MORPHOLOGY

p2230 *Yersinia* infections preferentially involve the ileum, appendix, and right colon (Fig. 17-28*B*). The organisms multiply extracellularly in lymphoid tissue, resulting in regional lymph node and Peyer patch hyperplasia as well as bowel wall thickening. The mucosa overlying lymphoid tissue may become hemorrhagic, and aphthous-like erosions and ulcers may develop, along with neutrophil infiltrates (Fig. 17-28*B*) and granulomas. This can result in diagnostic confusion with Crohn disease.

s0845 p2235 ***Clinical Features.*** People infected with *Yersinia* generally present with abdominal pain, but fever and diarrhea may also occur. Nausea, vomiting, and abdominal tenderness are common, and Peyer patch invasion with subsequent involvement of regional lymphatics can mimic acute appendicitis in teenagers and young adults. Enteritis and colitis predominate in younger children. *Extraintestinal symptoms of pharyngitis, arthralgia, and erythema nodosum occur frequently. Yersinia* can be detected by stool culture on *Yersinia*-selective agar. In cases with extraintestinal disease, cultures of lymph nodes or blood may also be positive. Postinfectious complications include reactive arthritis with urethritis and conjunctivitis, myocarditis, erythema nodosum, and kidney disease.

s0850 ## *Escherichia coli*

p2240 *E. coli* are gram-negative bacilli that colonize the healthy GI tract; most are nonpathogenic, but a subset cause human disease. The latter are classified according to morphology, mechanism of pathogenesis, and in vitro behavior. Subgroups with major clinical relevance include enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC), enteroinvasive *E. coli* (EIEC), and enteroaggregative *E. coli* (EAEC).

s0855 p2245 ***Enterotoxigenic* E. coli. ETEC organisms are the principal cause of traveler's diarrhea and spread via contaminated food or water.** In developing countries, children younger than 2 years of age are particularly susceptible. ETEC produce heat-labile toxin (LT) and heat-stable toxin (ST), both induce chloride and water secretion while inhibiting intestinal fluid absorption. The LT toxin is similar to cholera toxin and activates adenylate cyclase, resulting in increased intracellular cAMP. This stimulates chloride secretion and, simultaneously, inhibits absorption. ST toxins, which have homology to the mammalian regulatory protein guanylin, bind to guanylate cyclase and increase intracellular cGMP with resulting effects on transport that are similar to those produced by LT. Like cholera, the histopathology induced by ETEC infection is limited. The patients have secretory, noninflammatory diarrhea, dehydration, and, in severe cases, shock.

s9000 p9025 ***Enteropathogenic* E. coli. EPEC** are prevalent in developed and developing countries, where they are an important cause of endemic diarrhea as well as diarrheal outbreaks particularly in children less than 2 years of age. EPEC are characterized by their ability to produce attaching and effacing (A/E) lesions in which bacteria attach tightly to the enterocyte apical membranes and cause local loss, i.e. effacement, of the microvilli. The proteins necessary for creating A/E lesions are all encoded by large genomic pathogenicity island, the locus of enterocyte effacement (LEE), which is also present in many EHEC strains. These proteins include Tir, which is inserted into the intestinal epithelial cell plasma membrane. Tir acts as a receptor for the bacterial outer membrane protein intimin, which is encoded by the *espE* gene and is used for molecular detection and diagnosis of EPEC infection. The locus of enterocyte effacement also encodes a type III secretion system, similar to that in *Shigella*, that injects bacterial effector proteins into the epithelial cell cytoplasm. All EPEC strains lack genes to produce Shiga toxin.

s0870 p2250 ***Enterohemorrhagic* E. coli. EHEC are categorized as *E. coli* O157:H7 and non-O157:H7 serotypes.** Because cows are a natural reservoir, it is not surprising that large outbreaks of *E. coli* O157:H7 infection in developed countries are often associated with the consumption of inadequately cooked ground beef. However, contaminated milk and vegetables are also vehicles for infection. Both O157:H7 and non-O157:H7 serotypes produce Shiga-like toxins, and therefore lesions (Fig. 17-28*C*) and clinical symptoms are similar to those resulting from *S. dysenteriae* infection. O157:H7 strains of EHEC are more likely than non-O157:H7 serotypes to cause large outbreaks, bloody diarrhea, *hemolytic-uremic syndrome,* and ischemic colitis. Importantly, antibiotics are not recommended for treatment because killing the bacteria can lead to increased release of Shiga-like toxins that enhance the risk of hemolytic uremic syndrome, especially in children.

s0875 p2255 ***Enteroinvasive* E. coli. EIEC organisms are bacteriologically similar to *Shigella* and are transmitted via food, water, or by person-to-person contact.** While EIEC do not produce toxins, they invade epithelial cells and cause nonspecific features of acute self-limited colitis (Fig. 17-28*D*). EIEC infections are most common among young children in developing countries and are occasionally associated with outbreaks in developed countries.

s0880 p2260 ***Enteroaggregative* E. coli. EAEC organisms were identified on the basis of their unique pattern of adherence to epithelial cells.** These organisms are now recognized as a cause of diarrhea in children and adults in developed as well as developing countries. EAEC can also cause traveler's diarrhea. The organisms attach to enterocytes via adherence fimbriae and are aided by dispersin, a bacterial surface protein that neutralizes the negative surface charge of lipopolysaccharide. While the bacteria do produce enterotoxins related to *Shigella* enterotoxin and ETEC ST toxin, histologic damage is minimal and the characteristic adherence lesions are only visible by electron microscopy.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

EAEC organisms cause nonbloody diarrhea that may be prolonged in individuals with the acquired immunodeficiency syndrome.

Pseudomembranous Colitis

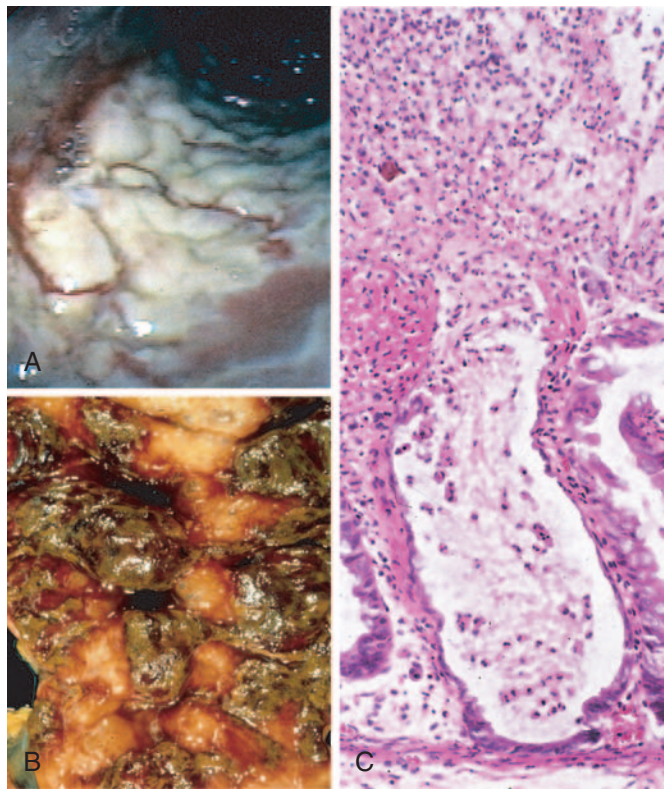
p2265 **Pseudomembranous colitis, generally caused by *C. difficile*, can also be referred to as antibiotic-associated colitis or antibiotic-associated diarrhea.** While antibiotic-associated diarrhea may also be caused by other organisms such as *Salmonella*, *C. perfringens* type A, or *Staphylococcus aureus* only *C. difficile* causes pseudomembranous colitis.

s0890 p2270 ***Pathogenesis.*** It is likely that disruption of the normal colonic microbiota by antibiotics allows *C. difficile* overgrowth. Almost any antibiotic may be responsible; the most important determinants of the disease are frequency of use and the affect on colonic microbiota. Immunosuppression is also a predisposing factor for *C. difficile* colitis. Toxins released by *C. difficile* cause the ribosylation of small GTPases, such as Rho, and lead to disruption of the epithelial cytoskeleton, tight junction barrier loss, cytokine release, and apoptosis. The mechanisms by which these processes lead to pseudomembranous colitis are incompletely understood.

MORPHOLOGY

p2275 Fully developed *C. difficile*–associated colitis is accompanied by formation of **pseudomembranes** (Fig. 17-29*A*, *B*), made up of an adherent layer of inflammatory cells and debris at sites of colonic mucosal injury. While pseudomembranes are not specific and may occur with ischemia or necrotizing infections, the histopathology of *C. difficile*-associated colitis is pathognomonic. The surface epithelium is denuded, and the superficial lamina propria contains a dense infiltrate of neutrophils and occasional fibrin thrombi within capillaries. Superficially damaged crypts are distended by a mucopurulent exudate that forms an eruption reminiscent of a volcano (Fig. 17-29*C*). These exudates coalesce to form pseudomembranes.

s0905 p2280 ***Clinical Features.*** *Risk factors for C. difficile–associated colitis include advanced age, hospitalization, and antibiotic treatment.* The organism is particularly prevalent in hospitals; as many as 30% of hospitalized adults are colonized with *C. difficile* (a rate tenfold greater than the general population), but most colonized patients are free of disease. Individuals with *C. difficile*–associated colitis present with fever, leukocytosis, abdominal pain, cramps, watery diarrhea, and dehydration. Protein loss can give rise to hypoalbuminemia. Fecal leukocytes and occult blood may be present, but grossly bloody diarrhea is uncommon. Diagnosis of *C. difficile*–associated colitis is usually accomplished by detection of *C. difficile* toxin, rather than culture, and is supported by the characteristic histopathology. Metronidazole or vancomycin are generally effective therapies, but antibiotic-resistant and hypervirulent *C. difficile* strains are increasingly common. Another major challenge in *C. difficile*–associated colitis is recurrent infection, which occurs in up to 40% of patients. New antibiotics, monoclonal antibodies against toxins A and B, and fecal microbial transplants can be effective therapies for recurrent *C. difficile* infection, but are not yet in widespread use.



f0150

Figure 17-29 *Clostridium difficile* colitis. **A,** The colon is coated by tan pseudomembranes composed of neutrophils, dead epithelial cells, and inflammatory debris (endoscopic view). **B,** Pseudomembranes are easily appreciated on gross examination. **C,** Typical pattern of neutrophils emanating from a crypt is reminiscent of a volcanic eruption.

Whipple Disease

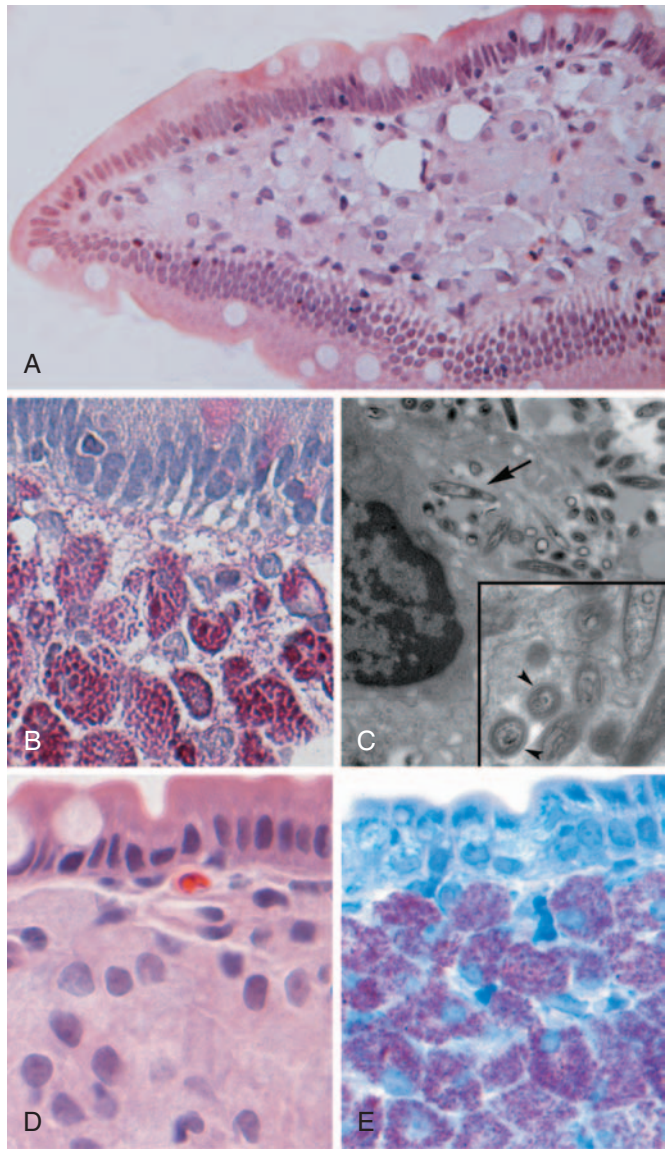
s0910

Whipple disease is a rare, multivisceral chronic disease first described as intestinal lipodystrophy in 1907 by George Hoyt Whipple. A mere 27 years later the pathologist went on to win the Nobel Prize for his work on pernicious anemia. He was a contemporary, but not a relative, of Allen Oldfather Whipple, the surgeon who pioneered the pancreatoduodenectomy.

p2285

s0915 p2290 ***Pathogenesis.*** Whipple's original case report described an individual with malabsorption, lymphadenopathy, and arthritis of undefined origin. Postmortem examination demonstrated the presence of foamy macrophages and large numbers of argyrophilic rods in the lymph nodes, suggesting that the disease was caused by a microbe. The gram-positive actinomycete, named *Tropheryma whippelii*, which is responsible for Whipple disease, was identified by PCR in 1992 and finally cultured in 2000. Clinical symptoms occur because organism-laden macrophages accumulate within the small intestinal lamina propria and mesenteric lymph nodes, causing lymphatic obstruction. Thus, *the malabsorptive diarrhea of Whipple disease is due to impaired lymphatic transport.*

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0155 **Figure 17-30** Whipple disease and mycobacterial infection. **A,** hematoxylin and eosin staining shows effacement of normal lamina propria by a sheet of swollen macrophages. **B,** PAS stain highlights macrophage lysosomes full of bacilli. Note the positive staining of mucous vacuoles in the overlying goblet cells. **C,** An electron micrograph of part of a macrophage shows bacilli within the cell (top arrow); also seen at higher magnification (inset). **D,** The morphology of mycobacterial infection can be similar to Whipple disease, particularly in the immunocompromised host. Compare with **A**. **E,** Mycobacteria are positive with stains for for acid-fast bacteria. (**C,** Courtesy George Kasnic and Dr. William Clapp, University of Florida, Gainesville, Fla.)

b0170 ## MORPHOLOGY

p2295 The morphologic hallmark of Whipple disease is a **dense accumulation of distended, foamy macrophages in the small intestinal lamina propria** (Fig. 17-30*A*). The macrophages contain periodic acid–Schiff (PAS)-positive, diastase-resistant granules that represent lysosomes stuffed with partially digested bacteria (Fig. 17-30*B*). Intact rod-shaped bacilli can also be identified by electron microscopy (Fig. 17-30*C*). A similar infiltrate of foamy macrophages is present in intestinal tuberculosis (Fig. 17-30*D*), and the organisms are PAS-positive in both diseases. The acid-fast stain can be helpful, since mycobacteria stain positively (Fig. 17-30*E*) while *T. whippelii* do not.

p2300 The **villous expansion** caused by the dense macrophage infiltrate imparts a shaggy gross appearance to the mucosal surface. Lymphatic dilatation and mucosal lipid deposition account for the common endoscopic detection of white to yellow mucosal plaques. In Whipple disease, bacteria-laden macrophages can accumulate within **mesenteric lymph nodes, synovial membranes of affected joints, cardiac valves, the brain,** and other sites.

p2305 Whipple disease is most common in Caucasian men, particularly farmers and others with occupational exposure to soil or animals. While there is no consistent familial clustering, the rarity of infection despite a large number of healthy carriers suggests that genetic risk factors may exist.

p2310 The clinical presentation of Whipple disease is usually a triad of diarrhea, weight loss, and arthralgia. Extraintestinal symptoms, which can exist for months or years before malabsorption, include arthritis, arthralgia, fever, lymphadenopathy, and neurologic, cardiac, or pulmonary disease.

p2315 Mycobacterial infections are considered in detail in Chapter 8.

Viral Gastroenteritis

s0930

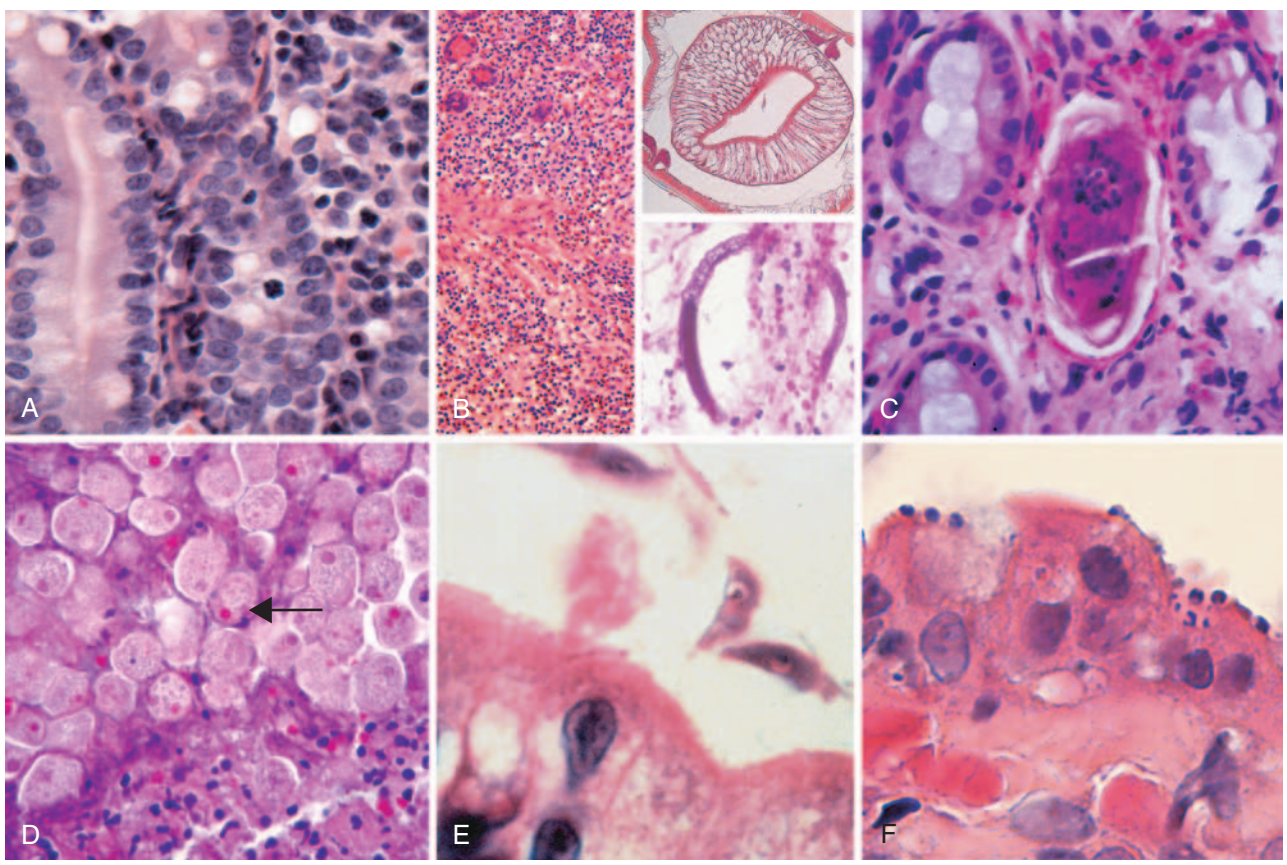
p2320 Symptomatic human infection is caused by several distinct groups of viruses. The most common are discussed here.

s0935 ***Norovirus.*** This was previously known as Norwalk-like virus and is a common cause of nonbacterial gastroenteri- p2325 tis. These are small icosahedral viruses with a single-stranded RNA genome that forms a genus within the Caliciviridae family. **Norovirus causes approximately half of all gastroenteritis outbreaks worldwide and is a common cause of sporadic gastroenteritis in developed countries.** In the United States, noroviruses are the most common cause of acute gastroenteritis requiring medical attention and are second only to rotavirus as a cause of severe diarrhea in infants and young children. In developing countries, noroviruses cause more than 200,000 childhood deaths annually. Norovirus is expected to become the most common cause of diarrhea worldwide in all age groups as rotavirus vaccination becomes widespread.

p2330 *Local norovirus outbreaks are usually related to contaminated food or water, but person-to-person transmission underlies most sporadic cases.* Infections spread easily within schools, hospitals, nursing homes, and other large groups in close quarters, such as those on cruise ships. In these environments, vehicles of infection include airborne droplets, environmental surfaces and fomites.

p9185 Following a short incubation period, affected individuals develop nausea, vomiting, watery diarrhea, and abdominal pain. Biopsy morphology is nonspecific. When present, abnormalities are most evident in the small intestine and include mild villous shortening, epithelial vacuolization, loss of the microvillus brush border, crypt hypertrophy, and lamina propria infiltration by lymphocytes (Fig. 17-31*A*). The disease is self-limited in immunocompetent hosts.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0160

Figure 17-31 Infectious enteritis. **A,** Histologic features of viral enteritis include increased numbers of intraepithelial and lamina propria lymphocytes and crypt hypertrophy. **B,** Diffuse eosinophilic infiltrates in parasitic infection. This case was caused by *Ascaris* (upper inset), but a similar tissue reaction could be caused by *Strongyloides* (lower inset). **C,** Schistosomiasis can induce an inflammatory reaction to eggs trapped within the lamina propria. **D,** *Entamoeba histolytica* in a colon biopsy specimen. Note some organisms ingesting red blood cells *(arrow)*. **E,** *Giardia lamblia*, which are present in the luminal space over nearly normal-appearing villi, are easily overlooked. **F,** *Cryptosporidia* organisms are seen as small blue spheres that appear to lie on top of the brush border but are actually enveloped by a thin layer of host cell cytoplasm.

p2335 Norovirus infection in immunocompromised patients is a significant problem. Some data suggest that nearly 20% of patients on immunosuppression after renal transplantation or as treatment for graft-versus-host disease after hematopoietic stem cell transplantation are infected with norovirus and have intermittent diarrhea. Many of these patients fail to clear the infection, and diarrhea persists for an average of 9 months. The resulting malnutrition and dehydration can increase morbidity of the underlying disease.

s0950 p2345 ***Rotavirus.*** **This encapsulated virus with a segmented, double-stranded RNA genome infects 140 million people and causes 1 million deaths each year, making rotavirus a common cause of severe childhood diarrhea and diarrheal mortality worldwide.** Children between 6 and 24 months of age are most vulnerable. Protection in the first 6 months of life is probably due to the presence of antibodies in breast milk, while protection beyond 2 years is due to immunity that develops following the first or second infection. However, protection conferred by maternal antibodies seems to be less effective in India, Asia and Africa. Thus, in these locales infections are common in those younger than 6 months of age, hence early vaccination has been suggested. Because live, attenuated virus is used, vaccination is contraindicated in patients with immunodeficiency. Vaccination has also been associated with intussusception, as discussed earlier.

