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9 CHAPTER

Infections of the Gastrointestinal Tract

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Introduction

The surgical pathologist plays a key role in the diagnosis of gastrointestinal infection. Virtually all types of pathogenic microbes can cause gastrointestinal infection, so the diagnostic pathologist must be cognizant of their varied histologic manifestations and acquainted with the complex morphologic features of viruses, bacteria, fungi, and parasites. Because certain noninfectious inflammatory conditions can mimic infection, recognizing their at times subtle distinctions is a critical aspect of the surgical pathologist's charge.

Infections of the Esophagus

Bacteria

Bacterial infection of the esophagus is uncommon; it is usually seen in neutropenic patients or as infection extending from the lung. Most cases occur after epithelial injury by acid reflux or previous viral infection. Neutropenia secondary to hematologic malignancy, intensive chemotherapy, or bone marrow transplantation predisposes to bacterial esophagitis.[1,2] Approximately 15% of infectious esophagitis is seen in immunocompromised patients, but it is less common in patients with the acquired immunodeficiency syndrome (AIDS) than in the oncology setting because of the relative sparing of granulocyte counts in AIDS.[3]

Clinical symptoms include odynophagia, dysphagia, and retrosternal pain. Fever is reported in a minority of cases.[2,4] Endoscopic findings are nonspecific and include mucosal friability, pseudomembranes, plaques, and ulcerations. Significant complications include perforation, fistula formation, and sepsis.[5]

The most common bacterial agents involved in gastrointestinal infection belong to the normal flora of the mouth and upper respiratory tract, including *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus viridans,* and *Bacillus* species. Polymicrobial infection is common.

Bacterial infection evokes a marked neutrophilic exudate, cellular necrosis, and degeneration (Fig. 9-1). In severely neutropenic patients, ulcers and pseudomembranes without substantial acute inflammation can be seen. Most bacteria can be identified in tissue sections by light microscopy with tissue Gram stain and oil immersion optics. The diagnosis of bacterial esophagitis is based on the presence of confluent bacteria invading subepithelial tissues (see Fig. 9-1B).[2] Bacterial cultures of endoscopic biopsy samples are usually of little value due to bacterial contamination by the endoscope.

Mycobacterium tuberculosis

Esophageal tuberculosis is usually caused by extension of infection from contiguous organs or from miliary spread.

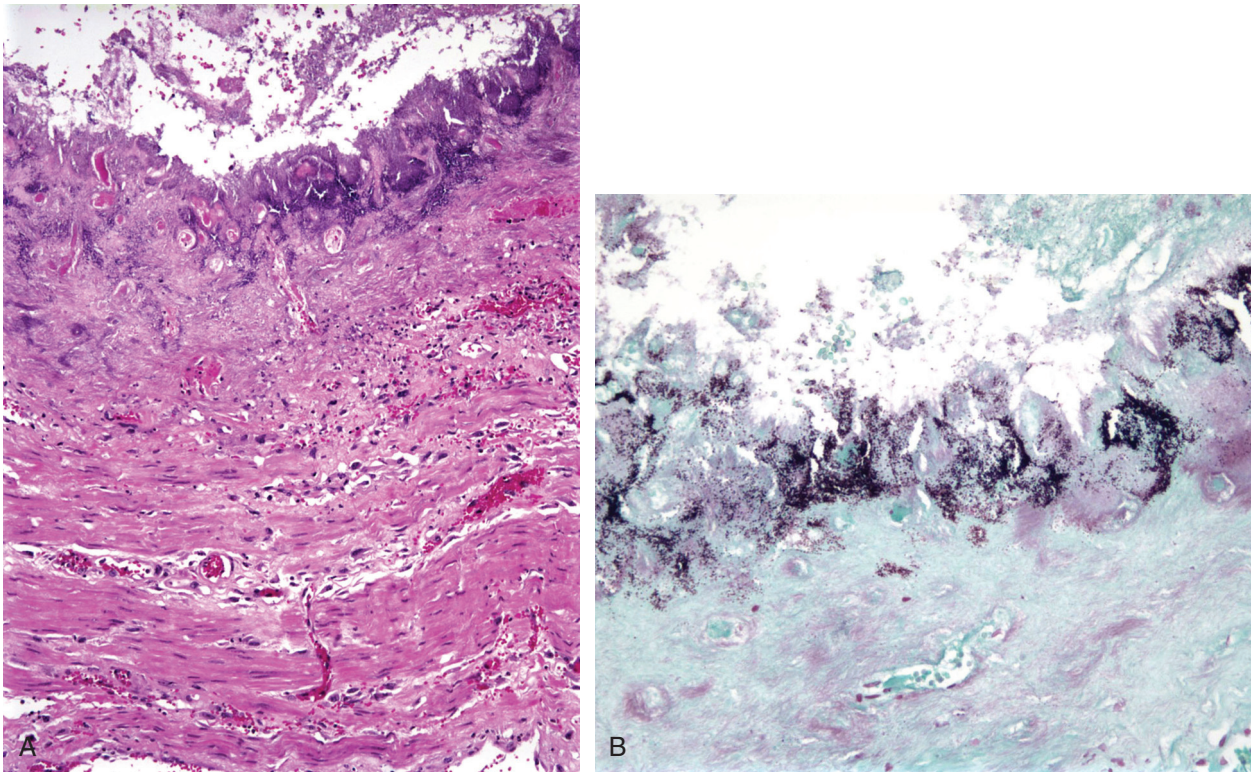

Figure 9-1. Nonspecific bacterial esophagitis. **A,** Esophageal mucosa is replaced by cellular necrosis and a fibrinopurulent exudate. **B,** Brown-Hopps stain highlights bacteria in subepithelial tissues. (Courtesy of Dr. Laura Lamps.)

Autopsy studies show esophageal involvement in 0.15% of patients dying with tuberculosis. Primary esophageal tuberculosis is extremely rare.[6-8] The most common symptoms of esophageal tuberculosis are dysphagia, weight loss, and retrosternal pain.[9] Imaging modalities may show extrinsic compression by involved lymph nodes in the mediastinum, traction diverticula, stricture, kinking of the esophagus, sinus or fistulous tract, and pseudotumoral masses.[10] Chest computed tomography and endoscopic ultrasonography reveal extrinsic nodular masses, consistent with mediastinal lymphadenopathy showing central hypodensity, rim enhancement, and calcification.[6,11] Endoscopic examination shows shallow ulcers with smooth border, a gray purulent base, and irregularly infiltrated edges.[12,13]

The differential diagnosis includes carcinoma, fungal infection, syphilis, and Crohn disease.[14] In some cases, no preoperative diagnosis is established before esophagectomy[15,16]; however, even if a developed stricture has formed, antimycobacterial treatment can successfully save the patient from a complex surgical intervention.[17]

The characteristic histologic features of esophageal tuberculosis include necrotizing, often confluent granulomas, which can be present at any level of the esophagus (Fig. 9-2). A rim of lymphocytes may be present at the periphery. In some cases, granulomas are sparse, or hyalinized and calcified. Acid-fast stains may demonstrate the organisms, but culture confirmation is often required.[18] Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* can be a rewarding diagnostic approach.[19-22]

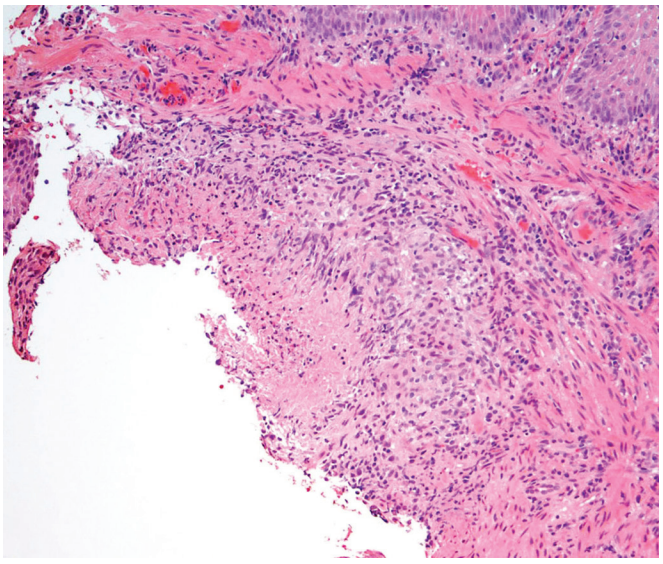

Figure 9-2. *Mycobacterium tuberculosis.* Caseating granuloma involving esophageal wall.

Other granulomatous conditions, including mycobacterial infection due to *Mycobacterium kansasii* or *Mycobacterium bovis*, fungal infection, and Crohn disease, should be excluded. Features favoring Crohn disease include the presence of transmural lymphoid aggregates with deep fistulas and fissures.

Table 9-1 Comparative Morphology of *Candida, Aspergillus,* and *Histoplasma* Species

Organisms	Morphologic Features
Candida albicans *Candida tropicalis*	Mixture of budding yeast and nonbranching pseudohyphae; occasional septate (true) hyphae
Candida glabrata	Budding yeast No hyphae No halo effect
Aspergillus species	Septate hyphae in uniform width True dichotomous branching with regular, acute angles
Histoplasma capsulatum	Intracellular Oval budding yeast with narrow-based buds Halo effect around organisms on H&E stain

H&E, hematoxylin and eosin.

Fungi

Fungal esophagitis is most frequently caused by *Candida* spp., but other pathogens, including *Histoplasma*, *Aspergillus*, *Cryptococcus*, *Coccidioides*, *Paracoccidioides*, *Trichosporon*, *Blastomyces*, and *Mucor,* can cause disease (Table 9-1). Fungal infection is often superimposed on other infections, and efforts at identifying all possible pathogens are mandatory to design optimal treatment. Debilitated and immunocompromised individuals are susceptible to fungal infections, and irradiation, chemotherapy, and chronic motility disorders are predisposing factors. Esophageal candidiasis is the most common cause of esophagitis in HIV-infected patients.[23,24]

Candidiasis

Candida albicans is a constituent of normal flora. Whereas it primarily affects patients with predisposing conditions, *Candida* esophagitis can occur in apparently normal hosts. A variety of *Candida* species are pathogenic, including *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida stellatoidea*, and *Candida krusei*. Of those, *C. tropicalis* tends to be more virulent, showing a propensity to invade submucosal blood vessels.[25] Patients with intact immunity usually develop inflammation at the infected site that limits penetration by the microorganisms.

Acute candidal esophagitis is the most common manifestation. Presenting symptoms are nonspecific and include odynophagia, dysphagia, and retrosternal chest pain. Esophageal bleeding, perforation, stricture, sinus formation (with secondary pulmonary abscess), extensive necrosis, and systemic invasion are rare.[26] Subacute candidal esophagitis is an uncommon disease that usually affects asymptomatic and immunocompetent patients, but it can cause esophageal strictures and pseudodiverticula. It typically follows an indolent course. Chronic candidal esophagitis is also rare and is usually seen as a feature of chronic mucocutaneous candidiasis. These patients usually have other gastrointestinal manifestations, including malabsorption and loss of parietal cell function.[27]

Candidal infections can result in significant morbidity and death, especially in high-risk patients. Patients who receive radiation therapy to the thorax for lung or esophageal cancer or inhaled corticosteroid for asthma or chronic obstructive pulmonary disease are predisposed to candidal esophagitis.

Candidal infections yield small, yellow-white, raised plaques with surrounding erythema in mild disease—and confluent linear and nodular plaques or membranes covering a friable, erythematous, ulcerated mucosa in extensive disease—particularly in the middle and distal esophagus.[26] Erosion, ulcers, and strictures can develop. Fungi are densely adherent to the inflamed mucosa. In advanced disease, the esophagus may become stenotic and show mucosal irregularities. In chronic cases, umbilicated, wartlike lesions may develop. The gross features are easily confused with pseudodiverticulosis, varices, or carcinoma. Rarely, fungal esophagitis leads to a botryoid appearance resembling clusters of grapes projecting from the mucosa, and. mucosal bridges may form. In severe candidiasis, necrosis of the entire esophageal mucosa may be seen.[28]

Candida species are characterized by a mixture of blastoconidial spores, 3 to 4 μm in diameter, and nonbranching pseudohyphae that may become quite large, up to 2 μm in diameter. True septate hyphae can also be seen. These structures are best seen with Grocott methenamine silver (GMS) or periodic acid–Schiff (PAS) stain, and the presence of all of these structures is diagnostic of *Candida* infection (Fig. 9-3). Isolated budding yeasts without pseudohyphae or evidence of tissue invasion are often seen in inflammatory exudates at the ulcer bed; however, pseudohyphae or true hyphae are required for accurate diagnosis. Superficial colonization, particularly of nonviable tissue, does not necessarily indicate clinically significant disease. Whereas cytologic brushings from the plaques are more sensitive for fungal detection, biopsies are required to ascertain whether the fungus has invaded tissue. For this reason, it is important to indicate in the pathology report the types of fungal forms that are present (yeast, pseudohyphae, or both) and whether they are only seen in exudates or actually invade tissue.

Candida infections also mimic other fungal infections, such as aspergillosis and histoplasmosis. *Candida* spp. can be differentiated from *Aspergillus* based on the width of hyphae, the presence of acute-angle dichotomous branching by *Aspergillus* spp., and the presence of blastoconidia in *Candida* infection. The presence of pseudohyphae in *Candida* generally differentiates it from *Histoplasma capsulatum*. But if only yeast forms are identified, the differentiation of *Candida* from *Histoplasma* may be difficult. However, tissue Gram stain almost always decorates the gram-positive yeast forms of *Candida*.

Aspergillosis

Aspergillus, which is a ubiquitous fungus, rarely causes esophagitis.[29-32] Several species can infect the esophagus, including *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus flavus*. *Aspergillus* commonly colonizes immunocompromised patients[33-35] but can invade tissues and disseminate via the bloodstream, posing a life-threatening condition. Patients with esophageal aspergillosis present with painful or difficult swallowing and weight loss. Concurrent mucosal candidiasis may be present.

