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The Gastrointestinal Tract

Frank A. Mitros
Emanuel Rubin

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THE ESOPHAGUS

Anatomy
Embryologically, the gut and respiratory tract arise from the same anlage and constitute a single tube. This structure divides into two separate tubes, the esophagus being dorsal and the future respiratory tract, ventral. Initially, columnar epithelium lines the esophagus in its early embryonic development, but it is replaced by a stratified squamous epithelium.

The adult esophagus is a 25-cm tube that is a conduit for the passage of food and liquid into the stomach. It contains striated and smooth muscle in its upper portion and smooth muscle alone in its lower portion. The organ is fixed superiorly at the cricopharyngeus muscle, which is considered the upper esophageal sphincter. It courses inferiorly through the posterior mediastinum behind the trachea and heart, and exits the thorax through the hiatus of the diaphragm. Tonic muscular contraction at its lower end creates an action like that of a one-way flutter valve. The so-called lower esophageal sphincter is not a true anatomical sphincter but rather a functional one.

The esophagus has a mucosa, submucosa, muscularis propria, and adventitia. The transition from the squamous mucosa of the esophagus to the gastric mucosa at the esophagogastric junction occurs abruptly at the level of the diaphragm. The esophageal submucosa contains mucous glands and a rich lymphatic plexus. The lymphatics of the upper third of the esophagus drain to cervical lymph nodes, those of the middle third to the mediastinal nodes, and those of the lower third to the celiac and gastric lymph nodes. These anatomic features are significant in the spread of esophageal cancer.

The venous drainage of the esophagus is important in portal hypertension, in which esophageal varices occur. These varices are invariably found in the lower third of the esophagus, because the veins of the upper third drain into the superior vena cava and those of the middle third drain into the azygous system. Only the veins of the lower third of the esophagus drain into the portal vein via the gastric veins.

Congenital Disorders

Tracheoesophageal Fistula Leads to Aspiration Pneumonia
Tracheoesophageal fistula is the most common esophageal anomaly (Fig. 13-1). It is frequently combined with some form of esophageal atresia. In some cases, it is associated with a complex of anomalies identified by the acronym VATER syndrome (vertebral defects, anal atresia, tracheoesophageal fistula, and renal dysplasia). Maternal hydramnios has been recorded in some cases of esophageal atresia and, less commonly, in cases of tracheoesophageal fistula. Esophageal atresia and fistulas are often associated with congenital heart disease.

PATHOLOGY: In 90% of tracheoesophageal fistulas, the upper portion of the esophagus ends in a blind pouch and the superior end of the lower segment communicates with the trachea. In this type of atresia, the upper blind sac soon fills with mucus, which the infant then aspirates. Surgical correction is feasible albeit difficult.

Among the remaining 10% of fistulas, the most common is a communication between the proximal esophagus and the
trachea; the lower esophageal pouch communicates with the stomach. Infants with this condition develop aspiration immediately after birth. In another variant, termed an H-type fistula, a communication exists between an intact esophagus and an intact trachea. In some cases, (see Fig. 13-1C) the lesion becomes symptomatic only in adulthood, when repeated pulmonary infections call attention to it.

Rings and Webs Cause Dysphagia

ESOPHAGEAL WEBS: Occasionally, a thin mucosal membrane projects into the esophageal lumen. Webs are usually single, but may be multiple, and can occur anywhere in the esophagus. They are often successfully treated by dilation with large rubber bougies; occasionally, they can be excised with biopsy forceps during endoscopy.

PLUMMER-VINSON (PATERSON-KELLY) SYNDROME: This disorder is characterized by (1) a cervical esophageal web, (2) mucosal lesions of the mouth and pharynx, and (3) iron-deficiency anemia. Dysphagia, often associated with aspiration of swallowed food, is the most common clinical manifestation. Ninety percent of cases occur in women. Carcinoma of the oropharynx and upper esophagus is a recognized complication of the Plummer-Vinson syndrome.

SCHATZKI RING: This lower esophageal narrowing is usually seen at the gastroesophageal junction (Fig. 13-2). The upper surface of the mucosal ring has stratified squamous epithelium; the lower, columnar epithelium. Although it has been noted in up to 14% of barium meal examinations, Schatzki ring is usually asymptomatic. Patients with narrow Schatzki rings however, may complain of intermittent dysphagia.

Esophageal Diverticula Often Reflect Motor Dysfunction

A true esophageal diverticulum is an outpouching of the wall that contains all layers of the esophagus. If a sac has no muscular layer, it is a false diverticulum. Esophageal diverticula occur in the hypopharyngeal area above the upper esophageal sphincter, in the middle esophagus, and immediately proximal to the lower esophageal sphincter.

ZENKER DIVERTICULUM: Zenker diverticulum is an uncommon lesion that appears high in the esophagus and affects men more than women. It was once believed to result from luminal pressure exerted in a structurally weak area and was therefore classed as a pulsion diverticulum. The cause is probably more complicated, but disordered function of cricopharyngeal musculature is still generally thought to be involved in the pathogenesis of this false diverticulum. Most affected persons who come to medical attention are older than 60, suggesting that this diverticulum is acquired.

Zenker diverticula can enlarge conspicuously and accumulate a large amount of food. The typical symptom is regurgitation of food eaten some time previously (occasionally days), in the absence of dysphagia. Recurrent aspiration pneumonia may be a serious complication. When symptoms are severe, surgical intervention is the rule.

TRACTION DIVERTICULA: Traction diverticula are outpouchings that occur principally in the midportion of the esophagus. They were so named because of their attachment to adjacent mediastinal lymph nodes, usually associated with tuberculous lymphadenitis. However, such adhesions are today uncommon and it is believed that these pouches often reflect a disturbance in the motor function of the esophagus. A diverticulum in the midesophagus ordinarily has a wide stoma and the pouch is usually higher than its orifice. Thus, it does not retain food or secretions and remains asymptomatic, with only rare complications.

EPIPHRENIC DIVERTICULA: These diverticula are located immediately above the diaphragm. Motor disturbances of the esophagus (e.g., achalasia, diffuse esophageal spasm) are found in two thirds of patients with this true diverticulum. In addition, reflux esophagitis may play a role in the pathogenesis of epiphrenic diverticula.

Unlike other diverticula, epiphrenic diverticula are encountered in young persons. Nocturnal regurgitation of large amounts of fluid stored in the diverticulum during the day is

![Figure 13-1. Congenital tracheoesophageal fistulas. A. The most common type is a communication between the trachea and the lower portion of the esophagus. The upper segment of the esophagus ends in a blind sac. B. In a few cases, the proximal esophagus communicates with the trachea. C. The least common anomaly, the H type, is a fistula between a continuous esophagus and the trachea.](image1)

![Figure 13-2. Schatzki mucosal ring. A contrast radiograph illustrates the lower esophageal narrowing.](image2)
typical. When symptoms are severe, surgical intervention directed toward correcting the motor abnormality (e.g., myotomy) is appropriate.

Motor Disorders

The automatic coordination of muscular movement during swallowing is termed a motor function and results in free passage of food through the esophagus. The hallmark of motor disorders is difficulty in swallowing, termed dysphagia. Dysphagia is often an awareness that a bolus of food is not moving downwards, and in itself is not painful. Pain on swallowing is often an awareness that a bolus of food is not moving downwards. The automatic coordination of muscular movement during swallowing is termed a motor function and results in free passage of food through the esophagus. The hallmark of motor disorders is difficulty in swallowing, termed dysphagia. Dysphagia is often an awareness that a bolus of food is not moving downwards, and in itself is not painful. Pain on swallowing is

Achalasia Features Impaired Function of the Lower Esophageal Sphincter

Achalasia, at one time termed cardiospasm, is characterized by failure of the lower esophageal sphincter to relax in response to swallowing and absence of peristalsis in the body of the esophagus. As a result of these defects in both the outflow tract and the pumping mechanisms of the esophagus, food is retained within the esophagus and the organ hypertrophies and dilates conspicuously (Fig. 13-3).

Achalasia is associated with loss or absence of ganglion cells in the esophageal myenteric plexus. Degenerative changes in the dorsal motor nucleus of the vagus and extraesophageal vagus nerves have also been described. Ganglion cell loss may be accompanied by chronic inflammation. In Latin America, achalasia is a common complication of Chagas disease, in which the ganglion cells are destroyed by the protozoa Trypanosoma cruzi.

Dysphagia, occasionally odynophagia, and regurgitation of material retained in the esophagus are common symptoms of achalasia. Squamous carcinoma is also a complication. Treatment is by dilation or surgical myotomy, which can lead to gastroesophageal reflux.

Scleroderma Causes Fibrosis of the Esophageal Wall

Scleroderma (progressive systemic sclerosis) causes fibrosis in many organs and produces a severe abnormality of esophageal muscle function. The disease mainly affects the lower esophageal sphincter, which may become so impaired that the lower esophagus and upper stomach are no longer distinct functional entities and are visualized as a common cavity. In addition, there may be a lack of peristalsis in the entire esophagus.

Microscopically, fibrosis of esophageal smooth muscle (especially the inner layer of the muscularis propria) and nonspecific inflammatory changes are seen. Intimal fibrosis of small arteries and arterioles is common and may play a role in the pathogenesis of the fibrosis. Clinically, patients have dysphagia and heartburn caused by peptic esophagitis, owing to reflux of acid from the stomach. Severe reflux changes may occur (see below).

Hiatal Hernia

Hiatal hernia is a herniation of the stomach through an enlarged esophageal hiatus in the diaphragm. Two basic types of hiatal hernia are observed (Fig. 13-4).

SLIDING HERNIA: An enlargement of the diaphragmatic hiatus and lacerity of the circumferential connective tissue allows a cap of gastric mucosa to move upward to a position above the diaphragm. This condition is common. Sliding hiatal hernia is asymptomatic in most patients: only 5% of patients diagnosed radiologically complain of symptoms referable to gastroesophageal reflux.

PARAESOPHAGEAL HERNIA: This uncommon form of hiatal hernia is characterized by herniation of a portion of gastric fundus alongside the esophagus through a defect in the diaphragmatic connective tissue membrane that defines the esophageal hiatus. The hernia progressively enlarges, and the hiatus grows increasingly wide. In extreme cases, most of the stomach herniates into the thorax.

CLINICAL FEATURES: Symptoms of hiatal hernia, particularly heartburn and regurgitation, are attributed to gastroesophageal reflux of gastric contents, primarily related to incompetence of the lower esophageal sphincter. Classically, symptoms are exacerbated when the affected person is recumbent, which facilitates acid reflux. Dysphagia, painful swallowing, and occasionally bleeding may also be troublesome. Large herniations carry a risk of gastric volvulus or intrathoracic gastric dilation.

Sliding hiatal hernias generally do not require surgical repair; symptoms are often treated medically. By contrast, an enlarging paraesophageal hernia should be surgically treated, even in the absence of symptoms.
CHAPTER 13: THE GASTROINTESTINAL TRACT

Esophagitis

Reflux Esophagitis Is Caused by Regurgitation of Gastric Contents

By far the most common type of esophagitis, reflux esophagitis is often found in conjunction with a sliding hiatal hernia, although it may occur through an incompetent lower esophageal sphincter without any demonstrable anatomical lesion.

**PATHOLOGY:** The first grossly evident change caused by gastroesophageal reflux is hyperemia. Areas affected by reflux are susceptible to superficial mucosal erosions and ulcers, which often appear as vertical linear streaks. Microscopically, mild injury to the squamous epithelium is manifested by cell swelling (hydropic change). The basal region of the epithelium is thickened, and the papillae of the lamina propria are elongated and extend toward the surface because of reactive proliferation. Capillary vessels within the papillae are often dilated. An increase in lymphocytes is seen in the squamous epithelium and eosinophils and neutrophils may be present. Esophageal stricture may eventuate in those patients in whom the ulcer persists and damages the esophageal wall deep to the lamina propria. In this circumstance, reactive fibrosis can narrow the esophageal lumen.

**Barrett Esophagus**

**PATHOLOGY:** Barrett esophagus is a result of chronic gastroesophageal reflux. Its incidence has been increasing in recent years, particularly among white men. This disorder occurs in the lower third of the esophagus but may extend higher.

There is a slight male predominance and a more than twofold increased risk for Barrett esophagus among smokers. Patients with Barrett esophagus are placed in a regular surveillance program to detect early microscopic evidence of dysplastic mucosa.

**PATHOGENESIS:** The principal barrier to reflux of gastric contents into the esophagus is the lower esophageal sphincter. Transient reflux is a normal event, particularly after a meal. When these episodes become more frequent and are prolonged, esophagitis results. Agents that decrease the pressure of the lower esophageal sphincter (e.g., alcohol, chocolate, fatty foods, cigarette smoking) are also associated with reflux. Certain central nervous system depressants (e.g., morphine, diazepam), pregnancy, estrogen therapy, and the presence of a nasogastric tube may lead to reflux esophagitis. Although acid is damaging to the esophageal mucosa, the combination of acid and pepsin may be particularly injurious. Moreover, gastric fluid often contains refluxed bile from the duodenum, which is harmful to the esophageal mucosa. Alcohol, hot beverages, and spicy foods also may damage the mucosa directly.

**Barrett Esophagus Is Replacement of Esophageal Squamous Epithelium by Columnar Epithelium**

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**PATHOLOGY:** Metaplastic Barrett epithelium may partially involve the circumference of short segments or may line the entire lower esophagus (Fig. 13-5A). Microscopically, the sine qua non of Barrett esophagus is the presence of a distinctive type of epithelium, referred to as "specialized epithelium." It consists of an admixture of intestine-like epithelium characterized by well-formed goblet cells interspersed with gastric foveolar cells (see Fig. 13-5B). Complete intestinal metaplasia, with Paneth cells and absorptive cells, occurs occasionally. Inflammatory changes are often superimposed on the epithelial alterations. Barrett esophagus may transform into adenocarcinoma, the risk correlating with the length of the involved esophagus and the degree of dysplasia (see below). The dysplastic change occurs in the "specialized epithelium."
**Pathology:**

In mild cases of candidiasis, a few small, elevated white plaques surrounded by a hyperemic zone are present on the mucosa of the middle or lower third of the esophagus. In severe cases, confluent pseudomembranes lie on a hyperemic and edematous mucosa. Microscopically, Candida sometimes involves only the superficial layers of the squamous epithelium. The candidal pseudomembrane contains fungal mycelia, necrotic debris, and fibrin. Involvement of deeper layers of the esophageal wall can lead to disseminated candidiasis or fibrosis, sometimes severe enough to create a stricture.

**Herpesvirus Type I:**

Esophageal infection with herpesvirus type I is most frequently associated with lymphomas and leukemias and is often manifested by odynophagia. However, it may occur in otherwise healthy individuals on occasion.

**Pathology:**

The well-developed lesions of herpetic esophagitis grossly resemble those of candidiasis. In early cases, vesicles, small erosions or plaques are seen; as infection progresses, these may coalesce to form larger lesions. Microscopically, lesions are superficial and epithelial cells exhibit typical nuclear herpetic inclusions and occasional multinucleation (see Fig. 9-6). Necrosis of infected cells leads to ulceration and candidal and bacterial superinfection results in the formation of pseudomembranes.

**Candida Esophagitis:**

This fungal infection has become commonplace because of an increasing number of immunocompromised persons who (1) receive chemotherapy for malignant disease, (2) are treated with immunosuppressive drugs after organ transplantation, or (3) have contracted acquired immunodeficiency syndrome (AIDS). Esophageal candidiasis also occurs in patients with diabetes, those receiving antibiotic therapy, and uncommonly in persons with no known predisposing factors. Dysphagia and severe pain on swallowing are usual.

**Pathology:**

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cytomegalovirus are present in endothelial cells and granulation tissue fibroblasts.

**Chemical Esophagitis Results from Ingestion of Corrosive Agents**

Chemical injury to the esophagus usually reflects accidental poisoning in children, attempted suicide in adults, or contact with medication. Ingestion of strong alkaline agents (e.g., lye) or strong acids (e.g., sulfuric or hydrochloric acid), both of which are used in various cleaning solutions, can produce chemical esophagitis. The alkaline solutions are particularly insidious, because they are generally odorless and tasteless and so easily swallowed before protective reflexes come into play.

**PATHOLOGY:** Microscopically, alkali-induced liquefactive necrosis is accompanied by conspicuous inflammation and saponification of membrane lipids in the epithelium, submucosa, and muscularis propria of the esophagus and stomach. Thrombosis of small vessels adds ischemic necrosis to the injury. Severe injury is the rule with liquid alkali, but less than 25% of those who ingest granular preparations have severe complications.

Strong acids produce immediate coagulation necrosis, which results in a protective eschar that limits injury and penetration. Nevertheless, half of patients who ingest concentrated hydrochloric or sulfuric acid have severe esophageal injury.

**Drug-related esophagitis** is most often caused by direct chemical effects on the squamous-lined mucosa, especially with capsules; esophageal dysmotility and cardiac enlargement (which impinges on the esophagus) may be contributing factors.

**Esophagitis May Complicate Systemic Illnesses**

Esophageal squamous mucosa resembles, and shares some reactions with, the epidermis.

The **dystrophic form of epidermolysis bullosa** involves all organs lined by, or derived from, squamous epithelium, including skin, nails, teeth, and esophagus. Bullae, which occur episodically, evolve from fluid-filled vesicles to weeping ulcers. Dysphagia and painful swallowing are the rule. Stricture, usually in the upper esophagus, may occur.

**Pemphigoid** produces subepithelial bullae in the skin and esophagus, but does not lead to scarring. Other dermatologic disorders associated with esophagitis include pemphigus, dermatitis herpetiformis, Behçet syndrome, and erythema multiforme.

**Graft-versus-host disease** in recipients of bone marrow transplants can cause esophageal lesions and dysphagia, odynophagia, and gastroesophageal reflux. The upper and middle thirds of the esophageal mucosa appear friable and esophageal motor function of the esophagus.

**Esophagitis May be Iatrogenic**

**External irradiation** for treatment of thoracic cancers may include portions of the esophagus and lead to esophagitis and even stricture. **Nasogastric tubes** may cause pressure ulcers when they are in place for prolonged periods, although acid reflux also plays a role in these cases.

**Esophageal Varices**

**Esophageal varices** are dilated veins immediately beneath the mucosa (Fig. 13-6) that are prone to rupture and hemorrhage (also see Chapter 14). They arise in the lower third of the esophagus, virtually always in patients with cirrhosis and portal hypertension. The lower esophageal veins are linked to the portal system through gastroesophageal anastomoses. If portal system pressure exceeds a critical level, these anastomoses become prominent in the upper stomach and lower esophagus. When varices are greater than 5 mm in diameter, they are prone to rupture, leading to life-threatening hemorrhage. Reflux injury or infective esophagitis can contribute to variceal bleeding.

**Lacerations and Perforations**

Lacerations of the esophagus result from external trauma, such as automobile accidents and falls from great heights as well as from medical instrumentation. However, the most common cause is severe vomiting, during which intraesophageal pressure may reach 300 mm Hg. The diaphragm descends rapidly, and a portion of the upper stomach is forced up through the hiatus. As a result, forceful retching may cause mucosal tears, beginning in the gastric epithelium and extending into the esophagus.

**Mallory-Weiss syndrome** refers to severe retching, often associated with alcoholism, that leads to mucosal lacerations of upper stomach and lower esophagus. These tears result in the vomiting of bright red blood and bleeding may be severe enough to require transfusion of many units of blood. The lacerations may also cause perforation into the mediastinum. Esophageal rupture due to vomiting is **Boerhaave syndrome**.

**Esophageal perforation** is a catastrophic event. It is a well-known occurrence in newborns, in whom it is caused occasionally by suctioning or feeding with a nasogastric tube. However, it may also occur spontaneously.

The major non-neoplastic disorders of the esophagus are summarized in Figure 13-7.
Benign Tumors of the Esophagus are Uncommon

Unlike the remainder of the gastrointestinal tract, most spindle cell submucosal tumors of the esophagus derive from smooth muscle (leiomyoma) rather than from interstitial cells of Cajal (gastrointestinal stromal tumors [GIST tumors]; see below). They are almost always benign. Squamous papilloma of the esophagus is rare.

Esophageal Carcinoma Varies Geographically and Histologically

**PATHOLOGY:** Worldwide, most esophageal cancers are squamous cell carcinomas but adenocarcinoma is now more common in the United States (see below). Esophageal cancer is uncommon and accounts for about 2% of cancer deaths in the United States.

Worldwide geographic variations in the incidence of esophageal carcinoma are striking, and areas of high incidence are located adjacent to areas of low incidence. There is an esophageal cancer belt extending across Asia from the Caspian Sea region of northern Iran and the former Soviet Union through Central Asia and Mongolia to northern China. In parts of China, the mortality rate from esophageal cancer in men may be 70 times that in the United States. American blacks have a much higher incidence than whites, and in the United States, urban dwellers are at greater risk than those in rural areas. Cancer of the esophagus is also common in certain regions of France, Finland, Switzerland, Chile, Japan, India, and Africa.

**PATHOGENESIS:** Geographic variations in esophageal cancer, even in relatively homogeneous populations, suggest that environmental factors contribute strongly to its development. However, no single factor has been incriminated.

- **Cigarette smoking** increases risk of esophageal cancer 5- to 10-fold. The number of cigarettes smoked correlates with the presence of esophageal dysplasia.
- **Excessive consumption of alcohol** is a major risk factor in the United States, even when cigarette smoking is taken into account.
- **Nitrosamines** and aniline dyes produce esophageal cancer in animals. Although high levels of nitrosamines and other potentially carcinogenic compounds have been found in the diets of persons living in high-incidence areas, direct evidence for their contribution to esophageal cancer is lacking. Moreover, such chemical agents have not been detected in many high-risk areas, such as northern Iran.
- **Diets low in fresh fruits, vegetables, animal protein, and trace metals** are described in areas with endemic esophageal cancer, and in some hyperendemic areas, as are deficiencies of various vitamins and minerals. However, the close proximity of endemic and nonendemic areas renders a causative role for these dietary factors unlikely.
- **Plummer-Vinson syndrome, celiac sprue, and achalasia** are associated with an increased incidence of esophageal cancer, for obscure reasons.
- **Chronic esophagitis** has been related to esophageal cancer in areas in which this tumor is endemic.
- **Chemical injury with esophageal stricture** is a risk factor. Of persons who have an esophageal stricture after ingestion of lye, 5% develop cancer 20 to 40 years later.
- **Webs, rings and diverticula** are sometimes associated with esophageal cancer.

**FIGURE 13-7. Nonneoplastic disorders of the esophagus.**

**EPIEDEMOLOGY:** Worldwide, most esophageal cancers are squamous cell carcinomas but adenocarcinoma is now more common in the United States (see below). Esophageal cancer is uncommon and accounts for about 2% of cancer deaths in the United States.

Grossly, the tumors are of three types: (1) polypoid, which projects into the lumen (Fig. 13-8B); (2) ulcerating, which is usually smaller than polypoid (Fig. 13-8A); and (3) infiltrating, in which the principal plane of growth is in the wall. The bulky polypoid tumors tend to obstruct early, whereas ulcerated ones are more likely to bleed. Infiltrating tumors gradually narrow the lumen by circumferential compression. Local extension of tumor into mediastinal structures is commonly a major problem.

Microscopically, neoplastic squamous cells range from well differentiated, with epithelial “pearls,” to poorly differentiated...
tumors that lack evidence of squamous differentiation. Occa-
sional tumors have a predominant spindle cell population of tu-
mors cells (metaplastic carcinoma).

The rich lymphatic drainage of the esophagus provides a
route for most metastases. Accordingly, tumors of the upper
third metastasize to cervical, internal jugular, and supraclavicu-
lar nodes. Cancer of the middle third metastasizes to the para-
tracheal and hilar lymph nodes and to nodes in the aortic,
cardiac, and paraesophageal regions. As the lower third of the
esophagus is fed by the left gastric artery, lower esophageal tu-
mors spread via accompanying lymphatics to retroperitoneal,
celiac, and left gastric nodes. Metastases to liver and lung are
common, but almost any organ may be involved.

CLINICAL FEATURES: The most common present-
ing complaint is dysphagia, but by this time most tu-
mors are unresectable. Patients with esophageal cancer
are almost invariably cachectic, owing to anorexia, difficulty in
swallowing, and the remote effects of a malignant tumor.
Odynophagia occurs in half of patients and persistent pain sug-
gests mediastinal extension of the tumor or involvement of
spinal nerves. Compression of the recurrent laryngeal nerve pro-
duces hoarseness and tracheoesophageal fistula is manifested
clinically by a chronic cough. Surgery and radiation therapy are
useful for palliation, but the prognosis remains dismal. Many pa-
tients are inoperable and of those who undergo surgery, only
20% survive for 5 years.

Adenocarcinoma of the Esophagus

As its incidence has recently increased, adenocarcinoma of the
esophagus is now more common (60%) in the United States than
squamous carcinoma. Virtually all adenocarcinomas arise in the
background of Barrett esophagus, although a rare case originates in
submucosal mucous glands. Endoscopic surveillance for aden-
ocarcinoma is now commonly done in patients with Barrett
esophagus, particularly in those with dysplasia. The symptoms
and clinical course of esophageal adenocarcinoma are similar to
those of squamous cell carcinoma.

THE STOMACH

Anatomy

The stomach, a J-shaped saccular organ with a volume of 1200 to
1500 mL., arises as a dilation of the primitive foregut. It is contin-
uous with the esophagus superiorly and the duodenum inferi-
orly. Situated in the upper abdomen, the stomach extends from
the left hypochondrium across the epigastrium. The convexity
of the stomach, extending leftward from the gastroesophageal
junction, is termed the greater curvature. The concavity of the
right side of the stomach, called the lesser curvature, is only
about one fourth as long as the greater curvature. The entire
stomach is invested in peritoneum, which descends from the
greater curvature as the greater omentum.

The stomach is divided into 5 regions, superiorly to inferiorly
(Fig. 13-9):

1. The cardia is a small, grossly indistinct zone that extends a
short distance from the gastroesophageal junction.
2. The fundus is the dome-shaped part of the stomach located
to the left of the cardia and extends superiorly above the level
of the gastroesophageal junction.
3. The body, or corpus, is two-thirds of the stomach and descends from the fundus to the most inferior region, where the organ turns right to form the bottom of the J.

4. The antrum is the distal third of the stomach. It is positioned horizontally and extends from the body to the pyloric sphincter.

5. The pyloric sphincter is the most distal tubular segment of the stomach. It is entirely surrounded by the thick muscular layer that controls passage of food into the duodenum.

The wall of the stomach is composed of a mucosa, submucosa, muscularis, and serosa. The lining of the fundus and body has prominent folds, the gastric rugae. Branches of the celiac, hepatic, and splenic arteries supply blood to the stomach. Gastric veins drain either directly into the portal system or indirectly through splenic and superior mesenteric veins. A rich plexus of lymphatic channels empties into gas-

Portal system or indirectly through splenic and superior mesenteric veins. A rich plexus of lymphatic channels empties into gast-

The histology of the gastric mucosa varies with the anatomic region. Surface mucus-secreting, columnar epithelium extends into numerous foveolae, or pits. These are the orifices of millions of branched, tubular glands. There are three types of glands:

- **Cardiac glands** are located in the cardia.
- **Parietal (oxyntic) glands** are found in the body and fundus of the stomach.
- **Pyloric glands** are situated in the antrum and the pyloric canal. The pyloric glands, the principal secretory elements of the stomach, are densely arranged perpendicular to the mucosa and enter the base of the foveola through a narrowed segment called the neck of the gland. Gastric glands contain 5 cell types:

- **Zymogen, or chief, cells:** These are primarily in the lower half of gastric glands. They are pyramidal, basophilic cells with zymogen granules that contain pepsinogen.
- **Parietal, or oxyntic, cells:** These cells occupy the upper half of the gastric gland. They are oval or pyramidal eosinophilic cells that secrete hydrochloric acid. They contain numerous mitochondria to provide energy for the ion transport needed for acid secretion. Ultrastructurally, parietal cells have many surface membrane invaginations, secretory canaliculi, which vastly expand the surface area for acid secretion. Parietal cells also produce intrinsic factor, which is necessary for intestinal absorption of vitamin B₁₂.
- **Mucous neck cells:** These mucus-secreting, basophilic components are interspersed among the parietal cells in the neck of the gastric gland.
- **Endocrine cells:** These cells are scattered in the gastric glands, mostly between the zymogen cells and the basement membrane. They are small, round, or pyramidal cells filled with granules. Endocrine cells are scattered among the pyloric glands and contain biogenic amines such as serotonin and polypeptide hormones (e.g., gastrin and somatostatin). The endocrine cells include gastrin-secreting cells (G cells). Vasoactive intestinal peptide (VIP) is found in neural elements of the mucosa but not within endocrine cells. These cells are best visualized by immunoperoxidase techniques, either with more generic markers such as chromogranin or synaptophysin or with antibodies directed against specific peptides, such as gastrin.
- **Pyloric glands** are branched and conspicuously coiled structures, emptying into foveolae that are substantially deeper than those elsewhere in the stomach. The glands are lined by pale cells similar in appearance to mucous neck cells and cells of Brunner glands in the duodenum. The endocrine cells include G cells.
- **Cardiac glands** are lined by cells that are similar to mucous neck cells and those of the pyloric glands but lack G cells.