Rotavirus outbreaks in hospitals and daycare centers p2350 are common, and infection spreads easily; the estimated minimal infective inoculum is only 10 viral particles. Rotavirus selectively infects and destroys mature enterocytes in the small intestine, and the villus surface is repopulated by immature secretory cells. Enterocyte damage may be mediated by a viral factor called nonstructural protein 4 (NSP4), which can induce epithelial apoptosis. The loss of absorptive function and net secretion of water and electrolytes is compounded by an osmotic diarrhea caused by the incomplete absorption of nutrients. Like norovirus, rotavirus has a short incubation period followed by several days of vomiting and watery diarrhea.

Adenovirus. A common cause of pediatric diarrhea, ade- s0955 novirus also affects immunocompromised patients. Small p2355 intestinal biopsy specimens can show epithelial degeneration but more often exhibit nonspecific villous atrophy and compensatory crypt hyperplasia. Viral nuclear inclusions are uncommon. Disease typically presents after an incubation period of 1 week with nonspecific symptoms that

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

include diarrhea, vomiting, and abdominal pain. Fever and weight loss may also be present. Symptoms generally resolve within 10 days.

s0960 Parasitic Enterocolitis

p2360 Although viruses and bacteria are the predominant enteric pathogens in the United States, parasitic disease and protozoal infections affect more than one half of the world's population on a chronic or recurrent basis. The small intestine can harbor as many as 20 species of parasites, including nematodes, such as the roundworms *Ascaris* and *Strongyloides*; hookworms and pinworms; cestodes, including flatworms and tapeworms; trematodes, or flukes; and protozoa. Parasitic infections are covered in Chapter 8; those that are common in the intestinal tract are discussed briefly here.

s0965 p2365 **Ascaris lumbricoides.** This nematode infects more than a billion individuals worldwide as a result of human fecal-oral contamination. Ingested eggs hatch in the intestine and larvae penetrate the intestinal mucosa. Larvae then migrate from splanchnic to systemic circulation and, finally, enter the lungs to grow within the alveoli. Approximately 3 weeks later, the larvae are coughed up and swallowed. Upon return to the small intestine, the larvae mature into adult worms, which induce an eosinophil-rich inflammatory reaction (Fig. 17-31*B*) that can cause physical obstruction of the intestine or biliary tree. Larvae can also form hepatic abscesses and cause *Ascaris* pneumonitis. Diagnosis is usually made by detection of eggs in stool samples.

s0980 p2370 **Strongyloides.** The larvae of *Strongyloides* live in fecally contaminated ground soil and can penetrate unbroken skin. They migrate through the lungs, where they induce inflammatory infiltrates, and then reside in the intestine while maturing into adult worms. Unlike other intestinal worms, which require an ova or larval stage outside the human, the eggs of *Strongyloides* can hatch within the intestine and release larvae that penetrate the mucosa, causing autoinfection (Fig. 17-31*B*). Hence, *Strongyloides* infection can persist for life, and immunosuppressed individuals can develop overwhelming autoinfection. *Strongyloides* incite a strong tissue reaction and induce peripheral eosinophilia.

s0985 p2375 **Necator duodenale *and* Ancylostoma duodenale.** These hookworms infect 1 billion people worldwide and cause significant morbidity. Infection is initiated by larval penetration through the skin and, after further development in the lungs the larvae migrate up the trachea and are swallowed. Once in the duodenum the worms attach to the mucosa, suck blood, and reproduce. This causes multiple superficial erosions, focal hemorrhage, and inflammatory infiltrates and, in chronic infection, iron deficiency anemia. Diagnosis can be made by detection of the eggs in fecal smears.

s0990 p2380 **Enterobius vermicularis.** Also known as pinworms, these parasites infect people in industrialized and developing countries; in the United States as many as 40 million people have pinworms. Because they do not invade host tissue and live their entire life within the intestinal lumen, they rarely cause serious illness. Infection by *E. vermicularis*, or enterobiasis, is primarily by the fecal-oral route. Adult worms living in the intestine migrate to the anal orifice at night, where the female deposits eggs on the perirectal mucosa. The eggs cause intense irritation. Rectal and perineal pruritus ensues. The intense itching leads to contamination of the fingers, which promotes human-to-human transmission. Both eggs and adult pinworms remain viable outside the body, and repeat infection is common. Diagnosis can be made by applying cellophane tape to the perianal skin and examining the tape for eggs under a microscope.

s0995 p2385 **Trichuris trichiura.** Whipworms primarily infect young children. Similar to *E. vermicularis*, *Trichuris trichiura* does not penetrate the intestinal mucosa and rarely cause serious disease. Heavy infections, however, may cause bloody diarrhea and rectal prolapse.

s1000 p2390 ***Schistosomiasis.*** This disease involving the intestines most commonly takes the form of adult worms residing within the mesenteric veins. Symptoms of intestinal schistosomiasis are caused by trapping of eggs within the mucosa and submucosa (Fig. 17-31*C*). The resulting immune reaction is often granulomatous and can cause bleeding and even obstruction. More details are presented in Chapter 8.

s1005 p2395 ***Intestinal Cestodes.*** The three primary species of cestodes that affect humans are *Diphyllobothrium latum*, fish tapeworms; *Taenia solium*, pork tapeworms; and *Hymenolepis nana*, dwarf tapeworms. They reside exclusively within the intestinal lumen and are transmitted by ingestion of raw or undercooked fish, meat, or pork that contains encysted larvae. Release of the larvae allows attachment to the intestinal mucosa through its head, or scolex. The worm derives its nutrients from the food stream and enlarges by formation of egg-filled segments termed proglottids. Humans are usually infected by a single worm, and since the worm does not penetrate the intestinal mucosa, peripheral eosinophilia does not generally occur. Nevertheless, the parasite burden can be staggering, since adult worms can grow to many meters in length. Large numbers of proglottids and eggs are shed in the feces. Clinical symptoms include abdominal pain, diarrhea, and nausea, but the majority of cases are asymptomatic. Occasionally, *D. latum* causes B_{12} deficiency and megaloblastic anemia because it competes with the host for dietary B_{12}. Identification of proglottids and eggs in stools is the most efficient method of diagnosis.

s1010 p2400 **Entamoeba histolytica.** This protozoan causes amebiasis and is spread by fecal-oral transmission. *E. histolytica* infects approximately 500 million people in countries such as India, Mexico, and Colombia, and causes 40 million cases of dysentery and liver abscess annually. *E. histolytica* cysts, which have a chitin wall and four nuclei, are resistant to gastric acid, a characteristic that allows them to pass through the stomach without harm. Cysts then colonize the epithelial surface of the colon and release trophozoites, ameboid forms that reproduce under anaerobic conditions.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

p2405 While amebiasis affects the cecum and ascending colon, most often, the sigmoid colon, rectum, and appendix can also be involved. Dysentery develops when the amebae attach to the colonic epithelium, induce apoptosis, invade crypts, and burrow laterally into the lamina propria. This recruits neutrophils, causes tissue damage, and creates a flask-shaped ulcer with a narrow neck and broad base. Histologic diagnosis can be difficult, since amebae are similar to macrophages in size and general appearance (Fig. 17-31*D*). Parasites may penetrate splanchnic vessels and embolize to the liver to produce abscesses in about 40% of patients with amebic dysentery. Amebic liver abscesses, which can exceed 10 cm in diameter, have a scant inflammatory reaction at their margins and a shaggy fibrin lining. The abscesses persist after the acute intestinal illness has passed and may, rarely, reach the lung and the heart by direct extension. Amebae may also spread to the kidneys and brain via the bloodstream.

p2410 Individuals with amebiasis may present with abdominal pain, bloody diarrhea, or weight loss. Occasionally, acute necrotizing colitis and megacolon occur, and both are associated with significant mortality. The parasites lack mitochondria or Krebs cycle enzymes and are thus obligate fermenters of glucose. Metronidazole, which inhibits pyruvate oxidoreductase, an enzyme required for fermentation, is the most effective treatment for systemic disease.

s1015 **Giardia lamblia.** These organisms, also referred to as
p2415 *G. duodenalis* or *G. intestinalis*, were initially described by van Leeuwenhoek, the inventor of the microscope, who discovered the pathogen in his own stool. *Giardia lamblia* are the most common parasitic pathogen in humans and are spread by fecally contaminated water or food. Infection may occur after ingestion of as few as 10 cysts. Because cysts are resistant to chlorine, *Giardia* are endemic in unfiltered public water supplies. They are commonly present in rural streams, explaining infection in campers who use these as a water source. Infection may also occur by the fecal-oral route and, because the cysts are stable, they may be accidentally swallowed while swimming in contaminated water.

p2420 *Giardia* are flagellated protozoans that cause decreased expression of brush-border enzymes, including lactase. In addition they cause microvillous damage and apoptosis of small intestinal epithelial cells. Secretory IgA and mucosal IL-6 responses are important for clearance of *Giardia* infections. Immunosuppressed, agammaglobulinemic, or malnourished individuals are often severely affected. *Giardia* can evade immune clearance through continuous modification of the major surface antigen, variant surface protein, and can persist for months or years while causing intermittent symptoms.

p2425 *Giardia* trophozoites can be identified in duodenal biopsies based on their characteristic pear shape and the presence of two equally sized nuclei. Despite large numbers of trophozoites, which are tightly bound to the brush border of villous enterocytes, there is no invasion and small intestinal morphology may be normal (Fig. 17-31*E*). However, villous blunting with increased numbers of intraepithelial lymphocytes and mixed lamina propria inflammatory infiltrates can develop in patients with heavy infections.

p2430 Giardiasis may be subclinical or accompanied by acute or chronic diarrhea, malabsorption, and weight loss. Infection is usually documented by immunofluorescent detection of cysts in stool samples. Although oral antimicrobial therapy is effective, recurrence is common.

s1020 **Cryptosporidium.** Like *Giardia,* cryptosporidia are an
p2435 important cause of diarrhea worldwide. Cryptosporidiosis was first discovered in the 1980s as an agent of *chronic diarrhea in AIDS patients* and is now recognized as a cause of acute, self-limited disease in immunologically normal hosts. Cryptosporidiosis also causes persistent diarrhea in residents of developing countries. The organisms are present worldwide, with the exception of Antarctica, perhaps because the oocysts are killed by freezing. The oocysts are resistant to chlorine and may, therefore, persist in treated, but unfiltered, water. Contaminated drinking water continues to be the most common means of transmission. The largest documented outbreak, a result of inadequate water purification, occurred in 1993 in Milwaukee, Wisconsin, and affected more than 400,000 people. Like giardiasis, cryptosporidiosis can be spread to water sport participants via contaminated water. Food-borne infection occurs less frequently.

p2440 Humans are infected by several different *Cryptosporidium* species, including *C. hominis* and *C. parvum*. All are able to go through an entire life cycle, with asexual and sexual reproductive phases, in a single host. The ingested encysted oocyte, of which 10 are sufficient to cause symptomatic infection, releases sporozoites following activation of proteases by gastric acid. The sporozoites are motile and have a specialized organelle that attaches to the brush border and causes changes in the enterocyte cytoskeleton. These changes induce the enterocyte to engulf the parasite, which takes up residence in an endocytic vacuole within the microvilli. The presence of the parasite leads to sodium malabsorption, chloride secretion, and increased tight junction permeability, which are responsible for the nonbloody, watery diarrhea that ensues.

p2445 Mucosal histology is often only minimally altered, but persistent cryptosporidiosis in children and heavy infection in immunosuppressed patients can result in villous atrophy, crypt hyperplasia, and inflammatory infiltrates. Although the sporozoite is intracellular, it appears, by light microscopy, to sit on top of the epithelial apical membrane (Fig. 17-31*F*). Organisms are typically most concentrated in the terminal ileum and proximal colon, but can be present throughout the gut, biliary tract, and even the respiratory tract of immunodeficient hosts. Diagnosis is based on finding oocysts in the stool.

KEY CONCEPTS b0175

Infectious Enterocolitis s9030

- ***Vibrio cholerae*** secrete a preformed toxin that causes massive chloride secretion. Water follows the resulting osmotic gradient, leading to *secretory diarrhea*. p2450
- ***Campylobacter jejuni*** is the most common bacterial enteric pathogen in developed countries and also causes traveler's diarrhea. Most isolates are noninvasive. u1070
- ***Salmonella* and *Shigella* spp.** are invasive and associated with and exudative bloody diarrhea (dysentery). u1075
- ***Salmonella* infection** is a common cause of food poisoning. u1080

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

u1085 ■ ***S. typhi*** can cause systemic disease (typhoid fever).

u1090 ■ **Pseudomembranous colitis** is often triggered by antibiotic therapy that allows colonization by ***Clostridium difficile***. The organism releases toxins that disrupt epithelial function. The associated inflammatory response includes characteristic volcano-like eruptions of neutrophils from colonic crypts that spread to form mucopurulent pseudomembranes.

u9180 ■ **Norovirus** is a very common cause of self limited diarrhea both in adults and children. It spreads from person to person in sporadic cases and by water in epidemic cases.

u1095 ■ **Rotavirus** is the most common cause of severe childhood diarrhea and diarrheal mortality worldwide. The diarrhea is caused by loss of mature enterocytes, resulting in malabsorption as well as secretion.

u1100 ■ **Parasitic and protozoal infections** affect more than one half of the world's population on a chronic or recurrent basis. Each parasite has a distinctive life cycle and tissue reaction. Most are associated with tissue and systemic eosinophilia.

s1025 ## Irritable Bowel Syndrome

p2545 **Irritable bowel syndrome (IBS) is characterized by chronic, relapsing abdominal pain, bloating, and changes in bowel habits.** Despite very real symptoms, the gross and microscopic evaluation is normal in most IBS patients. Thus, the diagnosis depends on clinical symptoms and functional testing. It should be recognized that IBS is a syndrome, and that multiple illnesses are represented under this global descriptor. IBS is currently divided into several subtypes, as defined by successive revisions of the Rome criteria.

s1030 p2550 ***Pathogenesis.*** The pathogenesis of IBS remains poorly defined, although there is clearly interplay between psychologic stressors, diet, perturbation of the gut microbiome, increased enteric sensory responses to gastrointestinal stimuli, and abnormal GI motility. For example, patients with *constipation-predominant* or *diarrhea-predominant* IBS tend to have decreased or increased colonic contractions and transit rates, respectively. Excess bile acid synthesis or bile acid malabsorption has been identified as one cause of diarrhea-predominant IBS, likely due to the effects of bile acids on intestinal motility.

p2555 Other data link disturbances in enteric nervous system function to IBS, suggesting a role for defective brain-gut axis signaling. Consistent with this, deep sequencing and genome wide association studies have linked several candidate genes to IBS, including serotonin reuptake transporters, cannabinoid receptors, and TNF-related inflammatory mediators. Further, 5-HT3 receptor anatagonists are effective in many cases of diarrhea-predominant IBS. Opioids and psychoactive drugs with anti-cholinergic effects are also commonly used to treat diarrhea-predominant IBS.

p9190 A separate group of IBS patients, relate onset to a bout of infectious gastroenteritis, suggesting that immune activation or, alternatively, a shift in the gut microbiome may trigger some cases. While unproven, this could explain the efficacy of fecal transplantation in some IBS cases.

There may be some overlap in mechanisms underlying p9195 constipation-predominant and diarrhea-predominant IBS. For example, single nucleotide polymorphisms in immune mediators have been detected in both.

Clinical Features. The peak prevalence of IBS is between s1050 20 and 40 years of age, and there is a significant female p2560 predominance. Variability in diagnostic criteria makes it difficult to establish the incidence, but most authors report prevalence in developed countries of between 5% and 10%. IBS is presently diagnosed using clinical criteria that require the occurrence of abdominal pain or discomfort at least 3 days per month over 3 months with improvement following defecation and a change in stool frequency or form. Other causes, such as enteric infection or inflammatory bowel disease, must be excluded.

IBS is not associated with serious long-term sequelae, p2565 but affected patients may undergo unnecessary abdominal surgery due to chronic pain and their ability to function socially may be compromised. The prognosis of IBS is most closely related to symptom duration, with longer duration correlating with reduced likelihood of improvement.

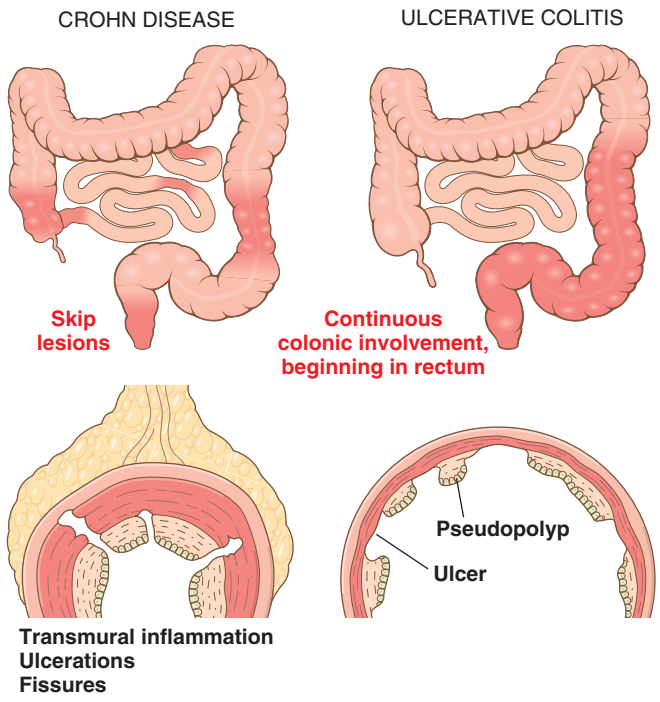
Inflammatory Bowel Disease s1055

Inflammatory bowel disease (IBD) is a chronic condition p2570 resulting from inappropriate mucosal immune activation. The two disorders that comprise IBD are *ulcerative colitis* and *Crohn disease.* Descriptions of ulcerative colitis and Crohn disease date back to antiquity and at least the sixteenth century, respectively, but it took modern microbiologic techniques to exclude conventional infectious etiologies for these diseases. As will be discussed later, however, the luminal microbiota likely play a role in the pathogenesis of IBD.

The distinction between ulcerative colitis and Crohn p2575 disease is based, in large part, on the distribution of affected sites (Fig. 17-32) and the morphologic expression of disease (Table 17-9) at those sites. **Ulcerative colitis is limited to the colon and rectum and extends only into the mucosa and submucosa. In contrast, Crohn disease, which has also been referred to as regional enteritis (because of frequent ileal involvement) may involve any area of the GI tract and is typically transmural.**

Epidemiology. Ulcerative colitis and Crohn disease fre- s1060 quently present in the teens and early 20s, with the former p2580 being slightly more common in females. IBD is most common among Caucasians and, in the United States, occurs 3 to 5 times more often among eastern European (Ashkenazi) Jews than the general population. This is at least partly due to genetic factors, as discussed later. The geographic distribution of IBD is highly variable, but it is most common in North America, northern Europe, and Australia. However, IBD incidence worldwide is on the rise, and it is becoming more common in regions such as Africa, South America, and Asia where its prevalence was historically low. The hygiene hypothesis suggests that this increasing incidence is related to improved food storage conditions, decreased food contamination, and changes in

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0165 **Figure 17-32** Distribution of lesions in inflammatory bowel disease. The distinction between Crohn disease and ulcerative colitis is primarily based on morphology.

gut microbiome composition. Apparently this results in inadequate development of regulatory processes that limit mucosal immune responses. This in turn allows some mucosa-associated microbial organisms to trigger persistent and chronic inflammation in susceptible hosts. Although many details to support this hypothesis are lacking, the observation that helminth infections, which are endemic in regions where IBD incidence is low, can prevent IBD development in animal models and even reduce disease in some patients, lends support to this idea.

s1080 p2585 ***Pathogenesis.*** Although precise causes are not yet defined **most investigators believe that IBD results from the combined effects of alterations in host interactions with intestinal microbiota, intestinal epithelial dysfunction, aberrant mucosal immune responses, and altered composition of the gut microbiome.** This view is supported by epidemiologic, genetic, and clinical studies as well as data from laboratory models of IBD (Fig. 17-33).

u1105 • **Genetics.** There is compelling evidence that genetic factors contribute to IBD. Risk of disease is increased when there is an affected family member and, in Crohn disease, the concordance rate for monozygotic twins approaches 50%. Genetic factors may also contribute to phenotypic expression of the disease, because twins affected by Crohn disease tend to present within a few years of each other and develop disease in similar regions of the GI tract. The concordance of monozygotic twins for ulcerative colitis is only about 15%, suggesting that genetic factors are less dominant than in Crohn disease. Concordance for dizygotic twins is less than 10% for both forms of IBD.

u1110 Population based genome wide association studies have identified over 160 IBD-associated genes. Most of these are shared between Crohn disease and ulcerative colitis, as well as other complex immune-mediated diseases. Interestingly, several IBD associated genes overlap with genes involved in responses to mycobacteria, including *Mycobacterium tuberculosis* and *Mycobacterium leprae*. This supports the idea that host-microbial interactions are critical to the pathogenesis of IBD and may explain some overlap in the histopathology of Crohn disease and mycobacterial infection. One of genes most strongly associated with Crohn disease is *NOD2* (nucleotide oligomerization binding domain 2), which encodes an intracellular protein that binds to bacterial peptidoglycans and activates signaling events, including the NF-κB pathway. Despite the increase in risk attributable to *NOD2* polymorphisms, it should be remembered that fewer than 10% of individuals carrying risk associated *NOD2* variants develop disease. Thus, as is the case with all IBD-associated genes, any one gene confers only a small increase in the risk of developing these diseases.

u1115 In addition to *NOD2*, two Crohn disease–related genes of particular interest are *ATG16L1* (autophagy-related 16-like), and *IRGM* (immunity-related GTPase M). Both are part of the autophagy pathways that are critical for cellular responses to intracellular bacteria; *ATG16L1* may also regulate epithelial homeostasis.