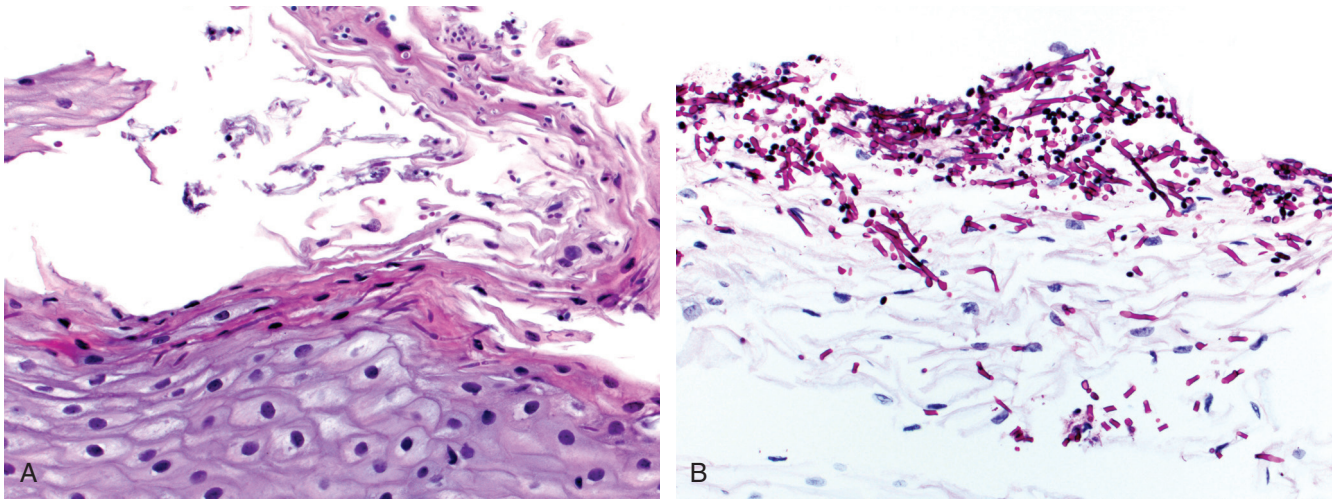

Figure 9-3. A, Candidal esophagitis is characterized by a mixture of spores and nonbranching pseudohyphae that invade the superficial layer of squamous epithelium. **B,** A PAS stain highlights the fungal elements.

Esophageal aspergillosis typically involves the mucosa and extends into the muscularis propria. When vascular invasion occurs, thrombosis and subsequent infarction may lead to perforation. Cytologically, *Aspergillus* is characterized by the presence of acute-angle branching septate hyphae with smooth, parallel walls, ranging in size from 2 to 4 mm in diameter. Characteristic conidiophores are rarely seen in this setting. *Aspergillus* can be differentiated from *Mucor* by its uniform thickness, mode of branching, and presence of frequent septation.

Other Fungal Infections

Blastomyces, *Histoplasma*, *Mucor*, and *Cryptococcus* species rarely involve the esophagus,[36] and usually only in patients with disseminated disease, but esophageal infection can arise from infections in contiguous structures, such as the lungs or mediastinum.[30] Patients with histoplasmosis can present with dysphagia resulting from esophageal compression by infected mediastinal lymph nodes or as a complication of mediastinal granuloma or sclerosing mediastinitis. Mediastinal granulomas can cause traction esophageal diverticuli.[36]

Viruses

Herpes Simplex Virus Types 1 and 2

Herpes infection may be seen throughout the gastrointestinal tract but is usually limited to squamous epithelium–lined structures (e.g., esophagus, anorectum). Herpes esophagitis has been reported with both herpes simplex virus type 1 (HSV-1) and HSV-2,[37,38] and it affects 0.5% to 6% of patients, primarily those who are immunocompromised due to AIDS, transplantation, or chemotherapy. However, immunocompetent adults and neonates also develop herpetic esophagitis.

Primary infections are common in neonates with disseminated HSV.[39] In adults, the disease typically manifests as a reactivation of latent disease. Usually, a previously healthy, immunocompetent patient with a history of recurrent "cold sores" (i.e., nasolabial herpetic lesions) who presents with concurrent esophageal symptoms most likely has HSV esophagitis. In this setting, infections are self-limited. However, immunocompromised individuals may experience severe prolonged infections, and they are at risk for serious complications, including mucosal necrosis, hemorrhage, strictures, tracheobronchial fistula, and disseminated infection.[40]

The endoscopic appearance of HSV esophagitis varies with the time of infection. Early lesions consist of rounded, 1- to 3-mm, clear vesicles seen predominantly in the middle to distal esophagus. Subsequently, the epithelial roof is eroded to leave small, 1- to 3-mm ulcers. After most of the HSV-infected squamous cells have sloughed off, characteristic sharply demarcated ulcers with raised margins and a yellow-gray base are seen (Fig. 9-4). The uninvolved mucosa usually appears normal. If infection progresses, the ulcers may coalesce to produce inflammatory exudates that grossly resemble *Candida* esophagitis.[41-44]

Typical histologic findings include focal ulceration, neutrophils in the lamina propria, and an inflammatory exudate with sloughed necrotic squamous cells. Aggregates of macrophages near the ulcer are characteristic of the inflammatory response.[45] Diagnostic cytopathic changes include nuclear molding, multinucleated giant cells, ballooning degeneration, and eosinophilic type A intranuclear inclusions showing margination of chromatin (Fig. 9-5). Cowdry type B inclusions are more frequently seen than type A inclusions. The edge of the ulcer and the sloughed squamous cells are the best places to sample for identification of the characteristic cytopathic changes. Viral culture is more sensitive than microscopic examination for diagnosis of HSV infection, and the combination of directed brushings and biopsy specimens submitted for culture and histology improves the sensitivity of endoscopic diagnosis compared with biopsy alone.[46,47] Accurate diagnosis can be confirmed in situ by immunostaining with commercially available specific monoclonal antibodies.

The differential diagnosis of HSV esophagitis includes other viral infections such as cytomegalovirus (CMV) and varicella-

zoster virus (VZV) infection. Their histologic features overlap, so immunostains and in situ hybridization are required to accurately distinguish them. It is important to distinguish HSV from other infections, because specific antimicrobial agents are required for effective treatment.

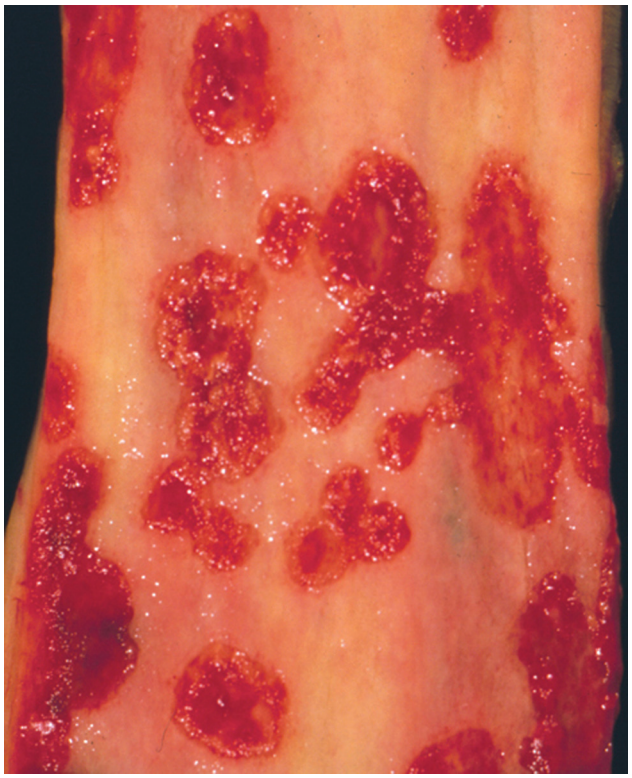

Figure 9-4. Gross appearance of esophageal ulcers due to herpes esophagitis in a patient with HIV infection. Numerous punched-out ulcers are present. (Courtesy of Dr. Rhonda Yantiss.)

Multinucleated squamous epithelial giant cells that are located predominantly in the proliferative basal and suprabasal zones of the preserved squamous epithelium have also been reported in the setting of reflux esophagitis, radiation therapy, and drug esophagitis. The epithelial giant cells may be confused with herpetic infection; however, the former typically lacks ground glass nuclear inclusions and peripheral condensation of chromatin at the nuclear membrane. The multinucleated cells in herpes esophagitis are generally more prominent in the superficial aspects of the epithelium and in luminal inflammatory debris. An immunostain for herpes virus antigen can help to exclude HSV infection.[48]

Cytomegalovirus

Because CMV infection is a systemic infection that involves multiple organs in addition to the esophagus, the clinical presentation of CMV esophagitis is often distinct. The onset of symptoms is more gradual than that of HSV esophagitis and includes fever, epigastric pain, nausea, vomiting, diarrhea, and weight loss, as opposed to the painful difficulties in swallowing and retrosternal pain commonly seen in HSV infection.[1,49,50] Endoscopically, CMV infection manifests as multiple, discrete, small, superficial ulcers in the middle or distal esophagus, but it may yield one or more large, flat, and elongated ulcers. Because HSV esophageal ulcers are rarely several centimeters in diameter, the presence of giant ulcers is suggestive of CMV esophagitis in patients with AIDS (Fig. 9-6A), although HIV-associated idiopathic ulcers may also become large.[51] Penetrating giant ulcers causing fistulas and pseudotumoral lesions may be seen in AIDS patients.[5] CMV esophagitis may coexist with both HSV and *Candida* infection in transplant recipients and in AIDS patients.[1,52]

CMV cytopathic effects typically develop in glandular epithelium, endothelial cells, and fibroblasts rather than in squamous cells (see Fig. 9-6). Therefore, superficial biopsy specimens that contain only squamous epithelium or brushings for cytology

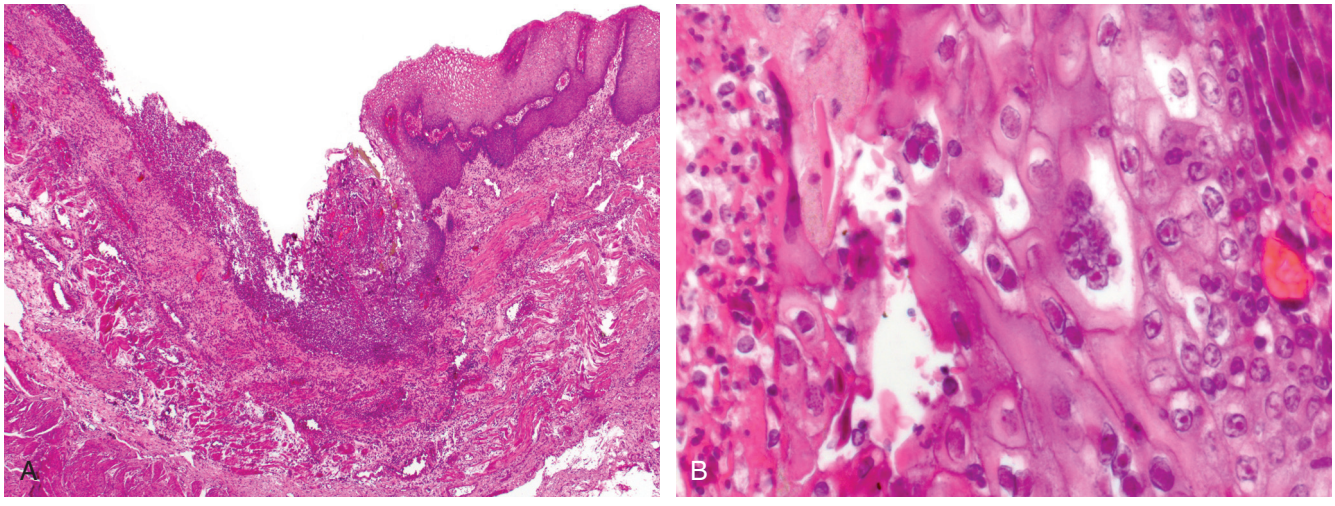

Figure 9-5. Herpes simplex virus (HSV) esophagitis. **A,** A resection specimen shows a sharply demarcated ulcer with raised margins. The ulcer bed is partially covered by inflammatory exudate that contains sloughed squamous cells. **B,** HSV cytopathic changes consist of nuclear molding, multinucleated giant cells, and type A intranuclear inclusions with margination of chromatin.

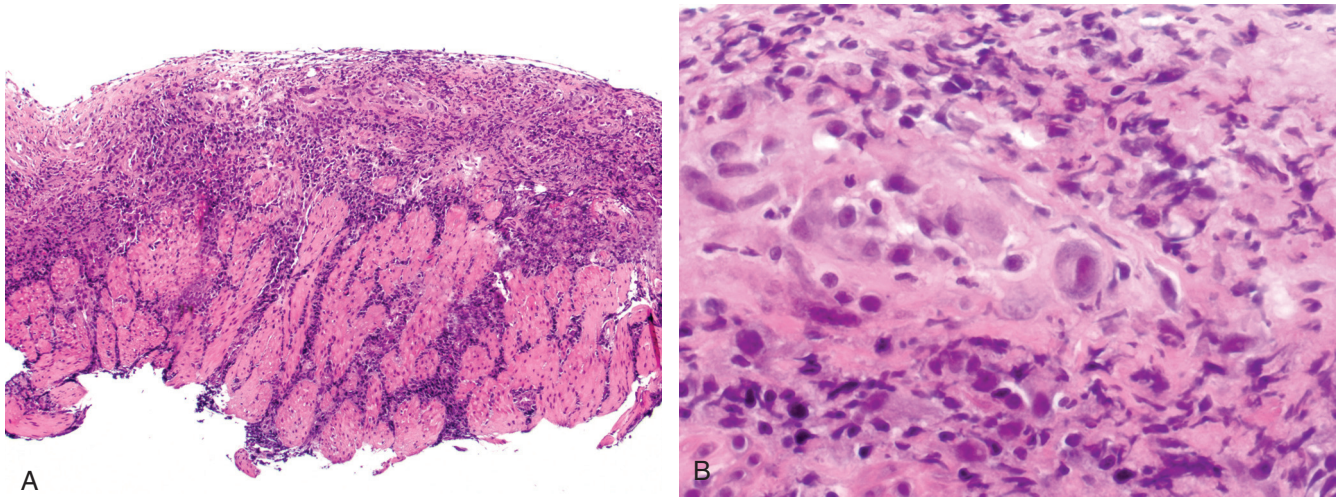

Figure 9-6. Cytomegalovirus (CMV) infection of esophagus. **A,** A mucosal biopsy from a large ulcer in a patient with AIDS demonstrates granulation tissue replacing lamina propria, as well as thickened and inflamed muscularis mucosae. **B,** High-power magnification reveals an endothelial cell with CMV cytopathic changes.

are usually insufficient for the evaluation of CMV infection, and it is recommended that biopsy include the granulation tissue of the ulcer bed. Classic cytopathic effects of CMV include intranuclear eosinophilic inclusions surrounded by a halo with margination of the chromatin to the nuclear membrane. In contrast to HSV and VZV, multiple small cytoplasmic inclusions may be seen with hematoxylin and eosin (H&E) stain, and to advantage with PAS and GMS. CMV can superinfect the ulcerations caused by HSV, and mixed infections are common in severely immunocompromised individuals (Fig. 9-7). Immunohistochemistry with specific antibodies or genetic probing for virus may be necessary to establish the diagnosis, especially if the patient has received antiviral agents prophylactically, because such agents can inhibit nuclear cytopathic changes.