### Congenital Disorders

**Congenital Pyloric Stenosis Causes Projectile Vomiting in Infancy**

*Congenital pyloric stenosis is concentric enlargement of the pyloric sphincter and narrowing of the pyloric canal that obstructs the gastric outlet.* This disorder is the most common indication for abdominal surgery in the initial 6 months of life. It is four times more common in boys than in girls and affects first-born children more than subsequent ones. It occurs in 1 in 250 white infants but is rare in blacks and Asians.

**PATHOGENESIS:** Congenital pyloric stenosis may have a genetic basis; there is a familial tendency, and the condition is more common in identical twins than in fraternal ones. It also has been seen together with other developmental abnormalities, such as Turner syndrome, trisomy 18, and esophageal atresia. Embryopathies associated with rubella infection and maternal intake of thalidomide have also been associated with congenital pyloric stenosis. In some cases, congenital pyloric stenosis is associated with a deficiency of nitric oxide synthase in the nerves of pyloric smooth muscle (nitric oxide mediates relaxation of smooth muscle).
**PATHOLOGY:** Gross examination of the stomach shows concentric pyloric enlargement, and narrowing of the pyloric canal. The only consistent microscopic abnormality is extreme hypertrophy of the circular muscle coat. After pyloromyotomy, the lesion disappears, although occasionally a small mass remains.

**CLINICAL FEATURES:** Projectile vomiting is the main symptom and is usually seen within the first month of life. Consequent loss of hydrochloric acid leads to hypochloremic alkalosis in one third of infants. A palpable pyloric lesion and visible peristalsis are common. Surgical incision of hypertrophied pyloric muscle is curative.

**Congenital Diaphragmatic Hernia**

Congenital diaphragmatic hernias of variable size and location are associated with defective closure of embryological foramina or abnormalities of the esophageal hiatus. These hernias are often associated with congenital malrotations of the intestine. The stomach, together with other abdominal organs, may eventrate into the thoracic cavity.

**Congenital Abnormalities Are Rare**

**DUPICATIONS, DIVERTICULA, AND CYSTS:** These lesions are usually lined by normal gastric mucosa and are distinctly uncommon. Whereas all layers of the stomach wall tend to be present in congenital duplications, muscle coats are often deficient in diverticula and cysts. Patients with these disorders are generally asymptomatic.

**SITUS INVERSUM:** This causes the stomach to be located to the right of the midline, as is the esophageal hiatus. Correspondingly, the duodenum is on the left.

**ECTOPIC PANCREATIC TISSUE:** Nodules of pancreatic tissue are common in the wall of the antrum and pylorus. Histologically, these embryonic rests are identical to normal pancreatic tissue, except that islets are rare. Heterotopic pancreatic tissue is usually asymptomatic, but pyloric obstruction and epigastric pain have been reported.

**PARTIAL GASTRIC ATRESIAS:** Lack of development of the body, antrum, and pylorus have been described, as have cases in which the stomach ends blindly.

**CONGENITAL PYLORIC AND ANTRAL MEMBRANES:** These lesions are presumably caused by failure of the stomach to canalize during embryogenesis. They may cause symptoms of obstruction in the neonatal period but more commonly become symptomatic in adults.

**Gastritis**

**Acute Hemorrhagic Gastritis Is Associated with Drugs and Stress**

Acute hemorrhagic erosive gastritis is characterized by mucosal necrosis. Erosion of the mucosa may extend into the deeper tissues to form an ulcer. The necrosis is accompanied by an acute inflammatory response and hemorrhage, which may be severe enough to result in exsanguination.

Acute hemorrhagic gastritis is most commonly associated with the intake of aspirin, other nonsteroidal anti-inflammatory agents, or excess alcohol, or with ischemic injury. These agents injure the gastric mucosa directly and exert their effects topically. Oral administration of corticosteroids also may be complicated by acute hemorrhagic gastritis. Uncommonly, accidental or suicidal ingestion of corrosive substances, such as those that produce erosive esophagitis, causes acute gastric injury. Any serious illness that is accompanied by profound physiologic alterations that require substantial medical or surgical intervention renders the gastric mucosa more vulnerable to acute hemorrhagic gastritis because of mucosal ischemia. The factor common to all forms of acute hemorrhagic gastritis is thought to be the breakdown of the mucosal barrier, permitting acid-induced injury.

**Stress ulcers and erosions** are occur in severely burned persons (Curling ulcer) and commonly result in bleeding. Ulceration may be deep enough to cause perforation of the stomach. Patients occasionally exhibit both gastric and duodenal ulcers.

**Central nervous system trauma,** accidental or surgical (Cushing ulcer), may also cause stress ulcers. These ulcers, which also may occur in the esophagus or duodenum, are characteristically deep and carry a substantial risk of perforation. Injury to the brain, particularly if it results in a decerebrate state, often leads to increased acid secretion in the stomach, presumably as a result of increased vagal tone. Severe trauma, especially if accompanied by shock, prolonged sepsis, and incapacitation from many debilitating chronic diseases also predisposes to development of acute hemorrhagic gastritis.

**Hypersecretion of gastric acid** has been incriminated in the pathogenesis of acute hemorrhagic gastritis, but its role is not clear. Acid secretion is often increased in some circumstances, such as neurologic trauma, but the development of stress ulcers is not generally accompanied by such an increase. Nevertheless, gastric acid plays a permissive role, because inhibition of gastric acid secretion (e.g., with histamine-receptor antagonists) protects against the development of stress ulcers. Microcirculatory changes in the stomach induced by shock or sepsis suggest that ischemic injury may contribute to the development of acute hemorrhagic gastritis.

Each of these defensive factors of the gastric mucosa has been individually investigated:

- **Corticosteroids and aspirin** lead to decreased mucus production and gastric ulcers after experimental administration.
- **Prostaglandin deficiency,** caused by nonsteroidal anti-inflammatory agents that inhibit prostaglandin synthesis, has been postulated to decrease mucosal resistance to gastric contents. By contrast, certain prostaglandins that stimulate mucus secretion also protect against gastric erosions.
- **Decreased intramural pH of the gastric mucosa** has been shown to protect from gastric erosions in hemorrhagic shock. Thus, acid-induced damage to the gastric mucosa is important in the pathogenesis of certain erosions.
PATHOLOGY: Acute hemorrhagic gastritis is characterized grossly by widespread petechial hemorrhages in any portion of the stomach or regions of confluent mucosal or submucosal bleeding (Fig. 13-10). Lesions vary from 1 to 25 mm across and appear occasionally as sharply punched-out ulcers. Microscopically, patchy mucosal necrosis, which can extend to the submucosa, is visualized adjacent to normal mucosa. Fibrinous exudate, edema and hemorrhage in the lamina propria are present in early lesions. Necrotic epithelium is eventually sloughed, but deeper erosions and hemorrhage may be present. In extreme cases, penetrating ulcers may reach the serosa.

CLINICAL FEATURES: Symptoms of acute hemorrhagic gastritis range from vague abdominal discomfort to massive, life-threatening hemorrhage, or clinical manifestations of gastric perforation. Patients with gastritis induced by aspirin and other nonsteroidal anti-inflammatory agents may be seen with hypochromic, microcytic anemia caused by undetected chronic bleeding. However, in patients with a severe underlying illness, the first sign of stress ulcers may be exsanguinating hemorrhage. Treatment with antacids and histamine-receptor antagonists has proved useful.

Chronic Gastritis is Autoimmune or Environmental

Chronic gastritis refers to chronic inflammatory diseases of the stomach, which range from mild superficial involvement of gastric mucosa to severe atrophy. This is a heterogeneous group of disorders with distinct anatomical distributions within the stomach, varying etiologies, and characteristic complications. The predominant symptom is dyspepsia. The diseases are also commonly discovered in asymptomatic persons undergoing routine endoscopic screening.

Autoimmune Atrophic Gastritis and Pernicious Anemia

Autoimmune atrophic gastritis is a chronic, diffuse inflammatory disease of the stomach that is restricted to the body and fundus and is associated with autoimmune phenomena. This disorder typically exhibits:

- Diffuse atrophic gastritis in the body and fundus of the stomach, with lack of, or minimal involvement of, the antrum
- Antibodies to parietal cells and intrinsic factor
- Significant reduction in or absence of gastric secretion, including acid
- Increased serum gastrin, owing to G-cell hyperplasia of the antral mucosa
- Enterochromaffin-like (ECL) cell hyperplasia in atrophic oxyntic mucosa, secondary to gastrin stimulation

Pernicious anemia is a megaloblastic anemia caused by malabsorption of vitamin B12, due to a deficiency of intrinsic factor. In most cases, pernicious anemia is a complication of autoimmune gastritis. The latter disorder is also associated with extragastric autoimmune diseases such as chronic thyroiditis, Graves disease, Addison disease, vitiligo, diabetes mellitus type I, and myasthenia gravis.

PATHOGENESIS: Autoimmune gastritis is so named because of the presence of autoantibodies and the association with other diseases that have a similar pathogenesis.

CYTOTOXIC ANTIBODIES: Circulating antibodies to parietal cells, some of which are cytotoxic in the presence of complement, occur in 90% of patients with pernicious anemia. Parietal cell autoantibodies react with $\alpha$ and $\beta$ subunits of the proton pump ($H^+/K^+$ ATPase). This enzyme is the major protein of the secretory canaliculi of parietal cells and mediates secretion of $H^+$ in exchange for $K^+$. Importantly, some 20% of persons over 60 years have parietal cell antibodies, but few have pernicious anemia.

INTRINSIC FACTOR ANTIBODIES: In addition to the postulated immunologic destruction of parietal cells, two types of autoantibodies to intrinsic factor are common in pernicious anemia. Two thirds of patients have an antibody to intrinsic factor that impedes its binding to vitamin B12, preventing formation of the complex that is absorbed in the ileum. About half of patients with this antibody also have an antibody against the intrinsic factor–vitamin B12 complex that interferes with its absorption.

OTHER ANTIBODIES: Half of patients with pernicious anemia have circulating antibodies to thyroid tissue. Conversely, about one third of patients with chronic thyroiditis possess gastric autoantibodies.

Multifocal Atrophic Gastritis (Environmental Metaplastic Atrophic Gastritis)

Multifocal atrophic gastritis is a disease of uncertain etiology that typically involves the antrum and adjacent areas of the body. This form of chronic gastritis has these features:

- It is considerably more common than the autoimmune variety of atrophic gastritis and is four times as frequent among whites as in other races.
- It is not linked to autoimmune phenomena.

FIGURE 13-10. Erosive gastritis. This endoscopic view of the stomach in a patient who was ingesting aspirin reveals acute hemorrhagic lesions.
Like autoimmune gastritis, it is often associated with reduced acid secretion (hypochlorhydria).

Complete absence of gastric secretion (achlorhydria) and pernicious anemia are uncommon.

**PATHOLOGY:** The pathologic features of autoimmune and multifocal atrophic gastritis are similar, except for the localization of the autoimmune type to the fundus and body and the multifocal variety mainly to the antrum.

**ATROPHIC GASTRITIS:** This condition is characterized by prominent chronic inflammation in the lamina propria. Occasionally, lymphoid cells are arranged as follicles, an appearance that has led to an erroneous diagnosis of lymphoma, especially in patients with *H. pylori* infection (see below). Involvement of gastric glands leads to degenerative changes in their epithelial cells and ultimately to a conspicuous reduction in the number of glands (thus the name *atrophic gastritis*; Fig. 13-11). Eventually, inflammation may abate, leaving only a thin atrophic mucosa, in which case the term *gastric atrophy* is applied.

**INTESTINAL METAPLASIA:** This lesion is a common and important histopathologic feature of both autoimmune and multifocal types of atrophic gastritis. In response to injury of the gastric mucosa, the normal epithelium is replaced by one composed of cells of the intestinal type (see Fig. 13-11C). Numerous mucin-containing goblet cells and enterocytes line cryptlike glands. Paneth cells, which are not normal inhabitants of the gastric mu-
cosa, are present. Intestinal-type villi may occasionally form. The metaplastic cells also contain enzymes characteristic of the intestine but not of the stomach (e.g., alkaline phosphatase, aminopeptidase).

In the fundus of the stomach with autoimmune atrophic gastritis, the normal parietal and zymogen cells may be replaced by clear mucous glands similar to those of the cardia or antrum, a change termed **psuedoplastic metaplasia**. Therefore, the pathologist must know the precise location from which a biopsy specimen was taken, because fundal pseudoplastic metaplasia may be mistaken for gastritis of the antrum.

**Atrophic Gastritis and Stomach Cancer**

Persons with autoimmune or multifocal atrophic gastritis have greater risk of carcinoma of the stomach. Atrophic gastritis is usually asymptomatic and so does not ordinarily come under medical scrutiny so this relationship is hard to quantify. However, patients with pernicious anemia, who invariably have atrophic gastritis, have a 3-fold greater risk for gastric adenocarcinoma and 13-fold higher risk of carcinoid (neuroendocrine) tumors. Cancer arises in the antrum several times more frequently than in the body of the stomach, suggesting that antral gastritis is related to gastric carcinogenesis.

**Intestinal metaplasia of the stomach has been identified as a preneoplastic lesion for several reasons:** (1) gastric cancer arises in areas of metaplastic epithelium, (2) half of all stomach cancers are of the intestinal cell type, and (3) many gastric cancers show aminopeptidase activity similar to that seen in areas of intestinal metaplasia. Moreover, all grades of dysplasia, from low-grade dysplasia to carcinoma in situ, have been observed in metaplastic intestinal epithelium, (2) half of all stomach cancers are of the intestinal cell type, and (3) many gastric cancers show aminopeptidase activity similar to that seen in areas of intestinal metaplasia.

Pathogenesis: Helicobacter pylori Gastritis

**Helicobacter pylori** is a chronic inflammatory disease of the antrum and body of the stomach caused by **H. pylori** and occasionally by **H. heilmannii**. It is the most common type of chronic gastritis in the United States. The organism causes one of the most frequent chronic infections. **H. pylori** infection is also strongly associated with peptic ulcer disease of the stomach and duodenum (see below).

**PATHOLOGY:** The curved rods of **H. pylori** are found in the surface mucus of epithelial cells and in gastric foveolae (Fig. 13-12). The uncommon bacterium **H. heilmannii** is long and has tight spirals, an appearance similar to that of spirochetes. Active gastritis features polymorphonuclear leukocytes in glands and their lumina and increased numbers of plasma cells and lymphocytes in the lamina propria (see Fig. 13-12A). Lymphoid hyperplasia with germinal centers is frequent.

**Reactive (Chemical) Gastropathy**

Reactive (chemical) gastropathy is being recognized with increasing frequency. It was first recognized in patients with bile reflux, but is currently most commonly seen in association with chronic nonsteroidal anti-inflammatory drug (NSAID) use. Reflux of bile is commonly occur after a gastroduodenostomy or gastrojejunostomy, but can be seen in intact stomachs.

**PATHOLOGY:** The normal flat mucosal surface is replaced by villiform projections in which the lamina propria shows fibromuscular proliferation. Surface foveolar cells show prominent reactive nuclear atypia out of proportion to the sparse inflammatory infiltrate. Unlike **H. pylori** gastritis, inflammatory infiltrates are minimal.

**Granulomatous Gastritis**

Granulomatous gastritis may be secondary to infection (e.g., Mycobacterium tuberculosis; fungus) or as a manifestation of systemic illness (e.g., sarcoidosis, Crohn disease). However, most cases of granulomatous gastritis are idiopathic.

**Miscellaneous Forms of Chronic Gastritis**

**Eosinophilic gastritis,** often in association with eosinophilic enteritis, is disease in which eosinophils involve all layers of the stomach wall or are selectively localized in a single layer. In classic cases, the antrum and pylorus are mainly affected: diffuse thickening of the wall, presumably by muscular hypertrophy, may narrow the pylorus and cause symptoms of obstruction. These are occasionally severe enough to require surgical relief. In some cases, ulceration in an affected area leads to chronic blood loss and anemia. Peripheral eosinophilia and a history of food allergies are common, but many patients have neither. Corticosteroid therapy is often effective.

**Lymphocytic gastritis** is characterized by prominent intraepithelial lymphocytes (>20 per 100 epithelial nuclei). It can
be associated with celiac disease, although in most cases the etiology is unknown. Some cases may be related to prior *H. pylori* infection.

**Vascular gastropathies** include gastric antral vascular ectasia (GAVE) and portal hypertensive gastropathy (see Chapter 14). GAVE is characterized by prominent lamina propria vessels with focal thrombosis. It has a characteristic endoscopic appearance termed “watermelon stomach”. GAVE mostly occurs in elderly patients, and may be associated with significant blood loss.

**Ménétrier Disease Causes Protein Loss**

*Ménétrier disease* (hyperplastic hypersecretory gastropathy) is an uncommon gastric disorder characterized by enlarged rugae. It is often accompanied by a severe loss of plasma proteins (including albumin) from the altered gastric mucosa. A childhood form is due to cytomegalovirus infection; an adult form is attributed to overexpression of transforming growth factor-α (TGF-α).

**PATHOLOGY:** The stomach is enlarged. The folds of the greater curvature in the fundus and body of the stomach, and occasionally in the antrum, are increased in height and thickness, forming a convoluted brainlike surface (Fig. 13-13). Microscopically, Ménétrier disease is restricted to the oxyntic mucosa. Hyperplasia of the gastric pits results in a conspicuous increase in their depth and a tortuous (corkscrew) structure. Mucus-secreting cells of the surface or neck type line the foveolae. The glands are elongated, and many appear cystic. These dilated glands, which are lined by superficial-type, mucus-secreting epithelial cells rather than parietal and chief cells, may penetrate the muscularis mucosae, and in so doing resemble the sinuses of Rokitansky-Aschoff in the gallbladder. Pseudopyloric metaplasia may be seen, but intestinal metaplasia does not occur. Lymphocytes, plasma cells, and occasional neutrophils are seen in the lamina propria. Concurrent lymphocytic gastritis is often present.

**CLINICAL FEATURES:** Ménétrier disease is four times more common in men than women and affects persons of all ages. The presenting symptom is usually postprandial pain, relieved by antacids. Weight loss, sometimes of rapid onset, occasionally occurs. Peripheral edema is com-
mon. In some cases, ascites and cachexia, which are related to a loss of plasma proteins from the gastric mucosa, may suggest a malignancy. The cause of the enormous protein loss into the lumen of the stomach is obscure, but treatment with anticholinergic agents or an inhibitor of acid secretion may be successful. Although gastric acidity is usually low, severe peptic ulceration associated with hyperacidity has occasionally been observed.

Ménétrier disease does not usually resolve spontaneously in adults, and in intractable cases, partial gastrectomy is necessary. The disorder is considered a precancerous condition, and periodic endoscopic surveillance is recommended. Cytomegalovirus-associated Ménétrier disease in children is often self-limited.

### Peptic Ulcer Disease

“Peptic ulcer disease” refers to focal destruction of gastric mucosa and small intestine, principally the proximal duodenum, caused by the action of gastric secretions. About 10% of the population of Western industrialized countries may develop such ulcers at some time during their lives. However, both the incidence and prevalence of duodenal ulcers have declined substantially during the past 30 years.

Although peptic ulceration can occur as high as Barrett esophagus and as low as Meckel diverticulum with gastric heterotopia, for practical purposes, peptic ulcer disease affects the distal stomach and proximal duodenum. Many clinical and epidemiologic features distinguish gastric from duodenal ulcers; the common factor that unites them is the gastric secretion of hydrochloric acid.

### EPIDEMIOLOGY: The peak age for peptic ulcer disease has progressively increased in the past 50 years, and for duodenal ulcer disease it is now between 30 and 60 years of age, although the disorder may occur in persons of any age and even in infants. Gastric ulcers afflict the middle-aged and elderly more than the young. For duodenal ulcers there is a male predominance. By contrast, the incidence of gastric ulcers is similar in men and women.

Racial differences in the incidence of peptic ulcers have been noted, but studies of different ethnic populations are confounded by variations in many other environmental factors. For example, in Africa, duodenal ulcers are rare among blacks, whereas in the United States, the incidence is the same in blacks and whites. The preponderance of evidence suggests that in an urban Western setting, all ethnic groups are susceptible.

Surveys in the United States and Great Britain suggest a trend towards an inverse relation between duodenal ulcers and socioeconomic status and education.

### PATHOGENESIS: Numerous etiologic factors have been implicated in the pathogenesis of peptic ulcers, but no single agent seems to be responsible.

#### Environmental Factors

**DIET:** Despite the folk wisdom that spicy food and caffeine are ulcerogenic, little evidence actually supports the contention that any food or beverage, including coffee and alcohol, contributes to the development or persistence of peptic ulcers. However, cirrhosis from any cause is associated with increased incidence of peptic ulcers.

**DRUGS:** Aspirin is an important contributing factor for duodenal, and especially gastric, ulcers. Other nonsteroidal anti-inflammatory agents and analgesics have been incriminated in production of peptic ulcers. Prolonged treatment with high doses of corticosteroids may also increase the risk of peptic ulceration slightly.

**CIGARETTE SMOKING:** Smoking is a definite risk factor for duodenal and gastric ulcers, particularly gastric ulcers.

### Genetic Factors

First-degree relatives of people with duodenal or gastric ulcers have a threefold increased risk of developing an ulcer, but only at the same site. These data are confirmed by a considerably higher concordance for these ulcers in monozygotic than in dizygotic twins. Identical twins show only a 50% concordance indicating that environmental factors must also be involved.

**Blood-group antigens** provide further evidence for the role of genetic factors. The risk of duodenal ulcer is 30% higher in persons with type O blood than in those with other types. Interestingly, patients with gastric ulcers do not exhibit a greater frequency of blood group O. People who do not secrete blood-group antigens in saliva or gastric juice carry a 30% increased risk for duodenal ulcers. Those who are both blood group O and nonsecretors (10% of white people) have a 2.5-fold increase in duodenal ulcers.

**Pepsinogen I** is secreted by gastric chief and mucous neck cells, and appears in gastric juice, blood, and urine. Serum levels of this proenzyme correlate with the capacity for gastric acid secretion and are considered a measure of parietal cell mass. A person with a high circulating level of pepsinogen I has 3 times the normal risk of developing a duodenal ulcer. Hyperpepsinogenemia occurs in half of children of ulcer patients with hyperpepsinogenemia and has been attributed to autosomal dominant inheritance. Thus, hyperpepsinogenemia may reflect an inherited tendency to increased parietal cell mass.

**Familial tendencies** for other features are reported in ulcer patients. Many patients with peptic ulcer have normal pepsinogen I secretion and familial aggregation has also been shown among such persons. Familial clustering of duodenal ulcers and rapid gastric emptying have been noted, and familial hyperfunction of antral G cells is also reported. Patients with a childhood duodenal ulcer are much more likely to have a family history of ulcers than persons in whom the disease begins when they are adults.

**Hydrochloric acid secretion** is necessary for formation and persistence of peptic ulcers in the stomach and duodenum. This is evidenced principally by: (1) all patients with duodenal ulcers and almost all with gastric ulcers are gastric acid secretors; (2) experimental ulcer production in animals requires acid; (3) hypersecretion of acid is present in many, but not all, patients with duodenal ulcers (there is no evidence that acid overproduction alone explains duodenal ulceration); and (4) surgical or medical treatment that reduces acid production results in the healing of peptic ulcers. Gastric secretion of pepsin, which may also play a role in peptic ulceration, parallels that of hydrochloric acid.
Physiologic Factors in Duodenal Ulcers

The maximal capacity for gastric acid production reflects total parietal cell mass. Patients with duodenal ulcers may have up to double normal parietal cell mass and maximal acid secretion. However, there is a large overlap with normal values, and only one third of these patients secrete excess acid. Increased chief cell mass often accompanies increased parietal cells, a situation that is consistent with the increased prevalence of hyperpepsinogenemia in patients with ulcers.

Gastric secretion of acid stimulated by food is increased in magnitude and duration in those with duodenal ulcers, although here, too, there is significant overlap with normal values. In a few patients this may involve, at least in part, altered G cell responses to meals. Such persons exhibit postprandial hypergastrinemia and increased numbers of antral G cells. Most patients with duodenal ulcers, however, show no evidence of G-cell hyperfunction.

Acid secretion in people with duodenal ulcers may also be more sensitive than normal to gastric secretagogues such as gastrin, possibly as due to increased vagal tone or increased affinity of parietal cells for gastrin. It is further possible that brisk secretion of acid after a meal is stimulated by increased vagal tone.

Accelerated gastric emptying has been noted in patients with duodenal ulcers. This condition might lead to excessive acidification of the duodenum. However, as with other factors, there is overlap with normal rates. Normally, duodenal bulb acidification inhibits further gastric emptying. In most patients with duodenal ulcer, this inhibitory mechanism is absent: duodenal acidification leads to continued, rather than delayed, gastric emptying. Rapid gastric emptying may in some cases be an inherited trait.

The pH of the duodenal bulb reflects the balance between delivery of gastric juice and its neutralization by biliary, pancreatic, and duodenal secretions. Duodenal ulceration requires an acidic pH in the bulb, that is, an excess of acid over-neutralizing secretions. In ulcer patients, duodenal pH after a meal decreases to a lower level and remains depressed for a longer time than in normal persons. Such duodenal hyperacidity certainly reflects the gastric factors discussed above. The role of neutralizing factors, particularly secretin-stimulated bicarbonate secretion by the pancreas and production of bicarbonate by the duodenal mucosa, is uncertain.

Impaired mucosal defenses have been invoked as contributing to peptic ulceration. These mucosal factors, including prostaglandin function, may or may not be similar to those protecting the gastric mucosa (see above).

Physiologic Factors in Gastric Ulcers

Gastric ulcers almost invariably arise in the setting of epithelial injury by H. pylori or chemical gastritis. The mechanisms by which chronic gastritis predisposes to gastric ulceration are obscure. Most patients with gastric ulcers secrete less acid than do those with duodenal ulcers and even less than normal persons. Factors implicated include (1) back-diffusion of acid into the mucosa, (2) decreased parietal cell mass, and (3) abnormalities of the parietal cells themselves. A minority of patients with gastric ulcers show acid hypersecretion. The ulcers in these persons are usually near the pylorus, and are considered variants of duodenal ulcers. Interestingly, the intense gastric hypersecretion that occurs in the Zollinger-Ellison syndrome is associated with severe ulceration of the duodenum and even the jejunum but rarely of the stomach.

The concurrence of gastric ulcers and gastric hyposecretion implies: (1) the gastric mucosa may in some way be particularly sensitive to low concentrations of acid; (2) something other than acid may damage the mucosa, e.g., NSAIDs; or (3) the gastric mucosa may be exposed to potentially injurious agents for unusually long periods. As discussed above, the mucosal barrier to the action of acid and perhaps to other contents of the stomach, may be impaired in some patients with gastric ulcers, although the evidence is far from conclusive. Bile reflux (particularly deoxycholic acid and lysolecithin) and pancreatic secretions have been suggested as causes of gastric ulcers.

The Role of Helicobacter pylori

H. pylori is isolated from the gastric antrum of virtually all patients with duodenal ulcers. The converse is not true; that is, only a small minority of persons infected with this bacterium have duodenal ulcer disease. Thus, H. pylori infection may be a necessary, but not sufficient, condition for development of peptic ulcers in the duodenum.