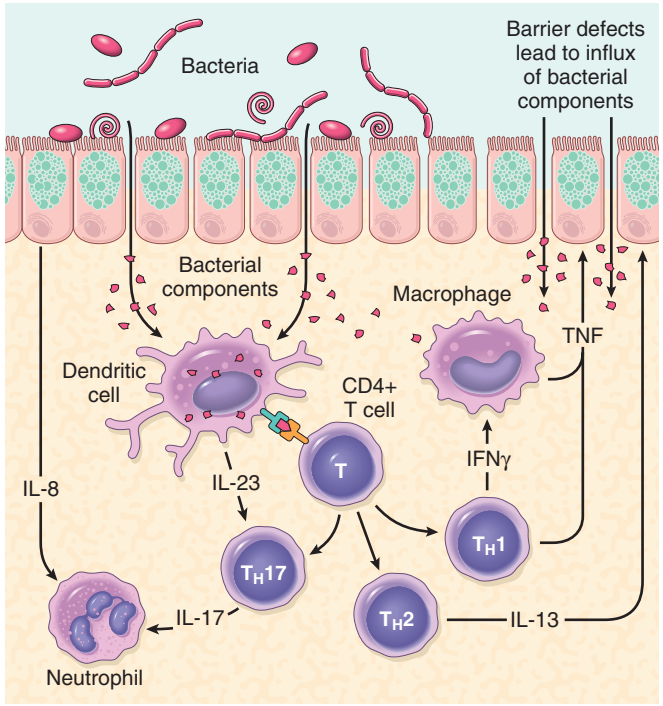
u1120 *NOD2, ATG16L1,* and *IRGM* are expressed in multiple cell types, and their precise roles in the pathogenesis of Crohn disease have yet to be defined. However, all

t0045 **Table 17-9** Features That Differ between Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Macroscopic		
Bowel region	Ileum ± colon	Colon only
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Wall appearance	Thick	Thin
Microscopic		
Inflammation	Transmural	Limited to mucosa
Pseudopolyps	Moderate	Marked
Ulcers	Deep, knife-like	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	Mild to none
Granulomas	Yes (~35%)	No
Fistulae/sinuses	Yes	No
Clinical		
Perianal fistula	Yes (in colonic disease)	No
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Recurrence after surgery	Common	No
Toxic megacolon	No	Yes

All features may not be present in a single case.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0170

Figure 17-33 One model of IBD pathogenesis. Aspects of both Crohn disease and ulcerative colitis are shown. See text for details.

three are involved in recognition and response to intracellular pathogens, supporting the hypothesis that inappropriate immune reactions to luminal bacteria are an important component of IBD pathogenesis.

u1125 • **Mucosal immune responses.** Several observations support a role for mucosal immune responses in the pathogenesis of IBD. Some of these are:

u9185 • T helper cells are activated in Crohn disease and the response is polarized to the T_H1 type (see Chapter 6)

u9190 • T_H17 T cells most likely contribute to disease pathogenesis. Consistent with this, certain polymorphisms of the IL-23 receptor, which is involved in the development and maintenance of T_H17 cells, confer marked reductions in the risk of both Crohn disease and ulcerative colitis.

u9195 • Many other pro-inflammatory cytokines, including TNF, interferon-γ and IL-13, as well as immunoregulatory molecules such as IL-10 and TGF-β, appear to be play a role the pathogenesis of IBD. The role of IL-10 is supported by the observations that autosomal recessive mutations of the IL-10 and IL-10 receptor genes are linked to severe, early onset IBD.

Overall, while details remain to be defined, it is clear that deranged mucosal immune activation and defective immunoregulation contribute to the development of ulcerative colitis and Crohn disease. Immunosuppresive agents remain the mainstay of treatment for these conditions.

u1135 • **Epithelial defects.** A variety of epithelial defects have been described in both Crohn disease and ulcerative colitis. Some examples follow:

u9200 • Defects in intestinal epithelial tight junction barrier function are present in Crohn disease patients and a subset of their healthy first-degree relatives. In patients with Crohn disease and their relatives, this barrier dysfunction is associated with specific disease-associated *NOD2* polymorphisms; experimental models demonstrate that barrier dysfunction can activate innate and adaptive mucosal immunity and sensitize subjects to disease.

u9205 • Some polymorphisms, such as those involving *ECM1* (extracellular matrix protein 1), which inhibits matrix metalloproteinase 9, are linked to ulcerative colitis but not Crohn disease. In this context it is notable that inhibition of matrix metalloproteinase 9 reduces the severity of colitis in experimental models.

u9210 • Certain polymorphisms in the transcription factor *HNFA* are associated with ulcerative colitis but not Crohn disease. These *HNFA* polymorphisms are also strongly associated with maturity onset diabetes of the young (MODY), which like IBD, is associated with reduced intestinal barrier function.

Together these data suggest that, derangements in epithelial function is an important component are critical to IBD pathogenesis.

u1140 • **Microbiota.** The abundance of microbiota in the GI lumen is overwhelming, amounting to as much as 10^{12} organisms per milliliter in the colon and 50% of fecal mass. In total, these organisms greatly outnumber human cells in our bodies, a sober reminder that at a cellular level, we may be only about 10% human. A sampling of data that supports the notion that microbiota play a role in the evolution of IBD follows:

• As mentioned earlier, linkage to NOD2, points to the involvement of microbes in the causation of Crohn disease.

• The presence of antibodies against the bacterial protein flagellin are most common in Crohn disease patients who have disease associated *NOD2* variants, stricture formation, perforation, and small-bowel involvement. In contrast, anti-flagellin antibodies are uncommon in ulcerative colitis patients.

• Microbial transfer studies are able to induce or reduce disease in animal models of IBD, and clinical trials suggest that probiotic (or beneficial) bacteria or even fecal microbial transplants from healthy individuals may benefit IBD patients.

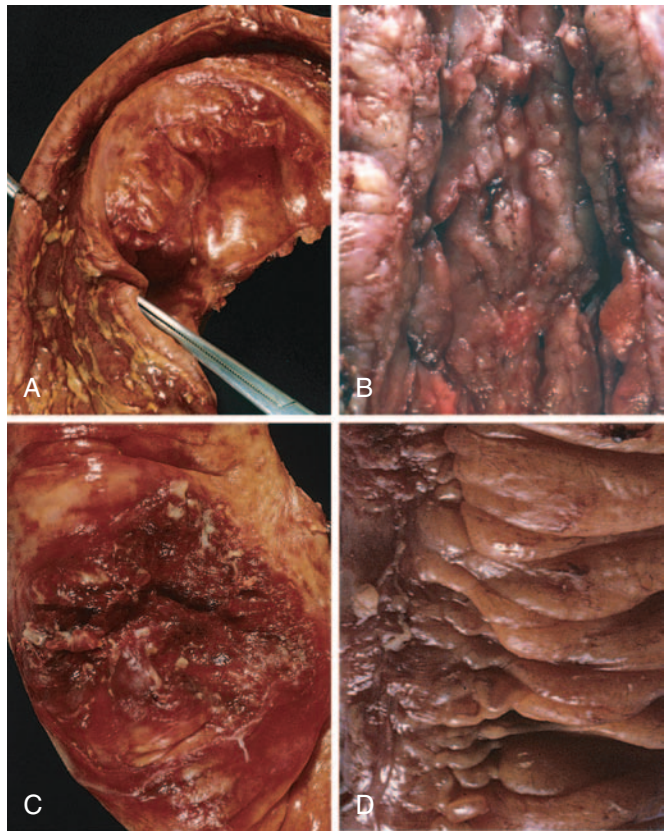
p2630 One model that unifies the roles of intestinal microbiota, epithelial function, and mucosal immunity suggests a cycle by which transepithelial flux of luminal bacterial components activates innate and adaptive immune responses. In a genetically susceptible host, the subsequent release of TNF and other immune-mediated signals direct epithelia to increase tight junction permeability, which causes further increases in the in flux of luminal material. These events may establish a self-amplifying cycle that gives rise to maladaptative and injurious immune responses.

Crohn Disease

s1085

p2635 Crohn disease, an eponym based on the 1932 description by Crohn, Ginzburg, and Oppenheimer, has existed for centuries. Louis XIII of France (1601-1643) suffered relapsing bloody diarrhea, fever, rectal abscess, small intestinal and colonic ulcers, and fistulae beginning at age 20 years, most likely due to Crohn disease.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



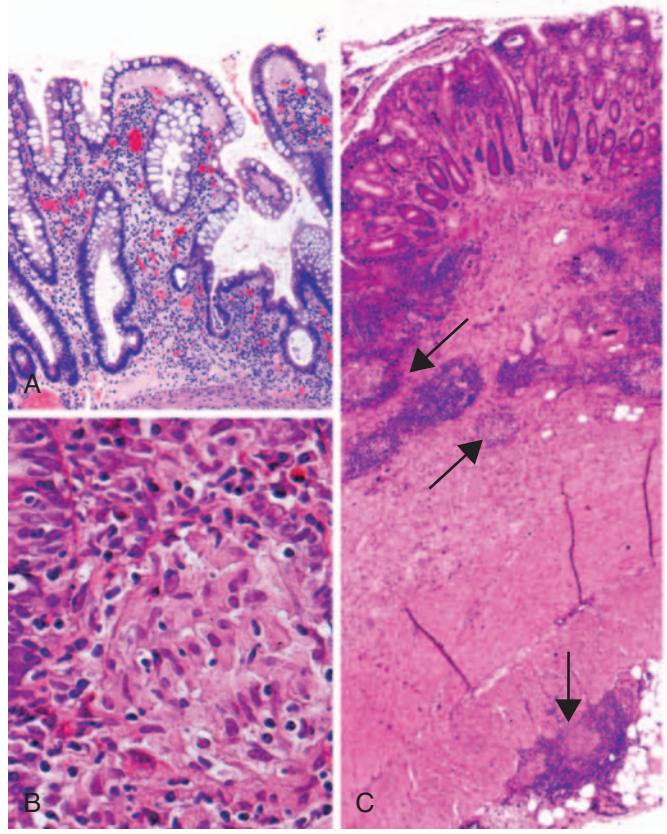
f0175 **Figure 17-34** Gross pathology of Crohn disease. **A,** Small-intestinal stricture. **B,** Linear mucosal ulcers, which impart a cobblestone appearance to the mucosa, and thickened intestinal wall. **C,** Perforation and associated serositis. **D,** Creeping fat.

b0180 ## MORPHOLOGY

p2640 Crohn disease may occur in any area of the GI tract, but the most common sites involved at presentation are the terminal ileum, ileocecal valve, and cecum. Disease is limited to the small intestine alone in about 40% of cases; the small intestine and colon are both involved in 30% of patients; the remainder have only colonic involvement. The presence of multiple, separate, sharply delineated areas of disease, resulting in **skip lesions**, is characteristic of Crohn disease and may help in the differentiation from ulcerative colitis. Strictures are common in Crohn disease, but do not generally develop in ulcerative colitis (Fig. 17-34*A*).

p2645 The earliest lesion, the **aphthous ulcer**, may progress, and multiple lesions often coalesce into elongated, serpentine ulcers oriented along the axis of the bowel (Fig. 17-34*B*). Edema and loss of the normal mucosal texture are common. Sparing of interspersed mucosa, a result of the patchy distribution of Crohn disease, results in a coarsely textured, **cobblestone** appearance in which diseased tissue is depressed below the level of normal mucosa (Fig. 17-34*B*). **Fissures** frequently develop between mucosal folds and may extend deeply to become fistula tracts or sites of perforation (Fig. 17-34*C*). The intestinal wall is thickened and rubbery as a consequence of transmural edema, inflammation, submucosal fibrosis, and hypertrophy of the muscularis propria, all of which contribute to stricture formation (Fig. 17-34*A*). In cases with extensive transmural disease, mesenteric fat frequently extends around the serosal surface **(creeping fat)** (Fig. 17-34*D*).

p2650 The microscopic features of active Crohn disease include abundant neutrophils that infiltrate and damage crypt epithelium. Clusters of neutrophils within a crypt are referred to as **crypt abscesses** and are often associated with crypt destruction. Ulceration is common in Crohn disease, and there may be an abrupt transition between ulcerated and adjacent normal mucosa. Even in areas where gross examination suggests diffuse disease, microscopic pathology can appear patchy. Repeated cycles of crypt destruction and regeneration lead to **distortion of mucosal architecture**; the normally straight and parallel crypts take on bizarre branching shapes and unusual orientations to one another (Fig. 17-35*A*). Epithelial metaplasia, another consequence of chronic relapsing injury, often takes the form of gastric antral-appearing glands, and is called pseudopyloric metaplasia. **Paneth cell metaplasia** may also occur in the left colon, where Paneth cells are normally absent. These architectural and metaplastic changes may persist even when active inflammation has resolved. Mucosal atrophy, with loss of crypts, may occur after years of disease. **Noncaseating granulomas** (Fig. 17-35*B*), a hallmark of Crohn disease, are found in approximately 35% of cases and may occur in areas of active disease or uninvolved regions in any layer of the intestinal wall (Fig. 17-35*C*). Granulomas may also be present in mesenteric lymph nodes. Cutaneous granulomas form nodules that are referred to as **metastatic Crohn disease** (a misnomer since there is no cancer). The absence of granulomas does not preclude a diagnosis of Crohn disease.



f0180 **Figure 17-35** Microscopic pathology of Crohn disease. **A,** Haphazard crypt organization results from repeated injury and regeneration. **B,** Noncaseating granuloma. **C,** Transmural Crohn disease with submucosal and serosal granulomas (arrows).

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

s1090 ***Clinical Features.*** The clinical manifestations of Crohn p2655 disease are extremely variable. In most patients disease begins with intermittent attacks of relatively mild diarrhea, fever, and abdominal pain. Approximately 20% of patients present acutely with right lower quadrant pain, fever, and bloody diarrhea that may mimic acute appendicitis or bowel perforation. Periods of active disease are typically interrupted by asymptomatic periods that last for weeks to many months. Disease re-activation can be associated with a variety of external triggers, including physical or emotional stress, specific dietary items, and cigarette smoking. The latter is a strong exogenous risk factor for development of Crohn disease and, in some cases, disease onset is associated with initiation of smoking. Unfortunately, smoking cessation does not result in disease remission.

p2660 Iron-deficiency anemia may develop in individuals with colonic disease, while extensive small bowel disease may result in serum protein loss and hypoalbuminemia, generalized nutrient malabsorption, or malabsorption of vitamin B_{12} and bile salts. *Fibrosing strictures,* particularly of the terminal ileum, are common and require surgical resection. Disease often recurs at the site of anastomosis, and as many as 40% of patients require additional resections within 10 years. *Fistulae* develop between loops of bowel and may also involve the urinary bladder, vagina, and abdominal or perianal skin. *Perforations* and peritoneal abscesses are common. Anti-TNF antibodies have revolutionized treatment of Crohn disease, and other biologic therapies are becoming available.

p2665 *Extraintestinal manifestations* of Crohn disease include uveitis, migratory polyarthritis, sacroiliitis, ankylosing spondylitis, erythema nodosum, and clubbing of the fingertips, any of which may develop before intestinal disease is recognized. Pericholangitis and primary sclerosing cholangitis occur in Crohn disease with a higher frequency than in those without Crohn disease, but are even more common in those who have ulcerative colitis (see below and Chapter 18). As discussed later, risk of colonic adenocarcinoma is increased in patients with long-standing IBD affecting the colon.

s1105 Ulcerative Colitis

p2670 Ulcerative colitis is closely related to Crohn disease. However, the disease in ulcerative colitis is limited to the colon and rectum. Common extraintestinal manifestations of ulcerative colitis overlap with those of Crohn disease and include migratory polyarthritis, sacroiliitis, ankylosing spondylitis, uveitis, and skin lesions. Approximately 2.5% to 7.5% of individuals with ulcerative colitis also have primary sclerosis cholangitis (Chapter 18). The long-term outlook for ulcerative colitis patients depends on the severity of active disease and disease duration.

b0185 MORPHOLOGY

p2675 Grossly, ulcerative colitis always involves the rectum and extends proximally in a continuous fashion to involve part or all of the colon. Disease of the entire colon is termed pancolitis (Fig. 17-36*A*), while left-sided disease extends no farther than the transverse colon. Limited distal disease may be referred to descriptively as ulcerative proctitis or ulcerative proctosigmoiditis. The small intestine is normal, although mild mucosal inflammation of the distal ileum, termed backwash ileitis, may be present in severe cases of pancolitis. Skip lesions are not seen (although focal appendiceal or cecal inflammation may occasionally be present in left-sided ulcerative colitis).

p2680 Grossly, involved colonic mucosa may be slightly red and granular or have extensive, **broad-based ulcers**. There can be an abrupt transition between diseased and uninvolved colon (Fig. 17-36*B*). Ulcers are aligned along the long axis of the colon but do not typically replicate the serpentine ulcers of Crohn disease. Isolated islands of regenerating mucosa often bulge into the lumen to create **pseudopolyps** (Fig. 17-36*C*), and the tips of these polyps may fuse to create **mucosal bridges** (Fig. 17-36*D*). Chronic disease may lead to **mucosal atrophy** with a flat and smooth mucosal surface that lacks normal folds. Unlike Crohn disease, **mural thickening is not present, the serosal surface is normal, and strictures do not occur**. However, inflammation and inflammatory mediators can damage the muscularis propria and disturb neuromuscular function leading to colonic dilation and **toxic megacolon**, which carries a significant risk of perforation.

p2685 Histologic features of mucosal disease in ulcerative colitis are similar to colonic Crohn disease and include inflammatory infiltrates, crypt abscesses (Fig. 17-37*A*), crypt distortion, and pseudopyloric epithelial metaplasia (Fig. 17-37*B*). However, **the inflammatory process is diffuse and generally limited to the mucosa and superficial submucosa** (Fig. 17-37*C*). In severe cases, extensive mucosal destruction may be accompanied by ulcers that extend more deeply into the submucosa, but the muscularis propria is rarely involved. Submucosal fibrosis, mucosal atrophy, and distorted mucosal architecture remain as residua of healed disease but histology may also revert to near normal after prolonged remission. **Granulomas are not present** in ulcerative colitis.

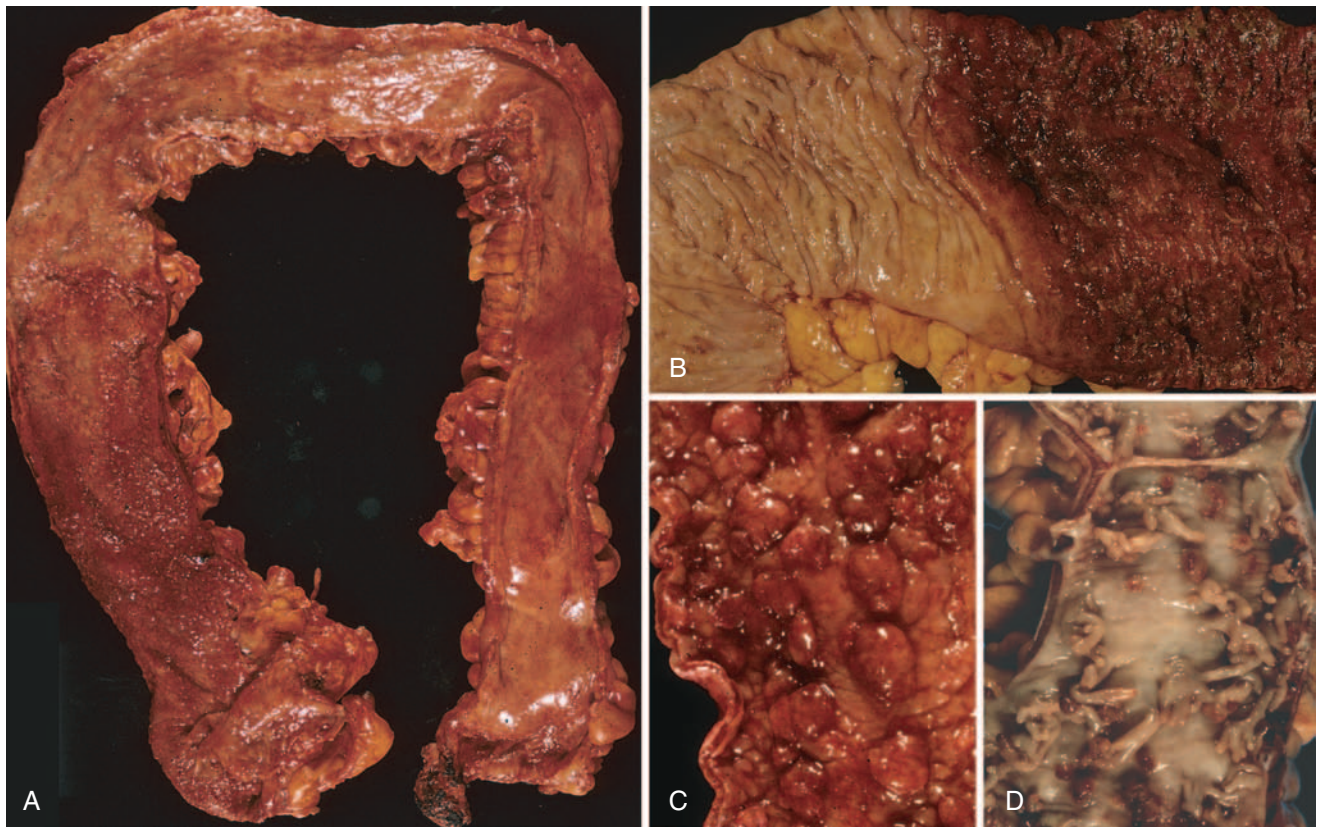
s1110 ***Clinical Features.*** Ulcerative colitis is a relapsing disorder p2690 characterized by attacks of bloody diarrhea with stringy, mucoid material, lower abdominal pain, and cramps that are temporarily relieved by defecation. These symptoms may persist for days, weeks, or months before they subside. The initial attack may, in some cases, be severe enough to constitute a medical or surgical emergency. More than half of patients have clinically mild disease, although almost all experience at least one relapse during a 10-year period, and up to 30% require colectomy within the first 3 years after presentation because of uncontrollable symptoms. Colectomy effectively cures intestinal disease in ulcerative colitis, but extraintestinal manifestations may persist.

p2695 The factors that trigger ulcerative colitis are not known, but infectious enteritis precedes disease onset in some cases. In other cases the first attack is preceded by psychologic stress, which may also be linked to relapse during remission. The initial onset of symptoms has also been reported to occur shortly after smoking cessation in some patients, and smoking may partially relieve symptoms. Unfortunately, studies of nicotine as a therapeutic agent have been disappointing.