Other Viral Infections

Primary VZV infection (chickenpox) in immunocompromised children is often associated with severe visceral dissemination and has a mortality rate of 7% to 30%.[53,54] VZV esophagitis is rare and occurs in severely ill patients, but not in AIDS patients.[3] VZV cytopathic changes are seen in epithelium, endothelium, and stroma cells and are indistinguishable from those of HSV.[55] Cytoplasmic rarefaction and vacuolization of the infected cells, as well as dissociation of the basal layer from the lamina propria, may be observed. To differentiate VZV infection from HSV infection, immunohistochemical staining with specific monoclonal antibodies is required.

Esophageal infections with human papillomavirus (HPV) may manifest as erythematous macules, white plaques, nodules, exuberant frondlike lesions, or even ulcerations.[56-59] Large lesions can be mistaken for malignancy on endoscopic examination, and small lesions may be confused with glycogen acanthosis.[60] Koilocytotic changes in squamous epithelium are characteristic. As in the cervix and anus, HPV infection is associated with well-defined papillomas (condylomas) and with mucosal hyperplasia.

Epstein-Barr virus (EBV) esophagitis is infrequently reported but can be seen in otherwise healthy patients with infectious mononucleosis. These patients present with odynophagia and hematemesis and develop multiple small (3-5 mm) midesophageal ulcerations that are deep and linear, with erythematous rims and a gelatinous base.[61] Histologically, EBV-infected esophageal mucosa is comparable to oral hairy leukoplakia seen in AIDS patients; it is characterized by epithelial hyperplasia, parakeratosis, and koilocytosis.[62,63] EBV infections confirmed by in situ hybridization are also seen in AIDS.[63]

Human Immunodeficiency Virus

Esophageal ulceration is an important cause of morbidity in patients with HIV/AIDS and may result from a variety of factors. A prospective study reported that 50% of esophageal ulcers in HIV-infected patients were caused by CMV infection, and about 40% were classified as idiopathic ulcers. Other causes included HSV infection, gastroesophageal reflux disease, and *Candida* infection. In 10% of patients, more than one etiology was discovered during long-term follow-up.[64] Acute seroconversion to HIV can produce multiple small esophageal ulcers with an intense inflammatory infiltrate. Based on the ultrastructural detection of viral-like particles in biopsy samples, it was hypothesized that HIV was responsible for the ulcerations in these individuals.[65,66]

Large idiopathic esophageal ulcerations have been documented in 4% to 12% of HIV-infected patients with esophageal symptoms, especially those in late stages of AIDS.[52,67] A thorough evaluation for other infectious agents was unrevealing.[68] Some have suggested that HIV is causative, based on demonstration of HIV by in situ hybridization[69] and positive immunohistochemistry and enzyme-linked immunosorbent assay (ELISA) for HIV p24 core protein in macrophages lining the ulcerations.[70,71] However, HIV PCR was also positive in the majority of the examined patients with CMV esophagitis, and HIV can be cultured in about 50% of esophageal specimens from otherwise asymptomatic HIV-infected patients,[72] raising doubt as to whether HIV is the cause of giant ulcerations. These patients may respond to systemic corticosteroid therapy,[69,71,73,74] but

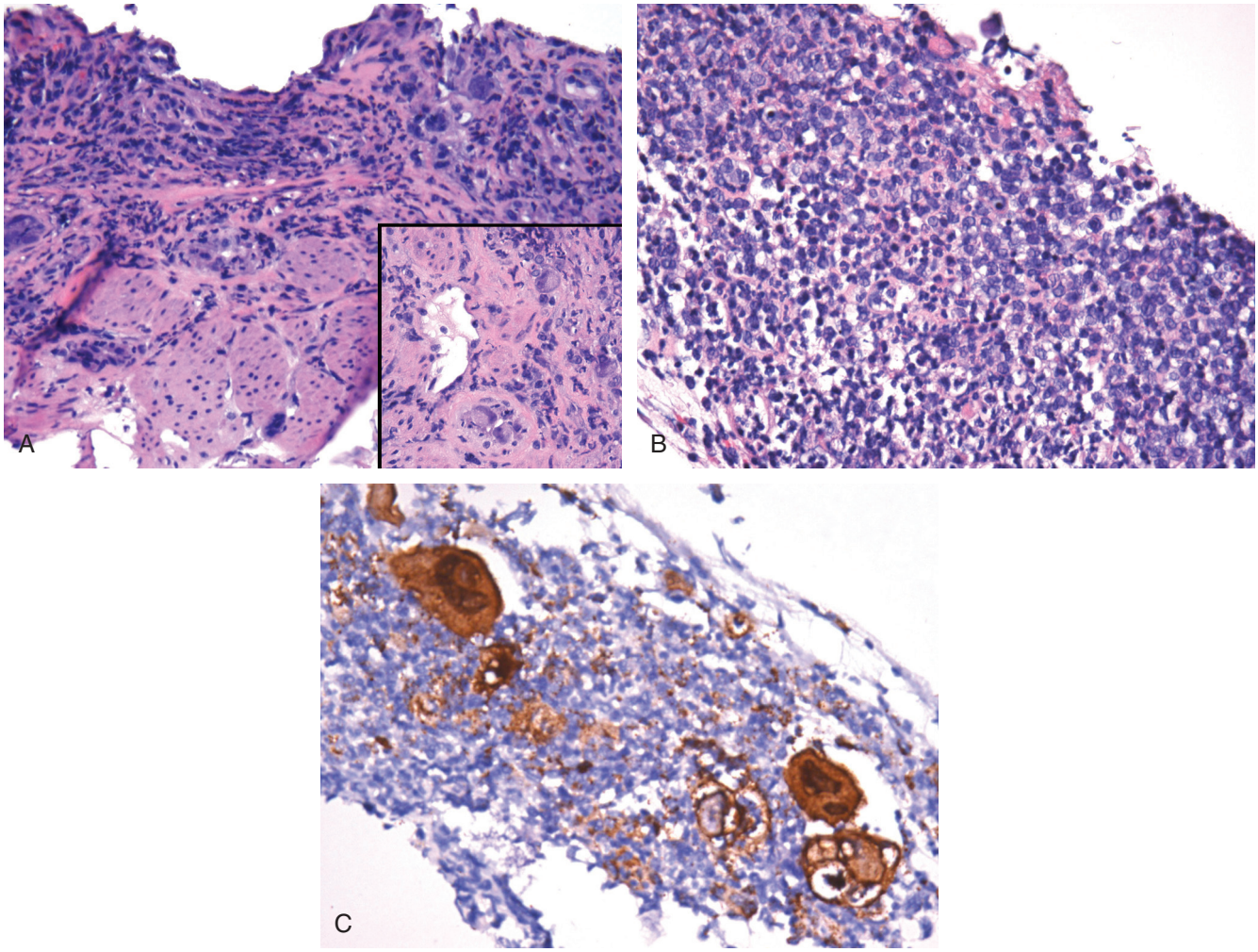

Figure 9-7. Mixed infection in a severely immunocompromised patient. The esophageal biopsy consisted of granulation tissue **(A),** with endothelial cells demonstrating characteristic cytomegalovirus cytopathic changes *(inset),* and detached fragment of fibrinopurulent exudate **(B)**. **C,** Immunostain for herpes simplex virus (HSV) performed on deeper sections also revealed positive multinucleated cells consistent with HSV cytopathic changes.

treatment also predisposes patients to infectious complications (Table 9-2).

Infections of the Stomach

Given the protective mechanism of low ambient gastric pH, only a limited number of infectious agents can thrive in the stomach, usually as a result of a high infectious burden or specific evolved protective mechanisms. Not surprisingly, patients in immunodeficient states are at greater risk for infectious gastritis. Although *Helicobacter pylori* is the most common cause of infectious gastritis, other agents also cause disease (Table 9-3).

Viruses

Cytomegalovirus

Although CMV infection may occur in immunocompetent patients,[75] gastrointestinal CMV usually occurs in immunocompromised individuals due to malignant disease, iatrogenic immunosuppression, or AIDS.[76] In these settings, CMV infection can be life-threatening.

Clinical symptoms include epigastric pain, fever, and atypical lymphocytosis. Endoscopically, the gastric mucosa is congested and edematous, with multiple erosions and ulcerations.[77] A pattern of hypertrophic gastritis resembling Ménétrièr disease and associated with protein-losing gastropathy has been described.[78]

The biopsy specimens demonstrate mixed inflammatory infiltrates with characteristically enlarged endothelial, stromal, or epithelial cells showing diagnostic owl's-eye intranuclear inclusions. However, cytopathic changes can be difficult to identify, and multiple granular basophilic cytoplasmic inclusions may be seen instead.[79] It has been noted that inclusions are usually observed in the endothelial cells if the mucosa is not ulcerated. Alternatively, they are commonly seen in endothelial and stromal cells when the mucosa is ulcerated.[80]

Gastric involvement with HSV or VZV is rare. Reactivation of infection acquired at an early age is often the result of radiation therapy, chemotherapy, or malignancies in immunocompro-

Table 9-2 Viral Pathogens of Esophagus

Virus	Location	Macroscopic Features	Histology
HSV, VZV	Middle to distal esophagus not extending to stomach (usually involves squamous mucosa)	Multiple small, sharply demarcated and shallow ulcers	Epithelial ballooning and inclusions at ulcer edge; only inflamed granulation tissue in ulcer bed
CMV	Part of multiple organ involvement (stomach, intestine > esophagus)	Resembles HSV; occasionally one or more giant ulcers	Cytopathic effects involving endothelium, stromal cells, and/or submucosal glands; infection of squamous cells rarely seen
HPV	Esophagus occasionally involved	Normal, elevated lesions, or papillomas	Koilocytosis in squamous epithelium; condyloma, epithelial hyperplasia, or normal-appearing mucosa
EBV	Middle esophagus	Multiple small, deep, and linear ulcers	Similar to oral hairy leukoplakia; epithelial hyperplasia, parakeratosis, and koilocytosis
HIV	Esophageal involvement hard to document	Large ulcers or small ulcers resembling HSV	No specific changes

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; VSV, varicella-zoster virus.

mised patients.[81] Symptoms include nausea, vomiting, fever, chills, and fatigue. Gastroscopic examination shows multiple small ulcers, at times yielding a cobblestone appearance, with ulcerated plaques or linear superficial ulcers. Microscopic examination reveals epithelial cells with ground glass nuclei and eosinophilic intranuclear inclusions surrounded by a clear halo. Acute gastritis due to EBV has been reported but is rarely biopsied. The pathology is characterized by prominent lymphoid hyperplasia. Rare cases of acute measles gastric infection with giant cells of Warthin-Finkeldey type have been described.[82]

Bacteria

Acute Suppurative Gastritis and Emphysematous Gastritis

Acute suppurative gastritis is a rare disorder caused by bacterial infection of the submucosa and muscularis propria. In severe cases, necrotizing gastritis may result.[83] It is associated with ethanol abuse, upper respiratory tract infection, AIDS and other immunocompromised states, and infected peritoneal-jugular venous shunts; it rarely occurs as a complication of surgical biopsy.[84,85]

Patients are acutely ill with acute upper abdominal pain, peritonitis, purulent ascitic fluid, fever, and hypotension. Ultrasonography and CT may establish the diagnosis.[86] Gastroscopic examination reveals a thick and edematous gastric wall. The mucosa may be granular with a dark green exudate. The diagnosis is commonly delayed, and the mortality rate is high. Gastric resection combined with broad antibiotic therapy directed against the most common organisms is the treatment of choice.

Microscopic examination reveals an edematous submucosa with a brisk polymorphonuclear infiltrate and numerous gram-positive and gram-negative organisms. Offending organisms include streptococci as well as *S. aureus*, *Escherichia coli*, Enterobacteriaceae, and other gram-negative bacilli.[87] Intravascular thrombosis is common, and extensive mucosal and mural necrosis can be seen.

Emphysematous gastritis is a rare variant resulting from infection by gas-forming organisms, most commonly *Clostridium perfringens*, *E. coli*, *Streptococcus*, *Enterobacter*, and *Pseudomonas aeruginosa*. Predisposing factors include gastroduodenal surgery, ingestion of corrosive material, gastroenteritis, and gastrointestinal infarction. In most cases, radiographic studies show gas bubbles conforming to the contours of the stomach.

Mycobacterium tuberculosis

Since the introduction of pasteurization, gastric infection due to *M. tuberculosis* has been rare; it is currently associated with pulmonary tuberculosis. The patient commonly presents with abdominal pain, nausea and vomiting, fever, and weight loss.

Endoscopic examination may demonstrate multiple bleeding ulcers or erosions; a narrowed, deformed antrum; and possibly gastric outlet obstruction due to a thickened wall. Microscopic examination may show an ulcerated mucosa, but the presence of necrotizing granulomas is diagnostic. The presence of acid-fast bacilli (AFB) can be confirmed on acid-fast staining,[88] but PCR for *M. tuberculosis* can also be a contributory tool.

Although *Mycobacterium avium* complex (MAC) infection is common in AIDS patients, the stomach is rarely involved. Gastric MAC may be associated with refractory chronic ulcers. Presenting symptoms include fever, night sweats, anorexia, weight loss, diarrhea, and abdominal pain. Abdominal CT scans may show mesenteric lymphadenopathy.[89] Microscopic examination shows a lamina propria expanded by numerous foamy histiocytes. These aggregate in ill-formed, non-necrotizing granulomas. AFB, often numerous, can be highlighted by Ziehl-Neelsen or Fite stain.