Just how H. pylori infection predisposes to duodenal ulcers is not completely known, but several mechanisms have been proposed. Cytokines produced by inflammatory cells that respond to H. pylori infection stimulate gastrin release and suppress somatostatin secretion. Interleukin (IL)-1β, an acid inhibitor, has also emerged as an important mediator of inflammation in H. pylori-infected gastric mucosa. These effects, together with release of histamine metabolites from the organism itself, may stimulate basal gastric acid secretion. In addition, luminal cytokines from the stomach may enter and injure duodenal epithelium. There is some evidence that H. pylori infection blocks inhibitory signals from the antrum to both the G cells and the parietal cell region, resulting in increased gastrin release and impaired inhibition of gastric acid secretion. Such an effect might lead to increased acid load in the duodenum, thereby contributing to duodenal ulceration. Acidification of the duodenal bulb leads to islands of metaplastic gastric mucosa in the duodenum in many patients with a peptic ulcer. This gastric epithelium in the duodenum is sometimes colonized with H. pylori, like the gastric mucosa. It has been postulated that infection of the metaplastic epithelium by H. pylori renders the mucosa more susceptible to peptic injury (Fig. 13-14).

Infection with H. pylori is probably also important in the pathogenesis of gastric ulcers, because this organism is responsible for most cases of the chronic gastritis that underlies this disease. About 75% of patients with gastric ulcers harbor H. pylori. The remaining 25% of cases may represent an association with other types of chronic gastritis. The various gastric and duodenal factors that have been implicated as possible mechanisms in the pathogenesis of duodenal ulcers are summarized in Figure 13-15.

Diseases Associated with Peptic Ulcers

CIRRHOSIS: The incidence of duodenal ulcers in patients with cirrhosis is 10 times that in normal persons.
CHRONIC RENAL FAILURE: End-stage renal disease with hemodialysis increases the risk of peptic ulceration. Patients subjected to renal transplantation also show a substantially increased incidence of peptic ulceration and its complications, such as bleeding and perforation.

HEREDITARY ENDOCRINE SYNDROMES: There is an increased incidence of peptic ulcers in persons with multiple endocrine neoplasia, type 1 (see Chapter 21). Zollinger-Ellison syndrome, a cause of severe peptic ulceration, is characterized by gastric hypersecretion caused by a gastrin-producing islet cell adenoma of the pancreas.

α₁-ANTITRYPSIN DEFICIENCY: Almost one third of patients with this disease have peptic ulcers, which incidence is even higher if patients also have lung disease. Moreover, peptic ulcer is increased in people heterozygous for mutant α₁-antitrypsin.

CHRONIC PULMONARY DISEASE: Long-standing pulmonary dysfunction significantly increases the risk of ulcers, and it is estimated that fully one fourth of those with such disorders have peptic ulcer disease. Conversely, chronic lung disease is increased 2- to 3-fold in persons who have peptic ulcers.

FIGURE 13-14. Possible mechanisms in the pathogenesis of duodenal ulcer disease associated with Helicobacter pylori infection.

FIGURE 13-15. Gastric and duodenal factors in the pathogenesis of duodenal peptic ulcers. *H. pylori* = *Helicobacter pylori*; HCl = hydrochloric acid; HCO₃⁻ = bicarbonate.
CHAPTER 13: THE GASTROINTESTINAL TRACT

PATHOLOGY: Most peptic ulcers arise in the lesser gastric curvature, in the antral and prepyloric regions and in the first part of the duodenum.

Gastric ulcers (Fig. 13-16) are usually single and smaller than 2 cm in diameter. Ulcers on the lesser curvature are commonly associated with chronic gastritis, whereas those on the greater curvature are often related to NSAIDs. Edges tend to be sharply punched out, with overhanging margins. Deeply penetrating ulcers produce a serosal exudate that may cause adherence of the stomach to surrounding structures. Scarring of ulcers in the prepyloric region may be severe enough to produce pyloric stenosis.

Grossly, chronic peptic ulcers may closely resemble ulcerated gastric carcinomas. Thus, the endoscopist must take multiple biopsies from the edges and bed of any gastric ulcer.

Duodenal ulcers (Fig. 13-17) are ordinarily on the anterior or posterior wall of the first part of the duodenum, close to the pylorus. Lesions are usually solitary, but it is not uncommon to find paired ulcers on both walls, so-called kissing ulcers.

Microscopically, gastric and duodenal ulcers are similar (Fig. 13-18). From the lumen outward, the following are noted: (1) a superficial zone of fibrinopurulent exudate; (2) necrotic tissue; (3) granulation tissue; and (4) fibrotic tissue at the base of the ulcer, which exhibits variable degrees of chronic inflammation. Ulceration may penetrate the muscle layers, causing them to be interrupted by scar tissue after healing. Blood vessels on the margins of the ulcer are often thrombosed. The mucosa at the margins tends to be hyperplastic, and with healing grows over the ulcerated area as a single layer of epithelium. Duodenal ulcers are usually accompanied by peptic duodenitis, with Brunner gland hyperplasia and gastric mucin cell metaplasia.

CLINICAL FEATURES: The symptoms of gastric and duodenal ulcers are sufficiently similar that the two conditions are generally not distinguishable by history or physical examination. The classic case of duodenal ulcer is characterized by epigastric pain 1 to 3 hours after a meal, or that awakens the patient at night. Both alkali and food relieve the symptoms. Dyspeptic symptoms commonly associated with gallbladder disease, including fatty food intolerance, distention, and belching, occur in half of patients with peptic ulcers. The major complications of peptic ulcer disease are hemorrhage, perforation with peritonitis and obstruction.
HEMORRHAGE: The most common complication of peptic ulcers is bleeding, which occurs in up to 20% of patients. Bleeding is often occult and, in the absence of other symptoms, may manifest as iron-deficiency anemia or occult blood in stools. Massive life-threatening bleeding is a well-known complication of active peptic ulcers.

PERFORATION: Perforation is a serious complication of peptic ulcers that occurs in 5% of patients; in one third of cases, there are no antecedent symptoms of a peptic ulcer. Perforations occur more often with duodenal than with gastric ulcers, mostly on the anterior wall of the duodenum. Because the anterior walls of the stomach and duodenum are unprotected by contiguous tissue, ulcers in these locations are more likely to be complicated by free perforation, which leads to generalized peritonitis and accumulation of air in the abdominal cavity, called pneumoperitoneum. Posterior gastric ulcers perforate into the lesser peritoneal sac, where the inflammatory reaction may be contained. When ulcers penetrate into the pancreas, liver or greater omentum, they cause intractable symptoms. They may also penetrate the biliary tract and fill it with air.

Perforation carries a high mortality rate. The risk of death for perforated gastric ulcers is 10% to 40%, two to four times more than for duodenal ulcers (10%). Perforations are occasionally complicated by hemorrhage. Although shock, abdominal distention, and pain are common symptoms, perforations are occasionally diagnosed for the first time at autopsy, particularly in institutionalized, elderly patients.

PYLORIC OBSTRUCTION (GASTRIC OUTLET OBSTRUCTION): Pyloric obstruction occurs in up to 10% of ulcer patients and peptic ulcer disease is its most common cause in adults. Narrowing of the pyloric lumen by an adjacent peptic ulcer may be caused by muscular spasm, edema, muscular hypertrophy, or contraction of scar tissue; most commonly it is due to a combination of these. Eventually obstruction may ensue.

DEVELOPMENT OF COMBINED ULCERS: Gastric and duodenal ulcers may occur together in the same patient far more often than can be accounted for by chance alone. Patients with either one have a much greater risk of developing the other later.

MALIGNANT TRANSFORMATION OF BENIGN GASTRIC ULCERS: It is extremely difficult to distinguish a cancer arising in a preexisting gastric ulcer from an ulcerated primary carcinoma. In contrast, malignant transformation of a duodenal ulcer is very uncommon. However, although cancers originating in benign peptic ulcers probably account for under 1% of all malignant tumors in the stomach, such tumors have been well documented.

TREATMENT: In the past, peptic ulcers were treated by subtotal gastrectomy. However, the disease is now cured using antibiotics to eliminate *H. pylori*, blocking gastric acid secretion, with histamine receptor blockers and proton pump inhibitors.

Benign Neoplasms

Stromal Tumors in the Stomach Tend to Be NonAggressive

Nearly all gastrointestinal stromal tumors (GISTs) are derived from the pacemaker cells of Cajal and include the vast majority of mesenchymal derived stromal tumors of the entire gastrointestinal tract. The pacemaker cells and the tumor cells express the *c-kit* oncogene (CD117) that encodes a tyrosine kinase that regulates cell proliferation and apoptosis. The criteria to evaluate aggressive behavior in all GISTs include size, necrosis, and the number of mitotic figures. Interestingly, many of gastric GISTs, independently of size, tend to behave in a nonaggressive fashion, as opposed to small and large bowel tumors, which more commonly behave in a malignant manner.

Gastric GISTs are usually submucosal (Fig. 13-19) and covered by intact mucosa or, when they project externally, by peri toneum. The cut surface is whorled. Microscopically, the tumors are variably cellular, and are composed of spindle-shaped cells with cytoplasmic vacuoles embedded in a collagenous stroma. The cells are disposed in whorls and interlacing bundles. Bizarre and giant nuclei do not necessarily suggest malignancy. GISTs

**FIGURE 13-19.** A. Gastrointestinal stromal tumor of the stomach. The resected tumor is submucosal and covered by a focally ulcerated mucosa. B. Microscopic examination of the tumor shows spindle cells with vacuolated cytoplasms.
Epithelial Polyps

HYPERPLASTIC POLYPS: These lesions are by far the most common of the gastric polyps. They may be single or multiple, and are seen as pedunculated or sessile lesions of variable sizes. Hyperplastic polyps are common in the atrophic oxyntic mucosa of the body and fundus of patients with autoimmune metaplastic atrophic gastritis, but they also occur in the antrum of patients with H. pylori gastritis. Microscopically, the polyps consist of elongated, branched crypts lined by foveolar epithelium, beneath which pyloric or gastric glands are present. They appear to represent a response to injury and their epithelium is not dysplastic. Hyperplastic polyps have no malignant potential.

TUBULAR ADENOMAS (ADENOMATOUS POLYPS): These are true neoplasms that occur most commonly in the antrum. They range from smaller than 1 cm in diameter to a considerable size. Many are about 4 cm. Most adenomatous polyps are sessile, and are usually solitary. Microscopically, adenomas show tubular structures or a combination of tubular and villous structures. The glands are usually lined by dysplastic epithelium, which is sometimes intestinalized. Adenomatous polyps manifest a malignant potential, variably reported at 9% to 70%. This risk increases with the size of the polyp and is greatest for lesions over 2 cm. Dysplasia can also occur in flat gastric mucosa. The presence of multiple tubular adenomas in patients with familial adenomatous polyposis greatly increases the risk of developing adenocarcinoma.

FUNDIC GLAND POLYPS: Fundic gland polyps are characterized by dilated oxyntic glands lined by parietal and chief cells and by mucus cell metaplasia. They were originally described in patients with familial adenomatous polyposis. Currently they are mostly seen in patients treated with proton pump inhibitors. These polyps are not considered preneoplastic, and patients have no increased risk of gastric carcinoma.

Malignant Tumors

Carcinoma of the Stomach Relates to Many Environmental Factors

**EPIDEMIOLOGY:** As recently as the mid-20th century, gastric carcinoma was the most common cause of cancer death in men in the United States. For reasons that are unclear, the incidence of gastric carcinoma has decreased steadily. It now accounts for only about 3% of cancer deaths in the United States. The incidence of stomach cancer remains exceedingly high in such countries as Japan and Chile, where rates are seven to eight times that in the United States. Emigrants from high-risk to low-risk areas show a decline in the incidence of cancer of the stomach (see Chapter 5), which observation strongly implicates environmental factors in its gastric carcinogenesis.

**PATHOGENESIS:** Although correlations have been demonstrated with a number of factors, the cause of gastric cancer remains elusive.

**DIETARY FACTORS:** Ingredients in the diet have been invoked to account for geographic variations in the incidence of gastric cancer. The tumor is more common among persons who eat large amounts of starch, smoked fish and meat, and pickled vegetables. Benzpyrene, a potent carcinogen, has been detected in smoked foods.

**NITROSAMINES:** Attention has focused on a possible role of nitrosamines, which are powerful carcinogens in animals. Secondary amines are nonenzymatically converted to nitrosamines in the presence of nitrates or nitrites. High concentrations of nitrate have been found in the soil and water in certain areas where incidence of gastric cancer is high, and processed meats and vegetables are high in nitrates and nitrites.

The decrease in gastric cancer in the United States parallels increased use of refrigeration, which inhibits conversion of nitrates to nitrites and also obviates the need for such food preservatives. Consumption of whole milk and fresh vegetables rich in vitamin C is inversely related to the occurrence of stomach cancer. Vitamin C inhibits the nitrosation of secondary amines in vivo.

**GENETIC FACTORS:** Although a few familial clusters and several cases in twins have been reported, heredity is not thought to play a role in most cases of gastric carcinoma. Gastric cancer occurs with higher frequency in hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, a disorder caused by germline mutations of genes responsible for DNA nucleotide mismatch repair. Blood type A is found in 38% of the general population, whereas half of patients with gastric cancer display this blood type.

**AGE AND SEX:** Gastric cancer is uncommon in persons younger than 30 years and shows a sharp peak in incidence in persons over 50. However, the age at onset is somewhat lower in Japan, where the disease is endemic. In the United States, there is only a slight male predominance, but in countries with a high incidence of this tumor, the male-to-female ratio is about 2:1.

**HELICOBACTER PYLORI:** Serologic studies have shown a high prevalence of gastric infection with H. pylori many years before the appearance of stomach cancer. Persons seropositive for H. pylori were three times more likely than seronegative persons to develop gastric adenocarcinoma in the ensuing 1 to 24 years of follow-up. In view of the observation that risk of stomach cancer is determined largely by environmental factors in the first decades of life, it is noteworthy that populations at high risk for this tumor show a high prevalence of childhood infection with H. pylori, while those at low risk do not. Since gastric adenocarcinoma develops in only a small proportion of persons infected with H. pylori, and since some stomach cancers are found in uninfected persons, H. pylori alone is neither sufficient nor necessary for gastric carcinogenesis.

**LOW SOCIOECONOMIC SETTINGS:** These situations pose an increased risk of gastric cancer, an observation that has been used to explain the higher frequency of the tumor among American blacks and the fact that the incidence of the disease in that population has not declined as rapidly as it has among whites.

**Atrophic gastritis, pernicious anemia, subtotal gastrectomy, and gastric adenomatous polyps** are discussed above as factors associated with a high risk of stomach cancer.
PATHOLOGY: Gastric adenocarcinoma accounts for over 95% of malignant gastric tumors. It occurs in two major but overlapping types: diffuse and intestinal. Cancers are most common in the distal stomach, the lesser curvature of the antrum and the prepyloric region. Adenocarcinoma may occur anywhere, but is rare in the fundus.

ADVANCED GASTRIC CANCER: By the time most gastric cancers in the Western world are detected, they are advanced; that is, they have penetrated beyond the submucosa into the muscularis propria and may extend through the serosa. The macroscopic appearance of these advanced cancers is of great importance not only to the pathologist but also to the radiologist and the endoscopist, who may be called on to distinguish carcinomas from benign lesions and to assess the degree of spread.

Advanced gastric cancers are divided into three major macroscopic types:

- **Polypoid (fungating) adenocarcinoma** accounts for one third of advanced cancers. It is a solid mass, often several centimeters in diameter, that projects into the stomach lumen. The surface may be partly ulcerated, and deeper tissues may or may not be infiltrated.

- **Ulcerating adenocarcinomas** comprise another third of all gastric cancers. They have shallow ulcers of variable size (Fig. 13-20). Surrounding tissues are firm, raised and nodular. Characteristically, the lateral margins of the ulcer are irregular and the base is ragged. This appearance stands in contrast to that of the usual benign peptic ulcer, which exhibits punched-out margins and a smooth base. Despite these differences, radiologic differentiation of ulcerating cancer from peptic ulcer is occasionally difficult.

- **Diffuse or infiltrating adenocarcinoma** accounts for one tenth of all stomach cancers. No true tumor mass is seen; instead, the wall of the stomach is thickened and firm (Fig. 13-21). If the entire stomach is involved, it is called a linitis plastica tumor. In the diffuse type of gastric carcinoma, invading tumor cells induce extensive fibrosis in the submucosa and muscularis. Thus, the wall is stiff and may be more than 2 cm thick.

Microscopically, the histologic pattern of advanced gastric cancer varies from a well-differentiated adenocarcinoma with gland formation (intestinal type) to a poorly differentiated carcinoma without glands. The polypoid variant typically contains well-differentiated glands, whereas linitis plastica is characteristically poorly differentiated. Particularly in the ulcerated type of cancer, tumor cells may be arranged in cords or small foci. Tumor cells may contain cytoplasmic mucin that displaces the nucleus to the periphery of the cell, resulting in the so-called signet ring cell (Fig. 13-22). Extracellular mucinous material may be so prominent that the malignant cells seem to float in a gelatinous matrix, in which case it is called a mucinous (colloid) carcinoma.

EARLY GASTRIC CANCER: Early gastric cancer is defined as a tumor limited to the mucosa or submucosa (Fig. 13-23). The older term, superficial spreading carcinoma, is synonymous with early gastric cancer. In Japan, early gastric cancer accounts for one third of all stomach cancers, but only 5% in the United States and Europe.

Early gastric cancer is strictly a pathologic diagnosis based on depth of invasion; the term does not refer to the duration of the disease, its size, presence of symptoms, absence of metastases or curability. Up to 20% of early gastric cancers have already metastasized to lymph nodes at the time of detection.

Like advanced cancer, most early gastric cancers are in the distal stomach and are classified according to their macroscopic appearance:

- **Type I** protrudes into the lumen as a polypoid or nodular mass.

- **Type II** is a superficial, flat lesion that may be slightly elevated or depressed.

- **Type III** is an excavated malignant ulcer that does not ordinarily occur alone but rather represents ulceration of type I or type II tumors.

The polypoid and superficial elevated varieties of early gastric cancer are typically well-differentiated intestinal-type adenocarcinomas. In flattened or depressed superficial early cancers, patterns range from well differentiated to poorly differentiated. The excavated lesions have the highest proportion of undifferentiated tumors.

Most intestinal type gastric cancers originate from areas of intestinal metaplasia. By contrast, less-differentiated and anaplastic tumors of the diffuse type are more likely to derive from the necks of gastric glands without intestinal metaplasia.

Intuitively, one would suppose that early gastric cancer would be the precancer of advanced gastric cancer. However, this is not always the case. Early gastric cancer may sometimes be a different disease from advanced cancer, with a more benign course and greater curability because it has an inherently lower biological potential for invasion. This difference in biology may reflect differences between intestinal and gastric cell types. For example, even if there are lymph node metastases, early gastric cancer has a much better prognosis than does advanced cancer.

The 10-year survival rate for surgically treated advanced gastric cancer is about 20%, compared with 95% for early gastric cancer.
cancer. Moreover, the mean age at onset of early gastric cancer is uniformly younger than that of advanced cancer, and the early variety shows a striking geographic distribution.

Gastric cancer metastasizes mainly via lymphatics to regional lymph nodes of the lesser and greater curvature, porta hepatis, and subpyloric region. Distant lymphatic metastases also occur, the most common being an enlarged supraclavicular node, called Virchow node. Hematogenous spread may seed any organ, including liver, lung, or brain. Direct extension to nearby organs is often seen. It can also spread to ovary, where it commonly elicits a desmoplastic response, which is termed a Krukenberg tumor.

Figure 13-24 schematically depicts the major types of gastric cancer.

**CLINICAL FEATURES:** In the United States and Europe, most patients with gastric cancer have metastases when they are first seen for examination. Thus, the symptoms and course are usually those of advanced cancer. The most frequent initial symptom is weight loss, usually with anorexia and nausea. Most patients complain of epigastric or back pain, a symptom that mimics benign gastric ulcer and is often relieved by antacids or H2-receptor antagonists. However, as the disease advances, symptomatic amelioration with medical therapy disappears.

Gastric outlet obstruction may occur with large tumors of the antrum or prepyloric region. Massive bleeding is uncommon, but chronic bleeding often leads to anemia and finding occult blood in the stools. Tumors involving the esophagogastric junction cause dysphagia and may mimic achalasia and esophageal adenocarcinoma.

Patients with early gastric cancer may be asymptomatic but usually complain of dyspepsia or epigastric pain. Weight loss, melena, and anemia are present in a minority.

**Gastric Neuroendocrine (Carcinoid) Tumors are Low-Grade Malignancies**

Various endocrine cells in the gastric mucosa may give rise to neoplasms, collectively termed carcinoid tumor (neuroendocrine tumors; NETs). These tumors may recur locally and metastasize. The probability of metastases depends more on tumor size than on histopathologic characteristics. Most gastric NETs are not hormonally functional but may occasionally secrete serotonin and metastases can cause carcinoid syndrome.

Gastric NETs arise in the setting of hypergastrinemia associated with autoimmune gastritis. In this context, NETs derive from hyperplastic neuroendocrine cells in the proximal stomach (ECL cells) in response to hypergastrinemia that follows loss of parietal cells. Sporadic gastric NETs tend to be more aggressive.

**Gastric Lymphoma Is the Most Common Extranodal Lymphoma**

Primary lymphoma of the stomach accounts for about 5% of all gastric malignancies, and 20% of all extranodal lymphomas. Clinically and radiologically, it mimics gastric adenocarcinoma. Presenting symptoms, as with gastric adenocarcinoma, are usually weight loss, dyspepsia, and abdominal pain. The age at diagnosis is usually 40 to 65 years and there is no sex predominance. The tumors grossly resemble carcinomas, because they may be polypoid, ulcerating or diffuse (Fig. 13-25). Most gastric lymphomas are low-grade B-cell neoplasms of the MALToma type and arise in the setting of chronic *H. pylori* gastritis with lymphoid hyperplasia. Some of actually regress after eradication of the *H. pylori* infection. Other histopathologic varieties are similar to those in primary nodal lymphomas.
Gastrointestinal Stromal Tumors Have Low Malignant Potential

These spindle cell tumors almost always arise from the interstitial cells of Cajal (pacemaker cells) in the muscularis propria. GISTs constitute about 1% of gastric cancers. They are seen as palpable masses in up to half of patients with this tumor. It is often difficult to predict the biological behavior of a GIST from its morphologic appearance in the absence of infiltration or metastases. Macroscopically malignant GISTs are larger than their benign counterparts. Cellular pleomorphism and hyperchromasia may be present in both benign and malignant tumors, but the size and number of mitoses are greater in malignant GISTs. In some cases, the biology of a tumor is apparent only after long-term follow-up. Metastases are usually to the liver and peritoneal surfaces. Direct spread to adjacent tissues may occur. Treatment is surgical excision. A drug that specifically inhibits the c-kit signal transduction pathway (imatinib) is an effective treatment in many patients with advanced metastatic GISTs.

Bezoars

Bezoars are foreign bodies made of food or hair altered by the digestive process.

PHYTOBEZOAR: These vegetable concretions are unusual, except in persons who eat many persimmons or swallow unchewed bubble gum. Phytozoos are usually seen in persons with delayed gastric emptying, as in the peripheral neuropathy of diabetes or gastric cancer, and in people undergoing therapy with anticholinergic agents.

Recently, phytozoos have been found principally in patients who display delayed gastric emptying and hypochlorhydria after partial gastrectomy, particularly when surgery includes vagotomy. Plant zoos contain vegetable or fruit fibers. Most patients with persimmon zoos have bleeding from an associated gastric ulcer.

The preferred treatment of phytozoos is chemical attack with cellulase; in some cases, manual disruption by endoscopic techniques, including jets of water, has been successful. However, enzymatic therapy is usually not effective for persimmon zoos, and surgery is required.

TRICHOBEZOAR: This mass is a hairball within a gelatinous matrix, usually seen in long-haired girls or young women who eat their own hair as a nervous habit. Trichobezoars may grow by accretion to form a complete cast of the stomach, potentially reaching 3 kg (Fig. 13-26).

THE SMALL INTESTINE

Anatomy

Early in development, the intestinal tract begins as a tube that joins the stomach to the cloaca. This tube progressively elongates and its cephalic portion becomes the segment that extends from the distal duodenum to the proximal ileum. The more caudal portion develops into distal ileum and the proximal two thirds of transverse colon. The vitelline duct, which connects the primitive duct with the yolk sac, may persist as a Meckel diverticulum. To achieve the final position of the intestine, the fetal gut undergoes a complex series of rotations.
CHAPTER 13: THE GASTROINTESTINAL TRACT

The small intestine extends from the pylorus to the ileocecal valve and, depending on its muscle tone, is from 3.5 to 6.5 m long. It is divided into three regions:

1. **The duodenum** extends to the ligament of Treitz.
2. **The jejunum** is the proximal 40% of the remainder of the small intestine.
3. **The ileum** is the distal 60%.

The duodenum is almost entirely retroperitoneal and therefore fixed. The remainder of small intestine, which is disposed in redundant loops, is movable.

The C-shaped duodenum surrounds the head of the pancreas. It receives biliary drainage of the liver and the pancreatic secretions through the common bile duct at the ampulla of Vater. The distal duodenum becomes invested by mesentery and merges with the jejunum at the ligament of Treitz. The proximity of the duodenum to its neighbors means that it may be affected by disorders such as cancer of the pancreas and choledochoduodenal fistulas. Conversely, duodenal ulcers may penetrate into the pancreas or liver. There is no demarcation between jejunum and ileum, which merge gradually. The wall of the jejunum is thicker and its lumen wider than that of the ileum.

**The plicae circularis,** the spiral folds that consist of mucosa and submucosa, are most prominent in the distal duodenum and proximal jejunum, usually disappearing in the terminal ileum. **Peyer patches** are lymphoid aggregates in the submucosa measuring up to 3 cm in diameter. They are located in the antimesenteric aspect of the distal half of the ileum. The ileocecal valve is not a true valve but rather a muscular sphincter that regulates the flow of intestinal contents into the cecum.

The duodenum is served by the pancreaticoduodenal branch of the hepatic artery, which arises from the celiac artery. The jejunum and ileum are supplied by the superior mesenteric artery (a branch of the aorta), which is arranged in arcades in the mesentery, thereby providing abundant collateral circulation in its distal reaches. The veins draining the small intestine empty into the portal venous system. Duodenal lymphatic channels drain into portal and pyloric lymph nodes; those of the jejunum and ileum communicate with mesenteric lymph nodes. The lymphatics of terminal ileum empty into ileocolic nodes.

The small intestine is innervated by sympathetic fibers from the celiac plexus and ganglia and by parasympathetic fibers from the vagus nerve. The small intestinal wall has four layers: mucosa, submucosa, muscularis, and serosa. In the retroperitoneal duodenum, however, only the anterior wall is covered by a serosa.

**SEROsa AND MUSCULARis PROPrIA:** The serosa contains loose connective tissue bounded by a single layer of mesothelial cells. The muscularis propria has an outer longitudinal layer and an inner circular layer, both of which function in a coordinated manner to propel the intestinal contents by peristalsis.

**SUBMUcOSA:** This region consists of vascularized connective tissue and a few scattered lymphocytes, plasma cells, and macrophages, with occasional mast cells and eosinophils. In the proximal duodenum, the submucosa is occupied by Brunner glands, branched structures that contain mucous and serous cells. These secrete mucus and bicarbonate, which protect the duodenal mucosa from peptic ulceration. The lymphatic and venous capillaries of the mucosa drain into a highly developed system of lymphatic and venous plexuses in the submucosa. The **myenteric nerve plexus of Auerbach,** which lies between the two layers of the muscularis, and **Meissner plexus** in the submucosa are interconnected.

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**FIGURE 13-25.** Mucosa-associated lymphoid tissue (MALT) lymphoma. **A.** There is loss of detail within the gastric mucosa as a MALT lymphoma infiltrates the mucosa over a large surface area, although a discrete mass was not formed. **B.** Microscopically, there is a monotonous population of lymphoid cells expands the lamina propria.

**FIGURE 13-26.** Trichobezoar (hairball). A mass of hair in a gelatinous matrix forms a cast of the stomach.
MUCOSA: The distinctive feature of intestinal mucosa is its arrangement in villi, fingerlike projections 0.5 to 1 mm in length that expand the absorptive area enormously. The macroscopic structure of the villi varies in different regions of the small intestine. In the proximal duodenum, villi tend to be broad and blunt, whereas in the distal duodenum and proximal jejunum, they are more slender, leaf-shaped. Shorter, finger-shaped villi are the rule in distal jejunum and ileum.