Indeterminate Colitis s1125

p2700 Because of the extensive pathologic and clinical overlap between ulcerative colitis and Crohn disease (Table 17-9),

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0185

Figure 17-36 Gross pathology of ulcerative colitis. **A,** Total colectomy with pancolitis showing active disease, with red, granular mucosa in the cecum (left) and smooth, atrophic mucosa distally (right). **B,** Sharp demarcation between active ulcerative colitis (right) and normal mucosa (left). **C,** Inflammatory polyps. **D,** Mucosal bridges.

definitive diagnosis is not possible in approximately 10% of IBD patients. These cases, termed indeterminate colitis, do not involve the small bowel and have colonic disease in a continuous pattern that would typically indicate ulcerative colitis. However, patchy histologic disease, fissures, a family history of Crohn disease, perianal lesions, onset after initiating use of cigarettes, or other features that are not typical of ulcerative colitis may prompt more detailed endoscopic, radiographic, and histologic examination. Serologic studies can be useful in these cases because perinuclear anti-neutrophil cytoplasmic antibodies are found in 75% of individuals with ulcerative colitis but only 11% with Crohn disease. In contrast, ulcerative colitis patients tend to lack antibodies to *Saccharomyces cerevisiae*, which are often present in those with Crohn disease. However, even the serologic results can be ambiguous in cases that are indeterminate on clinical grounds. Despite diagnostic uncertainty, extensive overlap in medical management of ulcerative colitis and Crohn disease allows patients carrying a diagnosis of indeterminate colitis to be treated effectively.

s1130 Colitis-Associated Neoplasia

p2705 **One of the most feared long-term complications of ulcerative colitis and colonic Crohn disease is the development of neoplasia.** The risk of dysplasia is related to several factors:

u1145 • *Duration of the disease.* Risk increases sharply 8 to 10 years after disease onset.

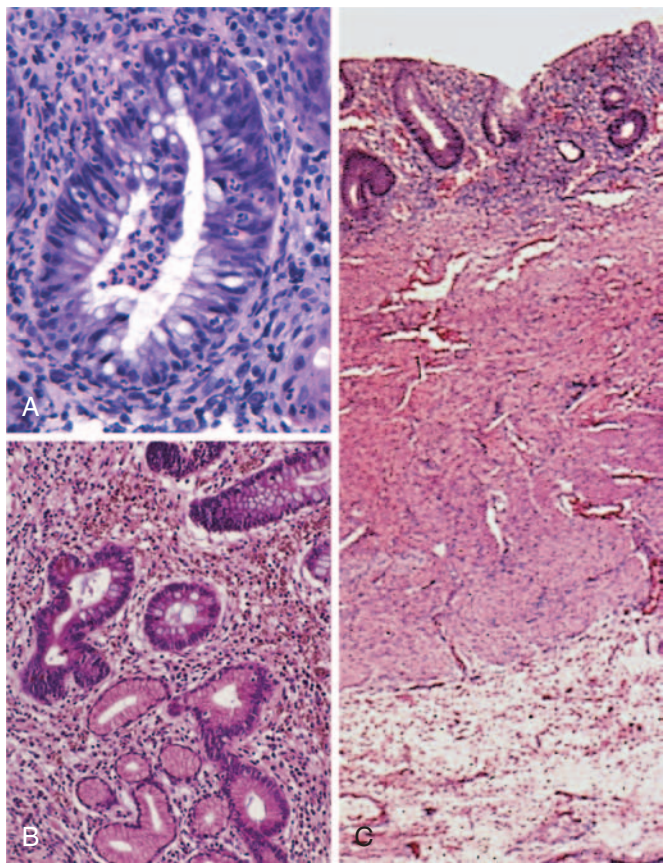
u1150 • *Extent of the disease.* Patients with pancolitis are at greater risk than those with only left-sided disease.

u1155 • *Nature of the inflammatory response.* Greater frequency and severity of active inflammation (characterized by the presence of neutrophils) confers increased risk.

p2730 To facilitate early detection of neoplasia, patients are typically enrolled in surveillance programs approximately 8 years after diagnosis of IBD. The major exception to this is patients with IBD and primary sclerosing cholangitis, who have an even greater risk of developing cancer and are generally enrolled for surveillance at the time of diagnosis. Surveillance requires regular and extensive mucosal biopsies, making it a costly practice. Research efforts are therefore focused on discovery of molecular markers of dysplasia.

p2735 **The goal of surveillance biopsies is to identify dysplastic epithelium, which is a precursor to colitis-associated carcinoma.** Dysplasia can develop in flat areas of mucosa that are not grossly recognized as abnormal. Thus, advanced endoscopic imaging techniques including chromoendoscopy and confocal endoscopy are beginning to be used to increase the sensitivity of detection. IBD-associated dysplasia is classified histologically as low grade or high grade (Fig. 17-38*A, B*) and may be multifocal. High-grade dysplasia may be associated with invasive carcinoma at the same site (Fig. 17-38*C*) or elsewhere in the colon and, therefore, often prompts colectomy. Low-grade dysplasia may be treated with colectomy or followed closely, depending on a variety of factors including patient age and the number of dysplastic foci present. Colonic

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0190 **Figure 17-37** Microscopic pathology of ulcerative colitis. **A,** Crypt abscess. **B,** Pseudopyloric metaplasia (bottom). **C,** Disease is limited to the mucosa. Compare to Figure 17-35*C*.

adenomas (discussed later) also occur in IBD patients, and in some cases these may be difficult to differentiate from a polypoid focus of IBD-associated dysplasia.

s1135 Other Causes of Chronic Colitis

s1140 Diversion Colitis

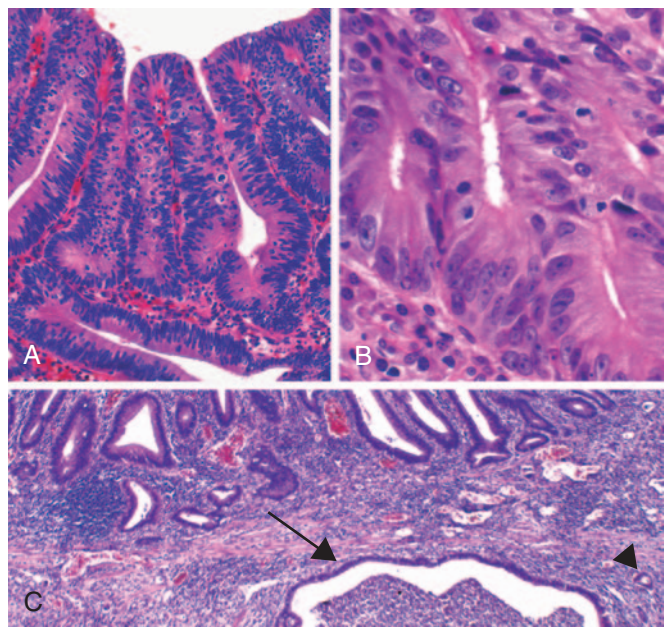
p2740 Surgical treatment of ulcerative colitis, Hirschsprung disease and other intestinal disorders sometimes require creation of a temporary or permanent ostomy and a blind distal segment of colon, from which the normal fecal flow is diverted. Colitis can develop within the diverted segment, particularly in ulcerative colitis patients. Besides mucosal erythema and friability, the most striking feature of diversion colitis is the development of numerous mucosal lymphoid follicles (Fig. 17-39*A*). Increased numbers of lamina propria lymphocytes, monocytes, macrophages, and plasma cells may also be present. In severe cases the histopathology may resemble IBD and include crypt abscesses, mucosal architectural distortion, or, rarely, granulomas. The mechanisms responsible for diversion colitis are not well understood, but changes in the luminal microbiota and diversion of the fecal stream that provides nutrients to colonic epithelial cells have been proposed. Consistent with this, enemas containing short-chain fatty acids, a product of bacterial digestion in the colon and an important energy source for colonic epithelial cells, can promote mucosal recovery in some cases. The ultimate cure is reanastomosis of the diverted segment.

Microscopic Colitis s1145

p2745 Microscopic colitis encompasses two entities, *collagenous colitis* and *lymphocytic colitis*. These idiopathic diseases both present with chronic, nonbloody, watery diarrhea without weight loss. Radiologic and endoscopic studies are typically normal. Collagenous colitis, which occurs primarily in middle-aged and older women, is characterized by the presence of a dense subepithelial collagen layer, increased numbers of intraepithelial lymphocytes, and a mixed inflammatory infiltrate within the lamina propria (Fig. 17-39*B*). Lymphocytic colitis is histologically similar, but the subepithelial collagen layer is of normal thickness and the increase in intraepithelial lymphocytes is greater, frequently exceeding one T lymphocyte per five colonocytes (Fig. 17-39*C*). Lymphocytic colitis shows a strong association with celiac disease and autoimmune diseases, including Graves disease, rheumatoid arthritis, and autoimmune or lymphocytic gastritis.

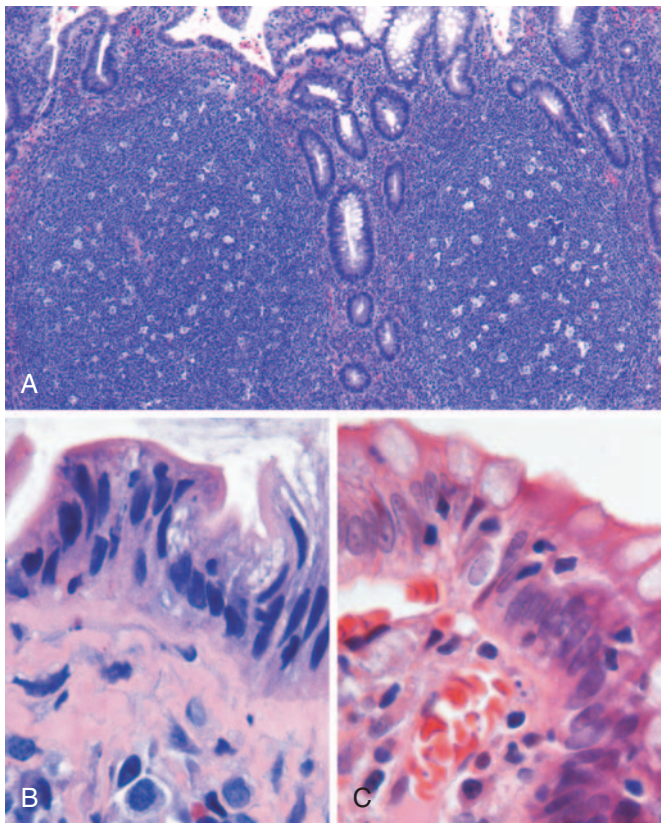
Graft-Versus-Host Disease s1150

p2750 Graft-versus-host disease occurs following hematopoietic stem cell transplantation. The small bowel and colon are involved in most cases. Although graft-versus-host disease is secondary to donor T cells targeting antigens on the recipient's GI epithelial cells, the lamina propria lymphocytic infiltrate is typically sparse. Epithelial apoptosis,



f0195 **Figure 17-38** Colitis-associated dysplasia. **A,** Dysplasia with extensive nuclear stratification and marked nuclear hyperchromasia. **B,** Cribriform glandular arrangement in high-grade dysplasia. **C,** Colectomy specimen with high-grade dysplasia on the surface and underlying invasive adenocarcinoma. A large cystic, neutrophil-filled space lined by invasive adenocarcinoma is apparent *(arrow)* beneath the muscularis mucosae. Also seen are small invasive glands *(arrowhead)*.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0200

Figure 17-39 Uncommon causes of colitis. **A,** Diversion colitis. Note the large lymphoid aggregates with germinal centers. **B,** Collagenous colitis with intraepithelial lymphocytes and a dense subepithelial collagen band. **C,** Lymphocytic colitis.

particularly of crypt cells, is the most common histologic finding. Rarely, total gland destruction occurs, although endocrine cells may persist. Intestinal graft-versus-host disease often presents as a watery diarrhea but may become bloody in severe cases.

s1155 ## Sigmoid Diverticular Disease

p2755 Diverticular disease generally refers to acquired pseudodiverticular outpouchings of the colonic mucosa and submucosa. Unlike true diverticula, such as Meckel diverticulum, they are not invested by all three layers of the colonic wall. Colonic diverticula are rare in persons younger than age 30, but the prevalence approaches 50% in Western adult populations older than age 60. Diverticula are generally multiple and the condition is referred to as diverticulosis. This disease is much less common in Japan as well as developing countries, probably because of dietary differences. Moreover, most diverticula in Asia and Africa occur in the right colon, while right-sided diverticula are uncommon in Western countries. The reasons for this difference in distribution are not well-defined.

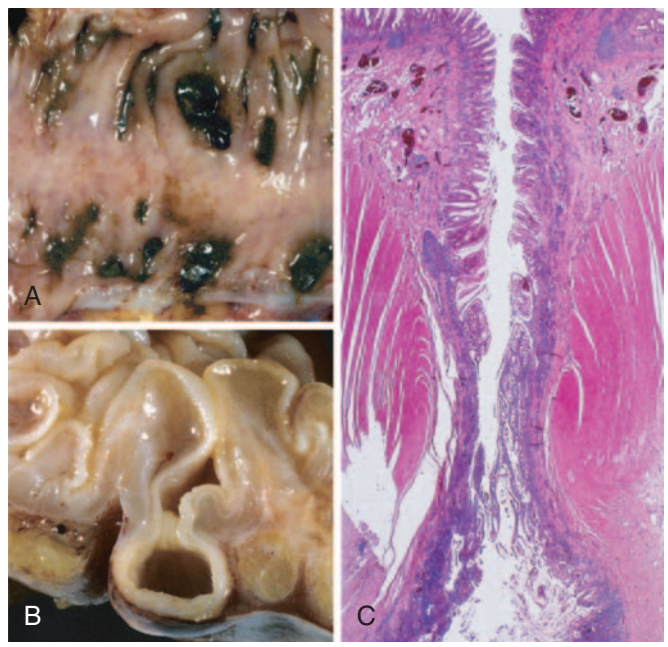
s1160 p2760 ***Pathogenesis.*** Colonic diverticula result from the unique structure of the colonic muscularis propria and elevated intraluminal pressure in the sigmoid colon. Where nerves, arterial vasa recta, and their connective tissue sheaths penetrate the inner circular muscle coat, focal discontinuities in the muscle wall are created. In other parts of the intestine these gaps are reinforced by the external longitudinal layer of the muscularis propria, but, in the colon, this muscle layer is gathered into the three bands termed taeniae coli. Increased intraluminal pressure is probably due to exaggerated peristaltic contractions, with spasmodic sequestration of bowel segments, and may be enhanced by diets low in fiber, which reduce stool bulk, particularly in the sigmoid colon.

MORPHOLOGY

b0190

p2765

Anatomically, colonic diverticula are small, flask-like outpouchings, usually 0.5 to 1 cm in diameter, that occur in a regular distribution alongside the taeniae coli (Fig. 17-40*A*). These are most common in the sigmoid colon, but more extensive areas may be affected in severe cases. Because diverticula are compressible, easily emptied of fecal contents, and often surrounded by the fat-containing epiploic appendices on the surface of the colon, they may be missed on casual inspection. Colonic diverticula have a thin wall composed of a flattened or atrophic mucosa, compressed submucosa, and attenuated or, most often, totally absent muscularis propria (Fig. 17-40*B, C*). Hypertrophy of the circular layer of the muscularis propria in the affected bowel segment is common. Obstruction of diverticula leads to inflammatory changes, producing diverticulitis and peridiverticulitis. Because the wall of the diverticulum is supported only by the muscularis mucosae and a thin layer of subserosal adipose tissue, inflammation and increased pressure within an obstructed diverticulum can lead to perforation. With or without perforation, diverticulitis may cause segmental diverticular disease-associated colitis, fibrotic thickening in and around the colonic wall, or stricture formation. Perforation is uncommon but it can result in pericolonic abscesses, sinus tracts, and, occasionally, peritonitis.



f0205

Figure 17-40 Sigmoid diverticular disease. **A,** Stool-filled diverticula are regularly arranged. **B,** Cross-section showing the outpouching of mucosa beneath the muscularis propria. **C,** Low-power photomicrograph of a sigmoid diverticulum showing protrusion of the mucosa and submucosa through the muscularis propria.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

s1180 p2770 ***Clinical Features.*** Most individuals with diverticular disease remain asymptomatic throughout their lives. However, about 20% of individuals with diverticuli develop manifestations of diverticular disease, such as intermittent cramping, continuous lower abdominal discomfort, constipation, distention, or a sensation of never being able to completely empty the rectum. Patients sometimes experience alternating constipation and diarrhea that can mimic IBS. Occasionally there may be minimal chronic or intermittent blood loss, and, rarely, massive hemorrhage. When present, bleeding is macroscopically visible in the stools. Whether a high-fiber diet prevents such progression or protects against diverticulitis is unclear, but diets supplemented with fiber may provide symptomatic improvement. Even when diverticulitis occurs, it most often resolves spontaneously and relatively few patients require surgical intervention.

b0195 **KEY CONCEPTS**

p2775 ■ **Irritable bowel syndrome (IBS)** is characterized by chronic, relapsing abdominal pain, bloating, and changes in bowel habits without obvious gross or histologic pathology. The pathogenesis of IBS is not defined, but includes contributions by psychologic stressors, diet, the gut microbiome, abnormal GI motility, and increased enteric sensory responses to gastrointestinal stimuli.

u1165 ■ **Inflammatory bowel disease (IBD)** is an umbrella term for **ulcerative colitis** and **Crohn disease**. **Indeterminate colitis** is used for cases of IBD without definitive features of either ulcerative colitis or Crohn disease.

u1170 ■ **Ulcerative colitis is limited to the colon**, is **continuous from the rectum**, and ranges from only rectal disease to pancolitis; neither skip lesions nor granulomas are present.

u1175 ■ **Crohn disease** most commonly affects the **terminal ileum and cecum**, but any site within the gastrointestinal tract can be involved; **skip lesions** are common and **noncaseating granulomas** also occur.

u1180 ■ Both forms of IBD typically present in the **teens and early 20s** and are associated with **extraintestinal manifestations**.

u1185 ■ IBD is thought to arise from a combination of alterations in host interactions with intestinal microbiota, intestinal epithelial dysfunction, and aberrant mucosal immune responses. Molecular analyses have identified more than 160 IBD-associated genes, of which the function of only a few is understood.

u1190 ■ The risk of colonic **epithelial dysplasia and adenocarcinoma** is increased in IBD patients who have had colonic disease for more than 8 to 10 years.

u1195 ■ The two forms of microscopic colitis, **collagenous colitis** and **lymphocytic colitis**, both cause chronic watery diarrhea. The intestines are grossly normal, and the diseases are identified by their characteristic histologic features.

u1200 ■ **Diverticular disease** of the sigmoid colon is common in western populations older than age 60. The causes include low fiber diets, colonic spasm, and the unique anatomy of the colon. Inflammation of diverticula, **diverticulitis**, affects a minority of those with **diverticulosis**, but can cause perforation in its most severe form.

Polyps

s1185

p2825 Polyps are most common in the colo-rectal region but may occur in the esophagus, stomach, or small intestine. Most, if not all, polyps begin as small elevations of the mucosa. These are referred to as sessile, a term borrowed from botanists who use it to describe flowers and leaves that grow directly from the stem without a stalk. As sessile polyps enlarge, proliferation of cells adjacent to the mass and the effects of traction on the luminal protrusion, may combine to create a stalk. Polyps with stalks are termed pedunculated. In general, intestinal polyps can be classified as nonneoplastic or neoplastic in nature. The most common neoplastic polyp is the adenoma, which has the potential to progress to cancer. The nonneoplastic polyps can be further classified as inflammatory, hamartomatous, or hyperplastic.

Hyperplastic Polyps

s1190

p2830 **Colonic hyperplastic polyps are benign epithelial proliferations that are typically discovered in the sixth and seventh decades of life.** The pathogenesis of hyperplastic polyps is incompletely understood, but they are thought to result from decreased epithelial cell turnover and delayed shedding of surface epithelial cells, leading to a "piling up" of goblet cells and absorptive cells. It is now appreciated that these lesions are without malignant potential. **Their chief significance is that they must be distinguished from sessile serrated adenomas, that are histologically similar but have malignant potential, as described later**. It is also important to remember that epithelial hyperplasia can occur as a nonspecific reaction adjacent to or overlying any mass or inflammatory lesion and, therefore, can be a clue to the presence of an adjacent, clinically important lesion.

b0200 **MORPHOLOGY**

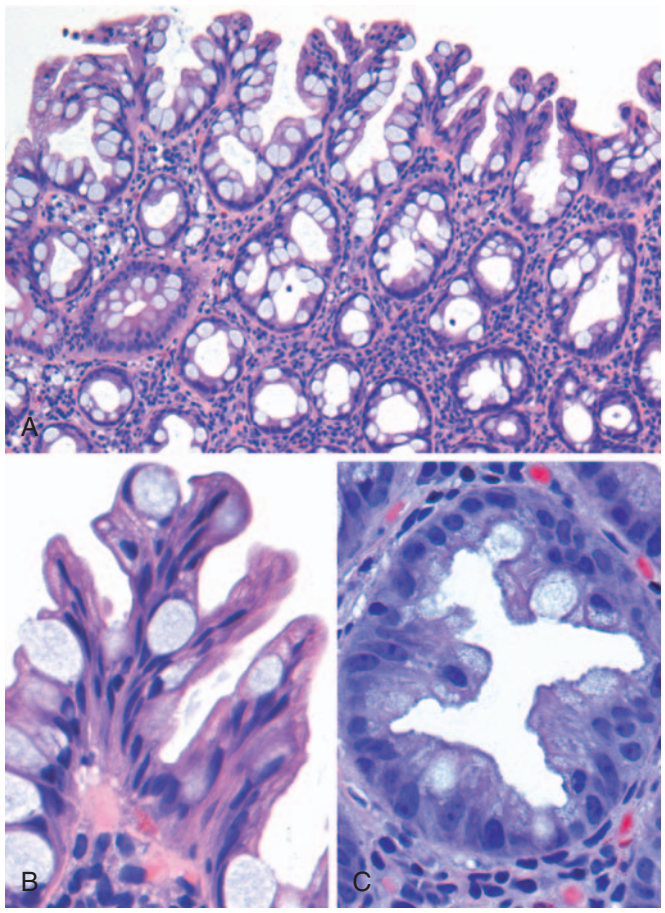
p2835 Hyperplastic polyps are most commonly found in the left colon and are typically less than 5 mm in diameter. They are smooth, nodular protrusions of the mucosa, often on the crests of mucosal folds. They may occur singly but are more frequently multiple, particularly in the sigmoid colon and rectum. Histologically, hyperplastic polyps are composed of mature goblet and absorptive cells. The delayed shedding of these cells leads to crowding that creates the serrated surface architecture that is the morphologic hallmark of these lesions (Fig. 17-41). Serration is typically restricted to the upper third, or less, of the crypt.