Actinomycosis

Primary gastric actinomycosis is a rare, chronic, suppurative disease. Symptoms include fever, epigastric pain, and bleeding. The stomach reveals a large, ill-defined ulcerative mass that mimics malignancy. Histologically, collections of neutrophils and sinuses are seen. *Actinomyces,* a gram-positive, filamentous,

Table 9-3 Pathogens Associated with Infectious Gastritis

Etiology	Clinical Setting	Histology
Viruses		
Cytomegalovirus Herpes simplex virus Varicella-zoster virus	Immunocompromised patients • AIDS • Cancer • Immunosuppressive therapies	Erosive gastritis
Bacteria		
Streptococcus *Escherichia coli* Enterobacteriaceae *Staphylococcus aureus*	• Large intake of alcohol • Upper respiratory tract infection, AIDS, and other immunocompromised states	Necrotizing gastritis
Mycobacterium tuberculosis	Endemic area	Erosive and fibrosing gastritis with necrotizing granulomas
Helicobacter pylori *Helicobacter heilmannii*	General population	Chronic active gastritis
Mycobacterium avium	AIDS	Ill-formed granulomas
Actinomyces		Suppurative and mass-forming gastritis
Syphilis	Sexually transmitted disease	Diffuse inflammatory gastritis
Clostridium perfringens, E. coli, Streptococcus, Enterobacter, Pseudomonas aeruginosa	• Gastroduodenal surgery • Corrosive material • Gastrointestinal infarction	Emphysematous gastritis
Fungi		
Candida	• Cancer • Immunocompromised patient • Severe alcoholism • Corrosive gastritis	Aphthous, or linear ulcerations or even larger ulcers.
Histoplasma capsulatum	• Cancer	Inflammatory mass.
Phycomycosis	• Immunocompromised patient • Corrosive gastritis	Ulceration and hemorrhagic necrosis
Parasites		
Cryptosporidiosis	AIDS	Minimal inflammation
Strongyloides stercoralis	Immunosuppressed patient (e.g., AIDS, diabetes)	Diffuse mucosal involvement
Anisakiasis	Consumption of raw shellfish	Eosinophilic and granulomatous gastritis
Ascaris lumbricoides		Gastric outlet obstruction

anaerobic bacterium, is best observed with a silver stain. The finding of sulfur granules containing long, filamentous, gram-positive bacilli is diagnostic.[90]

Syphilis

Syphilitic infection of the stomach is currently rare. Given the protean manifestations of this disease, gastric involvement in secondary or tertiary syphilis remains a diagnostic challenge. Endoscopic examination may show numerous shallow ulcerations with surrounding erythema, or a nodular mucosa with enlarged, thickened folds, suggestive of adenocarcinoma or lymphoma. Microscopic examination reveals severe gastritis with dense plasma cell infiltrates and varying numbers of neutrophils and lymphocytes. Gland destruction, vasculitis with endotheliitis, and ill-formed granulomas are seen. Warthin-Starry silver stain or modified Steiner stain may reveal numerous spirochetes. However, in many cases, immunofluorescence studies and PCR are required to establish a definitive diagnosis (Figs. 9-8 and 9-9).[91]

Fungi

Fungal colonization of the stomach may be seen in patients with underlying malignancy or in immunocompromised patients treated with antibiotics or corticosteroids. *Candida* infection also occurs in alcoholic patients and in those who have ingested corrosive chemicals. The organisms can be found on H&E-stained sections but are more readily seen with PAS with diastase or silver stains. The mucosa shows multiple, aphthous, and linear ulcerations, or single or multiple larger ulcers. Microscopically, the superficially necrotic, fibrinopurulent mucosa is infiltrated by yeast and pseudohyphae.

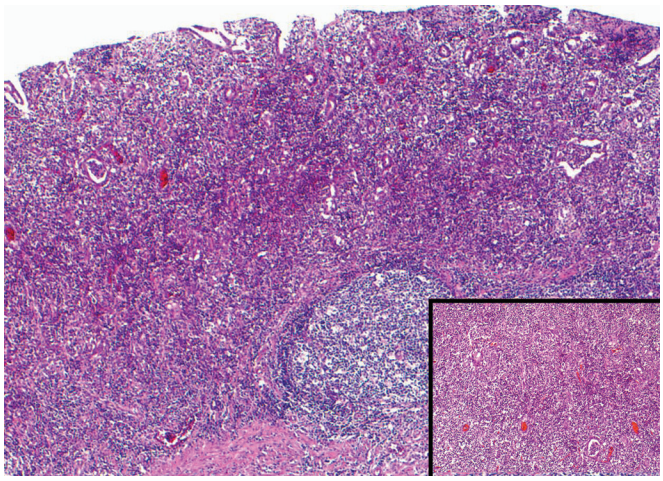

Figure 9-8. Syphilitic involvement of stomach. The mucosa is markedly thickened, and the normal architecture is effaced by a lymphoplasmacytic infiltrate *(inset)*.

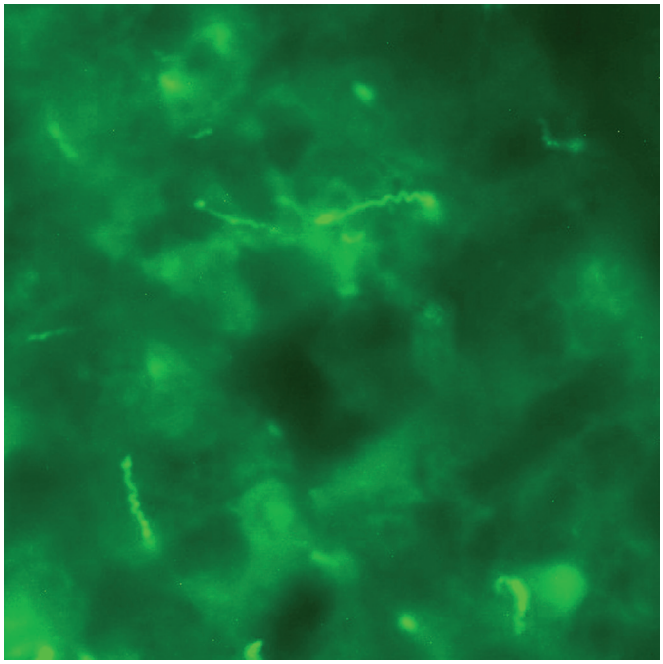

Figure 9-9. Syphilitic involvement of stomach. Immunofluorescence demonstrates numerous *Treponema pallidum*.

Fungal contamination of peptic gastric ulcer with *Candida* species is not uncommon and is likely of limited clinical significance, although it remains a matter of debate. These ulcers tend to be larger and are more often suspected of being malignant.[92]

Gastric histoplasmosis is a rare condition that manifests with hypertrophic gastric folds or masses mimicking adenocarcinoma. Biopsy shows intense infiltration by macrophages containing *H. capsulatum*. Fatal hemorrhage from gastric ulcer has been reported.[93]

Gastric phycomycosis is rare and highly lethal. It is classified as either invasive or noninvasive. The former type is characterized by deep invasion of the gastric wall and blood vessels. Ulceration and hemorrhagic necrosis of the mucosa and wall, with infiltrating pigmented nonseptate hyphae, are seen.[94]

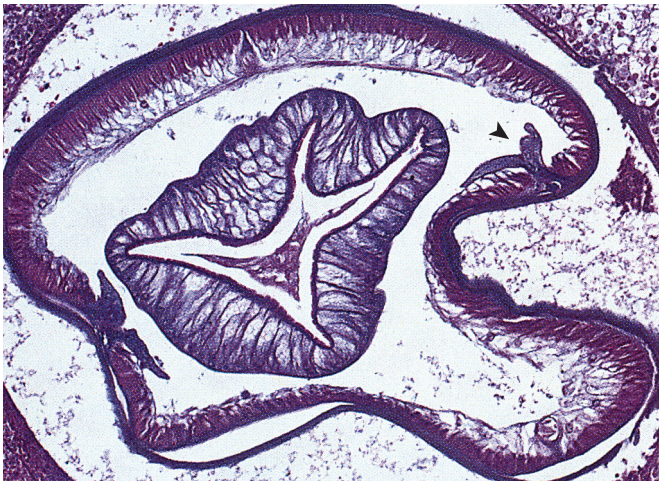

Figure 9-10. Anisakiasis. The helminth displays characteristic Y-shaped lateral cords *(arrowhead)*.

Parasites

Gastric parasitic infections are rare and are reported in specific clinical settings. Cryptosporidiosis, for example, has been reported in AIDS patients.[95,96] The stomach is rarely affected by *Strongyloides stercoralis,* although colonization of peptic ulcers has been reported, and diffuse mucosal involvement may be seen in immunosuppressed patients. On biopsy, the parasite is easily identified infiltrating the mucosa.[97]

Gastric invasive anisakiasis is commonly acquired after ingestion of raw shellfish containing the nematode larvae of *Anisakis*, although cases caused by *Pseudoterranova* spp. have also been reported in the United States. Typically, patients present with epigastric pain as the parasite migrates into the gastric wall. Mild peripheral blood eosinophilia is not universal. Small hemorrhagic erosions are detected endoscopically, and microscopic examination shows either a phlegmonous reaction or an eosinophilic abscess with granulomatous features. The offending nematode larvae of *Anisakis* can be identified based on the presence of characteristic Y-shaped lateral cords and a Y-shaped intestinal lumen at midsection (Fig. 9-10).[98] The lateral cords of *Pseudoterranova* are characteristically butterfly-shaped. Both lack the lateral alae of *Ascaris* larvae.

Rare examples of gastric infection by *Ascaris lumbricoides* have been reported in association with outlet obstruction caused by adult worms.[99]

Helicobacter pylori–associated Chronic Gastritis

H. pylori is a gram-negative rod that has a propensity to infect the gastric mucosa. *H. pylori* are 3.5-μm long and generally comma-shaped or slightly spiral in form.[100] The infection is usually acquired in childhood and causes chronic gastritis if the organisms are not eradicated. The majority of infected patients

carry and transmit *H. pylori* without any symptoms. The prevalence of the infection varies worldwide, ranging from less than 15% in some cohorts to almost 100% in underdeveloped countries.[101,102] Currently, despite a decrease of infection worldwide, at least 50% of the world's population is actively infected. The infection is transmitted by close personal contact.

H. pylori produces active and chronic gastritis. The lamina propria is expanded by a mononuclear cellular infiltrate, lymphocytes, and plasma cells, and lymphoid aggregates and follicles can also be seen (Figs. 9-11 and 9-12). If lymphoid inflammation is prominent, the term *follicular gastritis* has been adopted.[103] Normally, lymphocytes rarely enter the epithelium. Various degrees of neutrophilic infiltrate, reported as evidence of activity, may be seen. There are significant variations among infected individuals, based on host factors and the strain of infection.[104,105] *H. pylori* swim freely within the gastric mucus layer that overlays the apical side of the gastric surface cells, as well as in the foveolae.[105] In patients taking proton pump inhibitors, the organism translocates deep into the gastric glands (Fig. 9-13). Whereas *H. pylori*–induced damage is related to humoral and cell-mediated immune mechanisms, the morphologic activity varies significantly, from mild, with rare neutrophils seen, to severe, with glandular microabscesses.

H. pylori–associated chronic gastritis includes a heterogeneous group of clinical and pathologic changes. The most common phenotype observed at our institution is a mild antral gastritis or pangastritis with limited disruption of gastric acid secretion and usually no symptoms. A second syndrome, the duodenal ulcer phenotype, shows a marked antral gastritis with

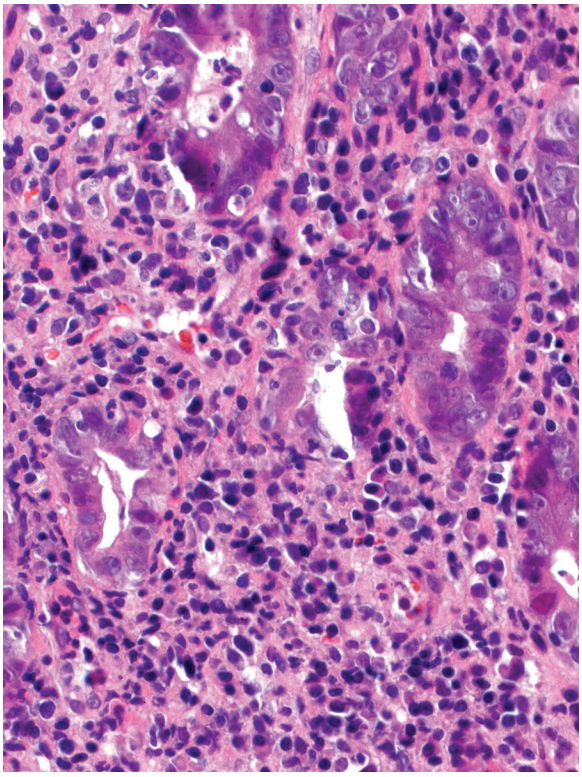

Figure 9-12. *Helicobacter pylori* gastritis. A dense lymphoplasmacytic infiltrate is seen around the foveolae, together with scattered neutrophils.

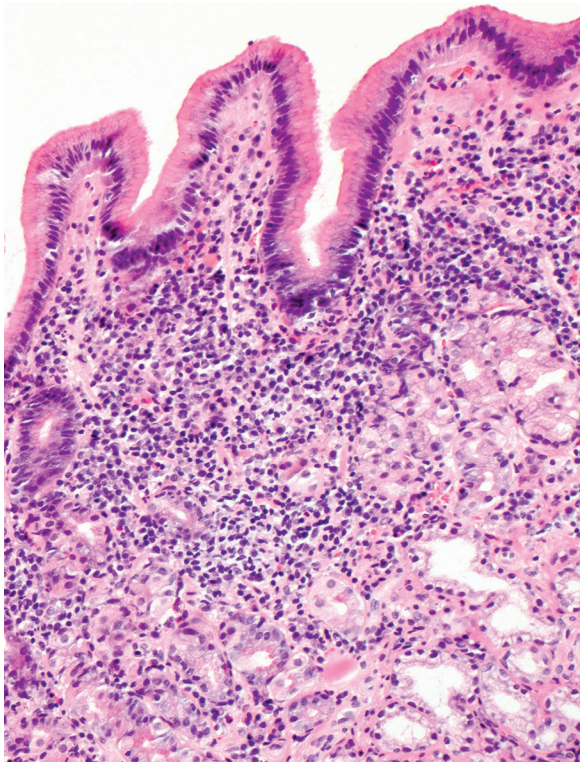

Figure 9-11. *Helicobacter pylori* infection. Low magnification of antral mucosa reveals a superficial band of dense chronic inflammation that is characteristic.