Villi are composed of columnar epithelium resting on a basement membrane, a lamina propria, and a muscularis mucosae, which separates the mucosa from the submucosa. The connective tissue of the lamina propria forms the core of the villus and surrounds the crypts of Lieberkühn at the base of the villi. The normal lamina propria contains lymphocytes, plasma cells and macrophages. Plasma cells in this location principally secrete immunoglobulin A (IgA) into the intestinal lumen or the lamina propria itself. Occasional eosinophils and mast cells are scattered throughout. A few smooth muscle cells and fibroblasts are also present. The cellular composition of the lamina propria reflects its role in protecting against invasion by bacteria that may penetrate the mucosa and segregating foreign material that breaches the mucosa.

Some IgA is produced by plasma cells in the lamina propria as a dimer that diffuses through the basement membrane of the crypt. IgA then reaches the basal or lateral surface of epithelial cells, where it combines with a secretory component produced by that cell. Resulting secretory IgA is taken up by epithelial cells and secreted into the lumen. Secretory IgA is more resistant to proteolysis than is serum IgA. It binds food antigens and prevents bacterial adherence to the intestinal epithelium. Moreover, it can neutralize bacterial toxins and inhibit viral replication and mucosal penetration.

Lymphoid nodules (MALT) are scattered throughout the mucosa and aggregate into visible Peyer patches. The villous columnar epithelial cells are mainly absorptive, whereas those lining the crypts are the source of cell renewal and secretion. There are normally a moderate number of intraepithelial T lymphocytes.

Absorptive cells, or enterocytes (Fig. 13-27), are the principal lining cells of intestinal villi. The villi also exhibit a few goblet and endocrine cells. Enterocytes are tall and display basally situated nuclei. Numerous microvilli extend from the surface of these cells into the lumen, thereby hugely increasing the absorptive surface. The plasma membrane of the microvilli is covered by a glycocalyx (fuzzy coat) produced by the absorptive cells. Disaccharidases and peptidases reside in this glycocalyx. Certain receptors, such as that for the intrinsic factor–vitamin B₁₂ complex in the ileum, are also present in the membrane–glycocalyx complex. The cyttoplasm just under the microvilli contains a network of actin filaments, termed the terminal web. These filaments, which are also associated with myosin and other contractile proteins, insert into the core of the microvilli and presumably serve as a contractile apparatus. The lateral borders of adjacent plasma membranes form tight junctions that are impermeable to macromolecules but permit passive transport of small molecules by the paracellular route. Absorbed material is transported from epithelial cells to the intercellular space between absorptive cells, through lateral or basal plasma membranes. It then penetrates the basement membrane, traverses the lamina propria and enters a capillary or a lymphatic channel.

Four cell types are recognized in the crypts:

- **Paneth cells** at the base of the crypts are similar to the zymogen cells of the pancreas and salivary glands that are actively engaged in exocrine secretion. Within Paneth cells, eosinophilic secretory granules fill a basophilic cytoplasm. These cells play a role in mucosal defense, as evidenced by the presence of lysozyme, antimicrobial products, including peptides called crypt defensins (cryptdins) and CD95 ligand, which is a member of the tumor necrosis factor (TNF) family of cytokines.

- **Goblet cells** of the lateral walls of the crypts are flask-shaped and filled with mucus granules. They are similar in structure and function to goblet cells elsewhere and contain neutral and acid mucins.

- **Endocrine cells** appear inverted, with an apical nucleus and basal granules. The granules are most likely secreted into the lamina propria. These cells make several gastrointestinal hormones and peptides, including gastrin, secretin, cholecystokinin, glucagon, VIP, and serotonin. These hormones are felt to regulate many gastrointestinal functions, and tumors derived from these cells often exhibit striking hormone secretion.

- **Undifferentiated cells** are located in the lateral crypt walls and are interspersed between the Paneth cells at their bases. They are the most numerous cells of the crypts. Small glycoprotein secretory granules are grouped in the apical cytoplasm of some of the undifferentiated cells. These cells function as reserve cells from which all other mucus cells are renewed, and thus mitoses are numerous among them.

**Cell renewal** in the small intestine is limited to the crypts, where undifferentiated cells divide. The newly formed cells migrate up the villus, where they terminally differentiate into absorptive cells and goblet cells and eventually undergo apoptosis or slough into the lumen at the tip of the villus. Their absorptive capacity is maximal when they reach the upper third of the villus. The mucosal epithelium of the small intestine is replaced within a period of 4 to 7 days. This rapid cell proliferation explains why the intestinal epithelium is particularly sensitive to radiation and chemotherapeutic agents.

### Congenital Disorders

**Atresia and Stenosis Cause Neonatal Intestinal Obstruction**

**ATRESIA:** Atresia is defined as a complete occlusion of the intestinal lumen, which may manifest as (1) a thin intraluminal diaphragm, (2) blind proximal and distal sacs joined by a cord, or (3) disconnected blind ends. One fourth of atresias are associated with meconium ileus and cystic fibrosis is involved in one tenth of the cases.

**STENOSIS:** This is an incomplete stricture, which narrows but does not occlude, the lumen. Stenosis may also be caused by an incomplete diaphragm. It is usually symptomatic in infancy, but cases presenting in middle-aged adults have been recorded.

One fourth of mothers of fetuses with high intestinal atresia develop polyhydramnios in their last trimester of pregnancy, presumably because the fetus does not swallow amniotic fluid. Intestinal atresia or stenosis is diagnosed on the basis of persistent vomiting of bile-containing fluid within the first day of life. Meconium is not passed. The obstructed fetal intestine is dilated and filled with fluid, which can be detected radiologically. Surgi-
cal correction is usually successful, but there are often other complicating anomalies.

**Duplications (Enteric Cysts) May Occur From the Esophagus to the Anus**

These cysts are spherical or tubular structures attached to the alimentary tract. They may be seen as cystic structures or may communicate with the gut lumen. Intestinal duplications are most common in the ileum and less so in the jejunum. They have a smooth muscle wall and gastrointestinal type epithelium. Communicating duplications are often lined by gastric mucosa, a situation that may lead to peptic ulceration, bleeding, or perforation.

**Meckel Diverticulum Causes Bleeding, Obstruction, and Perforation**

Meckel diverticulum, caused by persistence of the vitelline duct, is an outpouching of the gut on the antimesenteric ileal border, 60 to 100 cm from the ileocecal valve in adults. It is the most common and the most clinically significant congenital anomaly of the small intestine (Fig. 13-28). Two thirds of patients are younger than 2 years.

**PATHOLOGY:** Meckel diverticulum is about 5 cm long, slightly narrower than the ileum. A fibrous cord may hang freely from the apex of the diverticulum or
The complications of Meckel diverticulum are several.

- Hemorrhage: The most common complication is bleeding. Meckel diverticula are responsible for half of all lower gastrointestinal hemorrhage in children. Bleeding results from peptic ulceration of the ileum adjacent to the ectopic gastric mucosa.

- Intestinal obstruction: The diverticulum may be a lead point for intussusception and so cause intestinal obstruction. Obstruction can also be caused by volvulus around the fibrotic remnant of the vitelline duct.

- Diverticulitis: Inflammation of a Meckel diverticulum (i.e., diverticulitis) leads to symptoms indistinguishable from those of appendicitis. Thus, a surgeon suspecting acute appendicitis who encounters a normal appendix, is well advised to search for a Meckel diverticulum.

- Perforation: Peptic ulceration, either in the diverticulum or in the ileum, may cause perforation, and lead to rapidly spreading peritonitis.

- Fistula: A fecal discharge from the umbilicus may be observed.

Malrotation May Lead to Bowel Obstruction

Defective intestinal rotation in fetal life leads to abnormal positions of small intestine and colon, anomalous attachments, and bands. The clinical importance of such rotational anomalies lies in their propensity to cause catastrophic volvulus of the small and large intestine and incarceration of bowel in an internal hernia.

Meconium Ileus is an Early Complication of Cystic Fibrosis

Neonatal intestinal obstruction in cystic fibrosis is caused by accumulation of tenacious meconium in the small intestine. The abnormal consistency of the meconium reflects a deficiency in pancreatic enzymes and high viscosity of intestinal mucus. The distal ileum is usually contracted beyond the obstruction, whereas the midileum proximal to the inspissated meconium is dilated. In half of affected infants, meconium ileus is complicated by (1) volvulus, (2) perforation with meconium peritonitis, or (3) intestinal atresia. Meconium ileus must be differentiated from distal intestinal obstruction associated with cystic fibrosis, in which a small plug of meconium in the distal colon may eventually be passed, thereby relieving the obstruction.

Infections of the Small Intestine

Bacterial Diarrhea is a Major Cause of Death Worldwide

Infectious diarrhea is particularly lethal in underdeveloped countries and in infants. The small bowel normally has few bacteria (usually <10⁴/mL), mostly aerobic bacilli such as lactobacilli. These organisms travel in the food stream and ordinarily do not colonize the small intestine. Infectious diarrhea is caused by bacteria; colonization, e.g., with toxigenic strains of Escherichia coli and Vibrio cholerae.

The most significant factor in infectious diarrhea is increased intestinal secretion, stimulated by bacterial toxins and enteric hormones. Decreased absorption and increased peristaltic activity contribute less to the diarrhea.

The colon harbors an abundant bacterial flora, with a concentration seven orders of magnitude greater than that of the small intestine. Anaerobic bacteria in colon (e.g., Bacteroides and Clostridium species) outnumber aerobic organisms by a factor of 1000. With the more rapid transit of intestinal contents during a diarrheal episode, the flora is shifted to a more aerobic population, including E. coli, Klebsiella, and Proteus. Moreover, offending organisms themselves become conspicuous and pathogens of the small intestine such as V. cholerae may be the major isolate in the stools.

Several factors limit the numbers of bacteria in the stomach and small bowel: (1) gastric acid production is inimical to bacterial growth, which explains the overgrowth of bacteria in the stomach in the presence of achlorhydria; (2) bile has antimicrobial activity; (3) peristaltic propulsion of intestinal contents limits bacterial accumulation; (4) normal flora secrete their own antimicrobial substances to maintain an ecological balance (indeed, treatment with broad-spectrum antibiotics alters the natural flora and allows overgrowth of ordinarily harmless organisms); and (5) plasma cells of the lamina propria secrete IgA into the intestinal lumen.

Individual agents responsible for infectious diarrhea are discussed in Chapter 9. Here we only briefly review the major entities. The agents of infectious diarrhea are conveniently classified into toxigenic organisms, which produce diarrhea by elaborating toxins, adherent bacteria, and invasive bacteria.

Toxigenic Diarrhea

The prototypic organisms that produce diarrhea by secreting toxins are V. cholerae and toxigenic strains of E. coli. Toxigenic diarrhea is characterized by:

- Hemorrhage:
- Perforation:
- Diverticulitis:
- Intestinal obstruction:
- Fistula:
the lumen.

Possible that the damaged mucosa is unable to resorb fluid from

Prostaglandin synthesis seem to block fluid secretion. It is also

Invasion of the mucosa by bacteria increases the synthesis of

Invasive bacteria, as their name implies, cause diarrhea by directly injuring the intestinal mucosa. Among these organisms, Shigella, Salmonella, and certain strains of E. coli, Yersinia, and Campylobacter are the most widely recognized. Invasive organisms tend to infect distal ileum and colon, while toxigenic bacteria mainly involve the upper intestinal tract. The mechanism by which they produce diarrhea is uncertain. Enterotoxins have been identified, but their role in causing diarrhea has not been established. Invasion of the mucosa by bacteria increases the synthesis of prostaglandins in the affected tissue and inhibitors of prostaglandin synthesis seem to block fluid secretion. It is also possible that the damaged mucosa is unable to resorb fluid from the lumen.

Diarrhea Caused by Invasive Bacteria

Invasive bacteria, as their name implies, cause diarrhea by directly injuring the intestinal mucosa. Among these organisms, Shigella, Salmonella, and certain strains of E. coli, Yersinia, and Campylobacter are the most widely recognized. Invasive organisms tend to infect distal ileum and colon, while toxigenic bacteria mainly involve the upper intestinal tract. The mechanism by which they produce diarrhea is uncertain. Enterotoxins have been identified, but their role in causing diarrhea has not been established. Invasion of the mucosa by bacteria increases the synthesis of prostaglandins in the affected tissue and inhibitors of prostaglandin synthesis seem to block fluid secretion. It is also possible that the damaged mucosa is unable to resorb fluid from the lumen.

PATHOGENESIS AND PATHOLOGY: SHIGELLOSIS: Shigellosis principally affects the colon, although the terminal ileum is occasionally involved. Microscopically, a granular and hemorrhagic mucosa exhibits numerous shallow serpiginous ulcers. The inflammation, which is especially severe in the sigmoid colon and rectum, is usually superficial. In the early stage, the accumulation of neutrophils in damaged crypts (crypt abscesses) is similar to that in ulcerative colitis and the lymphoid follicles of the mucosa break down to form ulcers. As the infection recedes, the ulcers heal and the mucosa returns to normal.

TYPHOID FEVER: Typhoid fever (Salmonella enteritidis) is today uncommon in the industrialized world but is still a problem in underdeveloped countries. Necrosis of lymphoid tissue, principally in the terminal ileum, leads to scattered ulcers. Infection of Peyer patches results in oval ulcers, in which the longer dimension is in the long axis of the intestine. Occasionally, lymphoid follicles in the large bowel or the appendix are ulcerated. The base of the ulcer is composed of black necrotic tissue mixed with fibrin.

The early lesions of typhoid fever contain large basophilic macrophages filled with typhoid bacilli, erythrocytes, and necrotic debris. Necrosis of lymphoid follicles becomes confluent and mucosal ulceration follows. Similar lymphoid hyperplasia and necrosis are seen in regional lymph nodes. Within a week of the acute symptoms ulcers heal completely, leaving little fibrosis or other sequelae. Intestinal hemorrhage and perforation, principally in the ileum, are the most feared complications of typhoid fever and tend to occur in the third week and during convalescence. NONTYPHOIDAL SALMONELLOSIS: Formerly known as paratyphoid fever, this enteritis is caused by Salmonella strains other than Salmonella typhi and is generally far less serious than typhoid fever. The principal target is the ileum, although minor involvement of the colon may also occur. Organisms invade the mucosa, which shows mild ulceration, edema, and infiltration with neutrophils. Hematogenous dissemination from the intestine may carry infection to bones, joints, and meninges. Interestingly, people with sickle cell anemia tend to develop Salmonella osteomyelitis, presumably because phagocytosis of the products of hemolysis prevents further cellular ingestion of the Salmonella organisms and allows their dissemination through the bloodstream.

ENTEROINVASIVE AND ENTEROHEMORRHAGIC STRAINS OF E. COLI: These organisms may uncommonly cause bloody diarrhea similar to shigellosis. Certain strains of E. coli, particularly serotype O157:H7, produce Shigella-like toxins, but the role of these proteins in the pathogenesis of the enterocolitis is not understood. Serotype O157:H7 has also been implicated in the hemolytic–uremic syndrome in children.

YERSinia ENTEROCOLITIS: Yersinia enterocolitica and Yersinia pseudotuberculosis are transmitted by pets or contaminated food and infection is most common in young children. Yersinia infection causes diarrhea, cramps, and fever and lasts 1 to 3 weeks. Disease is characterized by hyperplasia of Peyer patches, with acute ulceration of overlying mucosa. A fibrinopurulent exudate covers the ulcers and often contains many organisms.

In addition to causing enterocolitis, Yersinia causes acute mesenteric adenitis and pain in the right lower quadrant. Infected children have undergone laparotomy because the disease was mistaken for appendicitis. Microscopically the lymph nodes show epithelioid granulomas with central necrotic zones in the case of infection with Y. pseudotuberculosis. The ileum and appendix may contain similar granulomas, causing an appearance that has been mistaken for Crohn disease.

Adults, who are less susceptible to infection with Yersinia than are children, have an acute diarrhea, often followed within a few weeks by erythema nodosum, erythema multiforme, or polyarthritis. Patients with chronic debilitating diseases may develop a fatal Yersinia bacteremia that is resistant to antibiotic treatment. Interestingly, persons with thalassemia have a propensity for Y. enterocolitica infection.

CAMPYLOBACTER JEJUNI: C. jejuni is one of the most common causes of bacterial diarrhea. Some investigators report a higher incidence of Campylobacter than of nontyphoidal Salmonella and Shigella infections in the United States. In one study from Great Britain, half of all bacterial diarrhea was caused by Campylobacter. Humans contract the disease mainly by contact with infected domestic animals or ingestion of poorly cooked or contaminated food. Adults usually recover in less than 1 week.

Food Poisoning

Infectious agents can produce diarrhea by elaborating enterotoxins in contaminated food that is then ingested.

STAPHYLOCOCCUS AUREUS: This bacterium is a common cause of food poisoning. Symptoms result from ingesting food contaminated with Staphylococcus strains that produce an exotoxin that damages the gastrointestinal epithelium. Within 6
hours, severe vomiting and abdominal cramps occur, often followed by diarrhea. Most patients recover in 1 to 2 days.

_Clostridium Perfringens:_ This bacterium elaborates an enterotoxin that causes vomiting and diarrhea. Although the organism is anaerobic, it tolerates exposure to air for up to 3 days. Enterotoxin activity is maximal in the ileum. In most cases, watery diarrhea and severe abdominal pain begin 8 to 24 hours after ingestion of contaminated food, and last only about 1 day.

**Rotavirus and Norwalk Virus are the Most Common Causes of Viral Gastroenteritis in the United States**

**Rotavirus:** Rotavirus infection is a common cause of infantile diarrhea. It accounts for about half of acute diarrhea in hospitalized children under 2 years. Rotavirus has been demonstrated in duodenal biopsy specimens and is associated with injury to the surface epithelium and impaired intestinal absorption for periods of up to 2 months.

**Norwalk Viruses:** These agents account for one third of the epidemics of viral gastroenteritis in the United States. The virus targets the upper small intestine, where it causes patchy mucosal lesions and malabsorption. Vomiting and diarrhea are usual, but the symptoms resolve within 2 days.

Other viruses implicated as etiological agents of infective diarrhea include echovirus, coxsackievirus, cytomegalovirus, adenovirus, and coronavirus.

**Intestinal Tuberculosis Occurs After Ingesting Mycobacterium Bovis**

Historically an important disease, gastrointestinal tuberculosis is now uncommon in industrialized countries, although it is still a problem in underdeveloped areas of the world. Intestinal tuberculosis usually involves infection with _M._ _bovis_, which was mainly transmitted by contaminated milk. However, the control of tuberculosis in dairy herds and pasteurization of milk have made infection with this organism a curiosity.

Most cases of intestinal tuberculosis are caused either by ingesting bacteria in food or by swallowing infectious sputum. The tubercle bacillus is protected from digestion by its waxy capsule, and passes into the small bowel. It then establishes a locus of infection, usually (90% of patients) in the ileocecal region, where lymphoid tissue is abundant. Infection also occurs in the colon, jejunum, appendix, rectum, and duodenum, in that order of frequency.

**Pathology:** Intestinal tuberculosis may present with circular ulcers of varying size in the transverse plane of the bowel. As the ulcers heal, reactive fibrosis may cause a circumferential ("napkin ring") stricture of the bowel lumen. Mesenteric lymph nodes are typically enlarged and display caseous necrosis.

Granulomas may also be found in all layers of the bowel wall, particularly in Peyer patches and lymphoid follicles. Tuberculous strictures are difficult to distinguish from other causes of stricture, such as ischemic enterocolitis or Crohn disease.

**CLINICAL FEATURES:** Almost all patients with intestinal tuberculosis complain of chronic abdominal pain and about two thirds have a palpable abdominal mass, usually in the right lower quadrant. Malnutrition, weight loss, fever, and weakness are common. Complications include obstruction, fistulas, perforation, and abscess.

**Intestinal Fungal Infections Occur Mainly in Immunocompromised Patients**

Since the gastrointestinal tract is not a hospitable environment for fungi and the number of commensal organisms is miniscule (mostly yeasts and anaerobic actinomycetes), gastrointestinal fungal infections are usually opportunistic. Suppression of normal bacterial flora by antibiotics also favors fungal growth. Under these circumstances, the most common mycosis is caused by Candida. Other fungi, including _Histoplasma_ and _Mucor_, are occasionally found.

**Pathology:** Candidiasis and mucormycosis typically cause mucosal erosions; these may progress to larger ulcers that are surrounded by hemorrhage and necrosis. The inflammation is characteristically neutrophilic and there may be remarkably little reaction to the fungi because of immunosuppression. Mucormycosis often invades blood vessels, with thrombosis and infarction, but hematogenous dissemination from the intestine is rare. Disseminated histoplasmosis may involve the bowel, where it causes elevated plaques that ulcerate and may even perforate.

**Small Intestinal Parasites Include Both Protozoan and Metazoan Species**

Parasitic diseases of the small bowel are discussed in detail in Chapter 9. These parasites include (1) _protozoa_, such as _Giardia lamblia_, _Coccidia_ species, and _cryptosporidia_; (2) _nematodes_ (roundworms) such as _Ascaris_, _Strongyloides_, and hookworms; and (3) _flatworms_. The latter are divided into tapeworms (cestodes), such as _Diphyllobothrium latum_, _Taenia solium_, _Taenia saginata_, and _Hymenolepis nana_. Flukes (trematodes) include various schistosomes and the giant intestinal fluke _Fasciolopsis buski_. In addition, trichinosis has an intestinal phase during which vomiting, diarrhea, and colic mimic acute food poisoning or bacterial enteritis.

**Vascular Diseases of the Small Intestine**

Decreased intestinal blood flow from any cause can lead to ischemic bowel disease. Analogous to coronary heart disease, there is a spectrum of manifestations. The most common type of ischemic bowel disease is acute intestinal ischemia, which is associated with injury ranging from mucosal necrosis to transmural bowel infarction. Chronic intestinal ischemic syndromes are less common and generally require the severe compromise of two or more major arteries, usually by atherosclerosis.

**Superior Mesenteric Artery Occlusion is the Most Common Cause of Acute Intestinal Ischemia**

**Pathogenesis:**

_Arterial Occlusion:_ Sudden occlusion of a large artery by thrombosis or embolization leads to small bowel infarction before collateral circulation comes into play. Depending on the size of the artery, infarction may be segmental or may lead to gangrene of virtually the entire small bowel (Fig. 13-29). Occlusive intestinal infarction is most often caused by embolic or thrombotic occlusion of the superior mesenteric artery. A lesser number are the result of vasculitis, which often involves small arteries.
In addition to intrinsic vascular lesions, volvulus, intussusception and incarceration of the intestine in a hernial sac may all lead to arterial as well as venous occlusion.

NONOCCLUSIVE INTESTINAL ISCHEMIA: Intestinal ischemic necrosis in which no acute vascular occlusion is evident is more common than the occlusive type. Nonocclusive intestinal infarction may be extensive and is seen in hypoxic patients with reduced cardiac output from shock of a variety of causes including hemorrhage, sepsis, and acute myocardial infarction. Shock leads to redistribution of blood flow to the brain and other vital organs. In addition, patients in shock often receive $\beta$-adrenergic agents, which may further shunt blood away from the intestine. The drastically lowered perfusion pressure in the arterioles leads to their collapse, thereby aggravating the ischemia.

THROMBOSIS OF MESENTERIC VEINS: Causes of mesenteric vein thrombosis include hypercoagulable states, stasis, and inflammation (pylephlebitis). Almost all thromboses affect the superior mesenteric vein; only 5% involve the inferior mesenteric vein. The collateral flow in the distribution of the superior mesenteric vein usually suffices to preclude infarction of the intestine.

PATHOLOGY: Infarcted bowel is edematous and diffusely purple. The demarcation between infarcted bowel and normal tissue is usually sharp, although venous occlusion may lead to a more diffuse appearance. Extensive hemorrhage is seen in the mucosa and submucosa. Hemorrhage is prominent especially in venous occlusion (e.g., mesenteric vein thrombosis). The mucosal surface shows irregular white sloughs, the wall becomes thin and distended and bubbles of gas (pneumatosis) may be present in the bowel wall and mesenteric veins. The serosal surface is cloudy and covered by an inflammatory exudate.

Dysfunction of smooth muscle interferes with peristalsis and leads to adynamic ileus, in which the bowel proximal to the lesion is dilated and filled with fluid. Intestinal organisms may pass through the damaged wall and cause peritonitis or septicemia.

In nonocclusive intestinal ischemia, the principal lesion is restricted initially to the mucosa. Mucosal changes range from foci of dilated capillaries with a few extravasated erythrocytes to severe hemorrhagic necrosis and bleeding into the lumen. If the patient survives the episode of hypoperfusion, the bowel may be completely repaired, or it may heal with granulation tissue and fibrosis, with eventual stricture formation.

CHRONIC INTESTINAL ISCHEMIA LEADS TO RECURRENT ABDOMINAL PAIN

Atherosclerotic narrowing of major splanchic arteries leads to chronic intestinal ischemia. As in the heart, it causes intermittent abdominal pain, termed intestinal (abdominal) angina. Characteristically, the pain begins within a half hour of eating and lasts for a few hours. Many cases of frank infarction of the intestine are preceded by abdominal angina. Recurrent abdominal pain may also reflect pressure on the celiac axis from surrounding structures and has been labeled the celiac compression syndrome.

PATHOLOGY: Chronic small bowel ischemia may lead to fibrosis and stricture formation. Ischemic strictures of the small bowel may be single or multiple, and produce intestinal obstruction or, occasionally, malabsorption due to stasis and bacterial overgrowth. These strictures are concentric, and the mucosa of this region is atrophic and often exhibits one or more small ulcers. The submucosa is thickened and fibrotic and displays granulation tissue, which may extend into the muscular layers. Hemosiderin deposition may be prominent, particularly near the muscularis mucosae.

Malabsorption

Malabsorption is a general term that describes a number of clinical conditions in which important nutrients are inadequately absorbed by the gastrointestinal tract. Although some nutrient absorption occurs in the stomach and colon, only absorption from the small intestine, mainly in the proximal portion, is clinically important. Two
substances are preferentially absorbed by the distal small intestine: bile salts and vitamin B₁₂.

Normal intestinal absorption is characterized by a luminal phase and an intestinal phase (Fig. 13-30). The **luminal phase**, consisting of those processes that occur within the lumen of the small intestine, alters the physicochemical state of the various nutrients so that they can be taken up by the small bowel absorptive cells. The **intestinal phase** includes those processes that occur in the cells and transport channels of the intestinal wall. Each phase includes several critical components; derangement of one or more leads to impaired absorption.

In the luminal phase of intestinal absorption, pancreatic enzymes and bile acids must be secreted into the duodenal lumen in adequate amounts and in a normal physicochemical condition. Two additional factors are important for optimal activity of both pancreatic enzymes and bile salts: a normal and regulated flow of gastric contents into the duodenum and an appropriately high pH of the duodenal contents. Normal pancreatic enzyme excretion into the duodenum requires adequate pancreatic exocrine function and an unobstructed flow of pancreatic juice.

Supply of a normal quantity and quality of bile to the duodenum requires (1) adequate hepatocellular function, (2) unobstructed flow of bile, and (3) intact enterohepatic circulation of bile salts. The enterohepatic circulation of bile begins with absorption of most intestinal bile salts from the distal ileum and ends with their excretion into the duodenum through the bile ducts. Normally, 95% of intestinal bile salts are recycled through the enterohepatic circulation; 5% are excreted in the stools. Normal functioning of the enterohepatic circulation requires (1) normal intestinal microflora, (2) normal ileal absorptive function, and (3) an unobstructed biliary system.

**Luminal-Phase Malabsorption Often Reflects Insufficient Bile Acids**

- ** Interruption of the normal continuity of the distal stomach and duodenum** occurs after gastroduodenal surgery (gastrectomy, antrectomy, pyloroplasty).
- **Pancreatic dysfunction** can occur as a result of chronic pancreatitis, pancreatic carcinoma, or cystic fibrosis.
Deficient or ineffective bile salts may result from three possible causes:

1. **Impaired excretion of bile** resulting from liver disease.
2. **Bacterial overgrowth** from a disturbance in gut motility. This is seen in such conditions as blind-loop syndrome, multiple diverticula of the small bowel, and muscular or neurogenic defects of the intestinal wall (e.g., amyloidosis, scleroderma, diabetic enteropathy). When gastrointestinal motility is defective, bile salts are deconjugated by the excess bacterial flora, after which they cannot form micelles, which are essential for normal absorption of monoglycerides and free fatty acids.
3. **Deficient bile salts** due to the absence or bypass of the distal ileum caused by surgical excision, surgical anastomoses, fistulas, or ileal disease (e.g., Crohn disease, lymphoma).