Inflammatory Polyps

s1195

p2840 Polyps that form as part of the solitary rectal ulcer syndrome are examples of purely inflammatory lesions. Patients present with a clinical triad of rectal bleeding, mucus discharge, and an inflammatory lesion of the anterior rectal wall. The underlying cause is impaired relaxation of the anorectal sphincter that creates a sharp angle at the anterior rectal shelf and leads to recurrent abrasion and ulceration of the overlying rectal mucosa. An inflammatory polyp may ultimately form as a result of chronic cycles of injury and healing. Entrapment of this polyp in

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0210

Figure 17-41 Hyperplastic polyp. **A,** Polyp surface with irregular tufting of epithelial cells. **B,** Tufting results from epithelial overcrowding. **C,** Epithelial crowding produces a serrated architecture when crypts are cut in cross-section.

the fecal stream leads to mucosal prolapse. The distinctive histologic features of a typical inflammatory polyp include mixed inflammatory infiltrates, erosion, and epithelial hyperplasia together with lamina propria fibromuscular hyperplasia (Fig. 17-42).

Hamartomatous Polyps s1200

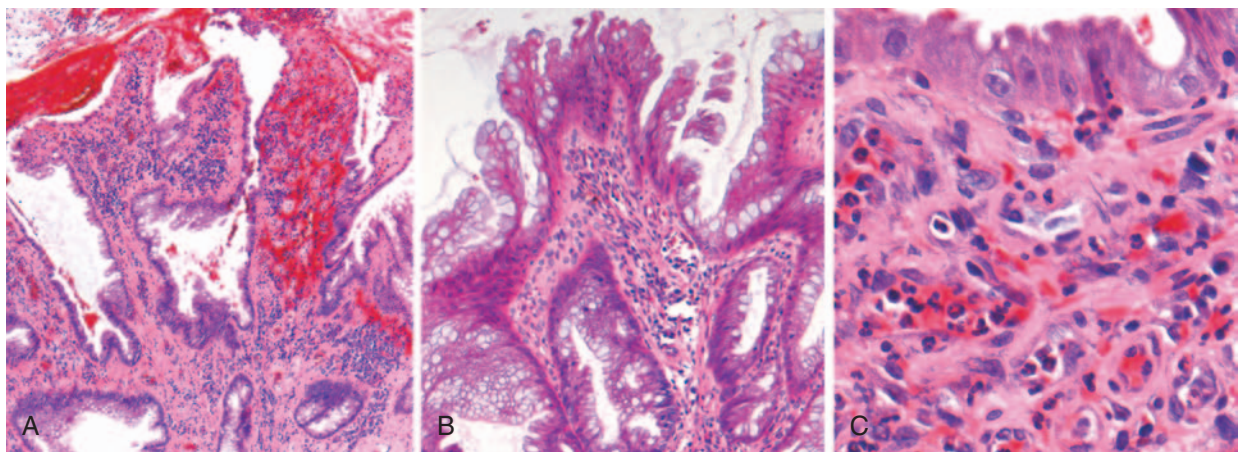
Hamartomatous polyps occur sporadically or as components of various genetically determined or acquired syndromes (Table 17-10)**.** p2845

Although they were originally thought to be caused by developmental abnormalities, it is now appreciated that many hamartomatous polyp syndromes are caused by germline mutations in tumor suppressor genes or proto-oncogenes. Some of these syndromes are associated with increased cancer risk, either within the polyps or at other intestinal or extra-intestinal sites. Thus, in some hamartomatous polyp syndromes, the polyps can be considered to be pre-malignant, neoplastic lesions, much like adenomas. In addition, it is important to recognize these polyps because of associated extraintestinal manifestations and the possibility that other family members are affected. Several of these syndromes are discussed below, while other syndromes are summarized in Table 17-10. p9200

Juvenile Polyps s1205

Juvenile polyps are focal malformations of the epithelium and lamina propria. These may be sporadic or syndromic, but the morphology of the two forms is often indistinguishable. The vast majority of juvenile polyps occur in children younger than 5 years of age but they can present at older ages as well. Most juvenile polyps are located in the rectum and typically present with rectal bleeding. In some cases intussusception, intestinal obstruction, or polyp prolapse (through the anal sphincter) may occur. p2850

Sporadic juvenile polyps are usually solitary lesions and may also be referred to as retention polyps. In contrast, individuals with the autosomal dominant syndrome of juvenile polyposis have from 3 to as many as 100 hamartomatous polyps and may require colectomy to limit the chronic and sometimes severe hemorrhage associated with polyp ulceration. A minority of patients also have polyps in the stomach and small bowel that can undergo malignant transformation. Pulmonary arteriovenous malformations and other congenital malformations are recognized extraintestinal manifestation of juvenile polyposis. p9205



f0215

Figure 17-42 Solitary rectal ulcer syndrome. **A,** The dilated glands, proliferative epithelium, superficial erosions, and inflammatory infiltrate are typical of an inflammatory polyp. However, the smooth muscle hyperplasia within the lamina propria suggests that mucosal prolapse has also occurred. **B,** Epithelial hyperplasia. **C,** Granulation tissue-like capillary proliferation within the lamina propria caused by repeated erosion.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

t0050 **Table 17-10** Gastrointestinal Polyposis Syndromes

Syndrome	Mean Age at Presentation (yr)	Mutated Gene(s); Pathway	Gastrointestinal Lesions	Selected Extra-Gastrointestinal Manifestations
Juvenile polyposis	<5	*SMAD4,BMPR1A*; TGF-β signaling pathway	Juvenile polyps; risk of gastric, small intestinal, colonic, and pancreatic adenocarcinoma	Congenital malformations, digital clubbing
Peutz-Jeghers syndrome	10-15	*STK11*; AMP kinase-related pathways	Arborizing polyps; Small intestine > colon > stomach; colonic adenocarcinoma	Pigmented macules; risk of colon, breast, lung, pancreatic, and thyroid cancer
Cowden syndrome, Bannayan-Ruvalcaba-Riley syndrome*	<15	*PTEN*: PI3K/AKT pathway	Hamartomatous/ inflammatory intestinal polyps, lipomas, ganglioneuromas	Benign skin tumors, benign and malignant thyroid and breast lesions; no increase in GI cancers
Cronkhite-Canada syndrome	>50	Nonhereditary, unknown cause	Hamartomatous polyps of stomach, small intestine colon; abnormalities in nonpolypoid mucosa	Nail atrophy, hair loss, abnormal skin pigmentation, cachexia, and anemia. Fatal in up to 50%.
Tuberous sclerosis		*TSC1* (hamartin), *TSC2* (tuberin); mTOR pathway	Hamartomatous polyps	Mental retardation, epilepsy. facial angiofibroma, cortical (CNS) tubers, renal angiomyolipoma
Familial adenomatous polyposis (FAP)				
Classic FAP	10-15	*APC*	Multiple adenomas	Congenital RPE hypertrophy
Attenuated FAP	40-50	*APC*	Multiple adenomas	
Gardner syndrome	10-15	*APC*	Multiple adenomas	Osteomas, thyroid and desmoid tumors, skin cysts
Turcot syndrome	10-15	*APC*	Multiple adenomas	Medulloblastoma, glioblastoma
MYH-associated polyposis	30-50	*MYH*	Multiple adenomas	

CNS, Central nervous system; mTOR, mammalian target of rapamycin; RPE, retinal pigmented epithelium.
*Also called PTEN Hamartoma-Tumor Syndromes.

b0205 ## MORPHOLOGY

p2855 Most juvenile polyps are less than 3 cm in diameter. They are typically pedunculated, smooth-surfaced, reddish lesions with characteristic cystic spaces apparent after sectioning. Microscopic examination shows these cysts to be dilated glands filled with mucin and inflammatory debris (Fig. 17-43). The remainder of the polyp is composed of lamina propria expanded by mixed inflammatory infiltrates. The muscularis mucosae may be normal or attenuated.

p2860 Although the morphogenesis of juvenile polyps is incompletely understood, it has been proposed that mucosal hyperplasia is the initiating event. This hypothesis is consistent with the discovery that mutations in pathways that regulate cellular growth cause autosomal dominant juvenile polyposis. The most common mutation identified is of *SMAD4*, which encodes a cytoplasmic intermediate in the TGF-β signaling pathway. *BMPR1A*, a kinase that is a member of the TGF-β superfamily, may be mutated in other cases (Table 17-10). However, these mutations account for fewer than half of patients, suggesting that other genes responsible for autosomal dominant juvenile polyposis remain to be discovered.

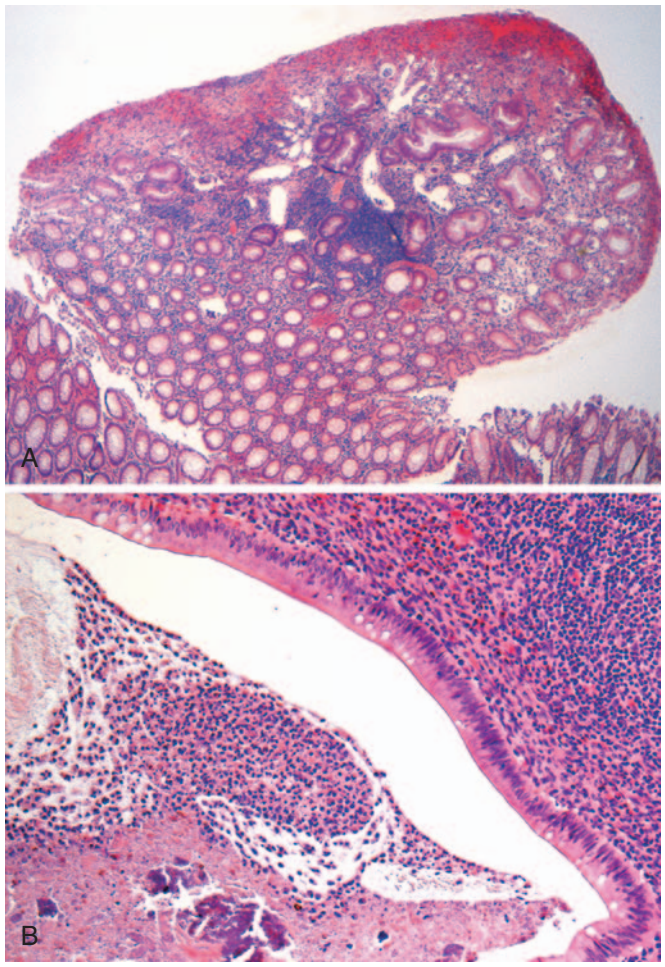
p2865 Dysplasia is extremely rare in sporadic juvenile polyps. In contrast juvenile polyposis syndrome is associated with dysplasia, both within the juvenile polyps and in separate adenomas. As a result, 30% to 50% of patients with juvenile polyposis develop colonic adenocarcinoma by age 45.

Peutz-Jeghers Syndrome s1210

p2870 **This rare autosomal dominant syndrome presents at a median age of 11 years with multiple GI hamartomatous polyps and mucocutaneous hyperpigmentation.** The latter takes the form of dark blue to brown macules on the lips, nostrils, buccal mucosa, palmar surfaces of the hands, genitalia, and perianal region. These lesions are similar to freckles but are distinguished by their presence in the buccal mucosa. Peutz-Jeghers polyps can initiate intussusception, which is occasionally fatal. Of greater importance, *Peutz-Jeghers syndrome is associated with a markedly increased risk of several malignancies.* Lifetime risk is approximately 40% for these, and regular surveillance is recommended beginning at birth, for sex cord tumors of the testes; late childhood for gastric and small intestinal cancers; and the second and third decades of life for colon, pancreatic, breast, lung, ovarian, and uterine cancers.

s1215 ***Pathogenesis.*** Germline heterozygous loss-of-function p2875 mutations in the gene *STK11* are present in approximately half of individuals with familial Peutz-Jeghers syndrome as well as a subset of patients with sporadic Peutz-Jeghers syndrome. You will recall from Chapter 7 that *STK11* is a tumor suppressor gene that encodes a kinase that regulates cell polarization and acts as a brake on growth and anabolic metabolism. As is common with other tumor suppressor genes, the function of the second "normal" copy of *STK11* is often lost through somatic mutation in cancers occurring in Peutz-Jeghers syndrome, providing an explanation for the high risk of neoplasia in affected patients. Importantly, colon cancers can also develop at sites without Peutz-Jeghers polyps.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0220 **Figure 17-43** Juvenile polyposis. **A,** Juvenile polyp. Note the surface erosion and cystically dilated crypts. **B,** Inspissated mucous, neutrophils, and inflammatory debris can accumulate within dilated crypts.

b0210 ## MORPHOLOGY

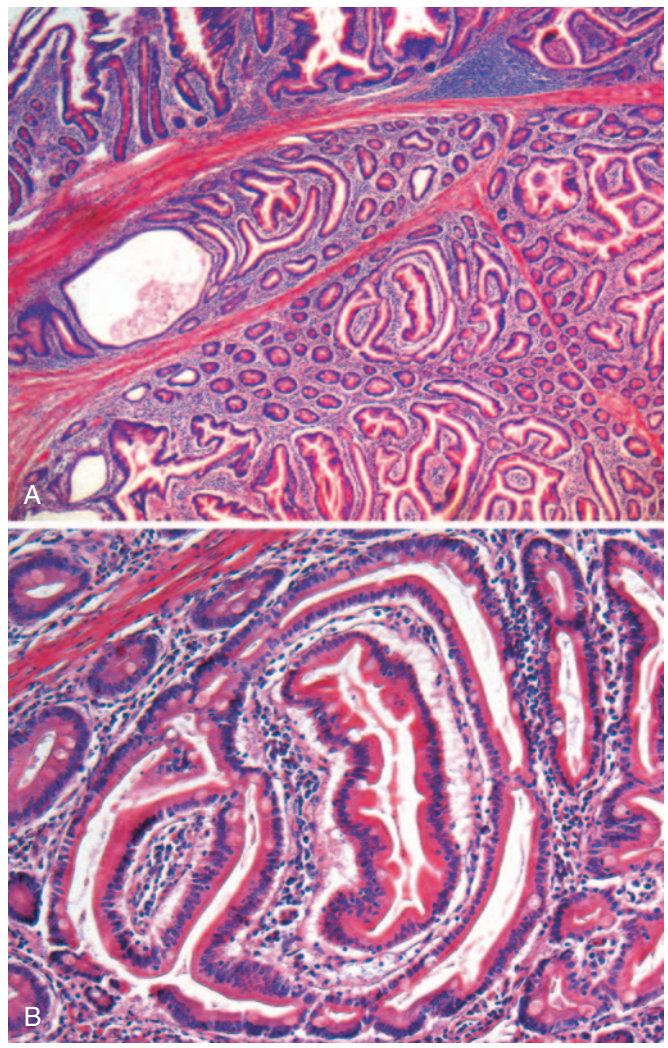
p2880 The polyps of Peutz-Jeghers syndrome are most common in the small intestine, although they may occur in the stomach and colon, and, with much lower frequency, in the bladder and lungs. Grossly, the polyps are large and pedunculated with a lobulated contour. Histologic examination demonstrates a characteristic arborizing network of connective tissue, smooth muscle, lamina propria, and glands lined by normal-appearing intestinal epithelium (Fig. 17-44). The arborization and presence of smooth muscle intermixed with lamina propria are helpful in distinguishing polyps of Peutz-Jeghers syndrome from juvenile polyps.

s1225 p2885 ***Clinical Features.*** Because the morphology of Peutz-Jeghers polyps can overlap with that of sporadic hamartomatous polyps, the presence of multiple polyps in the small intestine, mucocutaneous hyperpigmentation, and a positive family history are critical to the diagnosis. Detection of *STK11* mutations can be helpful diagnostically in patients with polyps who lack mucocutaneous hyperpigmentation. However, the absence of *STK11* mutations does not exclude the diagnosis, since mutations in other presently unknown genes can also cause the syndrome.

Neoplastic Polyps s1230

Any neoplastic mass lesion in the GI tract may produce a mucosal protrusion, or polyp. This includes adenocarcinomas, neuroendocrine (carcinoid) tumors, stromal tumors, lymphomas, and even metastatic cancers from distant sites. *The most common neoplastic polyps are colonic adenomas, which are precursors to the majority of colorectal adenocarcinomas.* p2890

Adenomas are intraepithelial neoplasms that range from small, often pedunculated, polyps to large sessile lesions. There is a small male predominance, and they are present in approximately 30% of adults living in the Western world by age 60. Because these polyps are precursors to colorectal adenocarcinoma, it is recommended that all adults in the United States undergo surveillance by age 50. Patients at increased risk, including those with a family history of colorectal adenocarcinoma, are typically screened colonoscopically at least 10 years before the youngest age at which a relative was diagnosed. The preferred approach to surveillance varies, but colonoscopy is most common. p2895



f0225 **Figure 17-44** Peutz-Jeghers polyp. **A,** Polyp surface (top) overlies stroma composed of smooth muscle bundles cutting through the lamina propria. **B,** Complex glandular architecture and the presence of smooth muscle are features that distinguish Peutz-Jeghers polyps from juvenile polyps. Compare to Figure 17-42.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

While adenomas are less common in Asia, their frequency has risen (in parallel with an increasing incidence of colorectal adenocarcinoma) in these populations as Western diets and lifestyles become more common.

p2900 **Colorectal adenomas are characterized by the presence of epithelial dysplasia.** Consistent with their being precursor lesions, the prevalence of colorectal adenomas correlates with that of colorectal adenocarcinoma and the distributions of adenomas and adenocarcinoma within the colon are similar. Large studies have demonstrated that regular surveillance colonoscopy and polyp removal reduces the incidence of colorectal adenocarcinoma. Despite this strong relationship, it must be emphasized that majority of adenomas do not progress to become adenocarcinomas. There are no tools presently available to distinguish between adenomas that will or will not undergo malignant transformation, and indeed it may be that transformation is stochastic, being dependent on acquisition of oncogenic mutations merely by chance. Most adenomas are clinically silent, with the exception of large polyps that produce occult bleeding and anemia and rare villous adenomas that cause hypoproteinemic hypokalemia by secreting large amounts of protein and potassium.

b0215 ## MORPHOLOGY

p2905 Typical adenomas range from 0.3 to 10 cm in diameter and can be pedunculated (Fig. 17-45*A*) or sessile, with the surface of both types having a texture resembling velvet or a raspberry (Fig. 17-45*B*). Histologically, the hallmark of epithelial dysplasia is nuclear hyperchromasia, elongation, and stratification (see Fig. 17-46*C*). These changes are most easily appreciated at the surface of the adenoma and are often accompanied by prominent nucleoli, eosinophilic cytoplasm, and a reduction in the number of goblet cells. Notably, epithelial cells fail to mature as they migrate from crypt to surface. Pedunculated adenomas have slender fibromuscular stalks (Fig. 17-45*C*) containing prominent blood vessels derived from the submucosa. The stalk is usually covered by nonneoplastic epithelium, but dysplastic epithelium is sometimes present.

p2910 Adenomas can be classified as **tubular, tubulovillous,** or **villous** based on their architecture. These categories, however, have little clinical significance in isolation. Tubular adenomas tend to be small, pedunculated polyps composed of rounded, or tubular, glands (Fig. 17-46*A*). In contrast, villous adenomas, which are often larger and sessile, are covered by slender villi (Fig. 17-46*B*). Tubulovillous adenomas have a mixture of tubular and villous elements. Although villous adenomas contain foci of invasion more frequently than tubular adenomas, villous architecture alone does not increase cancer risk when polyp size is considered.

p2915 **Sessile serrated adenomas** overlap histologically with hyperplastic polyps, but are more commonly found in the right colon. Despite their malignant potential, sessile serrated adenomas lack typical cytologic features of dysplasia that are present in other adenomas, prompting some to refer to these lesions as sessile serrated polyps. Histologic criteria for these lesions include serrated architecture throughout the full length of the glands, including the crypt base, crypt dilation, and lateral growth (Fig. 17-46*D*).

p2920 **Intramucosal carcinoma** occurs when dysplastic epithelial cells breach the basement membrane to invade the lamina propria or muscularis mucosae. Because functional lymphatic channels are absent in the colonic mucosa, intramucosal carcinomas have little or no metastatic potential and complete polypectomy is generally curative (Fig. 17-47*A*). Invasion beyond the muscularis mucosae, including into the submucosal stalk of a pedunculated polyp (Fig. 17-47*B*), constitutes invasive adenocarcinoma and carries a risk of spread to other sites. In such cases several factors, including the histologic grade of the invasive component, the presence of vascular or lymphatic invasion, and the distance of the invasive component from the margin of resection, must be considered in planning further therapy.