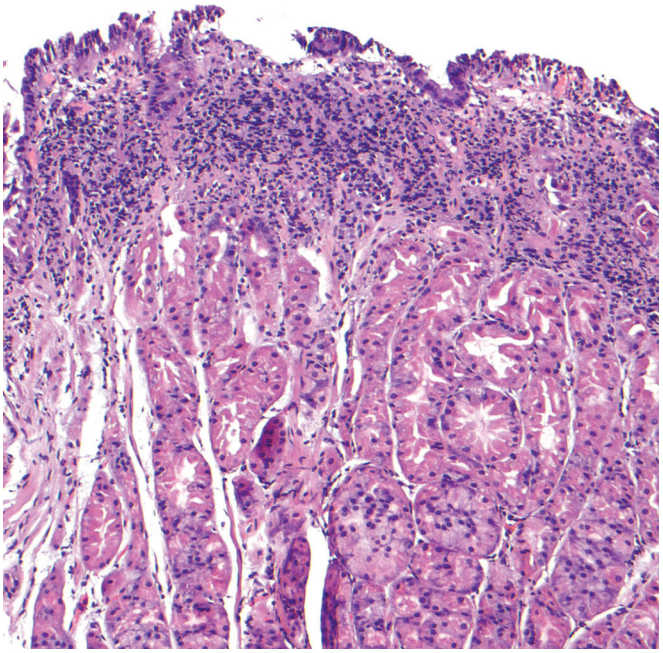

Figure 9-13. *Helicobacter pylori* infection of fundic mucosa. This is the characteristic appearance in a patient receiving proton pump inhibitor therapy without eradication of the bacteria.

high gastric secretion and preserved fundic mucosa. The patients commonly experience symptoms of duodenal ulceration.

Although about 10% of infected patients experience spontaneous regression,[106-108] in most cases gastritis progresses with time, yielding the gastric cancer phenotype. In this stage, the gastric mucosa typically undergoes changes that include glandular atrophy and intestinal metaplasia of the body fundus mucosa, accompanied by hypochlorhydria or achlorhydria. These changes increase the risk of gastric dysplasia and carcinoma. It has been calculated that patients with chronic atrophic gastritis have up to a 16-fold increased risk of developing gastric cancer. They are also at risk for development of mucosa-associated lymphoid tissue (MALT) lymphoma (extranodal marginal zone B-cell lymphoma).

In most cases, *H. pylori* can be identified in H&E-stained sections, although special stains (e.g., Giemsa, silver stains) and specific immunohistochemistry can aid in the detection of bacteria (Fig. 9-14).

Helicobacter heilmannii is a rare cause of diffuse, antral-predominant gastritis. The organism, in the past reported as *Gastrospirillum hominis*, is larger than *H. pylori* and shows corkscrew-like spirals. *H. heilmannii* infection has been associated with the development of MALT lymphoma but not with gastric cancer. Special stains used for *H. pylori* also highlight this organism (Fig. 9-15).[109-111]

Infections of the Small Bowel

Bacteria

Escherichia coli

Although most *E. coli* strains are harmless, some can cause serious food poisoning. The harmless strains belong to the normal intestinal flora and benefit the host by producing vitamin K_2[112] or by preventing the establishment of pathogenic bacteria within the intestine.[113,114] Virulent strains of *E. coli* that can cause gastroenteritis are classified on the basis of serologic characteristics and virulence properties. These are enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAggEC), enteroadherent *E. coli* (EAEC), enteroinvasive *E. coli* (EIEC), and enterohemorrhagic *E. coli* (EHEC). Of these, ETEC and EAggEC are noninvasive and induce diarrhea by

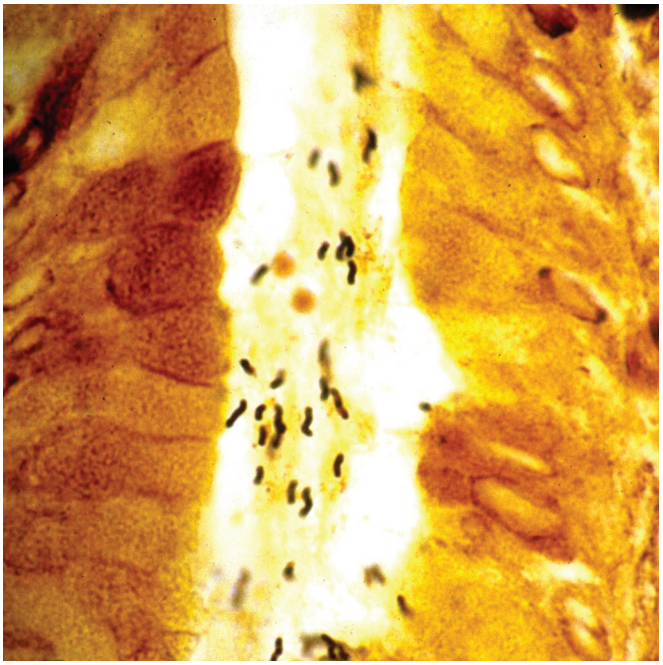

Figure 9-14. Silver stain demonstrating numerous curved *Helicobacter pylori*.

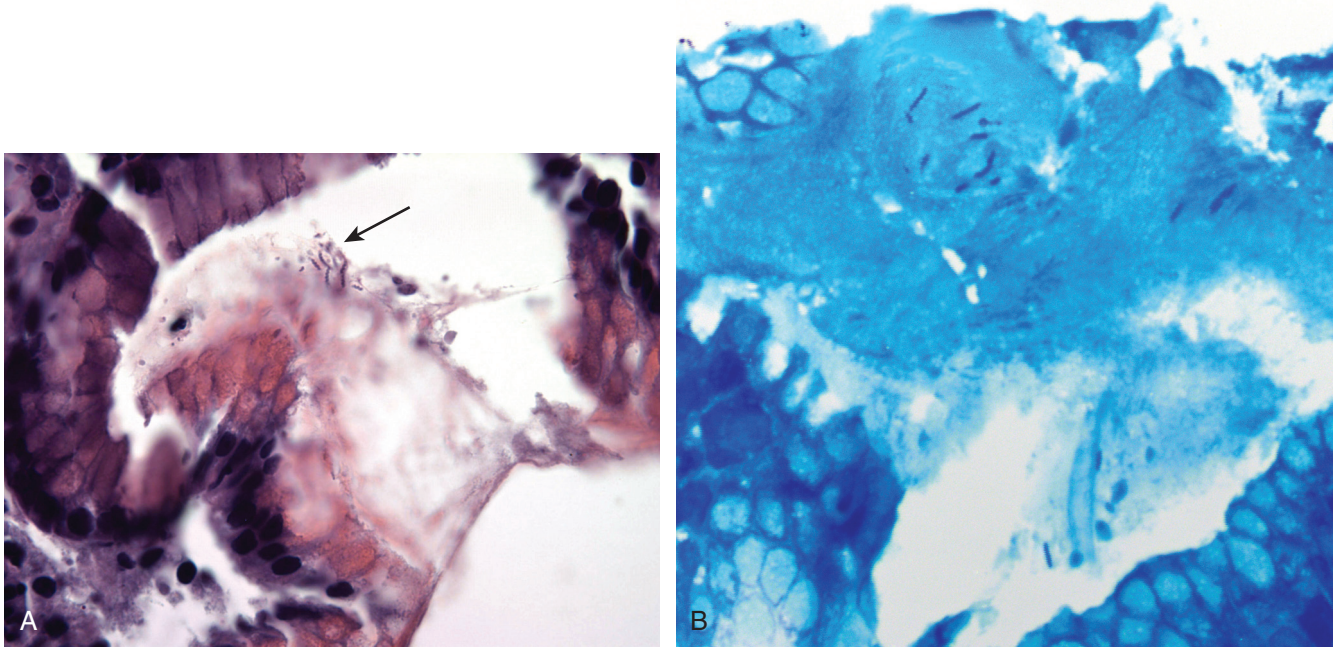

Figure 9-15. *Helicobacter heilmannii*. The thick, elongate, corkscrew bacteria are demonstrated in H&E-stained section (**A,** *arrow*) and with thiazine stain **(B)**.

producing enterotoxins or a hemolysin or both. EAEC are non toxigenic and noninvasive[115]; they avidly adhere to the epithelial brush border by means of specific receptors. Therefore, the histology of the intestine in infected individuals is often normal. Conversely, EPEC, EIEC, and EHEC are invasive. ETEC, EPEC, EAggEC, and EAEC colonize the small intestine. EIEC and EHEC preferentially colonize the large intestine before causing diarrhea. In this section, only the histology of EPEC is described.

Enteropathogenic Escherichia coli

EPEC is a leading cause of infantile diarrhea in developing countries, and some types of EPEC are also an important cause of traveler's diarrhea. The mucosal biopsy reveals moderate to severe damage with irregular atrophy of surface epithelium and subnuclear vacuolization of crypt epithelium. Ultrastructural study reveals bacteria adherent to mucosal cells with flattening of microvilli, loss of the cellular terminal web, and cupping of the plasma membrane around individual bacteria—characteristic attachment–effacement lesions.[116]

Salmonella

Salmonella typhi usually causes a mild, self-limited illness, but the elderly, infants, and immunocompromised patients may develop a serious course with sepsis and death. Nontyphoid species (*Salmonella paratyphi*, *Salmonella enteritidis*, *Salmonella typhimurium*, *Salmonella muenchen*, *Salmonella anatum*, and *Salmonella give*) infections result in milder, self-limited gastroenteritis.

Based on a study that examined intestinal function and jejunal biopsy specimens obtained soon after the recovery phase from acute disease in 29 patients with *Salmonella* infection, normal or near-normal small-intestinal histology was seen in more than 90% of cases, despite defective absorption, which was transiently observed in 50%. The remaining patients developed partial villous blunting with increased inflammation in the lamina propria and surface epithelium associated with reactive epithelium.[117] If the disease manifests with severe gastrointestinal bleeding that requires surgical intervention, *Salmonella* spp. commonly involve the ileum and cecum. In these cases, the bowel wall is thickened, and the mucosa displays erosions and ulcers that can be aphthous, linear, discoid, or full thickness in nature (Fig. 9-16A). Perforation with or without fistula formation may be seen.[118]

Microscopically, there is ileal and cecal mucosal thickening resulting from a predominantly monocytic infiltrate. Low-power examination shows nodular and diffuse areas of infiltration, with the latter present predominantly at the center of the lesion (see Fig. 9-16B). The nodules are of two types. The first is a germinal center rimmed by a ragged and compressed mantle zone. The second and predominant type of nodule consists of uniform sheets of monocyte-macrophages with numerous apoptotic bodies and cellular debris, surrounded by small lymphocytes. The centers of these monocytic-rich foci consist of amorphous eosinophilic debris and degenerating cells.

The interfollicular and diffuse areas are replaced by phagocytic monocytes showing round to irregularly shaped nuclei and intermingled with small mature lymphocytes. Neutrophils are rare, even in the areas of mucosal ulceration. The inflammatory process breaches the muscularis propria and may extend into the serosa. Small mucosal erosions in uninvolved portions of the ileum reveal a predominantly lymphoid infiltrate with germinal center formation and clusters of monocyte-macrophages, most likely representing early lesions.[118]

The regional lymph nodes show a necrotizing lymphadenitis and marked sinusoidal and paracortical expansion due to a

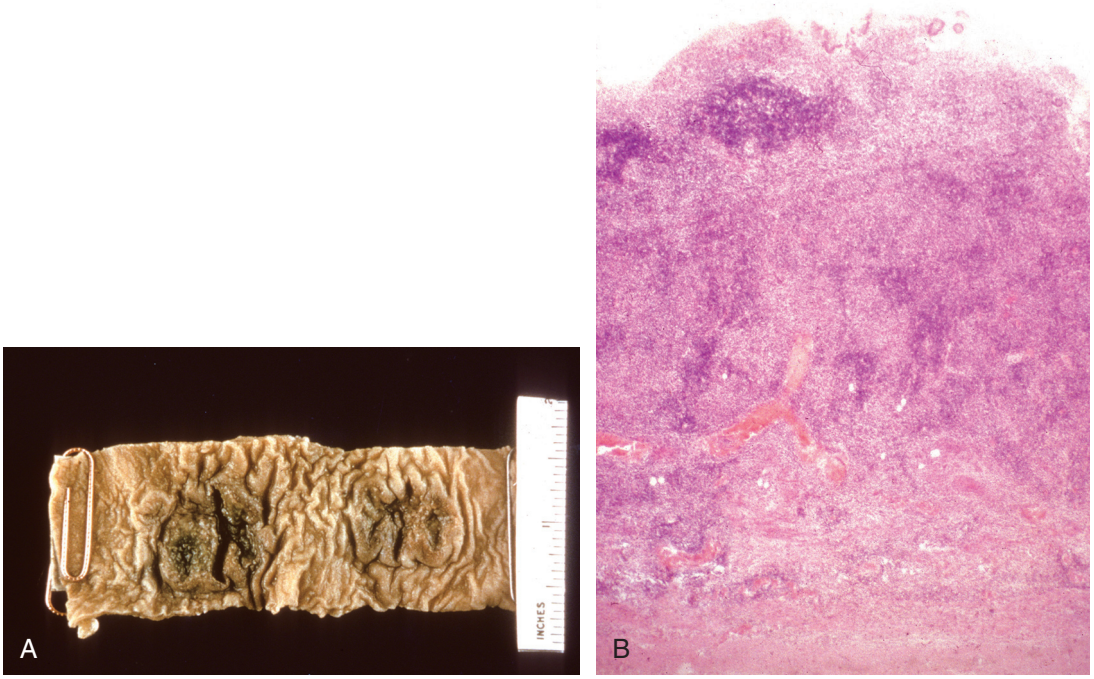

Figure 9-16. A, Opened, formalin-fixed specimen of terminal ileum from a patient with typhoid fever, showing ulceration of the Peyer patches. **B,** Low-power magnification of the ileum reveals diffuse inflammatory infiltrate transmurally involving the intestinal wall with surface ulceration, as well as nodular lymphoid aggregates.

proliferation of monocyte-macrophages identical to those seen in the intestine. Subcapsular sinuses are distended by monocytes but may be compressed or obliterated. Actively phagocytic macrophages are seen, many containing intracellular apoptotic bodies and cell fragments. The necrotic foci tend to be rounded and rimmed by foamy macrophages that blend smoothly with the reminder of the node.[118]

The closest mimic of *S. typhi* enterocolitis is *Yersinia* infection.[119-121] In both lesions, the terminal ileal mucosa and mesenteric lymph nodes are distorted by lymphoid and histiocytic hyperplasia; however, deep, penetrating ulcers and abundant epithelioid granulomas are characteristic features of *Yersinia* infections and not of *S. typhi* enterocolitis.