**Intestinal-Phase Malabsorption Frequently Reflects Specific Enzyme Defects or Impaired Transport**

Although abnormalities in any one of the four components of the intestinal phase may cause malabsorption, some diseases affect more than one of these components. Figure 13-30 summarizes the major causes of malabsorption.

**PATHOGENESIS:**

**MICROVILLI:** The intestinal disaccharidases and oligopeptidases are integrally bound to the microvillous membranes. Disaccharidases are essential for sugar absorption, because only monosaccharides can be absorbed by intestinal epithelial cells. Oligopeptides and dipeptides may be absorbed by alternate mechanisms that do not require peptidases. Abnormal function of the microvilli may be primary, as in primary disaccharidase deficiencies; or secondary, when there is damage to the villi, as in celiac disease (sprue). The various enzyme deficiencies (e.g., of lactase) are characterized by intolerance for the corresponding disaccharides.

**ABSORPTIVE AREA:** The considerable length of the small bowel and the amplification of its surface wall by the intestinal folds (valves of Kerkring) provide a large absorptive surface. Severe diminution in this area may result in malabsorption. The surface area may be diminished by (1) small bowel resection (short bowel syndrome), (2) gastroduodenal fistula (bypassing the small intestine), or (3) mucosal damage due to a number of small intestinal diseases (celiac disease, tropical sprue, and Whipple disease).

**METABOLIC FUNCTION OF THE ABSORPTIVE CELLS:** For their subsequent transport to the circulation, nutrients within the absorptive cells depend on their metabolism within these cells. Monoglycerides and free fatty acids are reassembled into triglycerides and coated with proteins (apoproteins) to form chylomicrons and lipoprotein particles. Specific metabolic dysfunction is seen in abetalipoproteinemia (associated with erythrocyte acanthocytosis), a disorder in which the absorptive cells cannot synthesize the apoprotein required for the assembly of lipoproteins and chylomicrons. Nonspecific damage to small intestinal epithelial cells occurs in celiac disease, tropical sprue, Whipple disease, and hyperacidity due to gastrinoma.

**TRANSPORT:** Nutrients are transported from the intestinal epithelium through the intestinal wall by way of blood capillaries and lymphatic vessels. Impaired transport of nutrients through these conduits is probably an important factor in the malabsorption associated with Whipple disease, intestinal lymphoma, and congenital lymphangiectasia.

**CLINICAL FEATURES:** Malabsorption may be either specific or generalized.

- **Specific or isolated malabsorption** refers to an identifiable molecular defect that causes malabsorption of a single nutrient. Examples of this group are the disaccharidase deficiencies (notably lactase deficiency) and deficiency of gastric intrinsic factor, which causes malabsorption of vitamin B₁₂ and consequently pernicious anemia. Specific deficiency states may present with anemia due to deficiency of iron, folic acid, or vitamin B₁₂, or a combination of these three. Patients may have a bleeding diathesis due to vitamin K deficiency or malabsorption of vitamin D and calcium may lead to tetany, osteomalacia (in adults), or rickets (in children). In some persons, a deficiency of water-soluble vitamins of the B group may occur.

- **Generalized malabsorption** describes a condition in which absorption of several or all major nutrient classes is impaired. It leads to generalized malnutrition. In adults, this appears as weight loss and sometimes cachexia; in children, it is expressed as “failure to thrive” with poor growth and weight gain.

Secondary effects of nonabsorbed or partially absorbed substances may lead to diarrhea. In disaccharidase deficiency, unhydrolyzed sugars in the gut are metabolized by colonic bacteria to lactic acid, carbon dioxide (CO₂), and water, causing explosive fermentative diarrhea. In patients with ileal dysfunction, bile salts that are not absorbed enter the colon and cause choleric diarrhea because they stimulate colonic secretion.

**Laboratory Evaluation Detects Specific Forms of Malabsorption**

Diverse laboratory tests are used to assess malabsorption. For example, disaccharidase deficiency is diagnosed by measuring blood sugar after oral administration of a standard amount of disaccharide, as in the lactose-tolerance test, or by quantitating disaccharidase activity in small bowel biopsy specimens. Vitamin B₁₂ absorption is assessed by the Schilling test, in which isotopically labeled vitamin B₁₂ is given orally and its blood level then determined. This test helps to distinguish between malabsorption resulting from intrinsic-factor deficiency and other causes of vitamin B₁₂ malabsorption.

In generalized malabsorption, there is almost always impaired absorption of dietary fat. Quantitative fecal fat analysis is the most reliable and sensitive test of overall digestive and absorptive function and is a standard for all other tests for malabsorption. Steatorrhea (fat in the stools) is the hallmark of generalized malabsorption, and the two terms are often used interchangeably.

A few of the tests currently in use for the evaluation of various causes of malabsorption merit mention.

- **D-Xylose Absorption:** Xylose is a 5-carbon sugar whose absorption does not require any of the components of the lu-
Lactase Deficiency Causes Intolerance to Milk Products

The intestinal brush border contains disaccharidases that are important for the absorption of carbohydrates. As a prominent constituent of milk and many other dairy products, lactose is one of the most common disaccharides in the diet. Acquired lactase deficiency is a widespread disorder of carbohydrate absorption. Typically, symptoms of the disease begin in adolescence. Patients complain of abdominal distention, flatulence, and diarrhea after the ingestion of dairy products. Eliminating milk and its products from the diet relieves these symptoms. Diseases that injure the intestinal mucosa (e.g., celiac disease or radiation enteritis) may also lead to acquired lactase deficiency. Congenital lactase deficiency is rare but may be lethal if not recognized.

Celiac Disease Reflects an Immune Response to Gluten in Cereals

Celiac disease (celiac sprue, gluten-sensitive enteropathy) is characterized by (1) generalized malabsorption, (2) small intestinal mucosal lesions, and (3) prompt clinical and histopathologic response to withdrawal of gluten-containing foods from the diet.

EPIDEMIOLOGY: Celiac disease is worldwide and affects all ethnic groups. There is a slight female predominance, 1.3:1. It may be seen any time after cereals are introduced into the diet. Most cases are diagnosed during childhood, although the disease may become clinically apparent for the first time as late as the seventh decade of life.

PATHOGENESIS: Genetic predisposition and gliadin exposure are crucial factors in the development of celiac disease.

ROLE OF CEREAL PROTEINS: Experiments on successfully treated, asymptomatic patients with celiac disease have shown that ingestion or instillation of wheat, barley, or rye flour into the small intestine is followed by the clinical and histopathologic features of celiac sprue. Other grains, such as rice and corn flour, do not have such an effect. Both the water-insoluble portion of wheat flour, gluten and an alcoholic extract called gliadin have the same effect.

GENETIC FACTORS: Celiac sprue is caused by an interplay of complex genetic factors plus an abnormal immune response to ingested cereal antigens. Overt and latent celiac disease run in families. Concordance for celiac disease in first-degree relatives ranges between 8% and 18% and reaches 70% in monozygotic twins. About 90% of patients with celiac disease carry the histocompatibility antigen human leukocyte antigen (HLA)-B8 and a comparable frequency has been reported for HLA DR8 and DQ2.

IMMUNOLOGIC FACTORS: The intestinal lesion in celiac disease is characterized by damage to the epithelial cells and a marked increase in the number of T lymphocytes within the epithelium and of plasma cells in the lamina propria. Gliadin challenge of persons with treated celiac sprue stimulates local immunoglobulin synthesis.

A region of amino acid sequence homology has been found between α-gliadin and a protein of an adenovirus (serotype 12) that infects the human gastrointestinal tract. Most (90%) untreated patients with celiac disease have serologic evidence of prior infection with this virus. Exposure of a genetically susceptible person to gluten-containing cereals might then stimulate an immune reaction to gliadin at the intestinal epithelial cell surface.

Serum antigliadin and anti-endomysial antibodies are present in almost all patients, but their role in the pathogenesis of the disease remains to be established.

ASSOCIATION WITH DERMATITIS HERPETIFORMIS: Celiac disease is occasionally associated with dermatitis herpetiformis (DH), a vesicular skin disease that typically affects extensor surfaces and exposed parts of the body. In DH, subepidermal neutrophil infiltration leads to local edema and blister formation. Basement membrane IgA deposits are detected. Almost all patients with DH have a small bowel mucosal lesion similar to that of celiac disease, although only 10% have overt malabsorption. Treatment with a strict gluten-free diet leads to improvement in both gastrointestinal symptoms and skin lesions. The histocompatibility antigen HLA-B8 is much more frequent in patients with dermatitis herpetiformis than in normal persons.

Malabsorption in celiac disease probably results from multiple factors, including reduced intestinal mucosa surface area (due to blunting of villi and microvilli) and impaired intracellular metabolism within damaged epithelial cells. A probable aggravating factor is secondary disaccharidase deficiency, related to damage to microvilli. A hypothetical mechanism for the pathogenesis of celiac disease is presented in Figure 13-31.

PATHOLOGY: A microscopic finding in small bowel biopsies that can precede the more characteristic findings is an intraepithelial lymphocytic infiltrate involving crypts and surface epithelium in normal appearing villi. The hallmark of fully developed celiac disease is a flat mucosa, with (1) blunting or total disappearance of villi, (2) damaged mucosal surface epithelial cells with numerous intraepithelial lymphocytes (T cells), and (3) increased plasma cells in the lamina propria but not in deeper layers (Fig. 13-32). The most severe histologic abnormalities in untreated celiac disease usually occur in the duodenum and proximal jejunum. There is a progressive decrease in severity distally and in some cases the ileal mucosa appears virtually normal. The clinical severity of the disease is related to the length of the affected intestine.
The total mucosal thickness may not be decreased, because lengthening of the crypts compensates for villous shortening. The absorptive cells are flattened and more basophilic than normal, and the basal polarity of their nuclei is lost. Lymphocytes and plasma cells in the lamina propria are markedly increased. Most of the plasma cells produce IgA (as in the normal small bowel). Polymorphonuclear leukocytes and eosinophils may also be increased in the epithelium and lamina propria.

**CLINICAL FEATURES:** Fully developed celiac disease is characterized by generalized malabsorption. Not infrequently, overt signs of malabsorption in children are lacking, and the disease is suspected only because of growth retardation. In adults, iron deficiency anemia resistant to oral therapy is often the clue to celiac disease. The symptoms and signs of generalized malabsorption are often initially manifested in older children, adolescents, and adults. With the application of IgA anti-endomysial and IgA anti-tissue transglutaminase antibodies, it has become evident that celiac disease is more common than previously thought.

The systemic manifestations of celiac disease are related to the various deficiency states that result from generalized malabsorption. Late complications in some cases include ulcerative jejunitis and small bowel T-cell lymphoma. Adenocarcinoma of the small bowel and carcinoma of the oropharynx and esophagus also occur and an increased risk for colorectal carcinoma is reported. Other extraintestinal manifestations include follicular keratosis, peripheral neuropathy, and infertility. Treatment with a strict gluten-free diet is usually followed by a complete and prolonged clinical and histopathologic remission. Some patients have refractory sprue and respond only to corticosteroids.

**Collagenous sprue** refers to a rare disorder characterized by the deposition of collagen in the lamina propria of the small bowel. The disorder initially mimics celiac disease but does not respond to removal of gluten from the diet. The prognosis in collagenous sprue is grave: all reported patients have died of the disease.

**Whipple Disease** is a rare infection of the small bowel. Malabsorption is the most prominent feature of Whipple disease. White men in their 30s and 40s are most affected. The disease is systemic, and other clinical findings include fever, increased skin pigmentation, anemia, lymphadenopathy, arthritis, pericarditis, pleurisy, endocarditis, and central nervous system involvement.

**PATHOGENESIS:** Whipple disease typically shows infiltration of the small bowel mucosa by macrophages packed with small, rod-shaped bacilli. The causative organism is one of the actinomycetes, *Tropheryma whippelii*. Interestingly, *T. whippelii* is distantly related to mycobacteria such as *Mycobacterium avium-intracellulare* and *Mycobacterium paratuberculosis*, both of which have been associated with illnesses resembling Whipple disease. The results of several studies suggest that host susceptibility factors, possibly defective T-lymphocyte function, may be important in predisposing to the disease. Macrophages from patients with Whipple disease exhibit decreased ability to degrade intracellular microorganisms. Circulating cells expressing CD11b, a cell-adhesion and complement-receptor molecule on macrophages, are reduced. CD11b is involved in activating macrophages to kill intracellular pathogens. Dramatic clinical remissions occur with antibiotic therapy.
FIGURE 13-32. Celiac disease. **A.** Normal proximal small intestine shows tall slender villi with crypts present at the base. **B.** Normal surface epithelium shows an occasional intraepithelial lymphocyte as well as an intact brush border. **C.** A mucosal biopsy from a patient with advanced celiac disease shows complete loss of the villi with infiltration of the lamina propria by lymphocytes and plasma cells. The crypts are increased in height. **D.** At higher power the surface epithelium is severely damaged with large numbers of intraepithelial lymphocytes and loss of the brush border.

**PATHOLOGY:** The bowel wall is thickened and edematous, and mesenteric lymph nodes are usually enlarged. Villi are flat and thickened, and the lamina propria is extensively infiltrated with large foamy macrophages (Fig. 13-33A) whose cytoplasm is filled with large glycoprotein granules that stain strongly with periodic acid–Schiff (PAS) (see Fig. 13-33B). The other normal cellular components of the lamina propria (i.e., plasma cells and lymphocytes) are depleted. The lymphatic vessels in the mucosa and submucosa are dilated and large lipid droplets abound within lymphatics and in extracellular spaces, a finding that suggests lymphatic obstruction. In contrast to the striking distortion of the villous architecture, epithelial cells show only patchy abnormalities, including attenuation of microvilli and accumulation of lipid droplets within the cytoplasm.

Electron-microscopic examination reveals numerous small bacilli within macrophages and free in the lamina propria (see Fig. 13-33C). The PAS-positive granules seen by light microscopy correspond to lysosomes engorged with bacilli in various stages of degeneration. Many bacilli cluster immediately beneath the epithelial basement membrane.

Mesenteric lymph nodes draining affected segments of small bowel reveal similar microscopic changes. A characteristic infiltration by macrophages containing bacilli may also be found in most other organs. Heart lesions may include valvular vegetations which contain bacilli-laden macrophages, sometimes with superimposed streptococcal endocarditis. Treatment of Whipple disease is with appropriate antibiotics.

**Abetalipoproteinemia Involves Failure to Make Apoprotein B**

Abetalipoproteinemia is inherited as an autosomal recessive disease. The missing apoprotein B is a constituent of the membrane coat of low-density lipoproteins. Small intestinal absorptive cells that lack
Hypogammaglobulinemia May Lead to Malabsorption

The small intestine in hypogammaglobulinemia contains few or no plasma cells in the lamina propria, and often displays nodular lymphoid hyperplasia. Occasionally, there is a flat mucosa, similar to the lesion of celiac sprue; in this case, the disorder is termed hypogammaglobulinemic sprue.

Most hypogammaglobulinemic patients with malabsorption have small intestinal infection with *Giardia lamblia*. Treatment with metronidazole is followed by improved intestinal absorption.

**Congenital Lymphangiectasia Is a Generalized Malformation That Causes Malabsorption**

Congenital lymphangiectasia is a poorly understood disease that usually begins in childhood. In addition to steatorrhea caused by impaired transport of chylomicrons by intestinal lymphatics, these patients have protein-losing enteropathy, i.e., excessive loss of plasma proteins into the gut. A syndrome of intestinal lymphangiectasia and peripheral lymphedema is known as Milroy disease.

Other important features of congenital lymphangiectasia are lymphopenia and impaired cell-mediated immunity, caused by loss of small lymphocytes into the bowel lumen. Chylous ascites (milky, lipid-containing peritoneal fluid), due to leakage of lymph from the mesenteric or serosal lymphatic vessels into the peritoneal cavity may occur.

Grossly, lesions of congenital lymphangiectasia are opalescent white spots which microscopically are dilated lymphatics (lacteals) in the lamina propria. The submucosal lymphatics also tend to be dilated. The epithelium is normal, but the villi may be blunted or even absent in areas overlying severe lymphatic dilation.

Acquired intestinal lymphangiectasia, with all or some of the clinical features described above, may be a secondary manifestation of small intestinal or retroperitoneal lymphoma, other retroperitoneal tumors, tuberculosis, sarcoidosis, chronic pancreatitis, and retroperitoneal fibrosis.

**Tropical Sprue Is a Disease of Unknown Etiology That Causes Folate Deficiency**

Tropical sprue is endemic in certain tropical areas and is characterized by progressively severe malabsorption and nutritional deficiency. Cure, or at least amelioration of symptoms, usually follows treatment with oral tetracycline and folic acid. The cause of tropical sprue is not known. Some studies suggest that long-standing contamination of the bowel with bacteria, perhaps toxigenic strains of *E. coli*, may be important and that the resultant folate deficiency may play a role in perpetuating the intestinal lesion.

The histologic findings are variable, ranging from mild widening and blunting of villi to a completely flat mucosa similar to that seen in celiac sprue. The morphologic injury in the epithelium and the inflammation of the lamina propria usually parallel the severity of the alterations in the villi.

Typically, steatorrhea, anemia, and weight loss are followed by progressively severe manifestations of folic acid and vitamin B₁₂ deficiencies, and hypoalbuminemia. Laboratory findings include increased fecal fat, impaired D-xylose absorption, megalo-loblastic anemia, and decreased disaccharidase activity in the intestinal mucosa.

**Radiation Enteritis Results From Abdominal Radiotherapy**

Transient damage to the small intestinal mucosa is seen. Anorexia, abdominal cramps, and changes in bowel habits occur frequently during abdominal radiation treatments, and labora-
Pathology

The bowel loops and predisposes to normality. Malrotation of the bowel permits undue mobility of Volvulus virtually always indicates an underlying congenital ab-
mesentery, kinking the bowel and usually interrupting its blood supply.

Volvulus is a cause of an acute abdomen and is an exam-
ple of intestinal obstruction in which a segment of gut twists on its mesentry, kinking the bowel and usually interrupting its blood supply. Volvulus virtually always indicates an underlying congenital abnormality. Malrotation of the bowel permits undue mobility of the bowel loops and predisposes to midgut volvulus. When the cecum or right colon is invested with a mesentery rather than being retroperitoneal, the result may be cecal volvulus. An unusually long sigmoid colon, which occurs sometimes in patients with idiopathic chronic constipation, permits the development of sigmoid volvulus.

**ADHESIONS:** Fibrous scars caused by previous surgery or peritonitis cause obstruction by kinking or angulating the bowel or directly compressing the lumen.

**HERNIA:** Loops of small bowel may be incarcerated in an inguinal or femoral hernia, in which case, the lumen may become obstructed and the vascular supply compromised. Similarly, portions of the bowel may be trapped internally by hernias that represent congenital or surgically acquired defects in the mesentery.

**PSEUDO-OBSTRUCTION:** Patients who have signs and symptoms of intestinal obstruction but who lack overt mechanical causes are said to have pseudo-obstruction. The process may be familial or sporadic. There may be an underlying myopathy or a neuropathy, but in many cases no anatomic lesion is found. The myopathies feature fibrosis around muscle cells in the lamina propria. Neuronal inclusions are occasionally seen in the neuropathies.

A particularly common form of pseudo-obstruction is limited to the colon in which no morphologic lesion is usually demonstrable, referred to as severe idiopathic constipation. Pseudo-obstruction may be secondary to intestinal involvement by diseases such as scleroderma, amyloidosis, hypothyroidism, or adverse drug effect. Such cases are often referred to as secondary pseudo-obstruction.

**Mechanical Obstruction**

Mechanical obstruction to the passage of intestinal contents can be caused by (1) a luminal mass, (2) an intrinsic lesion of the bowel wall, or (3) extrinsic compression.

**INTUSSUSCEPCION:** In this form of intraluminal small bowel obstruction a segment of bowel (intussusceptum) protrudes distally into a surrounding outer portion (intussuscipiens) (Fig. 13-34). Intussusception usually occurs in infants or young children, in whom it occurs without a known cause. In adults, the leading point of an intussusception is usually a lesion in the bowel wall, such as Meckel diverticulum or a tumor. Once the leading point is entrapped in the intussuscipiens, peristalsis drives the intussusceptum forward. In addition to acute intestinal obstruction, intussusception compresses the blood supply to the intussusceptum, which may become infarcted. If the obstruction is not relieved spontaneously, treatment requires surgery.

**VOLVULUS:** This is a cause of an acute abdomen and is an example of intestinal obstruction in which a segment of gut twists on its mesentry, kinking the bowel and usually interrupting its blood supply. Volvulus virtually always indicates an underlying congenital abnormality. Malrotation of the bowel permits undue mobility of the bowel loops and predisposes to midgut volvulus. When the cecum or right colon is invested with a mesentery rather than being retroperitoneal, the result may be cecal volvulus. An unusually long sigmoid colon, which occurs sometimes in patients with idiopathic chronic constipation, permits the development of sigmoid volvulus.

**Neoplasms**

Less than 5% of all gastrointestinal tumors arise in the small intestine.

**Benign Tumors Include Adenomas, Peutz-Jeghers Polyps, and Stromal Tumors**

**Adenomas**

Small bowel adenomas resemble those of the colon. Depending on the predominant component, adenomatous polyps of the small intestine may be tubular, villous, or tubulovillous. Villous adenoma is rare in the small intestine, usually occurring in the duodenum, especially the periampullary region. Adenomas, especially the villous type, may undergo malignant transformation. Benign adenomas are frequently asymptomatic, but bleeding and intussusception are occasional complications.

**Peutz-Jeghers Syndrome**

Peutz-Jeghers syndrome is an autosomal dominant hereditary disorder characterized by intestinal hamartomatous polyps and mucocutaneous melanin pigmentation, which is particularly evident on the face; buccal mucosa, hands, feet, and perianal and genital areas. Except for the buccal pigmentation, the frecklelike macular lesions usually fade at puberty. The polyps occur mostly in the proximal small intestine but are sometimes seen in the stomach and the colon. Patients usually have symptoms of obstruction or intussusception; in as many as one fourth of cases, however, the diagnosis is suggested by pigmentation in an otherwise asymptomatic person.

Peutz-Jeghers syndrome is associated with inactivating mutations of a gene (LKB1) on chromosome 19p that encodes a protein kinase. Carriers of the defective gene are also at increased risk for cancers of the breast, pancreas, testis, and ovary.
Peutz-Jeghers polyps are hamartomas, with branching networks of smooth muscle fibers continuous with the muscularis mucosae supports the glandular epithelium of the polyp (Fig. 13-35). Peutz-Jeghers polyps are generally considered benign, but 3% of patients develop adenocarcinoma, although not necessarily in the hamartomatous polyps.

Gastrointestinal Stromal Tumors
GISTs occur throughout the small intestine but most often in the jejunum. They grow as intramural masses covered by intact mucosa and are similar to those in other locations. Intestinal obstruction is uncommon, but volvulus may be a complication. Small intestinal GIST tumors are more likely to behave aggressively than their gastric counterparts.

Malignant Tumors of the Small Bowel are Uncommon

Adenocarcinoma

**EPIDEMIOLOGY:** Although small intestinal adenocarcinomas are a minute proportion of all gastrointestinal tumors, they account for half of all malignant small bowel tumors. Most are located in the duodenum and jejunum. The majority occur in middle-aged persons, and there is a moderate male predominance. Interestingly, the geographic variation in the incidence of small bowel adenocarcinoma correlates with that of colon cancer but not with that of stomach cancer.

*Crohn disease of the small bowel is a risk factor for adenocarcinoma.* For such patients, the mean age for developing adenocarcinoma is 10 years younger than the average. Such cancers tend to occur in the same area as the inflammatory lesions, namely the ileum. Familial adenomatous polyposis, HNPCC syndrome (Lynch syndrome), and celiac disease are additional risk factors.

**PATHOLOGY AND CLINICAL FEATURES:** Adenocarcinoma of the small intestine may be polyoid or ulcerative or simply annular and stenosing. In addition to causing intestinal obstruction directly, a polypoid tumor may be the lead point of an intussusception. Adenocarcinomas originate from crypt epithelium, rather than the villi and, therefore, resemble colorectal cancers.

The symptoms of small bowel adenocarcinoma commonly relate to progressive intestinal obstruction. Occult bleeding is common and often leads to iron-deficiency anemia. If adenocarcinoma of the duodenum involves the papilla of Vater, it is termed **ampullary carcinoma.** This tumor causes obstructive jaundice or pancreatitis. By the time the patient becomes symptomatic, most adenocarcinomas have metastasized to local lymph nodes and overall 5-year survival is less than 20%. This neoplasm is the second most common cause of death in patients with familial adenomatous polyposis.

**Primary Intestinal Lymphoma**
Primary lymphoma originates in nodules of lymphoid tissue normally present in the mucosa and superficial submucosa, termed mucosa-associated lymphoid tissue (MALT). Lymphoma is the second most common malignant tumor of the small intestine in industrialized countries, where it accounts for about 15% of small bowel cancers.

Another type of primary lymphoma comprises more than two-thirds of all cancers of the small intestine in less developed countries. The latter variety of intestinal lymphoma was originally described in Mediterranean populations, but it is now clear that it is distributed throughout the poorer parts of the world. These two types of lymphoma have distinct epidemiologic, clinical, and pathologic features and are respectively termed, **Western type** and **Mediterranean lymphoma.**

The cause of primary lymphoma of the small bowel is unknown, but association with celiac disease is well documented, occurring in as many as one tenth of patients with primary lymphoma. The persistent activation of lymphocytes in the bowel is felt to predispose to subsequent development of T-cell lymphoma. However, while a gluten-free diet usually improves the inflammatory component of the enteropathy, T-cell lymphoma can still occur.

The risk of intestinal lymphoma is also increased in conditions that favor development of nodal lymphoma, particularly immunodeficiency following treatment with immunosuppressive drugs.

**MEDITERRANEAN LYMPHOMA:** Mediterranean lymphoma typically occurs in poor countries in young men of low socioeconomic status; it is therefore thought by some to have an environmental cause. This neoplasm is associated with **α-heavy chain disease,** a proliferative disorder of intestinal B lymphocytes that secrete the heavy chain of IgA without light chains. Mediterranean lymphoma and α—chain disease are believed to be the same disorder, termed **immunoproliferative small intestinal disease.**

Mediterranean intestinal lymphoma predominantly involves the duodenum and proximal jejunum. A long segment of small intestine, or even the entire small bowel, is characteristically affected. Typically a diffuse infiltrate of plasmacytoid lymphocytes or plasma cells is seen in the mucosa and submucosa (Fig. 13-36). Lymphomatous infiltration of the mucosa leads to mucosal atrophy and severe malabsorption.

**WESTERN-TYPE INTESTINAL LYMPHOMA:** This disorder usually affects adults older than 40 and children younger than 10. It is most common in the ileum, where it is seen as (1) a fungating mass that projects into the lumen, (2) an elevated ulcerated lesion, (3) a diffuse segmental thickening of the bowel wall, or (4) plaquelike mucosal nodules. As a result, intestinal...
Pathology

obstruction, intussusception, and perforation are important complications. Occult bleeding is common, although massive acute hemorrhage may also occur. Microscopically, all varieties of malignant lymphoma are encountered. Those associated with celiac disease tend to be T-cell lymphomas. When extraintestinal spread is present, the 5-year survival rate is less than 10%.

Chronic abdominal pain, diarrhea, and clubbing of fingers are the most frequent clinical signs of intestinal lymphoma. Diarrhea and weight loss reflect the underlying malabsorption. Patients with Mediterranean lymphoma tend to survive longer than those with the Western type of lymphoma.

Carcinoid Tumor (Neuroendocrine Tumors)
The term *carcinoid tumor* has been largely replaced by the term *neuroendocrine tumors* (NETs). These tumors are all considered malignant, but usually with low metastatic potential. The gut is the most common site for NETs (the bronchus is the next most common site). The site of origin is a major determinant of behavior. Other important considerations include size, depth of invasion, hormonal responsiveness, and presence or absence of function.