p2925 Although most colorectal adenomas are benign lesions, a small proportion may harbor invasive cancer at the time of detection. *Size is the most important characteristic that correlates with risk of malignancy.* For example, while cancer is extremely rare in adenomas less than 1 cm in diameter, some studies suggest that nearly 40% of lesions larger than 4 cm in diameter contain foci of cancer. High-grade dysplasia is also a risk factor for cancer in an individual polyp,

f0230

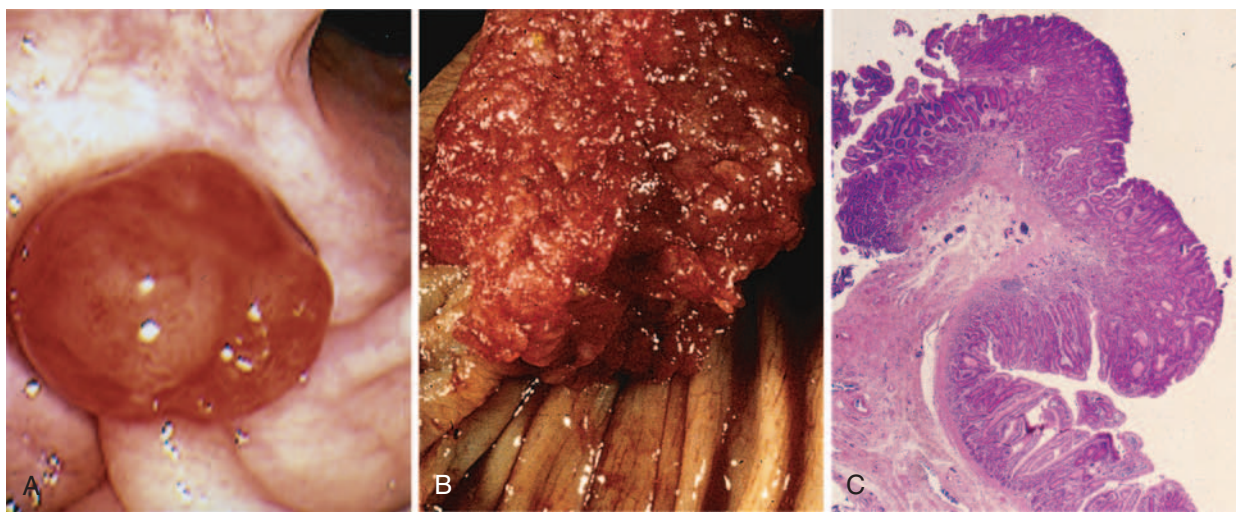
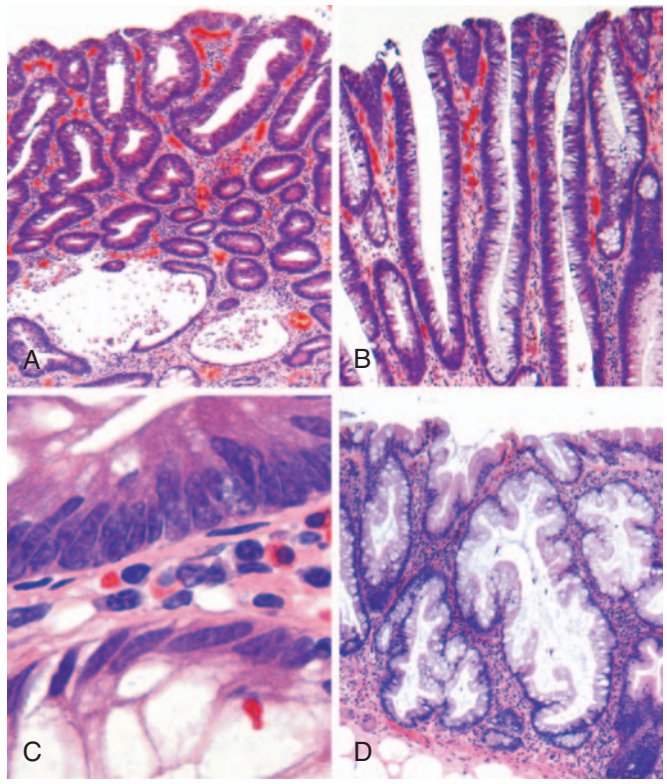


Figure 17-45 Colonic adenomas. **A,** Pedunculated adenoma (endoscopic view). **B,** Adenoma with a velvety surface. **C,** Low-magnification photomicrograph of a pedunculated tubular adenoma.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0235

Figure 17-46 Histologic appearance of colonic adenomas. **A,** Tubular adenoma with a smooth surface and rounded glands. Active inflammation is occasionally present in adenomas, in this case, crypt dilation and rupture can be seen at the bottom of the field. **B,** Villous adenoma with long, slender projections that are reminiscent of small intestinal villi. **C,** Dysplastic epithelial cells (top) with an increased nuclear-to-cytoplasmic ratio, hyperchromatic and elongated nuclei, and nuclear pseudostratification. Compare to the non-dysplastic epithelium below. **D,** Sessile serrated adenoma lined by goblet cells without cytologic features of dysplasia. This lesion is distinguished from a hyperplastic polyp by extension of the neoplastic process to the crypts, resulting in lateral growth. Compare to the hyperplastic polyp in Figure 17-44A.

but does not confer an increased risk of cancer in other polyps within the same patient.

s1245

Adenomatous Polyposis

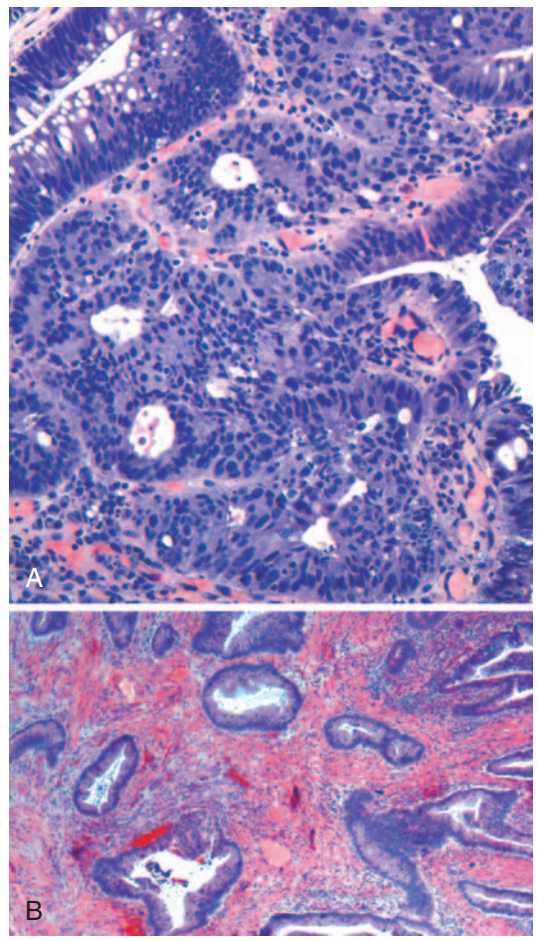
p2935 **Familial adenomatous polyposis (FAP) is an autosomal dominant disorder in which patients develop numerous colorectal adenomas as teenagers.** It is caused by mutations of the adenomatous polyposis coli, or *APC*, gene, which you will recall is a key negative regulator of the Wnt signaling pathway (Chapter 7). Approximately 75% of cases are inherited, while the remaining appear to be caused by de novo mutations.

p2940 At least 100 polyps are necessary for a diagnosis of classic FAP, but as many as several thousand may be present (Fig. 17-48). Except for their remarkable numbers, these growths are morphologically indistinguishable from sporadic adenomas. In addition, however, flat or depressed adenomas are also prevalent in FAP, and microscopic adenomas, consisting of only one or two dysplastic crypts, are frequently observed in otherwise normal-appearing mucosa.

p2945 **Colorectal adenocarcinoma develops in 100% of untreated FAP patients, often before age 30 and nearly always by age 50.** As a result, prophylactic colectomy is the standard therapy for individuals carrying *APC* mutations. Colectomy prevents colorectal cancer, but patients remain at risk for neoplasia at other sites. Adenomas may develop elsewhere in the GI tract, particularly adjacent to the ampulla of Vater and in the stomach.

p2950 FAP is associated with a variety of extraintestinal manifestations including congenital hypertrophy of the retinal pigment epithelium, which can generally be detected at birth, and therefore may be an adjunct to early screening. Specific *APC* mutations have been associated with the development of other manifestations of FAP and partly explain variants such as Gardner syndrome and Turcot syndrome (Table 17-11).

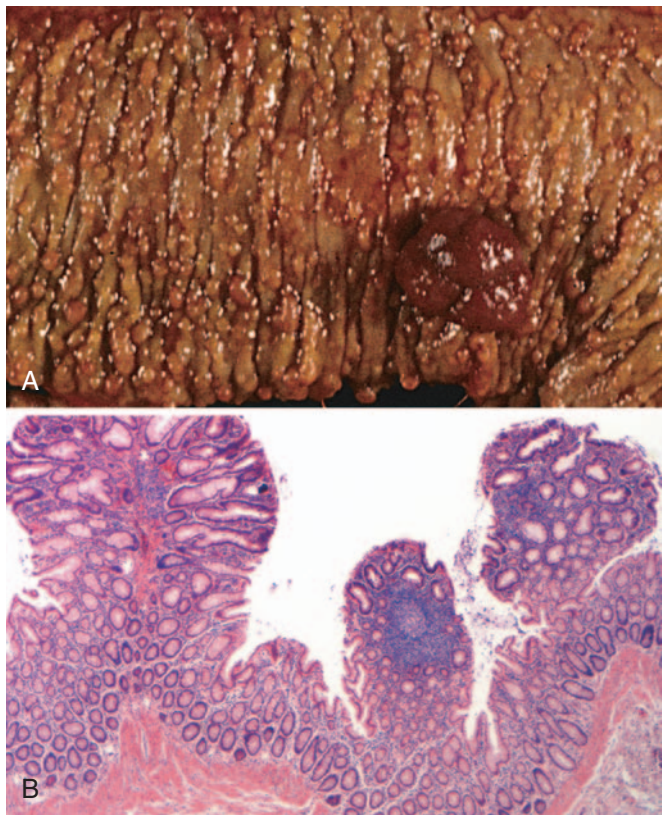
p2955 Some polyposis patients without *APC* loss have bi-allelic mutations of the base-excision repair gene *MYH* (also referred to as *MUTYH*). This autosomal recessive disorder is termed *MYH*-associated polyposis. The colonic phenotype is similar to attenuated FAP, with polyp development at later ages, the presence of fewer than 100 adenomas, and the delayed appearance of colon cancer, often at ages of 50 or older. In addition, serrated polyps, often with *KRAS*



f0240

Figure 17-47 Adenoma with intramucosal carcinoma. **A,** Cribriform glands interface directly with the lamina propria without an intervening basement membrane. **B,** Invasive adenocarcinoma (left) beneath a villous adenoma (right). Note the desmoplastic response to the invasive components.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0245 **Figure 17-48** Familial adenomatous polyposis. **A,** Hundreds of small polyps are present throughout this colon with a dominant polyp (right). **B,** Three tubular adenomas are present in this single microscopic field.

mutations, are frequently present in MUTYH-associated polyposis.

s1250

Hereditary Non-Polyposis Colorectal Cancer

p2960 Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, was originally described based on familial clustering of cancers at several sites including the colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, pancreas, and skin. HNPCC is thought to account for 2% to 4% of all colorectal cancers, making it the most common syndromic form of colon cancer. Colon cancers in HNPCC patients tend to occur at younger ages than sporadic colon cancers and are often located in the right colon (Table 17-11). Just as identification of *APC* mutations in FAP has provided molecular insights into the pathogenesis of the majority of sporadic colon cancers, unraveling the defects in HNPCC has shed light on the mechanisms responsible for most of the remaining sporadic cases. **HNPCC is caused by inherited mutations in genes that encode proteins responsible for the detection, excision, and repair of errors that occur during DNA replication** (Chapter 7). There are at least five such mismatch repair genes, but majority of patients with HNPCC have mutations in *MSH2* or *MLH1*. Patients with HNPCC inherit one mutant gene and one normal allele. When the second copy is lost through mutation or epigenetic silencing, defects in mismatch repair lead to the accumulation of mutations at rates up to 1000 times higher than normal, mostly in regions containing short repeatings sequences referred to as microsatellites. The human genome contains approximately 50,000 to 100,000 microsatellites, which are prone to undergo expansion during DNA replication and represent the most frequent sites of mutations in HNPCC. The consequences of mismatch repair deficiency and the resulting microsatellite instability are discussed next in the context of colonic adenocarcinoma.

Adenocarcinoma

s1255

Adenocarcinoma of the colon is the most common malig- p2965
nancy of the GI tract and is a major cause of morbidity and mortality worldwide. In contrast, the small intestine, which accounts for 75% of the overall length of the GI tract, is an uncommon site for benign and malignant tumors. Among malignant small intestinal tumors, adenocarcinomas and well-differentiated neuroendocrine (carcinoid) tumors have roughly equal incidence, followed by lymphomas and sarcomas.

Epidemiology. Approximately 1.2 million new cases of s1260
colorectal adenocarcinoma, and 600,000 associated deaths, p2970
occur each year worldwide. Thus, colorectal adenocarcinoma is responsible for nearly 10% of all cancer deaths. The

t0055 **Table 17-11** Common Patterns of Sporadic and Familial Colorectal Neoplasia

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
MYH-associated polyposis	DNA mismatch repair	*MYH*	Autosomal recessive	None	Sessile serrated adenoma; mucinous adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (70%-80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%-15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (5%-10%)	Hypermethylation	*MLH1, BRAF*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

incidence of these tumors is highest in North America, with the United States accounting for approximately 10% of worldwide cases and cancer deaths. This represents nearly 15% of all cancer-related deaths in the United States, second only to lung cancer. Australia, New Zealand, Europe, and, with changes in lifestyle and diet, Japan, also have high incidences of colorectal adenocarcinoma. In contrast, rates are lower in South America, India, Africa, and South Central Asia. Colorectal cancer incidence peaks at 60 to 70 years of age, with fewer than 20% of cases occuring before age 50.

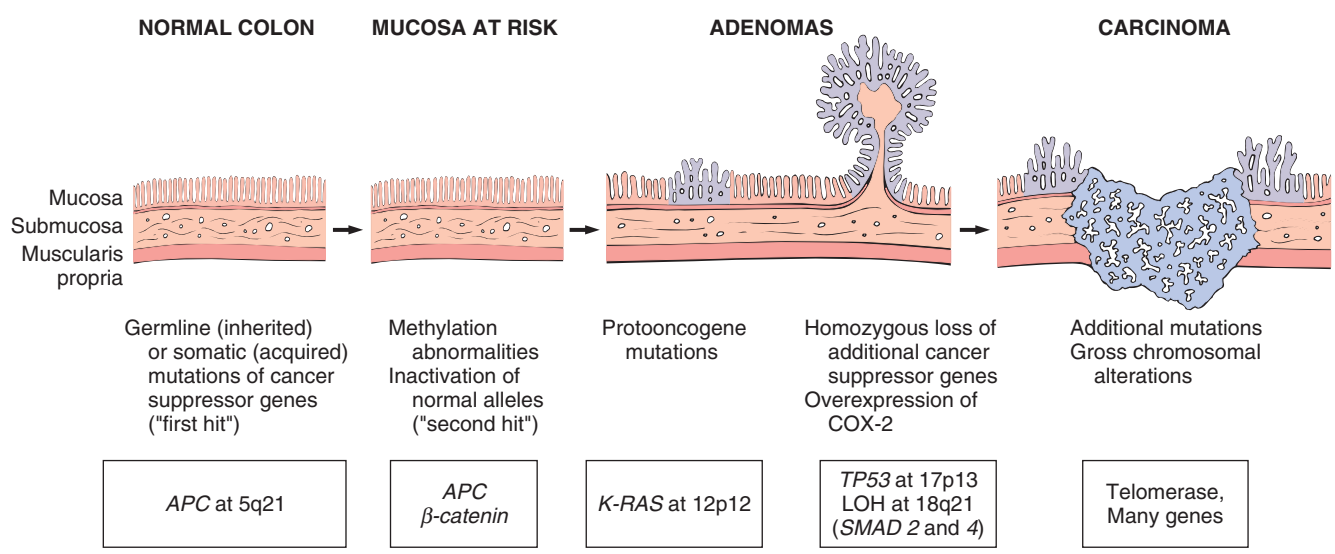
p2975 The *dietary factors* most closely associated with increased rates of colorectal cancer are low intake of unabsorbable vegetable fiber and high intake of refined carbohydrates and fat. Although these associations are clear, the mechanistic relationship between diet and risk remains poorly understood. It is theorized that reduced fiber content leads to decreased stool bulk and altered composition of the intestinal microbiota. This change may increase synthesis of potentially toxic oxidative by-products of bacterial metabolism, which would be expected to remain in contact with the colonic mucosa for longer periods of time as a result of reduced stool bulk. High fat intake also enhances hepatic synthesis of cholesterol and bile acids, which can be converted into carcinogens by intestinal bacteria.

p2980 In addition to dietary modification, *pharmacologic chemoprevention* has become an area of great interest. Several epidemiologic studies suggest that aspirin or other NSAIDs have a protective effect. This is consistent with studies showing that some NSAIDs cause polyp regression in FAP patients in whom the rectum was left in place after colectomy. It is suspected that this effect is mediated by inhibition of the enzyme cyclooxygenase-2 (COX-2), which is highly expressed in 90% of colorectal carcinomas and 40% to 90% of adenomas. COX-2 is necessary for production of prostaglandin E_2, which promotes epithelial proliferation, particularly after injury. Of further interest, COX-2 expression is regulated by TLR4, which recognizes lipopolysaccharide and is also overexpressed in adenomas and carcinomas.

Pathogenesis. Studies of colorectal carcinogenesis have s1280 provided fundamental insights into the general mecha- p2985 nisms of cancer evolution. These were discussed in Chapter 7; concepts that pertain specifically to colorectal carcinogenesis will be reviewed here.

The combination of molecular events that lead to p2990 colonic adenocarcinoma is heterogeneous and includes genetic and epigenetic abnormalities. At least two genetic pathways have been described. In simplest terms, these are the *APC/β-catenin pathway,* which is activated in the classic adenoma-carcinoma sequence; and the *microsatellite instability pathway*, which is associated with defects in DNA mismatch repair and accumulation of mutations in microsatellite repeat regions of the genome (Table 17-11). Both pathways involve the stepwise accumulation of multiple mutations, but differ in the genes involved and the mechanisms by which mutations accumulate. Epigenetic events, the most common of which is methylation-induced gene silencing, may enhance progression along either pathway.

- **The classic adenoma-carcinoma sequence, accounts** u1205 **for up to 80% of sporadic colon tumors and typically includes mutation of *APC* early in the neoplastic process** (Fig. 17-49)**.** Both copies of the *APC* gene must be functionally inactivated, either by mutation or epigenetic events, for adenomas to develop. *APC is a key negative regulator of β-catenin, a component of the Wnt signaling pathway* (Chapter 7)**.** The APC protein normally binds to and promotes degradation of β-catenin. With loss of APC function, β-catenin accumulates and



f0250 **Figure 17-49** Morphologic and molecular changes in the adenoma-carcinoma sequence. Loss of one normal copy of the tumor suppressor gene *APC* occurs early. Individuals born with one mutant allele are therefore at increased risk of developing colon cancer. Alternatively, inactivation of *APC* in colonic epithelium may occur later in life. This is the "first hit" according to the Knudson hypothesis (Chapter 7). The loss of the intact second copy of *APC* follows ("second hit"). Other changes, including mutation of *KRAS*, losses at 18q21 involving *SMAD2* and *SMAD4*, and inactivation of the tumor suppressor gene *TP53*, lead to the emergence of carcinoma, in which further mutations occur. Although there seems to be a temporal sequence of changes, the accumulation of mutations, rather than their occurrence in a specific order, is most critical.

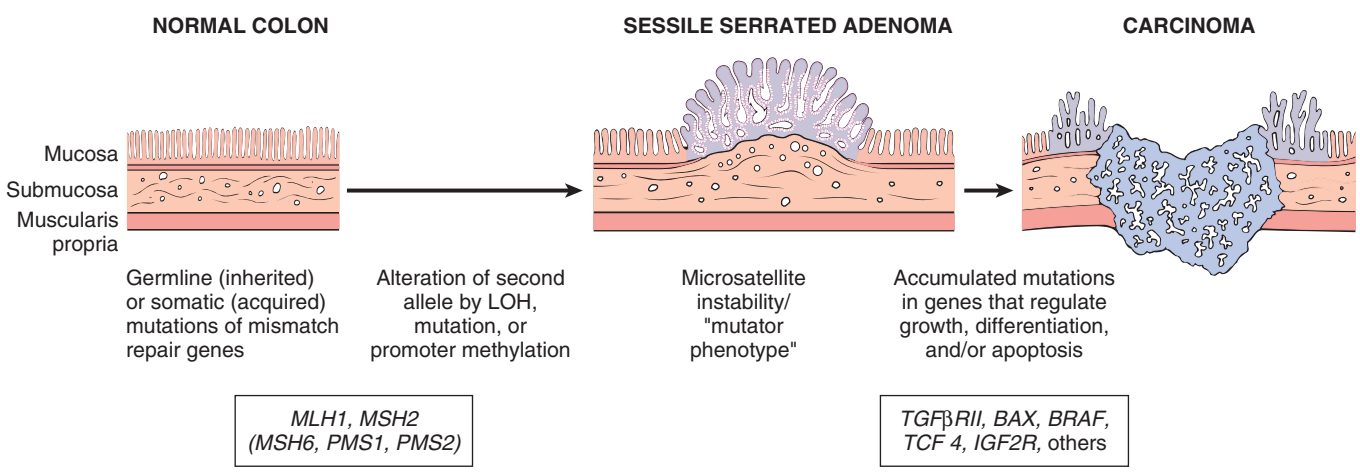
ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

translocates to the nucleus, where it forms a complex with the DNA-binding factor TCF and activates the transcription of genes, including MYC and cyclin D1, that promote proliferation. The critical role of β-catenin in this pathway is demonstrated by the fact that many colon cancers without *APC* mutations harbor β-catenin mutations that allow them to avoid APC-dependent degradation, thereby having the same impact as loss of APC function. Additional mutations accumulate, including activating mutations in *KRAS* that promote growth and prevent apoptosis. The idea that mutation of *KRAS* is a late event in carcinoma development is supported by the observation that such mutations are present in fewer than 10% of adenomas less than 1 cm in diameter but are found in 50% of adenomas greater than 1 cm in diameter and in 50% of invasive adenocarcinomas. Neoplastic progression is also associated with mutations in other tumor suppressor genes such as those encoding SMAD2 and SMAD4, which are effectors of TGF-β signaling. Because TGF-β signaling normally inhibits the cell cycle, loss of these genes may allow unrestrained cell growth. The tumor suppressor gene *TP53* is mutated in 70% to 80% of colon cancers, but is uncommonly affected in adenomas, suggesting that *TP53* mutations also occur at later stages of tumor progression. Loss of function of *TP53* and other tumor suppressor genes is often caused by chromosomal deletions, supporting the idea that chromosomal instability is a hallmark of the APC/β-catenin pathway. Alternatively, tumor suppressor genes may be silenced by methylation of a CpG-rich zone, or CpG island, a 5′ region of some genes that frequently includes the promoter and transcriptional start site. Expression of telomerase also increases as lesions become more advanced.

u1210 • **In patients with DNA mismatch repair deficiency, mutations accumulate in microsatellite repeats, a condition referred to as microsatellite instability (MSI).** These are referred to as MSI high, or MSI-H, tumors. Some microsatellite sequences are located in the coding or promoter regions of genes involved in regulation of cell growth, such as those encoding the type II TGF-β receptor and the pro-apoptotic protein BAX (Fig. 17-50). Because TGF-β inhibits colonic epithelial cell proliferation, mutation of type II TGF-β receptor can contribute to uncontrolled cell growth, while loss of *BAX* may enhance the survival of genetically abnormal clones.