Also in the differential diagnosis, especially of the nodal involvement, are histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease) and sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). These entities; however, rarely involve the intestine in a primary fashion.[118]

Vibrio

Eleven *Vibrio* species are recognized to cause human infection.[122-127] Infection with *Vibrio cholerae* results in cholera, an important cause of watery diarrhea and dysentery that may lead to significant dehydration and death. Although the disease is widespread, the role of intestinal biopsy is limited, because *V. cholerae* is a noninvasive, toxin-producing organism that causes minimal or no histologic changes. The intestinal mucosa appears to be intact, with mucin-depleted, dilated crypts in a background of edematous lamina propria with vascular dilatation and no significant inflammation. Ultrastructural examination reveals widening of the intercellular spaces and alteration of apical junctional complexes prominently in the villus epithelium, whereas blebbing of the microvillus border and mitochondrial changes occur in the crypt epithelium. The extent of the changes correlates with clinical severity.[128]

Clostridium

Clostridial infections are discussed more extensively in the infectious colitis section. Only a unique form of clostridial infection of the small intestine, enteritis necroticans, is discussed here.

Enteritis necroticans is a life-threatening infectious disease caused by *C. perfringens*, type C, a β-toxin–producing strain. It is characterized by segmental necrosis of the proximal jejunum and a high mortality rate if not diagnosed early and appropriately treated. In addition to antibiotics, advanced cases require surgical resection of necrotic bowel. The disease was first reported as Darmbrand (burnt bowels) in Northern Germany after World War II, where starved children and adults developed it after ingestion of large meals of meats and vegetables. It was prevalent between 1944 and 1948 but then disappeared in Europe as the nutritional status of its population improved. In 1963, a similar disease was reported from the Highlands of Papua New Guinea, where predominantly male children and young adults presented with severe abdominal pain after ceremonial feasting on large amounts of sweet potatoes and inadequately cooked pork contaminated with pig intestine. It was termed "pigbel," a pidgin English term for abdominal pain following a pig feast. Nowadays, enteritis necroticans is rarely seen in developed countries, and the majority of affected subjects are diabetics.[129,130] An impaired ability to degrade exogenous toxins due to decreased secretion of pancreatic protease in diabetics and individuals on low-protein diets, or the presence of natural protease inhibitors in sweet potato or soybean flour, together with delayed transit through the small intestine, may contribute to this unique form of clostridial infection.[129]

Histopathologically, the lesion starts abruptly in the proximal jejunum and usually extends distally to the ileum and cecum. Affected bowel segments are dilated, edematous, markedly congested, and thickened. Unaffected skip segments may be seen. Sloughing of the necrotic mucosa leaves severely ulcerated lesions, and transmural inflammation may be seen in severe cases.

The pathology varies depending on the severity and duration of disease, but common findings include severe mucosal necrosis with or without pseudomembrane formation, marked submucosal edema and hemorrhage, and fibrinous or fibrous serosal exudate (Fig. 9-17). Pneumatosis may be observed. The necrosis tends to be more prominent at the crown of plicae circulares, whereas the mucosa may appear normal at the vale of plicae circulares.[130] The necrotic mucosa is often covered by large numbers of club-shaped, gram-positive rods, ranging in length from 0.5 to 1.2 μm. Immunohistochemistry or PCR for the α and β toxins of *C. perfringens*, type C (designated *cpa* and *cpb*, respectively) confirms the diagnosis.[129,130]

Yersinia

The genus of *Yersinia* includes three species that are pathogenic for humans and rodents: *Yersinia pestis* (the causative agent of plague), *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis*. These enteropathogens most often cause self-limited enterocolitis and mesenteric lymphadenitis in humans.[131] An acute abdomen presentation due to acute gastroenteritis, colitis, or pseudoappendicitis resulting from acute terminal ileitis is the most characteristic manifestation of the disease. Patents with iron overload,[132-134] those receiving desferrioxamine,[135-137] those with liver disease,[133] and those who are immunocompromised or debilitated[138] are at increased risk for severe disease. *Yersinia* can occasionally cause extraintestinal manifestations such as arthritis and erythema nodosum,[135-137] as well as fulminate septicemia and peritonitis.[132-134,139]

Enteropathogenic *Yersinia* strains have a tropism for lymphoid tissue.[140] Bacteria bind to and invade M cells within the epithelium overlying the lymphoid follicles of Peyer patches.[141,142] Following their entry into the Peyer patches, the bacteria induce a host immune response characterized by infiltration of neutrophils and macrophages.[143] Because of its lymphoid tropism, *Yersinia* infections preferentially involve the ileocecal and appendiceal regions, although any segment of the small or large intestine can be affected.[144] The intestinal wall is congested and edematous. Diffuse or focal aphthous mucosal ulcers can develop. The serosa appears dull and hyperemic. Enlarged lymph nodes contain yellowish microabscesses that may become matted.

Microscopically, severe active enteritis with cryptitis, crypt abscesses, and ulceration can be seen in both *Y. enterocolitica* and *Y. pseudotuberculosis* infections. Crypt hyperplasia occurs throughout the small intestine, with villous atrophy.[120] Sharply demarcated areas of lymphoid hyperplasia contain prominent

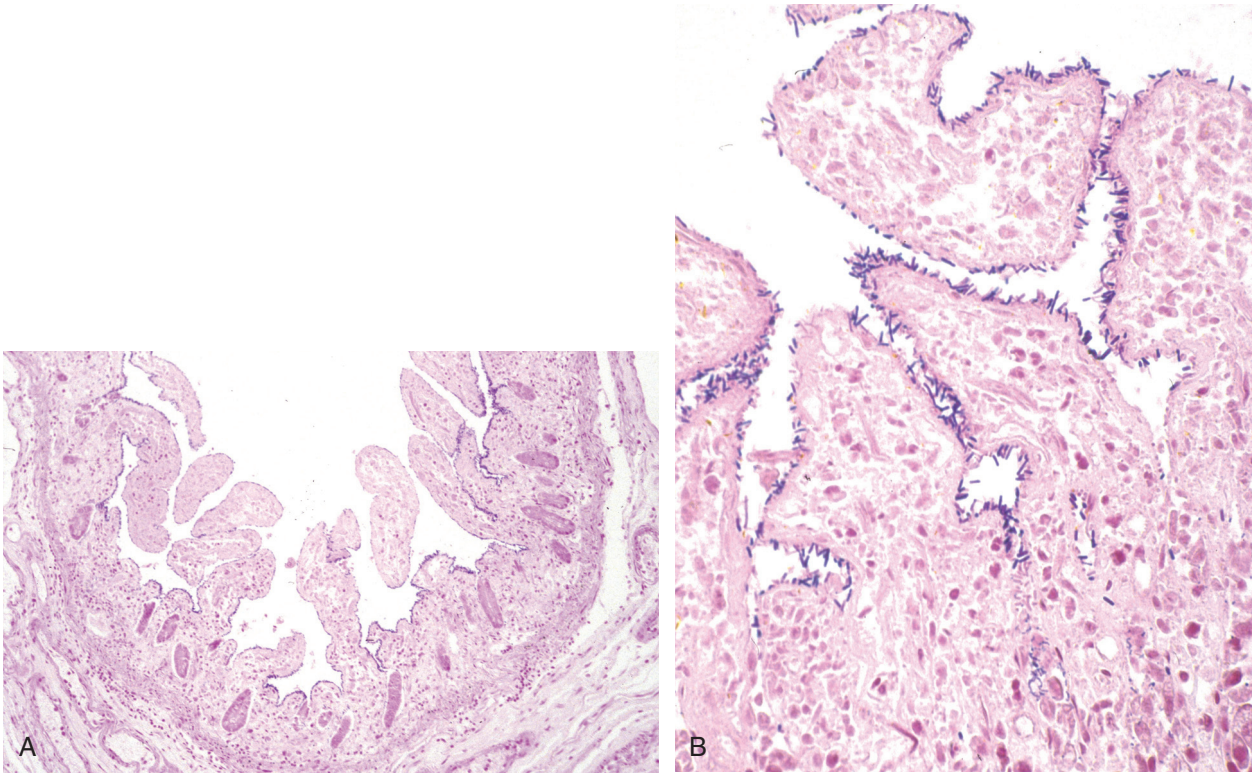

Figure 9-17. *Enteritis necroticans.* **A,** Severe mucosal necrosis. **B,** The necrotic mucosa is covered by numerous club-shaped, gram-positive rods. (Courtesy of Dr. Elena Brachtel.)

germinal centers. The follicular ileitis may persist for months. Notably, the mucosa overlying the follicles develops small, punctate, aphthoid ulcers resembling the early mucosal lesions of Crohn disease.[120] The ulcers are covered by fibrinopurulent exudates and large numbers of gram-positive coccobacilli. Epithelioid granulomas with central necrosis and prominent lymphoid cuffing are usually present in the mucosa, submucosa, and lymph nodes but can be seen on the serosa and lymph nodes as well (Fig. 9-18). The muscularis propria and serosa may be infiltrated by mixed inflammatory cells including eosinophils. Acute vasculitis as well as intussusception has been reported to cause segmental bowel ischemia.

The differential diagnosis includes Crohn disease, and this can be difficult to distinguish on histologic grounds alone. Cultures requiring special media,[144] serologic titers, and PCR assays must be considered in the evaluation of a patient for inflammatory bowel disease (e.g., Crohn disease), or a patient with suspected inflammatory bowel disease for whom steroid therapy has failed, before more aggressive immunosuppressive therapy is elected.[144] Features favoring a diagnosis of Crohn disease include crypt distortion, hyperplasia of the muscularis mucosa, and prominent neural hyperplasia; these features are evidence of chronic changes.

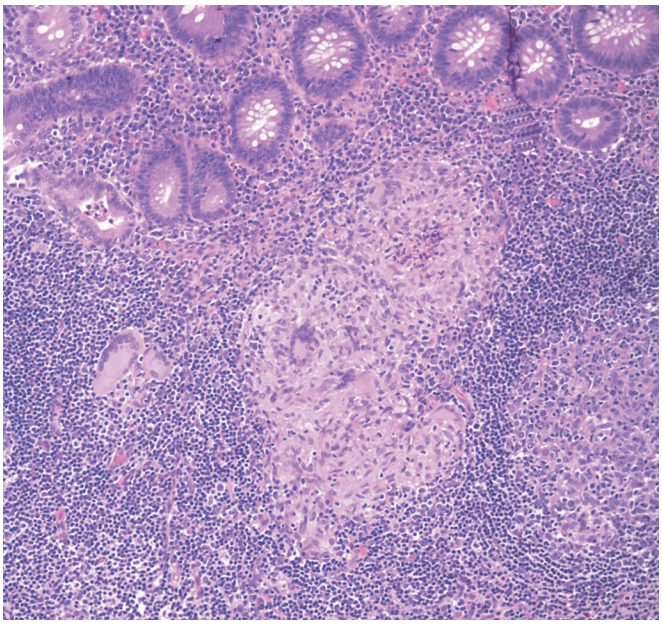

Figure 9-18. *Yersinia* infection. Epithelioid granulomas surrounded by prominent lymphoid infiltrate are seen in the deep mucosa and submucosa. (Courtesy of Dr. Laura Lamps.)

Mycobacterium tuberculosis

In accord with the distribution of lymphoid tissue, the ileocecal region is affected in 90% of patients infected by *M. tuberculosis* who present with gastrointestinal involvement. Grossly, intesti-

nal tuberculosis displays an ulcerative, hypertrophic, or mixed pattern. The ulcerative form is present in most cases and exhibits multiple superficial ulcers. Patients with this morphology tend to have a virulent clinical course with high mortality. The hypertrophic form is least common and mimics Crohn disease because of its scarring, fibrosis, and heaped-up mass lesions.[145] In the ulcerohypertrophic form, the intestinal wall becomes thickened and ulcerated by an inflammatory mass centered on the ileocecal valve.[146] In this form, the ileocecal valve is frequently obscured by a mass consisting of mesenteric fat, fibrotic tissue, and inflamed lymph nodes.

Tubercles begin in the Peyer patches or lymphoid follicles, giving the mucosa a cobblestone appearance. As disease progresses, they involve the entire intestinal wall with multiple nodules that may also produce serosal and mesenteric "studs." The ulcerative form of the disease begins as ragged ulcers that are varied in number and size. In contrast to Crohn disease, tuberculous ulcers are circumferential, with a long axis perpendicular to the lumen; fissure formation that extends into the muscularis propria may be seen.[145] The ulcers may contain AFB, even in the absence of granulomas. The mucosa appears edematous and hemorrhagic.

Hypertrophic lesions are caused by pronounced intramural thickening with ulceration and obstruction. Ulcers heal with fibrosis, strictures, and stenosis that may be broad, at times several centimeters in length. Epithelioid granulomas with obvious caseation (Fig. 9-19) occur more frequently in ulcerative than in hyperplastic lesions and are distributed throughout the entire thickness of the intestinal wall. Regional mesenteric lymph nodes become enlarged and contain areas of caseous necrosis as well.

Isolated organisms can be visualized in the granulomas and lymph nodes with the use of special stains and are recoverable in tissue culture. However, it is often difficult to detect the bacteria in suspected cases of tuberculosis, even with AFB-stained sections, due to the scarcity of the organisms. In this setting, the detection of mycobacterial DNA in formalin-fixed paraffin-embedded tissue by duplex PCR reactions can confirm the diagnosis. Other mycobacteria (e.g., *M. kansasii, M. bovis*) can produce similar pathologic features.

Although tuberculosis classically produces granulomas, other causes include fungal disease and Crohn disease. The latter may be difficult to distinguish from tuberculosis; transmural lymphoid aggregates, deep fistulas, and fissures favor Crohn disease (Table 9-4).