The appendix is the most common gastrointestinal site of origin, followed by the rectum. Tumors of these sites are usually small and rarely aggressive. The next most common site is ileum, where they are often multiple, and more aggressive. NETs account for about 20% of all small intestinal malignancies. They are also seen in association with the multiple endocrine neoplasia (MEN) syndromes, usually type I.

**PATHOLOGY:** Macroscopically, small carcinoid tumors present as submucosal nodules covered by intact mucosa. Large carcinoids may grow in a polypoid, intramural, or annular pattern (Fig. 13-37A) and often undergo secondary ulceration. The cut surface is firm and white to yellow. As they enlarge, carcinoid tumors invade the muscular coat and penetrate the serosa, often causing a conspicuous desmoplastic reaction. This fibrosis is responsible for peritoneal adhesions and kinking of the bowel, which may lead to intestinal obstruction.

Microscopically, these neoplasms appear as nests, cords and rosettes of uniform small, round cells (see Fig. 13-37B). Occasional glandlike structures are also seen. Nuclei are remarkably regular and mitoses are rare. Abundant eosinophilic cytoplasm contains cytoplasmic granules, which by electron microscopy are typically of the neurosecretory type. Goblet cell carcinoids or adenocarcinoid tumors have glandular differentiation. These tumors have a higher rate of aggressive behavior than do typical carcinoids.

NETs metastasize first to regional lymph nodes. Subsequently, hematogenous spread produces metastases at distant sites, particularly the liver.

**CLINICAL FEATURES:** Carcinoid syndrome is a unique but uncommon clinical condition caused by release of a variety of active tumor products that marks a small percentage of carcinoid tumors. Most NETs are to some extent functional, but this syndrome mainly occurs in patients with extensive hepatic metastases. Classic symptoms include diarrhea (often the most distressing symptom), episodic flushing, bronchospasm, cyanosis, telangiectasia, and skin lesions. Half of patients also have right-sided cardiac valvular disease. Diarrhea is thought to be caused by serotonin.

After its release into the blood, serotonin is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase either in the tumor or in other tissues. Urine 5-HIAA is a diagnostic test

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**FIGURE 13-36. Mediterranean intestinal lymphoma.** The villi are short and blunted, and the lamina propria is filled with lymphoid cells.

**FIGURE 13-37. Neuroendocrine tumor of small intestine.** A. A resected segment of distal ileum shows multiple neuroendocrine tumors (arrows). B. A photomicrograph of the lesion in A demonstrates cords of uniform small, round cells.
for the carcinoid syndrome. Whereas liver, lung, and brain all have high levels of activity of monoamine oxidase and (presumably) of enzymes that inactivate other tumor secretions, the right side of the heart is exposed to the full effects of tumor products that released into the vena cava from hepatic metastases. As a result, endocardial fibrosis occurs, probably as a reaction to endothelial damage. Fibrous plaques form on the tricuspid and pulmonic valves, the endocardium of the right-sided cardiac chambers, the vena cava, the coronary sinus, and the pulmonary artery. Distortion of the valves leads to pulmonic stenosis and tricuspid regurgitation.

Metastatic Tumors
The most common malignant tumors in the small intestine are metastatic. Cancer of adjacent organs (e.g., stomach, pancreas, or colon) may spread to the small intestine by direct extension. Lung and female genital organs and skin (melanomas) are the most frequent primary sites of small-intestinal metastases. Secondary involvement of the small intestine with systemic lymphoma may simulate metastatic carcinoma. Solitary, submucosal metastatic tumors may easily be mistaken for a primary cancer, and the symptoms may be indistinguishable.

Pneumatosis Cystoides Intestinalis
Pneumatosis cystoides intestinalis is an uncommon disorder in which numerous pockets of gas are found in the gut wall anywhere in the gastrointestinal tract. Most cases are associated with an underlying gastrointestinal disease, including intestinal obstruction, peptic ulcer, Crohn disease, mesenteric ischemia, volvulus, and neonatal necrotizing enterocolitis. Some are associated with chronic obstructive pulmonary disease or mechanical ventilation. Pneumatosis in adults is ordinarily benign, depending on the underlying disease. However, intestinal pneumatosis associated with neonatal necrotizing enteritis has a high mortality.

The cause of intestinal pneumatosis depends on the associated conditions. A mechanical break in mucosal continuity allows entry of air from the lumen to the submucosa. Alternatively, the gas can be a product of bacterial action, particularly in neonatal necrotizing enterocolitis. Dissection of air bubbles along the mesentery is common in patients with obstructive pulmonary disease or ventilation.

**PATHOLOGY:** Macroscopically, cysts appear as bubbles under the serosa of the intestine, and the bowel wall feels spongy. In some cases, air cysts are located principally in the submucosa, in which case, the cut surface of the bowel wall appears to be honeycombed. The cysts vary from a few millimeters to several centimeters in diameter. Cysts may also occur in the stomach and the mesentery. Microscopic examination reveals cystic spaces in the submucosa or beneath the serosa, which are often lined by large macrophages and multinucleated giant cells.

**CLINICAL FEATURES:** Many cases are found during investigation of symptoms unrelated to the pneumatosis. Some patients have episodic diarrhea. There is often blood in the stools, and rectal bleeding may be brisk. When intestinal pneumatosis is a complication of neonatal necrotizing enterocolitis, bowel perforation and peritonitis are frequent, but these complications are rare in adults.

Gas cysts may disappear spontaneously or may persist for years. Relief of symptoms may be obtained by oxygen inhalation or treatment with metronidazole.

**THE LARGE INTESTINE**

**Anatomy**

The large intestine is the portion of the gastrointestinal tract from the ileocecal valve to the anus. It is 90 to 125 cm in length in adults and includes the colon and rectum. Like the small intestine, the proximal colon is derived from embryonic midgut and supplied by the superior mesenteric artery. The distal half of the large intestine derives from embryonic hindgut, is supplied by the inferior mesenteric artery, and is mainly for storage.

**MACROSCOPIC FEATURES:** The large intestine is divided into six regions proceeding distally from the ileocecal valve: (1) cecum, (2) ascending colon, (3) transverse colon, (4) descending colon, (5) sigmoid colon, and (6) rectum. The bend between the ascending and transverse colon in the right upper quadrant is the hepatic flexure, and that between the transverse and descending segments in the left upper quadrant is the splenic flexure. The caliber of the lumen progressively diminishes from the cecum to the sigmoid colon.

Like the small intestine, the colon has outer longitudinal and inner circular muscle coats. However, in the colon, the longitudinal muscle has three separate bundles, the *taeniae coli*. Evaginations of the colonic wall between the taeniae, the *haustra*, appear as external sacculations. The appendices epiploicae are small serosal masses of fat, invested by peritoneum. The vermiform appendix arises at the apex of the cecum and terminates as a blind tube; it averages about 8 cm in length but occasionally measures up to 20 cm.

The ileocecal valve is a sphincter that regulates the flow of intestinal contents into the cecum. However, it is an incompetent sphincter, and reflux of cecal contents into the ileum is usual. The internal sphincter of the anal canal is continuous with colonic smooth muscle. The external anal sphincter is the major mechanism by which bowel continence is maintained. It surrounds the anal canal with a layer of skeletal muscle. The mucosal surface of the large bowel has prominent folds, which are less pronounced in the rectum.

**MICROSCOPIC FEATURES:** Histologically, the colonic mucosal surface is flat and punctuated by numerous pits, the *crypts of Lieberkuhn*. Both are lined by tall columnar epithelium. The surface epithelium is primarily simple columnar cells with occasional goblet cells. The crypts mostly contain goblet cells, except at their bases, where a few undifferentiated cells and a variety of neuroendocrine cells are located. The basal undifferentiated cells constitute the reserve cell population of the colonic mucosa and exhibit numerous mitoses. Mucosal cells migrate from the bases of the crypts toward the luminal surface. Programmed cell death (apoptosis) and sloughing of the mucosal cells balance proliferation in maintaining the crypt epithelial cell population.

The lamina propria contains lymphocytes, plasma cells, macrophages and fibroblasts, with occasional eosinophils. Lymphoid aggregates interrupt the continuity of the muscularis mucosae and extend into the submucosa. The submucosa is similar to that in small intestine, but lymphatic channels are far less prominent. The lymphatics drain into paracolic nodes in the serosal fat, intermediate nodes along the course of the colic
blood vessels and central nodes near the aorta. Parasympathetic and sympathetic innervations terminate in Meissner submucosal and Auerbach myenteric plexuses.

### Congenital Disorders

**Congenital Megacolon (Hirschsprung Disease) Reflects a Segmental Absence of Ganglion Cells**

Hirschsprung disease is a disorder in which colon dilation (Fig. 13-38) results from a defect in colorectal innervation: congenital absence of ganglion cells, in most cases in the wall of the rectum (Fig. 13-39). In one fourth of cases, ganglion cells are deficient in moreproximal portions of the colon and in unusual instances, the lesion may extend as far as the small intestine. The incidence of the disorder is estimated to be 1 in 5000 live births, and 80% of patients are male.

**PATHOLOGY:** The large intestine in Hirschsprung disease has a constricted and spastic segment that is the aganglionic zone. Proximal to this, the bowel is very dilated. The definitive diagnosis of Hirschsprung disease is made on the basis of absence of ganglion cells in a rectal biopsy specimen (see Fig. 13-39B). There is also a striking increase in nonmyelinated cholinergic nerve fibers in the submucosa and between the muscle coats (neural hyperplasia). The absence of ganglion cells leads to accumulation of acetylcholine and acetylcholinesterase. Histochemical demonstration of this enzyme, which is not visualized in normal rectal mucosa, enhances the reliability of a diagnosis based on rectal biopsy.

**PATHOGENESIS:** The pathogenesis of Hirschsprung disease can be traced to an interruption of the developmental sequence that leads to inner-

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**FIGURE 13-38. Hirschsprung disease.** A contrast radiograph shows marked dilation of the rectosigmoid colon proximal to the narrowed rectum.

Interestingly, like achalasia, which is caused by destruction of esophageal ganglion cells, Chagas disease may cause aganglionic megacolon.

**CLINICAL FEATURES:** Hirschsprung disease is the most common cause of congenital intestinal obstruction. The clinical signs are delayed passage of meconium by a newborn and development of vomiting in the first few days of life. In some cases, complete intestinal obstruction requires immediate surgical relief. In children who have short rectal segments lacking ganglion cells and who have only partial obstruction, constipation, abdominal distention, and recurrent fecal impactions are characteristic.

The most serious complication of congenital megacolon is an enterocolitis, in which necrosis and ulceration affect the dilated proximal segment of the colon and may extend into the small intestine. The treatment for Hirschsprung disease is surgical removal of the aganglionic segment and reconstruction.

**Acquired Megacolon Often Reflects Laxative Use**

Acquired megacolon sometimes occurs in children and often has a psychogenic background. It is frequently associated with chronic constipation and prolonged laxative use (“cathartic colon”). However, some cases in which ganglion cells are seen by rectal biopsy begin in infancy and are associated with fecal incontinence. The cause is not well understood, but it is thought to represent a functional abnormality of colonic motility. Acquired megacolon in adults can result from disorders that interfere with bowel innervation or smooth muscle function, such as diabetic neuropathy, Parkinsonism, myotonic dystrophy, scleroderma, amyloidosis, and hypothyroidism.

**Anorectal Malformations Are Common Developmental Defects**

These malformations vary from minor narrowing to serious and complex defects. The lesions result from arrested development of the caudal region of the gut in the first 6 months of fetal life. These anomalies are classified based on the relation of the terminal bowel to the levator ani muscle: (1) high or supralevator deformities, in which the bowel ends above the pelvic floor; (2) intermediate deformities; and (3) low or translevator deformities, in which the bowel ends below the pelvic floor.

- Anorectal agenesis and rectal atresia are supralevator deformities.
- Anal agenesis and anorectal stenosis are classified as intermediate deformities.
- Imperforate anus is a low or translevator deformity in which the opening is covered by a cutaneous membrane behind which meconium is visible. Anal stenosis is a variant of imperforate anus.
- Fistulas between the malformation and the bladder, urethra, vagina, or skin may occur in all types of anorectal anomalies.

**Infections of the Large Intestine**

The principal infections of the colon, including tuberculosis and amebiasis, are discussed in Chapter 9 or above in the context of small intestine infectious diarrhea. Most of the remaining infectious diseases are transmitted sexually and involve the anorectal region, often in male homosexuals, including gonorrhea, syphilis, lymphogranuloma venereum, anorectal herpes, and venereal warts (condylomata acuminata). Immunosuppressed people have a high incidence of colonic infections (e.g., amebiasis and shigellosis). Bone marrow transplant recipients often contract cytomegalovirus and herpes infection of the gastrointestinal tract.

**Pseudomembranous Colitis Usually Follows Antibiotic Treatment**

Pseudomembranous colitis is a generic term for an inflammatory condition of the colon that is characterized by exudative plaques on the mucosa.

**PATHOGENESIS:** After the introduction of antibiotics in the early 1950s, it became clear that administration of these drugs, principally tetracycline and chloramphenicol, often led to pseudomembranous colitis. *Clostridium difficile*, which is also implicated in neonatal necrotizing enterocolitis, is the offending organism. It is not invasive, but produces toxins that damage the colonic mucosa.

Other conditions which can produce pseudomembranes include various diseases of the colon, shock, burns, uremia, and chemotherapy.

The mechanism by which *C. difficile* becomes pathogenic is not entirely clear. Alteration of fecal flora by antibiotics contributes. Only 2% to 3% of healthy adults harbor the organism, while 10% to 20% of those who were recently treated with antibiotics are infected. However, the microbe can be isolated from the stools of 95% of patients with antibiotic-associated pseudomembranous colitis.

**PATHOLOGY:** Macroscopically, the colon, particularly the rectosigmoid region, shows raised yellowish plaques up to 2 cm in diameter that adhere to the underlying mucosa (Fig. 13-40). The intervening mucosa appears congested and edematous but is not ulcerated. In severe cases, plaques coalesce into extensive pseudomembranes. Necrosis of the superficial epithelium is believed to be the initial pathologic event. Subsequently, crypts become disrupted and expanded by mucin and neutrophils. The pseudomembrane consists of the debris of necrotic epithelial cells, mucus, fibrin, and neutrophils. In milder cases, well formed pseudomembranes may be absent, and the pathology is more subtle, with focal damage to the surface epithelium.

When both small and large bowel are involved, the condition is referred to as pseudomembranous enterocolitis. Pseudomembranes occur occasionally in other enteric infections, involving *Staphylococcus aureus*, *Candida*, invasive bacteria, and verotoxin-producing *E. coli*. Ischemic bowel disease may also show pseudomembranes.

**CLINICAL FEATURES:** Antibiotic-associated infections with *C. difficile* are virtually always accompanied by diarrhea, but in most cases, the disorder does not progress to colitis. In patients with pseudomembranous colitis, fever, leukocytosis, and abdominal cramps are superimposed on the diarrhea. Before there were antibiotics, many patients with...
Pathology

FIGURE 13-40. Pseudomembranous colitis. A. The colon shows variable involvement ranging from erythema to yellow-green areas of pseudomembrane. B. Microscopically, the pseudomembrane consists of fibrin, mucin, and inflammatory cells (largely neutrophils).

this form of colitis died within hours or days from ileus and irreversible shock. Today, pseudomembranous colitis, although still serious, is usually controlled with antibiotics and supportive fluid and electrolyte therapy. Milder cases can be confused with an array of diarrheal diseases.

Neonatal Necrotizing Enterocolitis Complicates Prematurity

Necrotizing enterocolitis is one of the most common acquired surgical emergencies in newborns. It is particularly common in premature infants after oral feeding and is likely related principally to an ischemic event involving the intestinal mucosa, which is followed by bacterial colonization, usually with *C. difficile*. The lesions vary from those of typical pseudomembranous enterocolitis to gangrene and perforation of the bowel.

Diverticular Disease

Diverticulitis refers to two entities: a condition termed diverticulosis and an inflammatory complication called diverticulitis.

Diverticulosis Reflects Environmental and Structural Factors

Diverticulosis is an acquired herniation (diverticulum) of the mucosa and submucosa through the muscular layers of the colon.

Epidemiology: Diverticulosis shows a striking geographic variation, being common in Western societies and infrequent in Asia, Africa, and underdeveloped countries. Diverticulosis increases in frequency with age. Some 10% of persons in Western countries are afflicted.

Pathogenesis: The striking variation in the prevalence of diverticulosis implies that environmental factors are primarily responsible for the disease. Western populations consume a diet in which refined carbohydrates and meat have replaced crude cereal grains and it is widely assumed that the lack of indigestible fibers in some way predisposes to formation of diverticula in susceptible persons. In this respect, the larger fecal mass in those who ingest a high-fiber diet diminishes spontaneous motility and intraluminal pressure in the colon.

Increased Intraluminal Pressure: According to the fiber theory, Western diets lack dietary residue, leading to sustained bowel contractions and consequently increased intraluminal pressure. Such prolonged increased pressure is believed to lead to herniation of the superficial coats of the colon through the muscular layers into the serosa.

Defects in the Wall of the Colon: In addition to pressure, defects in the wall of the colon are required for the formation of a diverticulum. The circular muscle of the colon is interrupted by connective tissue clefs at the sites of penetration by the nutrient vessels that supply the submucosa and mucosa. In persons of advancing age, this connective tissue loses its resilience and, therefore, its resistance to the effects of increased intraluminal pressure. This concept is supported by the observation that persons with heritable disorders of connective tissue (e.g., Marfan syndrome, Ehlers-Danlos syndrome) acquire precocious diverticulosis, primarily of the small bowel.

Clinical Features: Diverticulitis is generally asymptomatic, and 80% of affected persons remain symptom free. Many patients complain of episodic colicky abdominal pain. Both constipation and diarrhea, sometimes
Crohn disease is chronic segmental transmural inflammation of the intestine. Crohn disease occurs principally in the distal small intestine, but may involve any part of the digestive tract and even extraintestinal tissues. The colon, particularly the right colon, may be affected.

Crohn disease has variously been referred to as terminal ileitis and regional ileitis when it involves mainly the ileum, and granulomatous colitis and transmural colitis when it principally affects the colon.

**Epidemiology:** Crohn disease is worldwide, with an annual incidence of 0.5 to 5 per 100,000. Reports from various countries indicate that the incidence has increased dramatically over the past 30 years. The disease usually appears in adolescents or young adults and is most common among persons of European origin, with a considerably higher frequency among Jews. There is a slight female predominance (1.6:1).

**Diverticulitis** refers to inflammation at the base of a diverticulum. Diverticulitis presumably results from irritation caused by retained fecal material. In 10% to 20% of patients with diverticulosis, diverticulitis supervenes at some point.

**Pathology:** Diverticulitis produces inflammation of the wall of the diverticulum, an event that may lead to perforation and release of fecal bacteria into the peridiverticular tissues. The resulting abscess is usually contained by the appendices epiploicae and the pericolonic tissue. Infrequently, free perforation leads to generalized peritonitis. Fibrosis in response to repeated episodes of diverticulitis may constrict the bowel lumen, causing obstruction. Fistulas may form between the colon and adjacent organs, including the bladder, vagina, small intestine, and skin of the abdomen. Additional complications include pylephlebitis and liver abscesses.

**Clinical Features:** The most common symptoms of diverticulitis, usually following microscopic or gross perforation of the diverticulum, are persistent lower abdominal pain and fever. Changes in bowel habits, ranging diarrhea to constipation, are frequent and dysuria indicates bladder irritation. Most patients have tenderness in the left lower quadrant, and a mass in that area may be palpated. Leukocytosis is the rule. Antibiotic treatment and supportive measures usually alleviate acute diverticulitis, but about 20% of patients eventually require surgical intervention.

**Inflammatory Bowel Disease**

Inflammatory bowel disease is a term that describes two diseases: Crohn disease and ulcerative colitis. Although these two disorders usually differ enough to be clearly distinguishable, they have certain common features. Similarities apart, Crohn disease and ulcerative colitis have different clinical courses and natural histories.

**Pathogenesis:** Epidemiologic studies, particularly concordance rates in twin pairs and siblings, strongly implicate a genetic predisposition to Crohn disease. A family history of inflammatory bowel disease is more common for Crohn disease than ulcerative colitis. A putative susceptibility locus for Crohn disease has been assigned to the centromeric region of chromosome 16, at least in non-Jewish patients. Other susceptibility loci may reside on chromosomes 3, 7, and 12. NOD2 and CARD15 mutations determine ileal disease, and the clinical pattern of Crohn disease has been linked to specific genotypes. Crohn disease has only rarely been described in both a husband and a wife, a fact that suggests that environmental factors alone do not suffice to cause the disease. Interestingly, smoking is associated with Crohn disease, but ulcerative colitis is uncommon in smokers. Several infectious agents have been suggested as possible causative agents, but definitive associations are lacking. Several studies report impaired cell-mediated immunity in patients with Crohn disease. Some investigators have suggested increased suppressor T cell activity, and others have claimed depressed phagocytic function.
The possibility that Crohn disease reflects immunologically mediated damage to the intestine is suggested by the chronic and recurrent nature of the inflammation and the association with systemic manifestations that often suggest autoimmune diseases. Most recent immunologic studies focus on the possible role of cell-mediated cytotoxicity. Some studies support the hypothesis that cytotoxic T cells sensitized to bacterial or other antigens damage the intestinal wall. In this respect, cyclosporine, a potent inhibitor of cell-mediated immunity that is widely used to prevent rejection of transplanted organs, has been reported to ameliorate the symptoms of Crohn disease.

TNF-α production is increased in vitro in mucosal cells derived from patients with Crohn disease, as is a shift in the mucosal balance of T-cell mediated cytokine production toward TNF-α. Administration of anti-TNF-α antibodies to patients with Crohn disease provides effective short-term symptom remission.

The fecal stream appears to be of prime importance in the pathogenesis of Crohn disease, as evidenced by (1) the beneficial effects of surgical bypass, (2) the pattern of pre-anastomotic recurrence in patients with side-to-end anastomotic sites, and (3) the frequency of early inflammatory lesions (aphthoid erosions) in the epithelium in association with mucosal lymphoid tissue.

**PATHOLOGY:** Two major characteristics of Crohn disease differentiate it from other gastrointestinal inflammatory diseases. First, the inflammation usually involves all layers of the bowel wall and is, therefore, referred to as **transmural inflammatory disease.** Second, the involvement of the intestine is discontinuous; that is, segments of inflamed tissue are separated by apparently normal intestine.

It is convenient to classify Crohn disease into four broad macroscopic patterns, although many patients do not fit any one of them precisely. The disease involves (1) mainly the ileum and cecum in about 50% of cases, (2) only the small intestine in 15%, (3) only the colon in 20%, and (4) mainly the anorectal region in 15%. Disease of the ileum and cecum is more frequent in young persons; colitis is common in older patients. Crohn disease is occasionally seen in the duodenum and stomach as focal acute inflammation with or without granulomas. More rarely, it occurs in the esophagus and oral cavity, almost always in association with small intestinal disease. In women with anorectal Crohn disease, the inflammation may spread to involve the external genitalia.

The macroscopic and microscopic pathologies of Crohn disease are variable and may comprise almost any combination of features characteristic of the disease. Grossly, the bowel and adjacent mesentery are thickened and edematous. Mesenteric fat often wraps around the bowel ("creeping fat"). Mesenteric lymph nodes are frequently enlarged, firm, and matted together. The intestinal lumen is narrowed by edema in early cases and by a combination of edema and fibrosis in long-standing disease. Nodular swelling, fibrosis, and mucosal ulceration lead to a "cobblestone" appearance (Fig. 13-42A). In early cases, ulcers have either an aphthous or a serpiginous appearance; later they become deeper and appear as linear clefs or fissures (see Fig. 13-42B).

The cut surface of the bowel wall shows the transmural nature of the disease, with thickening, edema, and fibrosis of all layers. Involved loops of bowel are often adherent and fistulas between such segments are frequent. These fistulas, presumably a late result of the deep mural ulcers, may also penetrate from the bowel into other organs, including the bladder, uterus, vagina, and skin. Most fistulas end blindly, forming abscess cavities in the peritoneal cavity, mesentery, or retroperitoneal structures. Lesions in the distal rectum and anus may create perianal fistulas, a well-known presenting feature.

Microscopically, Crohn disease appears as a chronic inflammatory process. During early phases of the disease, the inflammation may be confined to the mucosa and submucosa. Small, superficial mucosal ulcers (aphthous ulcers) are seen, together with mucosal and submucosal edema and an increase in the number of lymphocytes, plasma cells, and macrophages. Destruction of mucosal architecture, with regenerative changes in crypts and villous distortion, are frequent. Pyloric metaplasia and Paneth cell hyperplasia is common in the small intestine and colorectum. Later, long, deep, fissurelike ulcers are seen, and vascular hyalinization and fibrosis become apparent.

The microscopic hallmark of Crohn disease is transmural nodular lymphoid aggregates, accompanied by proliferative changes of the muscularis mucosae and nerves of submucosal and myenteric plexuses (Fig. 13-43). Discrete, noncaseating...
granulomas, mostly in the submucosa, may be present. These granulomas are like those of sarcoidosis and consist of focal aggregates of epithelioid cells, vaguely limited by a rim of lymphocytes. Multinucleated giant cells may be present. The centers of the granulomas usually display hyaline material and only very rarely necrosis.

Although the presence of discrete granulomas is strong evidence in favor of Crohn disease, the absence of granulomas does not exclude the diagnosis, as less than half the cases show the typical granulomas.

The pathologic features of Crohn disease are summarized in Figure 13-44.

CLINICAL FEATURES: The clinical manifestations and natural history of Crohn disease are highly variable and relate to the anatomical sites involved by the disease.

The most frequent symptoms are abdominal pain and diarrhea, which are seen in over 75% of patients, and recurrent fever, evident in 50%. When disease mainly involves the ileum and cecum, sudden onset may mimic appendicitis, and the diagnosis is occasionally first made at the time of abdominal surgery. If the disease predominantly involves the ileum, the major clinical features are right lower quadrant pain, intermittent diarrhea and fever, and frequently a tender mass in the right lower quadrant of the abdomen.

When the small intestine is diffusely involved, malabsorption and malnutrition may be major features. Lipid malabsorption may also result from interruption of enterohepatic cycle of bile salts because of ileal disease. Crohn disease of the colon leads to diarrhea and sometimes colonic bleeding. In a few patients, the major site of involvement is the anorectal region and recurrent anorectal fistulas are the presenting sign.

Intestinal obstruction and fistulas are the most common intestinal complications of Crohn disease. Occasionally, free perforation of the bowel occurs. Small bowel cancer is at least threefold more common in patients with Crohn disease, and the disease also predisposes to colorectal cancer. When Crohn disease begins in childhood, it may lead to retardation of growth and physical development. Systemic complications also include liver disease (sclerosing cholangitis), cholelithiasis, renal oxalate stones, and amyloidosis. The most frequent extraintestinal inflammatory features are in the eye (episcleritis or uveitis), medium-sized joints (arthritis), and skin (erythema nodosum).

No cure is available. Several medications suppress the inflammatory reaction, including corticosteroids, sulfasalazine, metronidazole, 6-mercaptopurine, cyclosporine, and anti-TNF antibodies. Surgical resection of obstructed areas or of severely involved portions of intestine and drainage of abscesses caused by fistulas are required in some cases. Preenanostomotic or prestomal recurrences after construction of an enterostomy is a hallmark of Crohn disease, a feature that makes clinical management difficult. The need for repeated resections can lead to short-bowel syndrome in some patients.

Ulcerative Colitis Is a Chronic Superficial Inflammation of the Colon and Rectum

Ulcerative colitis is characterized by chronic diarrhea and rectal bleeding, with a pattern of exacerbations and remissions and with the possibility of serious local and systemic complications. The disorder occurs principally, but not exclusively, in young adults.

EPIDEMIOLOGY: In Europe and North America, the incidence of ulcerative colitis is 4 to 7 per 100,000 population, and its prevalence is 40 to 80 per 100,000. It usually begins in early adult life, with peak incidence in the third decade. However, it also occurs in childhood and old age. In the United States, whites are affected more commonly than blacks.
PATHOLOGY: Three major pathologic features characterize ulcerative colitis and help to differentiate it from other inflammatory conditions:

- **Ulcerative colitis is a diffuse disease.** It usually extends from the most distal part of the rectum for a variable distance proximally (Fig. 13-45). When it involves the rectum alone, it

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**PATHOGENESIS:** The cause of ulcerative colitis is unknown. Attempts to implicate viruses or bacteria have given only inconsistent results. In some families, as many as six patients with this disease have been described, and concordance has been reported in monozygotic twins. However, available family studies do not suggest any distinct mode of genetic transmission and studies of HLA distribution in patients with ulcerative colitis have not demonstrated a consistent pattern.