- **A subset of microsatellite unstable colon cancers without mutations in DNA mismatch repair enzymes demonstrate the CpG island hypermethylation phenotype (CIMP).** In these tumors, the *MLH1* promoter region is typically hypermethylated, thereby reducing MLH1 expression and repair function. Activating mutations in the oncogene *BRAF* are common in these cancers. In contrast, *KRAS* and *TP53* are not typically mutated. Thus, the combination of microsatellite instability, *BRAF* mutation, and methylation of specific targets, such as *MLH1*, is the signature of this pathway of carcinogenesis. u1215
- **A small group of colon cancers display increased CpG island methylation in the absence of microsatellite instability.** Many of these tumors harbor *KRAS* mutations, but *TP53* and *BRAF* mutations are uncommon. In contrast, *TP53* mutations are common in colon cancers that do not display a CpG island methylator phenotype. u1220

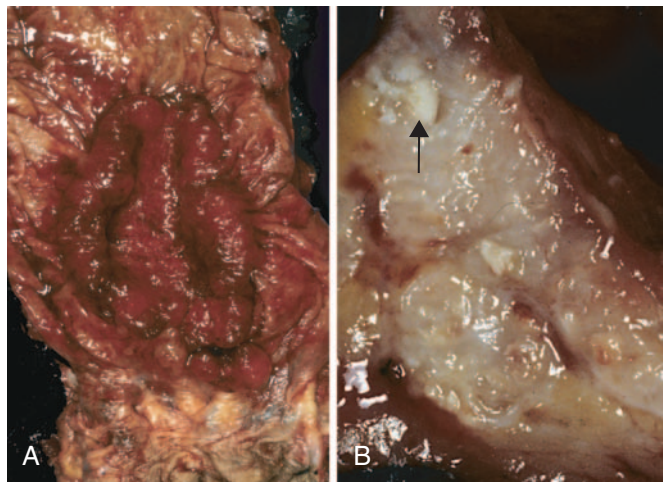
While morphology cannot reliably define the underlying molecular events that lead to carcinogenesis, certain correlations have been associated with mismatch repair deficiency and microsatellite instability. These molecular alterations are common in sessile serrated adenomas and cancers that arise from them. In addition, invasive carcinomas with microsatellite instability often have prominent mucinous differentiation and peritumoral lymphocytic infiltrates. These tumors, as well as those with a CpG island hypermethylation phenotype, are frequently located in the right colon. Tumors with microsatellite instability can be recognized by the absence of immunohistochemical staining for mismatch repair proteins or by molecular genetic analysis of microsatellite sequences. It is important to identify patients with HNPCC because of the implications for genetic counseling, the elevated risk of a second malignancy of the colon or other organs, and, in some settings, differences in prognosis and therapy. p3015



f0255

Figure 17-50 Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair genes result in microsatellite instability and permit accumulation of mutations in numerous genes. If these mutations affect genes involved in cell survival and proliferation, cancer may develop.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0260 **Figure 17-51** Colorectal carcinoma. **A,** Circumferential, ulcerated rectal cancer. Note the anal mucosa at the bottom of the image. **B,** Cancer of the sigmoid colon that has invaded through the muscularis propria and is present within subserosal adipose tissue (left). Areas of chalky necrosis are present within the colon wall *(arrow).*

b0220 ## MORPHOLOGY

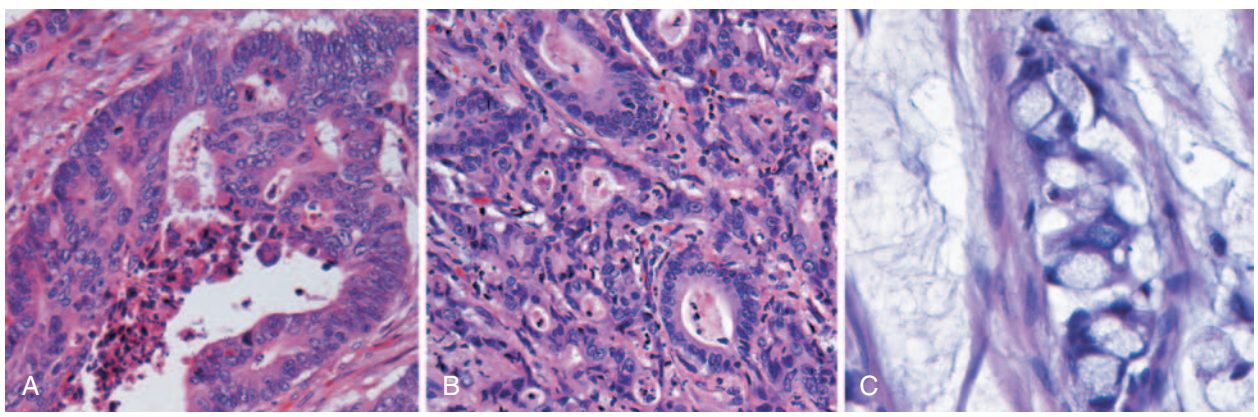
p3020 **Overall, adenocarcinomas are distributed approximately equally over the entire length of the colon.** Tumors in the **proximal colon often grow as polypoid, exophytic masses** that extend along one wall of the large-caliber cecum and ascending colon; these tumors rarely cause obstruction. In contrast, **carcinomas in the distal colon tend to be annular lesions** that produce "napkin-ring" constrictions and luminal narrowing (Fig. 17-51), sometimes to the point of obstruction. Both forms grow into the bowel wall over time. The general microscopic characteristics of right- and left-sided colonic adenocarcinomas are similar. Most tumors are composed of tall columnar cells that resemble dysplastic epithelium found in adenomas (Fig. 17-52*A*). The invasive component of these tumors elicits a strong stromal desmoplastic response, which is responsible for their characteristic firm consistency. Some poorly differentiated tumors form few glands (Fig. 17-52*B*). Others may produce abundant mucin that accumulates within the intestinal wall, and these are associated with poor prognosis. Tumors may also be composed of signet-ring cells that are similar to those in gastric cancer (Fig. 17-52*C*) or may display features of neuroendocrine differentiation.

Clinical Features. The availability of endoscopic screening s1285
combined with the knowledge that most carcinomas arise p3025
within adenomas presents a unique opportunity for cancer prevention. Unfortunately, colorectal cancers develop insidiously and may go undetected for long periods. Cecal and other *right-sided colon cancers* are most often called to clinical attention by the appearance of *fatigue and weakness due to iron deficiency anemia*. Thus, it is a clinical maxim that the underlying cause of iron deficiency anemia in an older man or postmenopausal woman is GI cancer until proven otherwise. *Left-sided colorectal adenocarcinomas* may produce *occult bleeding*, *changes in bowel habits*, or *cramping* and *left lower quadrant discomfort*.

Although poorly differentiated and mucinous histologies are associated with poor prognosis, *the two most important prognostic factors are depth of invasion and the presence of lymph node metastases.* Invasion into the muscularis propria confers significantly reduced survival that is decreased further by the presence of lymph node metastases (Fig. 17-53*A*). Metastases may involve regional lymph nodes, lungs (Fig. 17-53*B*) and bones, but as a result of portal drainage of the colon, the liver is the most common site of metastatic lesions (Fig. 17-53*C*). The rectum does not drain via the portal circulation, hence carcinomas of the anal region that metastasize often circumvent the liver. p3030

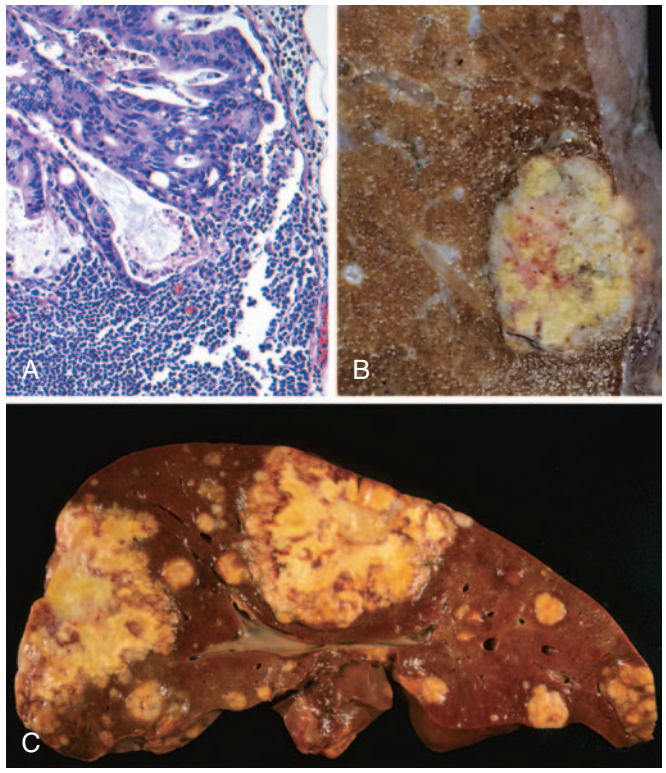
The prognostic factors were originally recognized by p3035
Dukes and Kirklin and form the core of the TNM (tumor-nodes-metastasis) classification (Table 17-12). The American Joint Committee on Cancer (AJCC) staging system is compared to the Astler-Coller modification of the Dukes system in Table 17-13. Regardless of stage, it must be remembered that some patients with small numbers of metastases do well for years following resection of distant tumor nodules.

Five-year survival rates vary widely worldwide. The p3040
overall 5-year survival rate in the United States is 65%, and ranges from 90% to 40% depending on stage. Survival rates in Europe, Japan and Australia are similar, ranging



f0265 **Figure 17-52** Histologic appearance of colorectal carcinoma. **A,** Well-differentiated adenocarcinoma. Note the elongated, hyperchromatic nuclei. Necrotic debris, present in the gland lumen, is typical. **B,** Poorly differentiated adenocarcinoma forms a few glands but is largely composed of infiltrating nests of tumor cells. **C,** Mucinous adenocarcinoma with signet-ring cells and extracellular mucin pools.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017



f0270

Figure 17-53 Metastatic colorectal carcinoma. **A,** Lymph node metastasis. Note the glandular structures within the subcapsular sinus. **B,** Solitary subpleural nodule of colorectal carcinoma metastatic to the lung. **C,** Liver containing two large and many smaller metastases. Note the central necrosis within metastases.

from 60% (Switzerland, Japan) to (40%) Poland. Overall survival rates are somewhat lower in other countries, such as China, India, the Philippines, and Thailand (30% to 42%). Sadly, the 5-year survival rate in Gambia is only 4%.

b0225

KEY CONCEPTS

s9035

Benign and malignant proliferative lesions of the colon

p3050 ■ **Intestinal polyps** can be classified as nonneoplastic or neoplastic. The nonneoplastic polyps can be further defined as hyperplastic, inflammatory, or hamartomatous.

u1230 ■ **Hyperplastic polyps** are benign epithelial proliferations most commonly found in the left colon and rectum. They have no malignant potential, and must be distinguished from sessile serrated adenomas.

u1235 ■ **Inflammatory polyps** form as a result of chronic cycles of injury and healing.

u1240 ■ **Hamartomatous polyps** occur sporadically or as a part of genetic diseases. The latter include **juvenile polyposis** and **Peutz-Jeghers Syndrome**, which are associated with **increased risk of malignancy**.

u1245 ■ Benign epithelial neoplastic polyps of the intestines are termed **adenomas**. The hallmark of these lesions, which are the precursors of colonic adenocarcinomas, is cytologic dysplasia.

u1250 ■ In contrast to traditional adenomas, **sessile serrated adenomas** lack cytologic dysplasia and share morphologic features with hyperplastic polyps.

t0060

Table 17-12 American Joint Committee on Cancer (AJCC) TNM Classification of Colorectal Carcinoma

TNM	
Tumor	
Tis	In situ dysplasia or intramucosal carcinoma
T1	Tumor invades submucosa
T2	Tumor invades into, but not through, muscularis propria
T3	Tumor invades through muscularis propria
T3a	Invasion < 0.1 cm beyond muscularis propria
T3b	Invasion 0.1 to 0.5 cm beyond muscularis propria
T3c	Invasion > 0.5 to 1.5 cm beyond muscularis propria
T3d	Invasion > 1.5 cm beyond muscularis propria
T4	Tumor penetrates visceral peritoneum or invades adjacent organs
T4a	Penetration into visceral peritoneum
T4b	Invasion into other organs or structures
Regional Lymph Nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N1a	Metastasis in one regional lymph nodes
N1b	Metastasis in two or three regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in four to six regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site
M1b	Metastases in more than one organ/site or the peritoneum

t0065

Table 17-13 Colorectal Cancer Staging Systems

	American Joint Committee on Cancer (AJCC) Stage			Astler-Coller Modification of Dukes Classification
	T	N	M	
I	T1 T2	N0 N0	M0 M0	A B1
IIA	T3	N0	M0	B2
IIB	T4a	N0	M0	B2
IIC	T4b	N0	M0	B3
IIIA	T1-T2 T1	N1/N1c N2a	M0 M0	C1 C1
IIIB	T3, T4a T2, T3 T1, T2	N1 (any) N2a N2b	M0 M0 M0	C2 C1/C2 C1
IIIC	T4a T3, T4a T4b	N2a N2b N1, N2	M0 M0 M0	C2 C2 C3
IVA	Any T	Any N	M1a	D*
IVB	Any T	Any N	M1b	D*

*Stages not included in original Dukes classification; added later for comparison with AJCC staging.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

u1255 ■ **Familial adenomatous polyposis** (FAP) and **hereditary non-polyposis colorectal cancer** (HNPCC) are the most common forms of familial colon cancer.

u1260 ■ **FAP** is caused by *APC* mutations. Patients typically have more than 100 adenomas and develop colon cancer before 30 years of age.

u1265 ■ **HNPCC** is caused by mutations in DNA mismatch repair enzymes. HNPCC patients have far fewer polyps and develop cancer at older ages than FAP patients but younger ages than those with sporadic colon cancer.

u1270 ■ FAP and HNPCC typify **distinct pathways of neoplastic transformation and progression** that also contribute to the majority of **sporadic colon cancers**.

u1275 ■ Nearly all colonic cancers are **adenocarcinomas**. The two most important prognostic factors are **depth of invasion** and the presence or absence of **lymph node metastases**.

s1290

Tumors of the Anal Canal

p3045 The anal canal can be divided into thirds. The upper zone is lined by columnar rectal epithelium; the middle third by transitional epithelium; and the lower third by stratified squamous epithelium. Carcinomas of the anal canal may have typical glandular or squamous patterns of differentiation, recapitulating the normal epithelium of the upper and lower thirds, respectively (Fig. 17-54*A*). An additional differentiation pattern, termed basaloid, is present in tumors populated by immature cells derived from the basal layer of transitional epithelium (Fig. 17-54*B*). When the entire tumor displays a basaloid pattern, the archaic term cloacogenic carcinoma is still often applied. Alternatively, basaloid differentiation may be mixed with squamous or mucinous differentiation. All are considered variants of anal canal carcinoma. Pure squamous cell carcinoma of the anal canal is frequently associated with HPV infection, which also causes precursor lesions such as condyloma acuminatum (Fig. 17-54*C*).

s1295

Hemorrhoids

p3110 Hemorrhoids affect about 5% of the general population and develop secondary to persistently elevated venous pressure within the hemorrhoidal plexus. The most frequent predisposing influences are straining at defecation, because of constipation, and the venous stasis of pregnancy. Hemorrhoids may also develop in association with portal hypertension. The pathogenesis of hemorrhoids (anal varices) in portal hypertension is similar to that of esophageal varices, although anal varices are both more common and much less serious. Variceal dilations of the anal and perianal venous plexuses form collaterals that connect the portal and caval venous systems, thereby relieving the venous hypertension.

p3115

MORPHOLOGY

b0230

p3120 Collateral vessels within the inferior hemorrhoidal plexus are located below the anorectal line and are termed **external hemorrhoids**, while those that result from dilation of the superior hemorrhoidal plexus within the distal rectum are referred to as **internal hemorrhoids.** Histologically, hemorrhoids consist of thin-walled, dilated, submucosal vessels that protrude beneath the anal or rectal mucosa. In their exposed position, they are subject to trauma and tend to become inflamed, thrombosed, and, in the course of time, recanalized. Superficial ulceration may occur.

p3125 Hemorrhoids often present with pain and rectal bleeding, particularly bright red blood seen on toilet tissue. Except for pregnant women, hemorrhoids are rarely encountered in persons younger than age 30. Hemorrhoidal bleeding is not generally a medical emergency and can be treated by sclerotherapy, rubber band ligation, or infrared coagulation. Extensive or severe internal or external hemorrhoids may be removed surgically by hemorrhoidectomy.

f0275

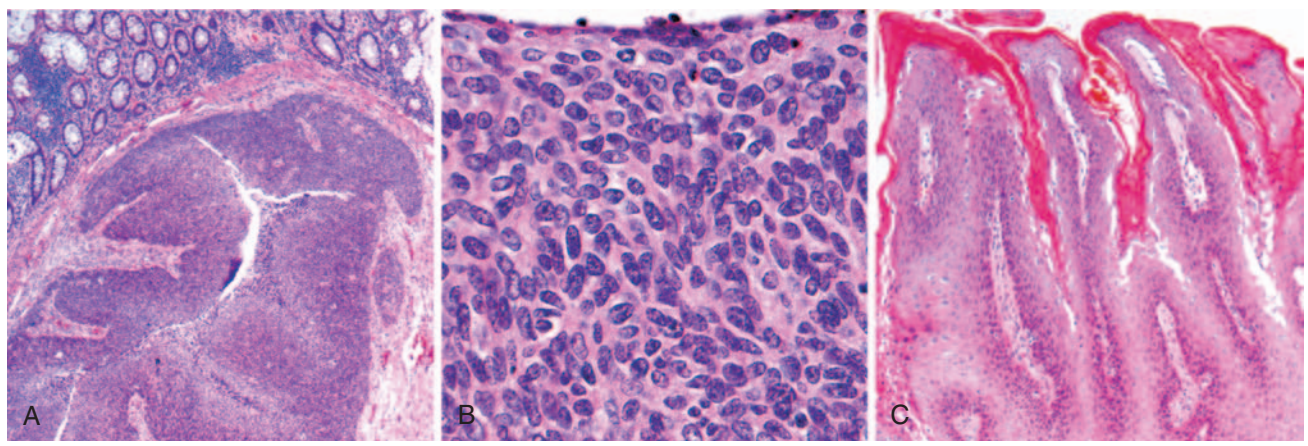


Figure 17-54 Anal tumors. **A,** This anal transition zone carcinoma demonstrates a multilayered organization reminiscent of benign squamous mucosa. The adjacent rectal mucosa is intact. **B,** This basaloid anal transition zone tumor is composed of hyperchromatic cells that resemble the basal layer of normal squamous mucosa. **C,** Condyloma acuminatum with verrucous architecture.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

Acute Appendicitis

The appendix is a normal true diverticulum of the cecum that is prone to acute and chronic inflammation. Acute appendicitis is most common in adolescents and young adults, with a lifetime risk of 7%; males are affected slightly more often than females. Despite the prevalence of acute appendicitis, the diagnosis can be difficult to confirm preoperatively and may be confused with mesenteric lymphadenitis (often secondary to unrecognized *Yersinia* infection or viral enterocolitis), acute salpingitis, ectopic pregnancy, mittelschmerz (pain caused by minor pelvic bleeding at the time of ovulation), and Meckel diverticulitis.

Pathogenesis. Acute appendicitis is thought to be initiated by progressive increases in intraluminal pressure that compromise venous outflow. In 50% to 80% of cases, acute appendicitis is associated with overt luminal obstruction, usually caused by a small stone-like mass of stool, or fecalith, or, less commonly, a gallstone, tumor, or mass of worms (oxyuriasis vermicularis). Stasis of luminal contents, which favors bacterial proliferation, triggers ischemia and inflammatory responses, resulting in tissue edema and neutrophilic infiltration of the lumen, muscular wall, and periappendiceal soft tissues.

MORPHOLOGY

In early acute appendicitis subserosal vessels are congested and there is a modest perivascular neutrophilic infiltrate within all layers of the wall. The inflammatory reaction transforms the normal glistening serosa into a dull, granular, erythematous surface. Although mucosal neutrophils and focal superficial ulceration are often present, these are not specific markers of acute appendicitis. Diagnosis of acute appendicitis requires **neutrophilic infiltration of the muscularis propria.** In more severe cases a prominent neutrophilic exudate generates a serosal fibrinopurulent reaction. As the process continues, focal abscesses may form within the wall (acute suppurative appendicitis). Further compromise of appendiceal vessels leads to large areas of hemorrhagic ulceration and gangrenous necrosis that extends to the serosa creating acute gangrenous appendicitis, which can be followed by rupture and suppurative peritonitis.

Clinical Features. Typically, early acute appendicitis produces periumbilical pain that ultimately localizes to the right lower quadrant, followed by nausea, vomiting, low-grade fever, and a mildly elevated peripheral white cell count. A classic physical finding is the *McBurney sign*, deep tenderness located two thirds of the distance from the umbilicus to the right anterior superior iliac spine (McBurney point).

Regrettably, classic signs and symptoms of acute appendicitis are often absent. In some cases, a retrocecal appendix may generate right flank or pelvic pain, while a malrotated colon may give rise to appendicitis in the left upper quadrant. As with other causes of acute inflammation there is neutrophilic leukocytosis. In some cases the peripheral leukocytosis may be minimal or, alternatively, so great that other causes are considered. The diagnosis of acute appendicitis in young children and the very old is particularly problematic, since other causes of abdominal emergencies are prevalent in these populations, and the very young and old are also more likely to have atypical clinical presentations.

Given these diagnostic challenges, it should be no surprise that even highly skilled surgeons remove normal appendices. This is preferred to delayed resection of a diseased appendix, given the significant morbidity and mortality associated with appendiceal perforation. Other complications of appendicitis include pyelophlebitis, portal venous thrombosis, liver abscess, and bacteremia.