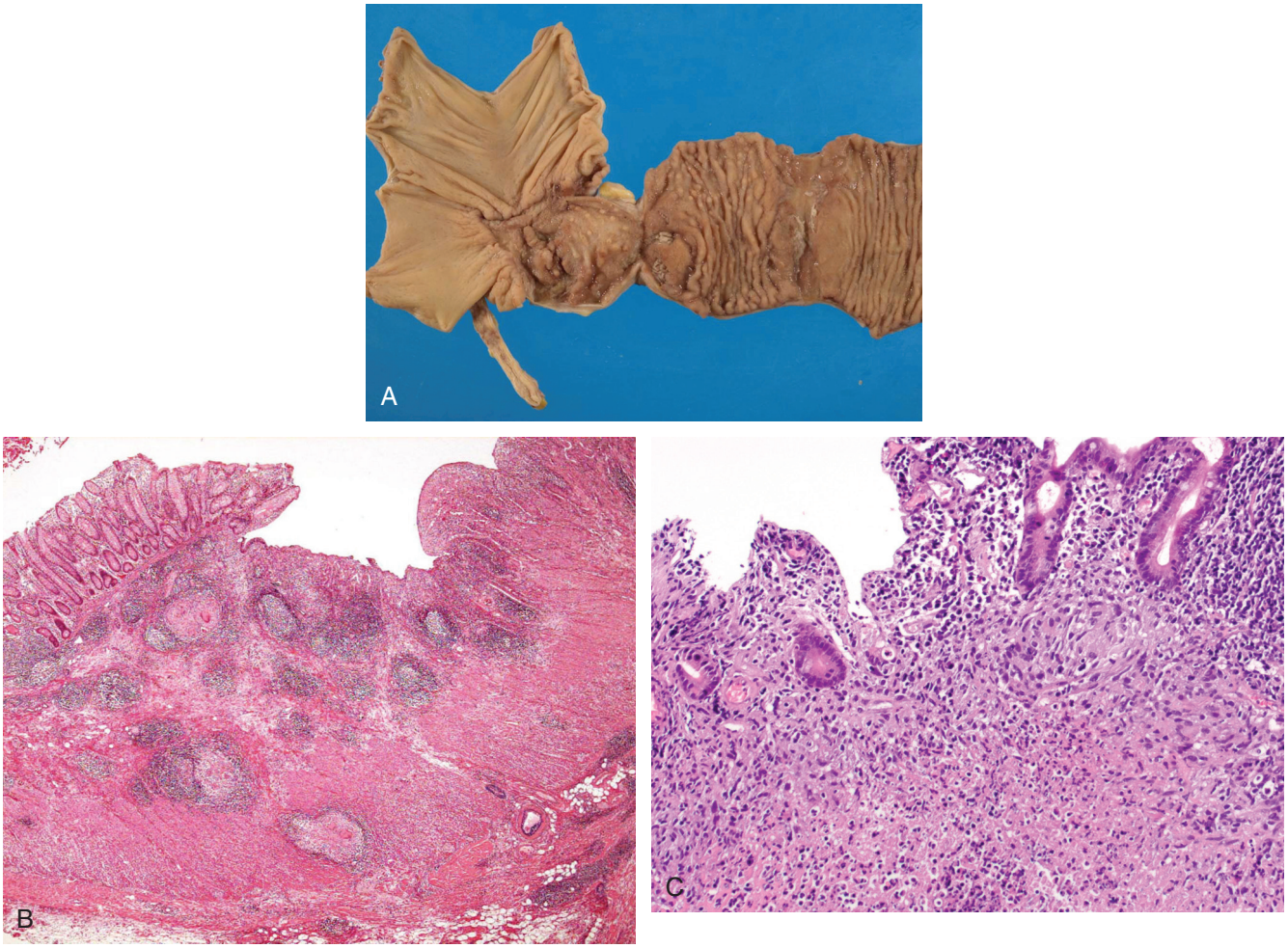

Figure 9-19. *Mycobacterium tuberculosis* of terminal ileum and ileocecal valve demonstrating ulcers that are circumferential, with their long axis perpendicular to the lumen **(A)**. **B,** The intestinal wall is thickened by epithelioid granulomas, lymphoid aggregates, and fibrosis. **C,** High power reveals caseous necrosis and epithelioid histiocytes. (Courtesy of Dr. Sachiko Minmiguchi.)

Table 9-4 Causes of Granulomas in Small Intestine

Crohn disease
Sarcoidosis
Infections
Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Mycobacterium bovis
Yersinia
Histoplasma
Schistosoma
Strongyloides
Actinomyces
Salmonella
Campylobacter
Brucella
Foreign material: sutures, barium, talc, feces due to fistula or perforation
Pneumatosis intestinalis
Malacoplakia
Langerhans cell histiocytosis

Mycobacterium avium-intracellulare Complex

MAC is an AIDS-defining opportunistic infection. Disseminated MAC infection is usually seen in patients with advanced HIV infection, generally those with CD4-positive T-lymphocyte counts lower than 50 cells/μL, and is associated with significant morbidity and mortality.[147,148] Since the induction of antimicrobial prophylaxis and highly active antiretroviral therapy (HAART), the incidence of disseminated MAC infection has dramatically declined, leading to improved survival.[149]

Disseminated MAC infection results from a primary infection, and a common portal of entry for MAC infection in AIDS patients appears to be the gastrointestinal tract.[150] The mycobacteria penetrate the gastrointestinal mucosa by yet undetermined mechanisms. This occurs rapidly, and solitary organisms can be seen in the lamina propria without apparent mucosal abnormality. Mycobacteria within the lamina propria are phagocytosed by macrophages, but intracellular killing does not occur. Instead, the macrophages become stuffed with organisms as they multiply intracellularly. With continued bacterial replication, the host cell ruptures. This process leads to the presence of sheets of macrophages laden with AFB. Unimpaired replication of mycobacteria results in massive thickening of the intestinal wall,[151] and infection spreads via mural lymphatics to involve lymph nodes. Mycobacteria replicate in the lymph nodes as well, and eventually the normal histology of the lymph nodes is effaced. Hematogenous dissemination occurs concurrently. Reticuloendothelial organs such as the liver, spleen, and bone marrow are the most frequent distant sites.[150]

The common presenting symptoms include diarrhea, fever, weight loss, and abdominal pain. Gastric ulcer, enterocolitis, enteric fistulas, intra-abdominal abscesses, and hemorrhage can also be seen as gastrointestinal manifestations.[152] Intussusception secondary to hyperplasia of Peyer patches can occur, and clinical and radiologic pictures resembling ileal Crohn disease may also be observed. The duodenum is most frequently involved, followed by the rectum, ileum, colon, esophagus, jejunum, and stomach, for reasons that are uncertain. On endoscopic examination, multiple raised, yellow-white nodules are seen in the duodenum, but the mucosa may appear normal. Other endoscopic findings include, in descending order, ulceration, erythema, edema, friability, confluent nodules, and strictures.[152]

Biopsy of nodular lesions reveals atrophic mucosa with villous blunting, as well as widening of lamina propria by an infiltrate of plump macrophages exhibiting granular foamy cytoplasm (Fig. 9-20). However, the overall architecture of the intestine is usually preserved. Other inflammatory cells, such as lymphocytes, plasma cells, and neutrophils, are sparse, if present. Regional lymph nodes display comparable infiltrates. Epithelioid granulomas are rarely seen[151]; if present, they are poorly circumscribed and rarely contain multinucleated giant cells. Small areas of necrosis are present in up to 30% of cases.[153] If necrosis is marked, the infiltrates are easily recognized on H&E stain even on low-power magnification. However, detection of focal involvement may require special stains. In addition to Ziehl-Neelsen and Fite stains, the PAS stain highlights mycobacteria. In contrast to *M. tuberculosis* infection, mycobacteria are usually present within macrophages, and not in giant cells or areas of caseous necrosis.

Whipple Disease (*Tropheryma whippelii*)

Whipple disease is a multisystem disease that results from infection with a gram-positive rod-shaped bacterium, *Tropheryma whippelii*. It is a rare disorder, and only about 1000 cases have been reported to date. Although it occurs in people of all ages, the typical patient is a middle-aged white man.[154] *T. whippelii* appears to be present in the general environment, although neither its source nor its mode of transmission is well established. Since an association between Whipple disease and *Giardia lamblia* infection has been reported, it is plausible that both microorganisms occupy the same ecologic niche.[155] Considering that many people may be exposed to *T. whippelii* but the disease develops in only some of them, it is likely that undefined predisposing immune factors exist.[156]

Several studies have demonstrated defective function of macrophages, with inability to degrade bacterial antigens efficiently, most likely due to inadequate production of interleukin-12 (IL-12),[157] which may lead to diminished production of interferon-γ by T cells and defective macrophage activation. A decrease in IL-12 production may prevent the development of an effective type 1 helper T-cell immune response and favor a shift toward a type 2 helper T-cell response. Replication of *T. whippelii* in macrophages is associated with apoptosis of the host cell that correlates with the expression and release of IL-16.[158]

Whipple disease is characterized by two stages: a prodromal stage and steady-state stage. The prodromal stage is marked by protean symptoms, along with chronic nonspecific findings, mainly arthralgia and arthritis. The steady-state stage is characterized by weight loss, diarrhea, or both, and occasionally by other manifestations affecting the many organs frequently involved.[159] The average time between the prodromal and the steady-state stage is 6 years. Patients on immunosuppressive therapy, such as corticosteroids or tumor necrosis factor antagonists, may experience more rapid clinical progression.[160,161]

Whipple disease frequently involves the small intestine, and jejunum and ileum more often than duodenum.[162] On endoscopic examination, pale yellow, shaggy mucosal changes, attrib-

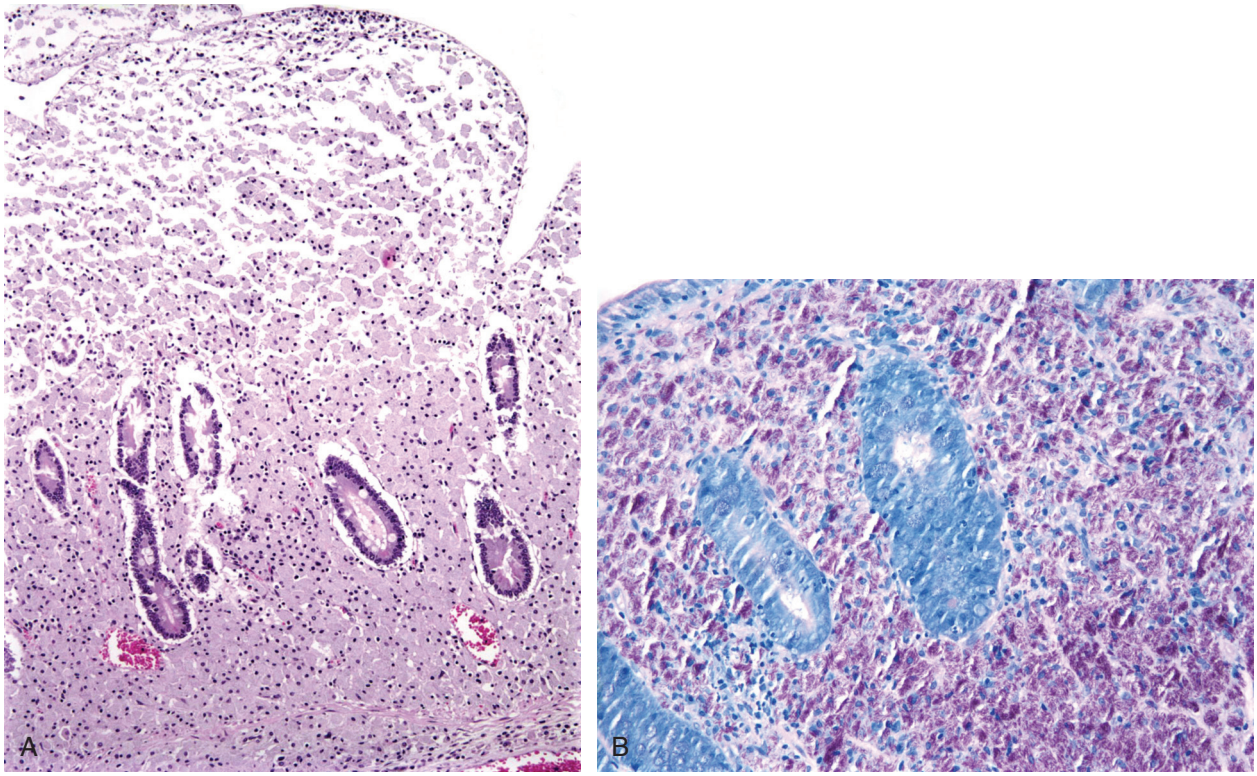

Figure 9-20. *Mycobacterium avium-intracellulare* complex infection. **A,** Intestinal villi are obliterated by infiltration of numerous plump macrophages with foamy cytoplasm in the lamina propria. **B,** The lamina propria macrophages are filled with PAS-positive mycobacteria.

uted to lipid deposits, alternating with eroded, erythematous, or mildly friable mucosal patches, are often seen in the distal aspect of the duodenum and jejunum.[163,164]

The histologic hallmark of Whipple disease is the presence of macrophages with cytoplasmic PAS-positive, diastase-resistant granules or sickle-form particles; these are known as sickle-form particle-containing cells, or SPC cells. Bacilli may also be seen within and between epithelial cells, especially before the initiation of antimicrobial therapy.[164] The intestinal villi are blunted and distorted by the collections of macrophage. In severe cases, subtotal or total villous atrophy can be seen. Conversely, the villous architecture is relatively normal in about one fifth of the cases.[164]

The majority of macrophages accumulate in the lamina propria of the villi, just beneath the luminal epithelial basement membrane (Fig. 9-21). A small number of macrophages may also be seen in the pericryptal lamina propria or submucosa or both.[164] Lymphocytes, neutrophils, eosinophils, and plasma cells can be seen infiltrating among the macrophages. Although rare, nonnecrotizing granulomas composed of epithelioid cells, which are PAS-negative in 40%, may be present in the mucosa, lymph nodes, and other organs, resembling sarcoidosis.[163,165,166] Lymphatic obstruction can cause dilatation of lacteals and can produce lipid deposits in the mucosa.