The possibility that an abnormal immune response may be involved has been studied extensively. There is abundant lymphoid tissue throughout the colon, and this disorder may have autoimmune-like concomitants, such as uveitis, erythema nodosum, and vasculitis. Several studies have demonstrated increased circulating antibodies against antigens in colonic epithelial cells and against cross-reacting antigens in enterobacteria. Furthermore, in vitro studies have shown that mononuclear cells from the colonic mucosa and blood of patients with ulcerative colitis are toxic for autologous colonic epithelial cells. Antineutrophil cytoplasmic antibodies (ANCAs) are found in 80% of patients with ulcerative colitis. However, these abnormalities are not unique for ulcerative colitis, nor are they a prerequisite for the development of the disease. It is, therefore, possible that some or all of these immune features are, the result, not the cause, of mucosal damage.
Mucosal excrescences are termed ulceration adjacent to hanging fragments of mucosa. Such crypt abscesses can undermine the mucosa, leaving areas of folds are lost (atrophy). Lateral extension and coalescence of crypt epithelium gives rise to the characteristic ulcerative proctitis. When the process extends toward the splenic flexure, the terms proctosigmoiditis and left-sided colitis are used. Sparing of the rectum or involvement of the right side of the colon alone is rare and suggests the possibility of another disorder, such as Crohn disease.

- Inflammation in ulcerative colitis is generally limited to the colon and rectum. It rarely involves the small intestine, stomach, or esophagus. If the cecum is affected, the disease ends at the ileocecal valve, although minor inflammation of the adjacent ileum is sometimes noted (backwash ileitis).

- Ulcerative colitis is essentially a mucosal disease. Deeper layers are uncommonly involved, mainly in fulminant cases, usually in association with toxic megacolon.

The microscopic features of early ulcerative colitis correlate with colonoscopic appearances and include (1) mucosal congestion, edema, and microscopic hemorrhages; (2) a diffuse chronic inflammatory infiltrate in the lamina propria; and (3) damage and distortion of the colorectal crypts, which are often surrounded and infiltrated by neutrophils. Suppurative necrosis of the crypt epithelium gives rise to the characteristic crypt abscess, which appears as a dilated crypt filled with neutrophils (Fig. 13-46).

**Progressive Colitis:** As the disease continues, mucosal folds are lost (atrophy). Lateral extension and coalescence of crypt abscesses can undermine the mucosa, leaving areas of ulceration adjacent to hanging fragments of mucosa. Such mucosal excrescences are termed inflammatory polyps (Fig. 13-47). Tissue destruction is accompanied by manifestations of tissue repair. Granulation tissue develops in denuded areas. Importantly, the strictures characteristic of Crohn disease are absent. Microscopically, colorectal crypts may appear tortuous, branched, and shortened in the late stages and the mucosa may be diffusely atrophic.

**Advanced Colitis:** In long-standing cases, the large bowel is often shortened, especially in the left side. Mucosal folds are indistinct and are replaced by a granular or smooth mucosal pattern. Microscopically, advanced ulcerative colitis is characterized by mucosal atrophy and a chronic inflammatory infiltrate in the mucosa and superficial submucosa. Paneth metaplasia is common.

**Clinical Features:** The clinical course and manifestations are very variable. Most patients (70%) have intermittent attacks, with partial or complete remission between attacks. A small number (<10%) have a very long remission (several years) after their first attack. The remaining 20% have continuous symptoms without remission.

**Mild Colitis:** Half of patients with ulcerative colitis have mild disease. Their major symptom is rectal bleeding, sometimes accompanied by tenesmus (rectal pressure and discomfort). The disease in these patients is usually limited to the rectum but may extend to the distal sigmoid colon. Extraintestinal complications are uncommon, and in most patients in this category, disease remains mild throughout their lives.

**Moderate Colitis:** About 40% of patients have moderate ulcerative colitis. They usually have recurrent episodes of loose bloody stools, crampy abdominal pain, and frequently low-grade fever, lasting days or weeks. Moderate anemia is a common result of chronic fecal blood loss.

**Severe Colitis:** About 10% of patients have severe or fulminant ulcerative colitis, sometimes from its onset but often during a flare of activity. They may have more than 6 and sometimes more than 20, bloody bowel movements daily, often with fever and other systemic manifestations. Blood and fluid loss rapidly leads to anemia, dehydration, and electrolyte depletion. Massive hemorrhage may be life-threatening. A particularly dangerous complication is toxic megacolon, which is characterized by extreme dilation of the colon. Patients with this condition are at high risk for perforation of the colon. Fulminant ulcerative colitis is a medical emergency requiring immediate, intensive medical therapy, and, in some cases, prompt colectomy. About 15% of patients with fulminant ulcerative colitis die of the disease.

The medical treatment of ulcerative colitis depends on the sites involved and the severity of the inflammation. The 5-aminosalicylate–based compounds are the mainstays of treatment for patients with mild-to-moderate ulcerative colitis. Corticosteroids and immunosuppressive and immunoregulatory agents (azathioprine or mercaptopurine) are used in patients who have severe and refractory disease.

**Extraintestinal Manifestations**

**Arthritis** is seen in 25% of patients with ulcerative colitis. Eye inflammation (mostly uveitis) and skin lesions develop in about 10%. The most common cutaneous lesions are erythema nodosum and pyoderma gangrenosum, the latter a serious, noninfective disorder characterized by deep, purulent, necrotic ulcers in the skin.

Liver disease occurs in about 4% of patients, most commonly primary sclerosing cholangitis. Those with primary sclerosing cholangitis are at risk for the development of cholangiocarcinoma. Thromboembolic phenomena, mostly deep vein thromboses of the lower extremities, occur in 6% of ulcerative colitis patients.

The various complications of ulcerative colitis are shown in Figure 13-48.
Differential Diagnosis
The most important conditions to be distinguished from ulcerative colitis are other forms of chronic colitis due to specifically treatable causes, and Crohn disease. Other conditions that should be considered in the differential diagnosis of ulcerative colitis are bacterial infections and amebic colitis, especially in areas where it is endemic. When inflammation is limited to the rectum, other infectious agents, including viruses, Chlamydia, fungi, and other parasites merit consideration. Proctitis due to these agents is common in male homosexuals and a variety of opportunistic infections of the bowel are encountered in patients with AIDS. Other conditions that may mimic ulcerative colitis are ischemic colitis, antibiotic-associated colitis, radiation injury, and solitary rectal ulcer syndrome.

The distinction between ulcerative colitis and Crohn colitis is based on different anatomical localization and histopathology (Table 13-1). Ulcerative colitis is a diffuse process, usually more severe distally, while Crohn colitis is patchy or segmental and often spares the rectum. The inflammation in ulcerative colitis is superficial (i.e., usually limited to the mucosa) and is characterized by an acute inflammatory infiltrate, with neutrophils and crypt abscesses. By contrast, Crohn colitis is transmural and involves all layers, with granulomas in some of the specimens.

If the disease stops at the ileocecal valve or is limited to the colon distal ulcerative colitis is more likely. Involvement of the terminal ileum suggests Crohn colitis.

In 10% of cases, definitive discrimination is not possible. This occurs mostly in fulminant colitis; the inflammatory bowel disease is then termed indeterminate colitis. The distinction between ulcerative colitis and Crohn colitis is important because of (1) different surgical therapy (Crohn disease often has recurrences, so that continent ileostomy and ileoanal pouch procedures may be contraindicated), (2) a higher risk of cancer in ulcerative colitis, and (3) different medical therapy.

Ulcerative Colitis and Colorectal Cancer
Persons with long-standing ulcerative colitis have a higher risk of colorectal cancer than the general population. The risk is related to the extent of colorectal involvement and the duration of the inflammatory disease. Thus, if the entire colon is involved, the
risk of developing colorectal cancer is greater. If the inflammatory disease is limited to the rectum, the risk of colorectal cancer is like that of the general population. Incidence of colorectal cancer in the United States is estimated to be between 5% to 10% for each decade of pancolitis. Young age at the onset of colitis is not an independent risk factor, but since patients in whom ulcerative colitis develops at a young age have a longer duration of disease, they also have a high cumulative incidence of cancer.

Colorectal epithelial dysplasia is a neoplastic epithelial proliferation and precursor to colorectal carcinoma in patients with long-term ulcerative colitis (Fig. 13-49). The histopathologic criteria include (1) alteration of mucosal architecture, (2) epithelial abnormalities (hypercellularity and stratification of nuclei), and (3) epithelial dysplasia (variation in the size, shape, and staining qualities of nuclei). Dysplasia is divided into low-grade and high-grade dysplasia. High-grade epithelial dysplasia reflects a high risk for the development of colorectal cancer and when identified in a biopsy, it is a strong indication for colectomy. Routine surveillance by colonoscopic biopsy of all patients with ulcerative colitis is, therefore, recommended.
Collagenous Colitis and Lymphocytic Colitis Cause Chronic Diarrhea

Collagenous colitis is an inflammatory disorder of the colon characterized clinically by chronic watery diarrhea and pathologically by a thickened subepithelial collagen band. The disorder mainly affects middle-aged and elderly women.

The colonic mucosa appears grossly normal. The histopathologic diagnosis of collagenous colitis is made by demonstrating a chronic inflammatory cell infiltrate in the mucosa and a band of collagen immediately beneath the surface epithelium that measures up to 80 μm (Fig. 13-50). The surface epithelium shows flattened or cuboidal cells and even separation of epithelial cells from underlying structures. Intraepithelial lymphocytes are common. The lamina propria contains increased numbers of chronic inflammatory cells and neutrophils are also found in some patients. Lymphocytic colitis also features prominent infiltration of the damaged colonic epithelium by lymphocytes but lacks the collagen table and has an equal sex distribution. Patients with lymphocytic colitis have more than 10 lymphocytes for every 100 epithelial cells for every 100 epithelial cells.

The etiologies of collagenous colitis and lymphocytic colitis are unknown. The fibrosis of collagenous colitis may result from persistent inflammation. Although the diseases have not been consistently linked to other systemic disorders, an autoimmune etiology also has been suggested, based on a putative association with rheumatoid arthritis and thyroid dysfunction. Compared with patients with collagenous colitis, those with lymphocytic colitis have an increased frequency of HLA-A1 and decreased HLA-A3. Many patients with these diseases have taken nonsteroidal anti-inflammatory drugs. Lymphocytic colitis is common in patients with celiac disease.

Vascular Diseases

The Colon is Subject to the Same Types of Ischemic Injury as the Small Intestine

Unlike the small bowel, extensive infarction of the colon is uncommon and chronic segmental disease is the rule. The most vulnerable areas are those between adjacent arterial distributions, so-called watershed areas. For example, the splenic flexure lies between the regions supplied by the superior and inferior mesenteric arteries, and the rectosigmoid area shares blood from the inferior mesenteric and internal iliac arteries. However, the rectum itself is usually spared in ischemic colitis. Most cases of ischemic colitis are caused by atherosclerosis of major intestinal arteries, and the disease usually occurs in persons older than 50.

PATHOLOGY: Some patients with symptoms and complications of bowel infarction require immediate surgical intervention. However, in most patients, the acute signs stabilize, and radiographic examination shows only the pattern associated with intramural hemorrhage and edema. On endoscopy, multiple ulcers, hemorrhagic nodular lesions, or a pseudomembrane is seen. Biopsy reveals ischemic necrosis of the bowel: mucosal ulceration, crypt abscesses, edema, and hemorrhage (Figure 13-51). Such patients may recover completely or may develop a colonic stricture, in which case, surgical removal of the obstructed segment is necessary. Segments of ischemic stricture show variable mucosal ulceration and inflammation, as well as submucosal widening by granulation tissue and fibrosis. Hemosiderin-laden macrophages may be noted, and patchy fibrosis of the muscular coats also may be present.

CLINICAL FEATURES: Ischemic disease of the rectosigmoid area typically manifests as abdominal pain, rectal bleeding, and a change in bowel habits. On clinical grounds alone, ischemic colitis often cannot be distinguished from some forms of infective colitis, ulcerative colitis, and Crohn colitis. Prognosis and treatment depend on the primary cause and extent of involvement. The goal is to improve blood supply to the colon by treating patients’ overall cardiovas-
abdominal pressure.

Hemorrhoids are common in pregnancy, presumably because of the increased venous pressure and capillaries are tortuous, thin walled, and dilated. The attenuated walls of these vessels are presumably responsible for their potential for malignant transformation.

Hemorrhoids Tend to Bleed

Hemorrhoids are dilated venous channels of the hemorrhoidal plexuses. They result from downward displacement of the anal cushions. Internal hemorrhoids arise from the superior hemorrhoidal plexus above the pectinate line, whereas external hemorrhoids originate from the inferior hemorrhoidal plexus below that line. Hemorrhoids are common in Western countries, to some degree afflicting at least half the population over 50 years. Hemorrhoids are common in pregnancy, presumably because of the increased abdominal pressure.

Angiodysplasia (Vascular Ectasia) May Cause Intestinal Bleeding

Angiodysplasia (vascular ectasia) refers to localized arteriovenous malformations, mainly in the cecum and ascending colon, which produce lower intestinal bleeding. The mean age at presentation is 60 years. Younger persons preferentially exhibit lesions at other sites, including the rectum, stomach, and small bowel. Interestingly, angiodysplasia is associated with aortic valve disease in some patients. It has been suggested that it may be the result of chronic circulatory insufficiency of the intestine, intestinal muscle hypertrophy, and consequent venous obstruction. Patients typically complain of multiple bleeding episodes, although chronic occult bleeding may also occur. Radiologic studies and examination at laparotomy are usually negative. Thus, the diagnosis is difficult and often requires selective mesenteric arteriography or colonoscopy. Surgical removal of the affected segment is curative.

PATHOLOGY: The resected specimen displays small, often multiple vascular lesions, usually smaller than 0.5 cm in diameter. Microscopically, the submucosal veins and capillaries are tortuous, thin walled, and dilated. The attenuated walls of these vessels are presumably responsible for their propensity to bleed.

Radiation Enterocolitis

Radiation therapy for malignant disease of the pelvis or abdomen may be complicated by injury to the small intestine and colon.

PATHOLOGY: Clinically significant radiation colitis is most common in the rectum. The lesions produced by radiation therapy range from a reversible injury of the intestinal mucosa to chronic inflammation, ulceration, and fibrosis of the intestine. In the short term, radiation results in epithelial and endothelial damage, including decreased mitoses and, in the small bowel, villous shortening. Mucosal inflammation is conspicuous and abscesses may be seen in the colorectal crypts. Failure of epithelial renewal may lead to ulceration. Subacute changes, occurring 2 to 12 months after radiation therapy, are noted after the mucosa has healed. Damage to submucosal vessels leads to thrombosis. The submucosa becomes fibrotic and often contains bizarre fibroblasts. As a result of radiation vascular injury, progressive ischemia further damages the bowel.

Complications of radiation enterocolitis include perforation and the subsequent development of internal fistulas, hemorrhage, and stricture, occasionally severe enough to lead to intestinal obstruction.

Solitary Rectal Ulcer Syndrome

Internal mucosal prolapse of the rectum can produce mucosal changes that can be mistaken clinically and pathologically for chronic inflammatory disease or a neoplasm. The hallmark of solitary rectal ulcer syndrome is smooth muscle proliferation from the muscularis mucosae into the lamina propria. Despite the name, some patients have no ulcers, whereas others display multiple erosions, ulcers, or even polypoid lesions. Mucosal abnormalities often appear as a mass that can simulate a neoplasm. Dilated glands can be entrapped in the rectal wall, a condition termed colitis cystica profunda.

Polyps of the Colon and Rectum

A gastrointestinal polyp is defined as a mass that protrudes into the lumen of the gut. Polyps are subdivided according to their attachment to the bowel wall (e.g., sessile or pedunculated, with a discrete stalk), their histopathologic appearance (e.g., hyperplastic or adenomatous) and their neoplastic potential (i.e., benign or malignant). By themselves, polyps are only infrequently symptomatic and their clinical importance lies in their potential for malignant transformation.

FIGURE 13-51. Ischemic colitis. A mucosal biopsy shows coagulative necrosis with “ghostly” outlines the preexisting crypts. Only a small portion of the base of several crypts remain.
Adenomatous Polyps Are Premalignant Lesions

Adenomatous polyps (tubular adenomas) are neoplasms that arise from the mucosal epithelium. They are composed of neoplastic epithelial cells that have migrated to the surface and have accumulated beyond the needs for replacement of the cells sloughed into the lumen.

**EPIDEMIOLOGY:** The prevalence of adenomatous polyps of the colon is highest in industrialized countries. As in diverticular disease, the diet is the only consistent environmental difference between high-risk and low-risk populations that has been identified. In the United States, it appears that at least one adenomatous polyp is present in half of the adult population, a figure that increases to more than two thirds among persons older than 65 years. There is a modest male predominance (1.4:1) and blacks have a higher proportion of right-sided adenomas and cancers. In one-fourth of those who have at least one adenoma, two or more are present.

**PATHOLOGY:** Almost half of all adenomatous polyps of the colon in the United States are located in the rectosigmoid region and can, therefore, be detected by digital examination or by sigmoidoscopy. The remaining half are evenly distributed throughout the rest of the colon. The macroscopic appearance of an adenoma varies from a barely visible nodule or small, pedunculated adenoma to a large, sessile (flat) adenoma. Adenomas are classified by architecture into tubular, villous, and tubulovillous types. They are the usual precursor to colon carcinoma, and their epithelium is often dysplastic.

**TUBULAR ADENOMAS:** These constitute two thirds of the benign large bowel adenomas. Tubular adenomas are typically smooth-surfaced lesions, usually less than 2 cm in diameter, which often have a stalk (Fig. 13-52). Some tubular adenomas, particularly the smaller ones, are sessile.

Microscopically, tubular adenoma has closely packed epithelial tubules, which may be uniform or irregular and excessively branched (see Fig. 13-52C). Tubules are embedded in a fibrovascular stroma similar to the normal lamina propria. Although most tubular adenomas show little epithelial dysplasia, one fifth (particularly larger tumors) may have dysplastic features, which vary from mild nuclear pleomorphism to frank invasive carcinoma (Fig. 13-53). In high-grade dysplasia, glands become crowded and highly irregular in size and shape. Papillary or cribriform (sievelike or perforated) growth patterns are common. As long as the dysplastic focus is confined to the mucosa, the lesion is cured by resection of the polyp.

The risk of invasive carcinoma correlates with the size of the tubular adenoma. Only 1% of tubular adenomas under 1 cm display invasive cancer at the time of resection; among those between 1 and 2 cm, 10% harbor malignancy; and among those over 2 cm, 35% are cancerous. Small flat adenomas may be missed during conventional endoscopy and have a high malignant potential.

**VILLOUS ADENOMAS:** These polyps constitute one tenth of colonic adenomas and are found predominantly in the rectosigmoid region. They are typically large, broad-based, elevated lesions with a shaggy, cauliflower-like surface (Fig. 13-54A), but they can be small and pedunculated. Most are over 2 cm in diameter. On occasion, they reach 10 to 15 cm across. Microscopically, villous adenomas are composed of thin, tall, fingerlike processes that superficially resemble the villi of the small intestine. They are lined externally by neoplastic epithelial cells and are supported by a core of fibrovascular connective tissue corresponding to the normal lamina propria (Fig. 13-54B).

The histopathology of dysplasia in villous adenomas is comparable to that in tubular adenomas. However, villous adenomas contain foci of carcinoma more often than tubular adenomas. In polyps less than 1 cm across, the risk is 10 times higher than that for comparably sized tubular adenomas. Of greater importance is the fact that 50% of villous adenomas larger than 2 cm harbor invasive carcinoma. Given that most villous adenomas measure more
FIGURE 13-53. Adenocarcinoma arising in a pedunculated adenomatous polyp. A. Both low-grade dysplasia and high-grade dysplasia are present. The latter is characterized by a cribriform pattern and increased nuclear pleomorphism (arrows). B. Trichrome stain showing tumor invading the stalk (blue). Since there was a margin of resection of over 1 mm, polypectomy was sufficient therapy.

FIGURE 13-54. Villous adenoma of the colon. A. The colon contains a large, broad-based, elevated lesion that has a cauliflower-like surface. A firm area near the center of the lesion proved on histologic examination to be an adenocarcinoma. B. Microscopic examination shows fingerlike processes with fibrovascular cores lined by hyperchromatic nuclei.
than 2 cm in greatest dimension, more than one third of all resected villous adenomas contain invasive cancer.

**TUBULOVLLOUS ADENOMAS:** Many adenomatous polyps have both tubular and villous features. Polyps with more than 25% and less than 75% villous architecture are termed tubulovillous. These adenomas tend to be intermediate in distribution and size between the tubular and villous forms, one fourth to one third being larger than 2 cm across. Tubulovillous polyps are also intermediate between tubular and villous adenomas in the risk of invasive carcinoma.

**PATHOGENESIS:** The precursor to colorectal carcinoma is dysplasia, usually in the form of an adenoma. The pathogenesis of adenomas of the colon and rectum involves neoplastic alteration of crypt epithelial homeostasis with (1) diminished apoptosis, (2) persistent cell replication, and (3) failure to mature and differentiate as the epithelial cells migrate toward the surface of the crypts (Fig. 13-55). Normally, DNA synthesis ceases when cells reach the upper third of the crypts, after which they mature, migrate to the surface, and become senescent. They then undergo apoptosis or are sloughed into the lumen. Adenomas represent focal disruption of this orderly sequence, so that epithelial cells retain their proliferative capacity throughout the entire depth of the crypt. Thus, mitotic figures are initially visualized not only along the entire length of the crypt but also on the mucosal surface. As the lesion evolves, cell proliferation exceeds the rate of apoptosis and sloughing and cells begin to accumulate in upper crypts and on the surface. Eventually, the accumulated cells on the mucosal surface form tubules or villous structures, in concert with stromal elements.

**ADENOMATOUS POLYPS AND COLORECTAL CANCER:** The origin of colon cancer in adenomatous polyps is supported by the following:

- The geographic coincidence in the frequencies of adenomatous polyps and colorectal cancer suggests a causal relation. In geographic regions in which there is a high risk of colorectal cancer, adenomatous polyps tend to be larger, are more often villous, and display more high-grade dysplasia than those in low-risk areas. The anatomical distributions of adenomas and carcinomas are similar, both being most frequent in the sigmoid colon in Western countries.
- Adenomatous polyps tend to antedate colon cancer by 10 to 15 years, suggesting that the latter follows the former.
- Carcinomas are found in adenomas, and some carcinomas have adenomatous remnants at their periphery.
- An associated carcinoma is commonly found in colons that harbor adenomas. Conversely, one third of colons resected for cancer contain an adenomatous polyp. Moreover, the presence of an adenomatous polyp in the same colon specimen resected for cancer doubles the risk that another carcinoma will develop in the remaining colon.
- In familial adenomatosis polyposis (see below), the innumerable adenomatous polyps are initially benign, but colorectal cancer invariably develops at a later age.

**Hyperplastic Polyps**

Hyperplastic polyps are small, sessile mucosal excrecences that with exaggerated crypt architecture. They are the most common polypoid lesions of the colon and are particularly frequent in the rectum. Hyperplastic polyps are present in 40% of rectal specimens in persons younger than 40 and in 75% of older persons. They are more common than usual in colons with adenomatous polyps and in populations with higher rates of colorectal cancer.
CHAPTER 13: THE GASTROINTESTINAL TRACT

PATHOLOGY:
Hyperplastic polyps are small, sessile, raised mucosal nodules, up to 0.5 cm in diameter but occasionally larger. They are almost always multiple and have even been mistaken for familial adenomatous polyposis (FAP). Histologically, the crypts of hyperplastic polyps are elongated and may show cystic dilation (Fig. 13-56). The epithelium contains goblet cells and absorptive cells, with no dysplasia. The surface cells are elongated giving a tufted appearance; this accounts for the serrated contour of the glands near the surface.

There are Several Variants of Hyperplastic Polyps (Serrated Adenomas)
There is debate over current nomenclature of these variants. One form has a serrated configuration like that of hyperplastic polyps but with nuclear features of adenomas, and is termed serrated adenoma (Fig. 13-57A). Another type is called sessile serrated adenoma, and resembles classic hyperplastic polyps, but does not show adenomatous features, and often appear as a large deformed mucosal fold (Fig. 13-57B and C). Yet a third variant exhibits juxtaposed areas of hyperplastic polyp and adenoma, referred to as mixed hyperplastic adenomatous polyps (Fig. 13-57D). Unlike classic hyperplastic polyps, patients with these variants have an increased risk for the development of carcinoma. These lesions have a high incidence of microsatellite instability. The carcinomas that arise from them tend to be bulky, mucinous, and right-sided.

Familial Adenomatous Polyposis (FAP) is an Autosomal Dominant Trait that Invariably Leads to Cancer
Also termed adenomatous polyposis coli (APC), FAP accounts for less than 1% of colorectal cancers. It is caused by a mutation of the APC gene on the long arm of chromosome 5 (5q21-22) (see below). Most cases are familial, but 30% to 50% reflect new mutations. FAP is characterized by hundreds to thousands of adenomas carpeting the colorectal mucosa, sometimes throughout its length, but particularly in the rectosigmoid area (Fig. 13-58). The adenomas are mostly of the tubular variety, although tubulovillous and villous adenomas are also present. Microscopic adenomas, sometimes involving a single crypt, are numerous. A few polyps are usually present by age 10, but the mean age for occurrence of symptoms is 36 years, by which time cancer is often already present. Carcinoma of the colon and rectum is inevitable, the mean age of onset being 40 years. Total colectomy before onset of cancer is curative, but some patients also have tubular adenomas in the small intestine and stomach that have the same malignant potential as those in the colon.

Genetic testing for FAP is available, but mutations are found in only 75% of familial cases. Subtypes of FAP include:
- **Attenuated FAP:** In this condition adenomas in the colon number less than 100.
- **Gardner syndrome:** This variant features extracolonic lesions including osteomas of the skull, mandible, and long bones; epidermoid cysts; desmoid tumors; and congenital hypertrophy of the retinal pigment epithelium. APC gene mutations do not predict this phenotype.
- **Turcot syndrome:** This rare disorder combines FAP with malignant tumors of the central nervous system. Many cases, especially those with medulloblastoma, are due to germline mutation of the APC gene. Some cases, especially those with glioblastoma multiforme, are part of the spectrum of the HNPCC syndrome (see below).

Non-neoplastic Polyps Are Acquired Lesions
Non-neoplastic polyps are entirely different entities and are grouped together solely because of their gross appearance as raised lesions of the colonic mucosa.

**Juvenile Polyps (Retention Polyps)**
Juvenile polyps are hamartomatous proliferations of the colonic mucosa. They are most common in children younger than 10 years, although one third occur in adults.

PATHOLOGY:
Juvenile polyps are single or (rarely) multiple. They mostly occur in the rectum, but may be seen anywhere in the small or large bowel. Grossly,
most are pedunculated lesions up to 2 cm in diameter. They have smooth, rounded surfaces, unlike fissured surfaces of adenomatous polyps. Microscopically, dilated and cystic epithelial tubules filled with mucus (hence the name “retention polyp”) are embedded in a fibrovascular lamina propria (Fig. 13-59). Surface epithelial erosion is common, and reactive epithelial proliferation is evident, but the epithelium usually lacks dysplasia.

Patients with five or more juvenile polyps, or juvenile polyps present outside the colon along with a family history of juvenile polyps have a high likelihood of the syndrome of familial juvenile polyposis. These patients have an increased risk for gastrointestinal carcinoma, not necessarily arising from the polyps or even the segment of the gastrointestinal tract in which they are located.

**Inflammatory Polyps**

Inflammatory polyps are not neoplasms but are elevated nodules of inflamed, regenerating epithelium. They are commonly found in association with ulcerative colitis and Crohn disease; they are also encountered in cases of amebic colitis and bacterial dysentery. Microscopically, inflammatory polyps are composed of a variable component of distorted and inflamed mucosal glands, often intermixed with granulation tissue.