Tumors of the Appendix

The most common tumor of the appendix is the well-differentiated neuroendocrine (carcinoid) tumor. It is usually discovered incidentally at the time of surgery or examination of a resected appendix. This neoplasm, which is almost always benign, most frequently forms a solid bulbous swelling at the distal tip of the appendix, where it can reach 2 to 3 cm in diameter. Although intramural and transmural extension may be evident, nodal metastases are very infrequent, and distant spread is exceptionally rare. Conventional adenomas or non–mucin-producing adenocarcinomas also occur in the appendix and may cause obstruction and enlargement that mimics acute appendicitis. Mucocele, a dilated appendix filled with mucin, may simply represent an obstructed appendix containing inspissated mucin or be a consequence of mucinous cystadenoma or mucinous cystadenocarcinoma. In the latter instance, invasion through the appendiceal wall can lead to intraperitoneal seeding and spread. In women the resulting peritoneal implants may be mistaken for mucinous ovarian tumors. In the most advanced cases the abdomen fills with tenacious, semisolid mucin, a condition called *pseudomyxoma peritonei* (Chapter 22). This disseminated intraperitoneal disease may be held in check for years by repeated debulking but, in most instances, follows an inexorably fatal course.

KEY CONCEPTS

- **Hemorrhoids** are collateral vessels that develop secondary to persistently elevated venous pressure within the hemorrhoidal plexus. They also occur in portal hypertension.
- **Acute appendicitis** is most common in children and adolescents. It is thought to be initiated by increased intraluminal pressure and compromised venous outflow
- The most common tumor of the appendix is the **benign carcinoid.**
- Peritoneal dissemination of mucinous tumors can cause **pseudomyxoma peritonei**.

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

s1360

PERITONEAL CAVITY

p3180 The peritoneal cavity houses the abdominal viscera and is lined by a single layer of mesothelial cells; these cover the visceral and parietal surfaces and are supported by a thin layer of connective tissue to form the peritoneum. Here we discuss inflammatory, infectious, and neoplastic disorders of the peritoneal cavity and retroperitoneal space. Although they are less common than inflammatory and infectious processes, tumors can carry a grave prognosis and, thus, also deserve discussion.

s1365

Inflammatory Disease

p3185 Peritonitis may result from bacterial invasion or chemical irritation and is most often due to:

u1300 • Leakage of bile or pancreatic enzymes, which produces *sterile peritonitis*

u1305 • *Perforation or rupture of the biliary system* that evokes a highly irritating peritonitis, usually complicated by bacterial superinfection

u1310 • *Acute hemorrhagic pancreatitis* (Chapter 19), which is associated with leakage of pancreatic enzymes and fat necrosis. Damage to the bowel wall may allow bacteria to spread to the peritoneal cavity.

u1315 • *Foreign material*, including that introduced surgically (e.g., talc and sutures), that induces foreign body-type granulomas and fibrous scarring

u1320 • *Endometriosis*, which causes hemorrhage into the peritoneal cavity, where it acts as an irritant

u1325 • *Ruptured dermoid cysts* that release keratins and induce an intense granulomatous reaction

u1330 • *Perforation* of abdominal viscera.

s1370

Peritoneal Infection

p3225 Bacterial peritonitis occurs when bacteria from the gastrointestinal lumen are released into the abdominal cavity, most commonly following perforation. *E. coli*, streptococci, *S. aureus*, enterococci, and *C. perfringens* are implicated most often.

p3230 Spontaneous bacterial peritonitis develops in the absence of an obvious source of contamination. It is seen most often in patients with cirrhosis and ascites and less frequently in children with nephrotic syndrome.

b0245

MORPHOLOGY

p3235 The cellular inflammatory response is composed primarily of dense collections of neutrophils and fibrinopurulent debris that coat the viscera and abdominal wall. Serous or slightly turbid fluid begins to accumulate and becomes suppurative as infection progresses. Subhepatic and subdiaphragmatic abscesses may be formed. With the exception of tuberculous peritonitis, the reaction usually remains superficial.

Sclerosing Retroperitonitis s1375

Sclerosing retroperitonitis, also known as idiopathic retroperitoneal fibrosis or Ormond disease, is characterized by dense fibrosis that may extend to involve the mesentery. Although the cause of sclerosing retroperitonitis is unknown, many cases are now thought to fall within the spectrum of IgG4-related sclerosing disease, an immunoinflammatory disorder that can lead to fibrosis in a wide variety of tissues. Because the process frequently compresses the ureters, this entity is described in more detail in Chapters 6 and 21. p3240

Tumors s1380

Primary malignant tumors arising from peritoneal lining are mesotheliomas that are similar to tumors of the pleura and pericardium. Peritoneal mesotheliomas are almost always associated with significant asbestos exposure. Rarely, primary benign and malignant soft-tissue tumors may also develop within the peritoneum and retroperitoneum. The most common of these is desmoplastic small round cell tumor. This is an aggressive tumor that occurs in children and young adults and bears resemblance to Ewing sarcoma and other small round cell tumors. It is characterized by a reciprocal translocation, t(11;22)(p13;q12) that results in the formation of a fusion gene involving *EWS* and *WT1* genes. p3245

Secondary tumors may involve the peritoneum by direct spread or metastatic seeding, resulting in peritoneal carcinomatosis. Mucinous carcinomas, particularly those of the appendix may cause pseudomyxoma peritonei. p3250

SUGGESTED READINGS

Congenital Abnormalities

Amin SC, Pappas C, Iyengar H, et al: Short bowel syndrome in the NICU. *Clin Perinatol* 40:53, 2013. *[A comprehensive discussion of the epidemiology and management of short bowel syndrome in neonates.]*

Kapur RP: Practical pathology and genetics of Hirschsprung's disease. *Semin Pediatr Surg* 18:212, 2009. *[A review of Hirschsprung disease etiology and diagnosis.]*

Peeters B, Benninga MA, Hennekam RC: Infantile hypertrophic pyloric stenosis–genetics and syndromes. *Nat Rev Gastroenterol Hepatol* 9:646, 2012. *[A review that focuses on disease mechanisms and clinical associations.]*

Esophagus

Esophageal Obstruction p9005

Clarke JO, Pandolfino JE: Esophageal motor disorders: how to bridge the gap between advanced diagnostic tools and paucity of therapeutic modalities? *J Clin Gastroenterol* 46:442, 2012. *[A diagnosis-based discussion of esophageal motor disorders.]*

Richter JE, Boeckxstaens GE: Management of achalasia: surgery or pneumatic dilation. *Gut* 60:869, 2011. *[A therapy-focused discussion of the etiology, pathophysiology, and management of achalasia.]*

Esophagitis

Abonia JP, Rothenberg ME: Eosinophilic esophagitis: rapidly advancing insights. *Annu Rev Med* 63:421, 2012. *[Comprehensive review of pathobiology and treatment of eosinophilic esophagitis.]*

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

Coss-Adame E, Erdogan A, Rao SS: Treatment of Esophageal (Non-cardiac) Chest Pain: Review. *Clin Gastroenterol Hepatol* 2013. *[A careful consideration of the approach to a patient with esophageal symptoms.]*

Kandulski A, Malfertheiner P: Gastroesophageal reflux disease–from reflux episodes to mucosal inflammation. *Nat Rev Gastroenterol Hepatol* 9:15, 2012. *[A mechanism-based update on gastroesophageal reflux.]*

Barrett Esophagus

Jankowski JA, Satsangi J: Barrett's esophagus: evolutionary insights from genomics. *Gastroenterol* 144:667, 2013. *[A detailed discussion of Barrett esophagus pathogenesis.]*

Kahrilas PJ: The problems with surveillance of Barrett's esophagus. *N Engl J Med* 365:1437, 2011. *[Analysis of the utility of current surveillance protocols for esophageal glandular dysplasia.]*

Shaheen NJ, Sharma P, Overholt BF, et al.: Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 360:2277, 2009. *[Clinical trial report for radiofrequency ablation of Barrett esophagus.]*

Sharma P: Clinical practice. Barrett's esophagus, *N Engl J Med* 361:2548, 2009. *[A comprehensive discussion of Barrett esophagus.]*

Spechler SJ, Fitzgerald RC, Prasad GA, et al: History, molecular mechanisms, and endoscopic treatment of Barrett's esophagus. *Gastroenterol* 138:854, 2010. *[Overarching review of Barrett esophagus.]*

Spechler SJ, Sharma P, Souza RF, et al: American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterol* 140:e18, 2011. *[Practice-based focus on management of Barrett esophagus.]*

Esophageal Tumors

Cook MB, Shaheen NJ, Anderson LA, et al: Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. *Gastroenterol* 142:744, 2012. *[Analysis of risk factors associated with Barrett esophagus.]*

Fleischer DE: Comparing apples with apples and oranges: the role of radiofrequency ablation alone versus radiofrequency ablation plus EMR for endoscopic management of Barrett's esophagus with advanced neoplasia. *Gastrointest Endosc* 76:740, 2012. *[Comparison of therapeutic options in Barrett esophagus with neoplasia.]*

Hvid-Jensen F, Pedersen L, Drewes AM, et al: Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 365:1375, 2011. *[Analysis of adenocarcinoma risk for Barrett esophagus patients.]*

Stomach

p9010

Gastropathy and Acute Gastritis

Ali T, Harty RF: Stress-induced ulcer bleeding in critically ill patients. *Gastroenterol Clin North Am* 38:245, 2009. *[Historically and clinically focused discussion of stress-related erosive syndrome.]*

Camilleri M, Bharucha AE, Farrugia G: Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clin Gastroenterol Hepatol* 9:5, 2011. *[Comprehensive discussion of diabetic gastroparesis.]*

Fourmy D, Gigoux V, Reubi JC: Gastrin in gastrointestinal diseases. *Gastroenterol* 141:814, 2011. *[Discussion of gastrin contributions to gastric physiology and disease.]*

Sostres C, Lanas A: Gastrointestinal effects of aspirin. *Nat Rev Gastroenterol Hepatol* 8:385, 2011. *[Mechanisms and management of NSAID toxicities are explored.]*

Tang SJ, Daram SR, Wu R, et al: Pathogenesis, Diagnosis, and Management of Gastric Ischemia. *Clin Gastroenterol Hepatol* 2013. *[All-encompassing review of gastric ischemic disease.]*

Chronic Gastritis

Arnold IC, Lee JY, Amieva MR, et al.: Tolerance rather than immunity protects from Helicobacter pylori-induced gastric preneoplasia. *Gastroenterol* 140:199, 2011. *[Consideration of host factors that contribute to outcomes of H. pylori infection.]*

Neumann WL, Coss E, Rugge M, et al: Autoimmune atrophic gastritis-pathogenesis, pathology and management. *Nat Rev Gastroenterol Hepatol* 10:529, 2013. *[All-encompassing review of atrophic gastritis.]*

Sonnenberg A, Lash RH, Genta RM: A national study of Helicobactor pylori infection in gastric biopsy specimens. *Gastroenterol* 139:1894, 2010. *[Pathology-based review of nearly 80,000 gastric biopsies.]*

Complications of Chronic Gastritis

Malfertheiner P, Chan FK, McColl KE: Peptic ulcer disease. *Lancet* 374:1449, 2009. *[Summary of current understanding of peptic ulcer disease.]*

Park JY, Cornish TC, Lam-Himlin D, et al: Gastric lesions in patients with autoimmune metaplastic atrophic gastritis (AMAG) in a tertiary care setting. *Am J Surg Pathol* 34:1591, 2010. *[Review of over 40,000 gastric biopsies and analysis of the incidence of autoimmune metaplastic atrophic gastritis and associated lesions.]*

Hypertrophic Gastropathies

Fiske WH, Tanksley J, Nam KT, et al: Efficacy of cetuximab in the treatment of Menetrier's disease. *Sci Transl Med* 1:8ra18, 2009. *[Analysis of series of patients treated for Menetrier's disease.]*

Nalle SC, Turner JR: Menetrier's disease therapy: rebooting mucosal signaling. *Sci Transl Med* 1:8ps10, 2009. *[Review of mechanisms of Menetrier's disease.]*

Rich A, Toro TZ, Tanksley J, et al: Distinguishing Menetrier's disease from its mimics. *Gut* 59:1617, 2010. *[Discussion of the differential diagnostic features of Menetrier's disease.]*

Simmons LH, Guimaraes AR, Zukerberg LR: Case records of the Massachusetts General Hospital. Case 6-2013. A 54-year-old man with recurrent diarrhea. *N Engl J Med* 368:757, 2013. *[Case report and discussion of Zollinger-Ellison syndrome.]*

Gastric Polyps and Tumors

Carmack SW, Genta RM, Graham DY, et al: Management of gastric polyps: a pathology-based guide for gastroenterologists. *Nat Rev Gastroenterol Hepatol* 6:331, 2009. *[Discussion of endoscopic characteristics, histopathology, pathogenesis, and clinical management gastric polyps.]*

Corless CL, Barnett CM, Heinrich MC: Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer* 11:865, 2011. *[Comprehensive review of gastrointestinal stromal tumor biology.]*

Lei Z, Tan IB, Das K, et al: Identification of Molecular Subtypes of Gastric Cancer With Different Responses to PI3-Kinase Inhibitors and 5-Fluorouracil. *Gastroenterol* 145:554, 2013. *[Expression profiling-based detection of gastric cancer subtypes and permanent characterization of chemotherapeutic responses.]*

Polk DB, Peek RM Jr: Helicobacter pylori: gastric cancer and beyond. *Nat Rev Cancer* 10:403, 2010. *[A good review of H. pylori and mechanisms by which it is linked to gastric cancer.]*

Sagaert X, Van Cutsem E, De Hertogh G, et al: Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development. *Nat Rev Gastroenterol Hepatol* 7:336, 2010. *[A discussion of gastric MALT lymphoma pathogenesis.]*

Turner ES, Turner JR: Expanding the Lauren Classification: A New Gastric Cancer Subtype? *Gastroenterol* 2013. *[Commentary exploring the interactions between molecular and morphologic analysis in gastric cancer characterization.]*

Small Intestine and Colon

Intestinal Obstruction

p9015

Hellebrekers BW, Kooistra T: Pathogenesis of postoperative adhesion formation. *Br J Surg* 98:1503, 2011. *[Review of adhesion pathogenesis and consideration of therapies to prevent adhesion formation.]*

Justice FA, Nguyen LT, Tran SN, et al: Recurrent intussusception in infants. *J Paediatr Child Health* 47:802, 2011. *[Review of over 600 cases of pediatric intussusception.]*

Osiro SB, Cunningham D, Shoja MM, et al: The twisted colon: a review of sigmoid volvulus. *Am Surg* 78:271, 2012. *[Review of colonic volvulus.]*

Patel MM, Lopez-Collada VR, Bulhoes MM, et al: Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med* 364:2283, 2011. *[Epidemiologic analysis of intussusception risk following rotavirus vaccination.]*

Ischemic Bowel Disease and Angiodysplasia

Barnert J, Messmann H: Diagnosis and management of lower gastrointestinal bleeding. *Nat Rev Gastroenterol Hepatol* 6:637, 2009. *[Discussion of clinical approaches to lower GI bleeding.]*

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

Brandt LJ, Feuerstadt P, Blaszka MC: Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology. *Am J Gastroenterol* 105:2245, 2010. *[Study of disease associations and clinical outcomes in colonic ischemia.]*

Longstreth GF, Yao JF: Diseases and drugs that increase risk of acute large bowel ischemia. *Clin Gastroenterol Hepatol* 8:49, 2010. *[Detailed clinical analysis of nearly 400 cases of colonic ischemia in older adults.]*

Swanson E, Mahgoub A, Macdonald R, et al: Medical and Endoscopic Therapies for Angiodysplasia and Gastric Antral Vascular Ectasia: a Systematic Review. *Clin Gastroenterol Hepatol* 2013. *[Comprehensive review of angiodysplasia and gastric antral vascular ectasia (GAVE).]*

Malabsorption and Diarrhea

Gelfond D, Borowitz D: Gastrointestinal complications of cystic fibrosis. *Clin Gastroenterol Hepatol* 11:333, 2013. *[Clinical review of cystic fibrosis associated lesions of the gastrointestinal tract.]*

Guerrant RL, DeBoer MD, Moore SR, et al: The impoverished gut–a triple burden of diarrhoea, stunting and chronic disease. *Nat Rev Gastroenterol Hepatol* 10:220, 2013. *[Review of mechanisms underlying growth failure (stunting).]*

Hammer HF, Hammer J: Diarrhea caused by carbohydrate malabsorption. *Gastroenterol Clin North Am* 41:611, 2012. *[Pathophysiology focused review of carbohydrate malabsorption-induced diarrhea.]*

Ludvigsson JF, Leffler DA, Bai JC, et al: The Oslo definitions for coeliac disease and related terms. *Gut* 62:43, 2013. *[Presentation of accepted terminology in diagnosis of celiac disease.]*

Meresse B, Malamut G, Cerf-Bensussan N: Celiac disease: an immunological jigsaw. *Immunity* 36:907, 2012. *[Immunology-focused review of disease mechanisms associated with celiac disease.]*

Moore SR, Lima NL, Soares AM, et al: Prolonged episodes of acute diarrhea reduce growth and increase risk of persistent diarrhea in children. *Gastroenterology* 139:1156, 2010. *[A detailed study of environmental enteropathy.]*

Infectious Enterocolitis

Barton Behravesh C, Mody RK, Jungk J, et al: 2008 outbreak of Salmonella Saintpaul infections associated with raw produce. *N Engl J Med* 364:918, 2011. *[Analysis of a Salmonella epidemic.]*

Barzilay EJ, Schaad N, Magloire R, et al: Cholera surveillance during the Haiti epidemic–the first 2 years. *N Engl J Med* 368:599, 2013. *[Study of cholera outbreak following following the 2010 Haitian earthquake.]*

de Jong HK, Parry CM, van der Poll T, et al: Host-pathogen interaction in invasive Salmonellosis. *PLoS Pathog* 8:e1002933, 2012. *[Mechanism-based review of salmonella pathobiology.]*

Kuehne SA, Cartman ST, Heap JT, et al: The role of toxin A and toxin B in Clostridium difficile infection. *Nature* 467:711, 2010. *[A detailed analysis of toxin function in C. difficile pathogenesis.]*

Madhi SA, Cunliffe NA, Steele D, et al: Effect of human rotavirus vaccine on severe diarrhea in African infants. *N Engl J Med* 362:289, 2010. *[Clinical trial demonstrating reduced efficacy of rotavirus vaccine in some patient groups.]*

Irritable Bowel Syndrome

Ford AC, Bercik P, Morgan DG, et al: Validation of the Rome III Criteria for the Diagnosis of Irritable Bowel Syndrome in Secondary Care. *Gastroenterol* 2013. *[Analysis of the sensitivity and specificity of current diagnostic criteria for IBS.]*

Sperber AD, Drossman DA, Quigley EM: The global perspective on irritable bowel syndrome: a Rome Foundation-World Gastroenterology Organisation symposium. *Am J Gastroenterol* 107:1602, 2012. *[An analysis of IBS from a global perspective.]*

Vazquez-Roque MI, Camilleri M, Smyrk T, et al: A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterol* 144:903, 2013. *[An analysis of gluten sensitivity in diarrhea predominant IBS patients.]*

Inflammatory Bowel Disease

Abraham C, Medzhitov R: Interactions between the host innate immune system and microbes in inflammatory bowel disease. *Gastroenterol* 140:1729, 2011. *[Immunology-focused review considering host microbe interactions in IBD.]*

Glocker EO, Kotlarz D, Boztug K, et al: Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 361:2033, 2009. *[Identification of IL-10 receptor mutations in a subset of ulcerative colitis patients.]*

Jostins L, Ripke S, Weersma RK, et al: Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491:119, 2012. *[A comprehensive analysis of 163 IBD-associated genes with new insight into the relationship to pathogen responses.]*

Marchiando AM, Graham WV, Turner JR: Epithelial barriers in homeostasis and disease. *Annu Rev Pathol* 5:119, 2010. *[Review of intestinal epithelial barrier function and its implications in IBD and other disorders.]*

Other Causes of Colitis

Pardi DS, Kelly CP: Microscopic colitis. *Gastroenterology* 140:1155, 2011. *[Review of collagenous and lymphocytic colitis pathobiology and diagnosis.]*

Turner JR: Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol* 9:799, 2009. *[Analysis of epithelial-immune interactions in gastrointestinal disease.]*

Sigmoid Diverticulitis

Strate LL, Modi R, Cohen E, et al: Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. *Am J Gastroenterol* 107:1486, 2012. *[Review of emerging epidemiology and pathophysiology of chronic diverticular disease.]*

Polyps

Beggs AD, Latchford AR, Vasen HF, et al: Peutz-Jeghers syndrome: a systematic review and recommendations for management. *Gut* 59:975, 2010. *[Review of Peutz-Jeghers disease etiology and management.]*

Rex DK, Ahnen DJ, Baron JA, et al: Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol* 107:1315, 2012. *[Clinical perspective on management of sessile serrated adenomas.]*

Adenocarcinoma

Boland CR, Goel A: Microsatellite instability in colorectal cancer. *Gastroenterology* 138:2073, 2010. *[Discussion of the microsatellite instability pathway of colon cancer.]*

Corley DA, Jensen CD, Marks AR, et al: Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 370:1298, 2014. *[Large study of the relationship between adenoma detection rates and colon cancer incidence.]*

Jasperson KW, Tuohy TM, Neklason DW, et al: Hereditary and familial colon cancer. *Gastroenterology* 138:2044, 2010. *[Comprehensive review of colon cancer syndromes.]*

Pino MS, Chung DC: The chromosomal instability pathway in colon cancer. *Gastroenterology* 138:2059, 2010. *[Review of colon cancer genetics.]*

Hemorrhoids

Sneider EB, Maykel JA: Diagnosis and management of symptomatic hemorrhoids. *Surg Clin North Am* 90:17, 2010. *[Clinically oriented review of hemorrhoids.]*

Acute Appendicitis and Tumors of the Appendix

Cartwright SL, Knudson MP: Evaluation of acute abdominal pain in adults. *Am Fam Physician* 77:971, 2008. *[Clinically oriented approach to the acute abdomen.]*

Deschamps L, Couvelard A: Endocrine tumors of the appendix: a pathologic review. *Arch Pathol Lab Med* 134:871, 2010. *[Pathology-focused review of appendiceal carcinoid tumors.]*

Peritoneal Cavity

Baratti D, Kusamura S, Deraco M: Diffuse malignant peritoneal mesothelioma: systematic review of clinical management and biological research. *J Surg Oncol* 103:822, 2011. *[Overarching review of diffuse malignant peritoneal mesothelioma.]*

Li PK, Chow KM: Infectious complications in dialysis–epidemiology and outcomes. *Nat Rev Nephrol* 8:77, 2012. *[A review of that includes discussion of peritoneal infections occurring in association with peritoneal dialysis.]*

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017

ISBN: 978-1-4557-2613-4; PII: B978-1-4557-2613-4.00017-7; Author: Kumar & Abbas & Aster; 00017