As healing proceeds, epithelial regeneration characterized by large, basophilic epithelial cells restores mucosal architecture. These lesions are not precancerous, but occur in chronic inflammatory diseases that are associated with a high incidence of cancer (e.g., ulcerative colitis) and must thus be distinguished from adenomatous polyps.

**FIGURE 13-57. Variants of hyperplastic polyps.**

A. Serrated adenoma. The epithelium shows contours typical of hyperplastic polyp with adenomatous nuclear features. B. Sessile serrated adenoma. A polypoid lesion appears to be an enlarged flattened fold. C. Microscopically, sessile serrated adenoma features irregular, asymmetric crypts that are often dilated by mucus. D. Mixed hyperplastic adenomatous polyp. Two adenomatous crypts in the upper right contrast with the three hyperplastic crypts.
Most cancers of the colon and rectum arise in adenomatous polyps and so factors associated with the development of such polyps are relevant to the genesis of colorectal cancer. The importance of environmental factors in the pathogenesis of colorectal cancer is emphasized by the high incidence of the disease in industrialized countries and among emigrants from low-risk to high-risk regions.

**DIETARY FIBER:** A diet low in indigestible fiber and high in animal fat has been implicated in the etiology of other colonic diseases, including diverticulosis and appendicitis. Such a diet is associated with slower transit of fecal contents through the colon, and some suggest that this permits longer exposure of the mucosa to possibly toxic substances in the stools. It has also been suggested that fiber may bind potential mutagens and dilute their concentration by increasing stool bulk. However, more recent analyses and clinical trials of diets high in fiber have cast doubt on such an explanation.

**DIETARY FAT:** Consumption of animal fats is paralleled in high-risk populations with a higher content of anaerobic bacteria than do those in low-risk populations. Some of these bacteria, particularly *Bacteroides* species, can convert bile into compounds that are potentially mutagenic. Repopulation of the colon with *Lactobacillus* protects experimental animals against chemically induced colon cancer.

**ANAEROBIC BACTERIA:** The feces of persons in high-risk populations have a higher content of anaerobic bacteria than do those in low-risk populations. Some of these bacteria, particularly *Bacteroides* species, can convert bile salts into compounds that are potentially mutagenic. Repopulation of the colon with *Lactobacillus* protects experimental animals against chemically induced colon cancer.

**OTHER DIETARY FACTORS:** A low prevalence of colorectal cancer has been correlated with high levels of selenium in the soil and plants in certain geographic areas. In this context, the endogenous antioxidant, glutathione peroxidase, is a selenium-containing enzyme. Exogenous antioxidants (e.g., butylated hydroxytoluene and vitamin E) and a reducing agent such as ascorbic acid have protected experimental animals from colonic cancer. Diets rich in cruciferous vegetables (e.g., cauliflower, Brussels sprouts, and cabbage) and those that provide vitamin A may be associated with a lower incidence of colorectal cancer.

**PATHOGENESIS:** Most cancers of the colon and rectum arise in adenomatous polyps and so factors associated with the development of such polyps are relevant to the genesis of colorectal cancer. The importance of environmental factors in the pathogenesis of colorectal cancer is emphasized by the high incidence of the disease in industrialized countries and among emigrants from low-risk to high-risk regions.

In recent decades, colon cancer shows a slight female preponderance, whereas rectal cancer is somewhat more common in men. The proportion of cancers in the distal colorectum has been declining in recent decades.

**Lymphoid Polyps**
Lymphoid polyps are submucosal accumulations of lymphoid tissue, almost invariably in the rectum, which are seen as single, sessile nodules measuring from pinpoint size to as large as 5 cm in diameter. On occasion, multiple lesions impart a cobblestone appearance to the mucosa. Microscopically, these polyps are covered by intact mucosa and are composed of prominent lymphoid follicles with germinal centers. In this context, lymphoid tissue is normally present in the colorectal mucosa. Lymphoid polyps are more common in women than men and occur at any age, including childhood. They are benign and usually asymptomatic.

**Nodular lymphoid hyperplasia** is seen primarily in children or with common variable immunodeficiency syndrome, and features excessive accumulation of the normal follicular lymphoid tissue of the colon. Macroscopically, the mucosa exhibits numerous small sessile or polypoid nodules up to 0.5 cm in diameter. The microscopic appearance is similar to that of lymphoid polyps. The condition is only rarely related to malignant lymphoma, but the radiologic appearance can be mistaken for FAP.

**Malignant Tumors**

**Adenocarcinoma of the Colon and Rectum Is an Example of Multistep Carcinogenesis**
In Western societies, colorectal cancer is the most common cause of cancer deaths that are not directly attributable to tobacco use. Some 5% of Americans develop this cancer during their lifetime. Although the widely used term colorectal implies a common biology, the differences between cancers of the colon and rectum seem to be more fundamental than simple location. For instance, whereas colon cancer is much more common in the United States than in Japan, the incidence of rectal cancer in the two populations is nearly the same. In general, rectosigmoid carcinoma accounts for a much higher proportion of large bowel cancers in populations at high risk for this tumor (including the United States) than in low-risk populations. Moreover, colon cancer shows a slight female preponderance, whereas rectal cancer is somewhat more common in men. The proportion of cancers in the distal colorectum has been declining in recent decades.

**Molecular Genetics of Colorectal Cancer**
In 85% of cases of colorectal carcinoma, it has been estimated that at least 8 to 10 mutational events must accumulate before an invasive cancer with metastatic potential develops. This process is initiated in histologically normal mucosa, proceeds through an adenomatous precursor stage, and ends as invasive adenocarcinoma.

The most important mutational events are illustrated in Figure 13-60 and involve:
- **Ras oncogene:** Activating mutations of the ras protooncogene occur early in tubular adenomas of the colon.
- **DCC gene:** A putative tumor-suppressor gene, DCC (“deleted in colon cancer”) is located on chromosome 18 and is often missing in colorectal cancers.
- **p53 tumor-suppressor gene:** In the most common type of adenocarcinoma of the colon, mutation of p53 participates in the transition from adenoma to carcinoma and is a late event in the carcinogenic pathway.

In 15% of colorectal cancers, DNA mismatch repair (MMR) is impaired, leading to deficient repair of spontaneous replication errors, particularly in simple repetitive sequences (microsatellites). MMR deficiencies can occur through two mechanisms in a hereditary form (HNPCC, Lynch syndrome), a germline mutation in one of the MMR genes is followed by a somatic mutation of the other allele (“second hit”) later in life. In a sporadic form, hypermethylation of the MMR promoter, MLH1, inactivates transcription of the gene.

**Risk Factors**

**AGE:** Increasing age is probably the single most important risk factor for colorectal cancer in the general population. Risk is low before age 40. It increases steadily to age 50, after which it doubles with each decade.

**PRIOR COLORECTAL CANCER:** Patients with a prior colorectal cancer are at increased risk for a subsequent tumor. In fact, 5% to 10% of patients treated for colorectal cancer subsequently develop a second colorectal malignancy. Moreover, 2% to 5% of
those with a new colorectal cancer harbor a second (synchronous) colorectal primary cancer.

**ULCERATIVE COLITIS AND CROHN DISEASE:** These chronic inflammatory diseases increase the risk of colorectal cancer in proportion to their duration and extent of involvement within the large bowel.

**GENETIC FACTORS:** Colorectal cancer is increased in frequency among relatives of patients with the disease, a finding that suggests a genetic contribution to tumorigenesis. Persons with two or more first- or second-degree relatives with colorectal cancer constitute 20% of all patients with this tumor. Some 5% to 10% of all colorectal cancers are inherited as autosomal dominant traits. A history of cancer at other sites, particularly breast or genital cancer in women, is associated with a higher than normal frequency of colorectal cancer.

**DIET:** As previously noted, prospective studies involving large populations in various countries have reported that the daily consumption of red meat and animal fat leads to a higher risk of colorectal cancer than that in persons who eat little or no meat.

**PATHOLOGY:** Grossly colorectal cancers resemble adenocarcinomas elsewhere in the gut. They tend to be polypoid and ulcerating or infiltrative and may be annular and constrictive (Fig. 13-61A). Polypoid cancers are more common in the right colon, particularly in the cecum, where the large caliber of the colon and the submucosal blood vessels allow unimpeded intraluminal growth. Annular constricting tumors are more common in the distal colon. Ulceration of tumors, irrespective of growth pattern, is common.

**CLINICAL FEATURES:** Initially, colorectal cancer is clinically silent. As the tumor grows, the most common sign is occult blood in the feces when the tumor is in the proximal portions of the colon. Both occult blood and bright red blood in the feces may occur if a lesion is in the distal colorectum.

Cancers on the left side of the colon, where the caliber of the lumen is small and the fecal contents more solid, often constriict the lumen, producing obstructive symptoms. These are manifested as changes in bowel habits and abdominal pain. Occasionally, colorectal cancer perforates early and induces peritonitis. By contrast, on the right side of the colon, particularly in the cecum, the colon lumen is large and fecal contents are liquid, tumors can grow to large size without causing symptoms of obstruction. In this situation, chronic asymptomatic bleeding may cause iron-deficiency anemia, which is often the first indication of colorectal cancer. When a tumor has extended beyond the confines of the colorectum, it may produce enterocutaneous and rectovaginal fistulas, tumor masses in the abdominal wall, bladder symptoms, and sciatic nerve pain. Spread within the abdomen may cause small intestinal obstruction and malignant ascites.

A positive test result for fecal occult blood predicts the presence of a cancer or an adenoma in 50% of cases. Periodic fiberoptic colonoscopy and testing for occult blood in feces improves the prognosis of colorectal cancer, because these methods can often detect the disease at an early stage.

The only curative treatment for colorectal cancer is surgery. Small polyps are easily removed endoscopically; large lesions require segmental resection. Tumors close to the anal verge
HNPCC is caused by germine mutations in a DNA mismatch repair gene. In most cases, hMSH2 (human MutS homolog 2) on chromosome 2p and hMLH1 (human MutL homolog 1) on chromosome 3p are affected. A smaller number of cases are caused by mutations in hMSH6 (human MutS homolog 6) and hPMS2 (human postmeiotic segregation 2) on chromosomes 2p and 7p, respectively. In patients with HNPCC there is a germine mutation in one allele of one of the mismatch repair genes, and the second allele is deleted in a somatic “second hit.” The result is that spontaneous replication errors are not repaired effectively. This leads to widespread genomic instability, particularly in simple repetitive sequences (microsatellites), which are particularly prone to replication errors. Thus, genes that regulate growth and differentiation, and other mismatch repair genes, are disabled by unrepaired mutations.

**Carcinoid Tumors (Neuroendocrine Tumors)**

Colorectal carcinoid tumors behave like similar tumors of the small intestine. Half of carcinoid tumors of the colorectum have metastasized at the time they are discovered.

**Large Bowel Lymphoma is Usually B-cell Lymphoma**

Primary lymphoma of the colorectum is uncommon. It may be seen as (1) segmental involvement of the mucosa, (2) diffuse polyloid lesions, or (3) a mass extending beyond the confines of the colorectum. Presenting symptoms are similar to those of other primary intestinal cancers, but the diffuse polyloid form may resemble inflammatory polyps or adenomatous polyps. Most large bowel lymphomas are derived from B cells.

**Cancers of the Anal Canal Are Epidermoid Carcinomas**

Carcinomas of the anal canal, which constitute 2% of cancers of the large bowel, may arise at or above the dentate line. These tumors occur in both sexes, but are more common in women and in blacks.

**PATHOLOGY:** Anal cancers have various histologic patterns, such as squamous, basaloid (cloacogenic) or mucoepidermoid, but the different tumor types exhibit similar clinical behavior and so are all classed as epidermoid carcinomas. **Bowen disease of the anus** is squamous carcinoma in situ, while **extramammary Paget disease** at this site reflects intraepithelial adenocarcinoma (either primary of the mucosa or metastatic). Carcinoma of the anus penetrates directly into surrounding tissues, including internal and external sphincters, perianal soft tissues, prostate, and vagina.

**CLINICAL FEATURES:** Infection with human papilloma virus (HPV) and chronic inflammatory disease of the anus (e.g., venereal disease), fissures, and trauma predispose to anal cancer. Factors associated with genital carcinoma (cancer of the penis, scrotum, cervix or vulva), poor hygiene, indiscriminate sexual practices, and genital warts also contribute to the development of anal cancer.

The usual symptoms of anal cancers include bleeding, pain, and an anal or rectal mass. Often a tumor is not clinically recognized as a malignant lesion and may be discovered only in a hemorrhoidectomy specimen. Combined chemotherapy and radiation therapy is the customary treatment, although abdominal–perineal resection is sometimes carried out. More than half of patients survive for at least 5 years.

**Miscellaneous Disorders**

**Endometriosis Involves the Colon and Rectum in 15% to 20% of Cases**

Colorectal endometriosis is mostly asymptomatic and discovered only incidentally during laparotomy for other reasons. When
Acute appendicitis relates to fibrosis. Repeated hemorrhage, the lesions are surrounded by reactive bowel, although they may penetrate the submucosa. As a result of malabsorption have been reported.

Kaposi sarcoma of the gut is found almost exclusively in patients with AIDS. One third to one half of AIDS patients with cutaneous Kaposi sarcoma show digestive tract involvement. In most patients, intestinal Kaposi sarcoma does not lead to symptoms, although gastrointestinal bleeding, obstruction, and malabsorption have been reported.

A common presentation of lymphoma complicating AIDS is involvement of the gastrointestinal tract. Any portion may be affected. The histologic appearance and prognosis of these tumors in AIDS patients are similar to those elsewhere.

The AIDS epidemic has resulted in numerous gastrointestinal infections previously considered rare. Most patients with AIDS (50%–90%) have chronic diarrhea. Virtually all forms of infectious agents—including bacteria, fungi, protozoa, and viruses—afflict patients with AIDS (Table 13-3).

Kaposi sarcoma of the gut is found almost exclusively in patients with AIDS. One third to one half of AIDS patients with cutaneous Kaposi sarcoma show digestive tract involvement. In most patients, intestinal Kaposi sarcoma does not lead to symptoms, although gastrointestinal bleeding, obstruction, and malabsorption have been reported.

A common presentation of lymphoma complicating AIDS is involvement of the gastrointestinal tract. Any portion may be affected. The histologic appearance and prognosis of these tumors in AIDS patients are similar to those elsewhere.

### PATHOLOGY: Acute appendicitis relates to obstruction of its orifice, with secondary distention of the lumen and bacterial invasion of the wall. Mechanical obstruction by fecaliths or solid fecal material in the cecum is found in one third of cases. Occasionally tumors, parasites such as Enterobius vermicularis or foreign bodies are incriminated. Lymphoid hyperplasia due to bacterial or viral infection (e.g., by Salmonella or measles) may obstruct the lumen and lead to appendicitis. However, no obstruction is demonstrated in up to half of patients with appendicitis, and the factor that precipitates the disease in these patients is unknown.

As secretions distend an obstructed appendix, intraluminal pressure increases and eventually exceeds the venous pressure. This causes venous stasis and ischemia, and leads to mucosal ulceration and invasion by intestinal bacteria. Neutrophil accumulation produces microabscesses. Interestingly, appendectomy protects against development of ulcerative colitis but not Crohn disease.

### PATHOGENESIS: Acute appendicitis

Acute appendicitis is an inflammatory disease of the wall of the vermiform appendix that leads to transmural inflammation and perforation and peritonitis. This condition is by far the most common disease of the appendix and is the most frequent cause of an abdominal emergency. Although incidence peaks in the second and third decades, acute appendicitis may occur in persons of any age.

### TABLE 13-3

<table>
<thead>
<tr>
<th>Gastrointestinal Pathogens Associated with AIDS</th>
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<tbody>
<tr>
<td><strong>Bacteria</strong></td>
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<tr>
<td>Mycobacterium avium-intracellulare</td>
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<tr>
<td>Shigella</td>
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<tr>
<td>Salmonella</td>
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<tr>
<td>Clostridium difficile</td>
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<tr>
<td><strong>Viruses</strong></td>
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<tr>
<td>Cytomegalovirus</td>
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<td>Herpes simplex</td>
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<td><strong>Fungi</strong></td>
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<td>Candida</td>
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<td>Aspergillus</td>
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<tr>
<td><strong>Protozoa</strong></td>
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<tr>
<td>Cryptosporidium</td>
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<tr>
<td>Toxoplasma</td>
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<tr>
<td>Giardia</td>
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<tr>
<td>Entameba histolytica</td>
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<tr>
<td>Microsporidia</td>
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<tr>
<td>Isopora belli</td>
</tr>
<tr>
<td><strong>Helminths</strong></td>
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<tr>
<td>Strongyloides</td>
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<tr>
<td>Enterobius</td>
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</tbody>
</table>

The appendix is congested, tense, and covered by a fibrinous exudate. Its lumen often contains purulent material. A fecalith may be evident (Fig. 13-62). Microscopically, early cases show mucosal microabscesses and a purulent exudate in the lumen. As infection progresses, the entire wall becomes infiltrated with neutrophils, which eventually reach the serosa. Perforation of the wall releases the luminal contents into the peritoneal cavity.

The complications of appendicitis are principally related to perforation, which occurs in one third of children and young adults. Almost all children under 2 years have a perforated appendix at the time of operation, as do three fourths of patients over 60.

- **Periappendiceal abscesses** are common, although abscesses may develop anywhere in the abdominal cavity.
Acute appendicitis.

The lumen of this acutely inflamed appendix is dilated and contains a large fecolith.

- Fistulous tracts may appear between the perforated appendix and adjacent structures, including the small and large bowel, bladder, vagina, or abdominal wall.
- Pylephlebitis (thrombophlebitis of the intrahepatic portal vein radicals) and secondary hepatic abscesses may occur, because venous blood from the appendix drains into the superior mesenteric vein.
- Diffuse peritonitis and septicemia are dangerous sequelae.
- Wound infection is the most common complication of acute appendicitis after surgery; it occurs in one fourth of patients with perforation and in one third of those who develop a periappendiceal abscess.

**CLINICAL FEATURES:** Acute appendicitis is typically manifested as epigastric or periumbilical cramping pain, but the pain may be diffuse or initially restricted to the right lower quadrant. Shortly thereafter, nausea and vomiting occur and the patient develops a low-grade fever and moderate leukocytosis. The pain shifts to the right lower quadrant, where point tenderness is the rule. A diseased retrocecal appendix is shielded from the anterior abdominal wall by the cecum and ileum; atypical symptoms are thus easily misinterpreted because of their poor localization. In the elderly, appendicitis may produce only vague symptoms, and the diagnosis is often not made until perforation occurs. Several conditions that do not require surgery may be misdiagnosed as appendicitis, especially mesenteric adenitis in children, Meckel diverticulitis, rupture of an ovarian follicle during ovulation and acute salpingitis.

Treatment is surgical in the vast majority of cases. As perforation carries a much higher risk of death than does laparoscopic surgery, early surgical intervention is warranted, even if the diagnosis of acute appendicitis is not entirely secure.

**Fistulous tracts**

Fistulous tracts may appear between the perforated appendix and adjacent structures, including the small and large bowel, bladder, vagina, or abdominal wall.

**Pylephlebitis** (thrombophlebitis of the intrahepatic portal vein radicals) and **secondary hepatic abscesses** may occur, because venous blood from the appendix drains into the superior mesenteric vein.

**Diffuse peritonitis and septicemia** are dangerous sequelae.

**Wound infection** is the most common complication of acute appendicitis after surgery; it occurs in one fourth of patients with perforation and in one third of those who develop a periappendiceal abscess.

**Mucocele**

Mucocele refers to a dilated mucus-filled appendix. The pathogenesis may be neoplastic or non-neoplastic. In the non-neoplastic variety chronic obstruction leads to retention of mucus in the appendiceal lumen.

Most mucoceles are associated with neoplastic epithelium. In the presence of a **mucinous cystadenoma** (Fig. 13-63) or a **mucinous cystadenocarcinoma**, the dilated appendix is lined by a villous adenomatous mucosa. Cystadenocarcinoma exhibits infiltrating neoplastic glands into the wall of the appendix. A mucocele may become secondarily infected and rupture, discharging mucus and debris into the peritoneum. This material may be mistaken at laparotomy for peritoneal tumor implants. However, when a mucocele results from mucus secretion by a cystadenoma or cystadenocarcinoma of the appendix, perforation may lead to seeding of the peritoneum by mucus-secreting tumor cells, a condition known as **pseudomyxoma peritonei**. In less than one third of cases, pseudomyxoma peritonei is caused by disease of the appendix; in half, it originates from ovarian mucinous cystadenocarcinoma.

**Neoplasms**

Carcinoid tumors of the appendix are common, and are unlikely to metastasize unless they are over 1.5 cm, which is very rare.

Figure 13-64 through Figure 13-67 summarize the causes of gastrointestinal bleeding and obstruction and the major benign and malignant tumors of the gastrointestinal tract.
CHAPTER 13: THE GASTROINTESTINAL TRACT

SMALL INTESTINAL BLEEDING
- Meckel diverticulum
- Ischemic bowel disease
- Intussusception
- Meckel diverticulum

LOWER INTESTINAL BLEEDING
- Angiodysplasia
- Colonic carcinoma
- Rectosigmoid carcinoma
- Hemorrhoids
- Anal fissure
- Diverticulosus
- Inflammatory bowel disease

Mallory-Weiss tear
- Gastric ulcer
- Hemorrhagic gastritis

FIGURE 13-64. Causes of gastrointestinal bleeding.

UPPER GASTRO-INTESTINAL BLEEDING
- Mallory-Weiss tear
- Gastric ulcer
- Hemorrhagic gastritis

Duodenal ulcer


SMALL INTESTINE
- Paralytic ileus
- Small bowel infarct (e.g., mesenteric thrombosis)
- Small intestinal volvulus
- Meconium ileus (neonatal cystic fibrosis)
- Intussusception
- Incarcerated inguinal hernia
- Stricture (e.g., Crohn disease)

Thrombus
- Adhesion

LARGE INTESTINE
- Megacolon
  - Toxic, ulcerative colitis
  - Hirschsprung disease
- Colonic carcinoma
- Diverticulitis (stricture)
- Fecal impaction

Nerve


THE PERITONEUM

The peritoneum is the mesothelial lining of the abdominal cavity and its viscera. The visceral peritoneum invests the gastrointestinal tract from stomach to rectum and encircles the liver. The parietal peritoneum lines the abdominal wall and retroperitoneal space. The omentum, which has a double layer of peritoneum, encloses blood vessels and a variable amount of fat.

Peritonitis

Bacterial Peritonitis Is Usually Caused by Intestinal Organisms

**PATHOGENESIS:**

**PERFORATION:** The most common cause of bacterial peritonitis is perforation of an abdominal viscus, as in an inflamed appendix, peptic ulcer, or colonic diverticulum. Peritonitis results in an acute abdomen, in which severe abdominal pain and tenderness predominate. Nausea, vomiting, and a high fever are usual, and in severe cases, generalized peritonitis, paralytic ileus, and septic shock ensue. Often the perforation becomes "walled off," in which case a peritoneal abscess results.

The bacteria released into the peritoneal cavity from the gastrointestinal tract vary according to the site of perforation and the duration of the peritonitis. Commonly, several aerobic and anaerobic species are cultured, including *E. coli*, *Bacteroides* species, various *Streptococcus* species, and *Clostridium*. Despite antibiotic treatment, surgical drainage is usually necessary, and the mortality is high. Often the perforation becomes "walled off," in which case a peritoneal abscess results.

**PERITONEAL DIALYSIS:** Chronic peritoneal dialysis is today a frequent cause of bacterial peritonitis, owing to contamination of instruments or dialysate. The clinical course is usually milder than that noted with a perforated viscus and the offending organisms are mostly *Staphylococcus* and *Streptococcus* species. One fourth of cases of peritonitis associated with chronic dialysis are aseptic; they are presumably caused by some chemical in the dialysate to which the peritoneum is sensitive.

**SPONTANEOUS BACTERIAL PERITONITIS:** This term refers to a peritoneal infection lacking a clear precipitating circumstance, such as a perforated viscus. The most common cause of spontaneous bacterial peritonitis in adults is cirrhosis complicated by portal hypertension and ascites. The pathogenesis appears to involve movement of enteric organisms, mainly gram-negative bacilli, from the gut to mesenteric lymph nodes. Seeding of ascitic fluid then ensues, with depressed phagocytic activity and low antibacterial activity in ascitic fluid.

Spontaneous bacterial peritonitis in children can be a complication of the **nephrotic syndrome**, in part because ascites is more common in nephrotic children than in adults. Most cases of spontaneous peritonitis in children are caused by gram-negative organisms, usually derived from urinary tract infections. The disease causes symptoms of an acute abdomen and ordinarily leads to surgical intervention, unless the child is known to have the nephrotic syndrome. Even with antibiotic treatment, mortality is 5% to 10%.

**TUBERCULOUS PERITONITIS:** This infection is rarely seen in industrialized countries today, but occasionally complicates tuberculosis in developing countries. Many patients with tuberculous peritonitis do not have apparent pulmonary or miliary tuberculosis, an observation that suggests activation of latent tuberculous foci in the peritoneum derived from previous hematogenous dissemination.

**PATHOLOGY:** Grossly, bacterial peritonitis resembles purulent infection elsewhere. A fibrinous exudate covers the surface of the intestines, and on organization, fibrinous and fibrous adhesions form between loops of bowel, which become joined to each other. Such adhesions may eventually be lysed, or they may lead to volvulus and **intestinal obstruction**.

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Familial Paroxysmal Polyserositis (Familial Mediterranean Fever) Leads to Peritonitis and Amyloidosis

Familial Mediterranean fever (FMF) is an inherited autosomal recessive disorder that features recurrent episodes of aseptic peritonitis with fever and abdominal pain. It is caused by mutations in a gene on the short arm of chromosome 16. FMF initially presents as peritonitis in half of cases, as arthritis in one-fourth, and as pleuritis in 5% of patients. However, almost all affected persons eventually manifest peritonitis, and more than half develop arthritis and pleuritis at some time. The disease predominates in Sephardic Jews and other Mediterranean populations, such as Armenians, Turks, and Arabs. The pathogenesis of FMF remains obscure, but in the absence of complications, the prognosis is good. Unfortunately, amyloidosis is a frequent complication (see Chapter 23).

**Chemical Peritonitis Usually Results from Endogenous Sources**

- **Bile peritonitis** is caused by escape of bile into the peritoneum, usually from a perforated gallbladder but sometimes from a needle biopsy of the liver. This abrupt insult may lead to shock.
- **Hydrochloric acid or hemorrhage** from a perforated peptic ulcer of the stomach or duodenum may elicit an inflammatory reaction in the peritoneum.
- **Acute pancreatitis** causes release and activation of potent lipolytic and proteolytic enzymes that produce severe peritonitis and fat necrosis. Shock is common and may be lethal unless adequately treated.
- **Foreign materials** introduced by surgery (e.g., talc) or by trauma are unusual causes of chemical peritonitis.
- **Leakage of urine** can produce ascites.
Retroperitoneal Fibrosis

Idiopathic retroperitoneal fibrosis, an uncommon fibrosing condition of the abdomen, becomes symptomatic when it causes obstruction of the ureters. Although no cause is discernible in most cases, it has been linked to treatment of migraine headaches with methysergide. A similar idiopathic fibrosis also has been described in the mediastinum and may affect the mesentery, causing secondary intestinal obstruction.

Neoplasms of the Peritoneum

Mesenteric and Omental Cysts are Usually of Lymphatic Origin

They may also derive from other embryonic tissues. Usually a slowly enlarging, painless mass is discovered in a child older than 10 years. The cyst may come to medical attention because of rupture, bleeding, torsion or intestinal obstruction. Surgical excision is curative.

Mesotheliomas are the Most Common Primary Peritoneal Tumor

One fourth of all mesotheliomas arise in the peritoneum. Like pleural mesotheliomas, most of these malignant tumors are associated with exposure to asbestos. The pathologic characteristics of peritoneal mesotheliomas are identical to those of their pleural counterparts (see Chapter 12).

Primary Peritoneal Carcinoma Resembles Ovarian Carcinoma

Primary peritoneal carcinoma presents as tumor masses involving the omentum and peritoneum. It is morphologically identical to ovarian serous carcinoma of the ovary, except that the ovaries are normal.

Metastatic Carcinoma is the Most Common Malignancy of the Peritoneum

Ovarian, gastric, and pancreatic carcinomas are particularly likely to seed the peritoneum, but any intra-abdominal carcinoma can spread to the peritoneum.