Antimicrobial treatment may affect the histology of the disease. With a decrease in the number of PAS-positive macrophages, a change occurs in the pattern of mucosal involvement. It may go from diffuse to patchy; the distribution of macrophages may shift from the villous interstitium to the pericryptal interstitium; and the intensity of PAS-positive staining may diminish.[163]

Other entities can yield PAS-positive macrophage collections in the intestinal lamina propria. These include *M. avium-intracellulare* infection, histoplasmosis, chronic granulomatous disease, xanthomas, storage disease, and common variable immunodeficiency. Although the macrophages may appear similar in these conditions, lipid deposits are seen only in Whipple disease. As for differentiating Whipple disease from MAC infection, acid-fast staining occurs only with MAC. Because characteristic histologic features are seen in only 90% of patients,[163] PCR assay is required to confirm the diagnosis in clinically suspicious cases that show nondiagnostic histologic changes (Table 9-5).

Tropical Sprue

Tropical sprue is an intestinal malabsorption syndrome that affects residents and visitors to the tropics, including Puerto Rico, the Caribbean, northern South America, West Africa, India, and southeast Asia.[167] Although its etiology and pathogenesis remain unclear, an infectious cause is strongly suspected because of the occurrence of tropical sprue particularly in rural areas with poor hygiene, susceptibility of visitors from developed countries in endemic regions,[168] and a favorable response to antibiotic therapy.[169] Patients also have been shown to have aerobic bacterial contamination of the small bowel, although no specific microorganisms are common to all patients.[170] In addition, preexisting prolonged orocecal transit time may contribute

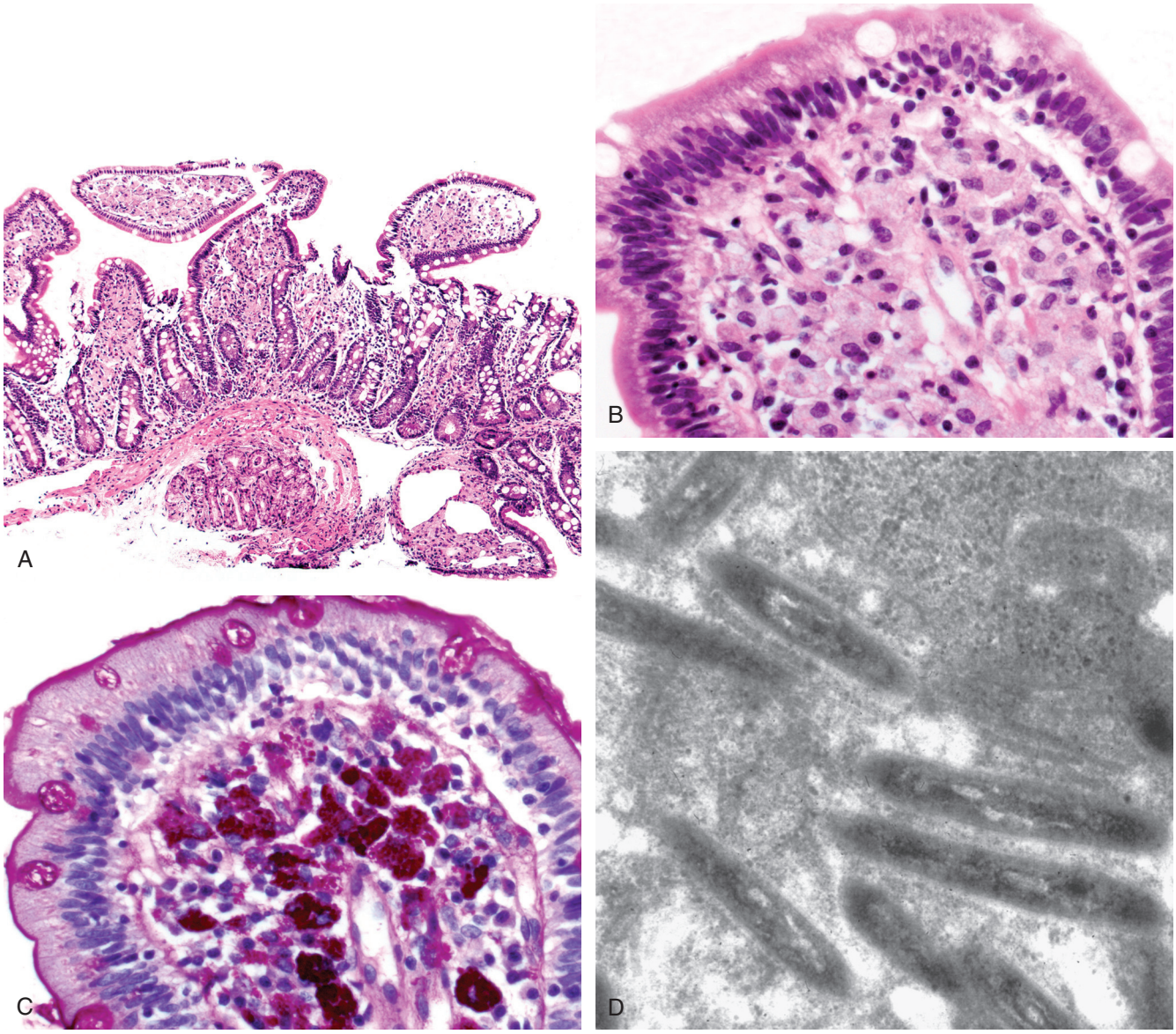

Figure 9-21. Whipple disease involving duodenum. **A,** A mucosal biopsy demonstrates partial villous blunting by collections of macrophages in the lamina propria. **B,** A large number of macrophages have accumulated in the lamina propria beneath the luminal epithelial basement membrane. **C,** PAS stain highlights intracytoplasmic granular particles that are resistant to diastase. **D,** Electron micrograph shows intact bacilli with characteristic thick walls and intracytoplasmic vacuoles.

to the disease process in some patients.[170] Diagnostic evaluation of tropical sprue requires its differentiation from infectious etiologies, especially parasitic diarrheal diseases and Whipple disease, and from other malabsorption syndromes such as celiac disease. Jejunal biopsies are necessary to establish the presence of characteristic histologic features and to exclude other diseases.

Histologic features of tropical sprue consist of villous atrophy, crypt hyperplasia, chronic inflammatory cell infiltration (particularly plasma cells, lymphocytes, eosinophils, and histiocytes), and increased numbers of intraepithelial lymphocytes. Nuclear-cytoplasmic maturational dissociation (i.e., nuclear enlargement and decreased mitotic figures) may be observed in the enterocytes.[171,172] The histologic findings, although similar to those of celiac disease, are not identical, and total villous atrophy is rare (<10%) in tropical sprue.[173-175]

The disease first involves the jejunum, then spreads distally to the ileum. In the early stage, the mucosa may appear normal or may show only increased numbers of intraepithelial lymphocytes. In well-established disease, the pathologic changes become equally prominent in the ileum.[175] Conversely, celiac disease commonly shows prominent mucosal changes in the proximal small intestine. This difference in disease distribution explains the more common association of tropical sprue with megaloblastic anemia caused by deficiencies of vitamin B_{12} and folate.

Fungi

Candida and *Aspergillus* species account for the majority of fungal infections of the small bowel. In comparison to *Candida*,

Aspergillus hyphae are often seen in submucosal vessels spreading within the bowel wall in a radiating pattern.[176] Other fungi that can involve the small bowel include *Histoplasma*, *Mucor*, *Paracoccidioides*, and *Penicillium marneffei*.

Of these, *H. capsulatum* is the most common endemic systemic mycosis in the United States; it occurs primarily, but not exclusively, in the central regions of the country. Gastrointestinal involvement occurs in 40% of patients with disseminated disease, and involvement of the small intestine is seen in 27%[177]; however, in contrast to other forms of disseminated histoplasmosis, fever and pulmonary involvement are unusual in gastrointestinal histoplasmosis.[178] Terminal ileal involvement is commonly seen. Deep ulcerative lesions with undercut margins are characteristic of *H. capsulatum* involvement,[178] but masses mimicking carcinoma, pseudopolyps, and lesions resembling xanthomas may also be seen.[179] Histologically, yeast forms ranging from 2 to 4 μm in size lie within well-formed granulomas or macrophages scattered in the lamina propria in a pattern resembling Whipple disease or early enteritis caused by *Mycobacterium avium-intracellulare* (Fig. 9-22).

Table 9-5 Comparison of *Mycobacterium avium-intracellulare* Infection and Whipple Disease

	M. avium-intracellulare	Whipple Disease
Distribution in small intestine	Duodenum > ileum > jejunum	Jejunum and ileum > duodenum
Macroscopic features	Yellow-white nodules or normal	Erythema alternating with pale yellow, shaggy mucosal changes
Villous architecture	Blunted or normal	Blunted
Lacteals	Not dilated	Dilated
Lipid deposits	–	+
PAS stain	+	+
AFB stain	+	–

AFB, acid-fast bacilli; PAS, periodic acid–Schiff.

Candida

Small intestinal candidal infections are rare in immunocompetent individuals with intact mucosal integrity, but they can be seen in up to 20% of autopsied patients with disseminated infection.[180] All *Candida* species can infect immunocompromised patients, but there is a higher frequency of disseminated *C. tropicalis*.[25] The gross appearance is variable; it includes mucosal flecks, sloughed membranes, ulcers of varying configuration, and nodular masses. Most invasive *Candida* infections are superficial[176] and must be carefully differentiated from benign colonization. In colonization, *Candida* spp. may be identified embedded in the fibrinopurulent exudate that covers blind loops or in devitalized tissues without invasion of viable tissue. In immunocompromised or chronically debilitated patients, *Candida* can also invade deep into the intestinal wall and gain entry to the microvasculature, leading to ischemia and sepsis.

Viruses

Enteric Virus Infections

Numerous viruses, including rotavirus, enteric adenovirus, Norwalk virus, coronavirus, echovirus, enterovirus, calicivirus, and astrovirus,[181-183] can cause gastroenteritis. Diagnosis is made based on viral culture, electron microscopy, ELISA of stool specimens, or genetic probes. Pathologists rarely obtain biopsies from patients with viral enteritis, but if they do, the bowel displays nonspecific findings such as reactive and degenerative changes of the epithelium and a mononuclear cell infiltrate in the lamina propria. Architectural changes of microvilli may also be seen.

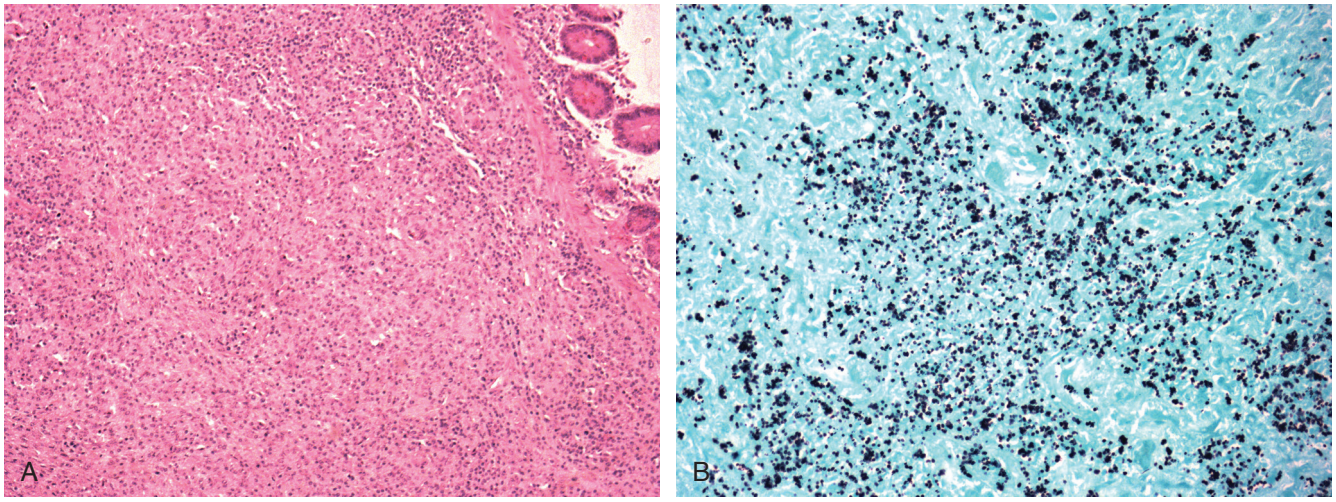

Figure 9-22. A, *Histoplasma capsulatum* infection of the small intestine shows ulceration of the mucosa with non-necrotizing granulomas in the bowel wall. **B,** GMS stain reveals innumerable budding yeast forms.

Cytomegalovirus

CMV infection of the small intestine accounts for only 4% of all CMV infections, and CMV infection of the duodenum accounts for 22% of all CMV infections of the gastrointestinal tract.[184] Immunosuppressed patients, including not only those with HIV infection but also those who undergo small bowel transplantation for short bowel syndrome, are prone to CMV infection. The latter group of patients show a high incidence of recurrence due to the heavy immunosuppression required to manage the graft.[185,186] In this setting, PCR analysis of small-intestinal biopsy specimens may be a sensitive method for early detection of CMV and can be useful for preemptive therapy.[187] The clinical manifestations of CMV infection include a wide spectrum of symptoms such as malaise, anorexia, fever, nausea, diarrhea, abdominal pain, ileus, gastrointestinal bleeding, and perforation. Severe complications such as hemorrhage and perforation are often preceded by vague symptoms for up to 2 weeks.[188,189] The mortality associated with CMV enteritis is related to older age (>65 years) and delay in instituting therapy but not to the anatomic site of the infection.[190]

CMV enteritis tends to involve only a single region, rather than causing a panenteric infection.[191] The pathologic changes range from few stromal or endothelial cells exhibiting CMV viral inclusions with no tissue reaction to frank ulceration and perforation. Almost any cell type may be infected, although CMV most frequently involves vascular endothelial or stromal cells (Fig. 9-23). The infected and swollen endothelial cells lead to luminal compromise, with fibrin thrombi formation that results in ischemic mucosal injury and, subsequently, ulceration.[188]

Human Immunodeficiency Virus–related Enteropathy

HIV enteropathy is a poorly defined clinical entity that represents pathogen-negative diarrhea in an HIV-infected individual. The possibility that it is related directly to local HIV infection is

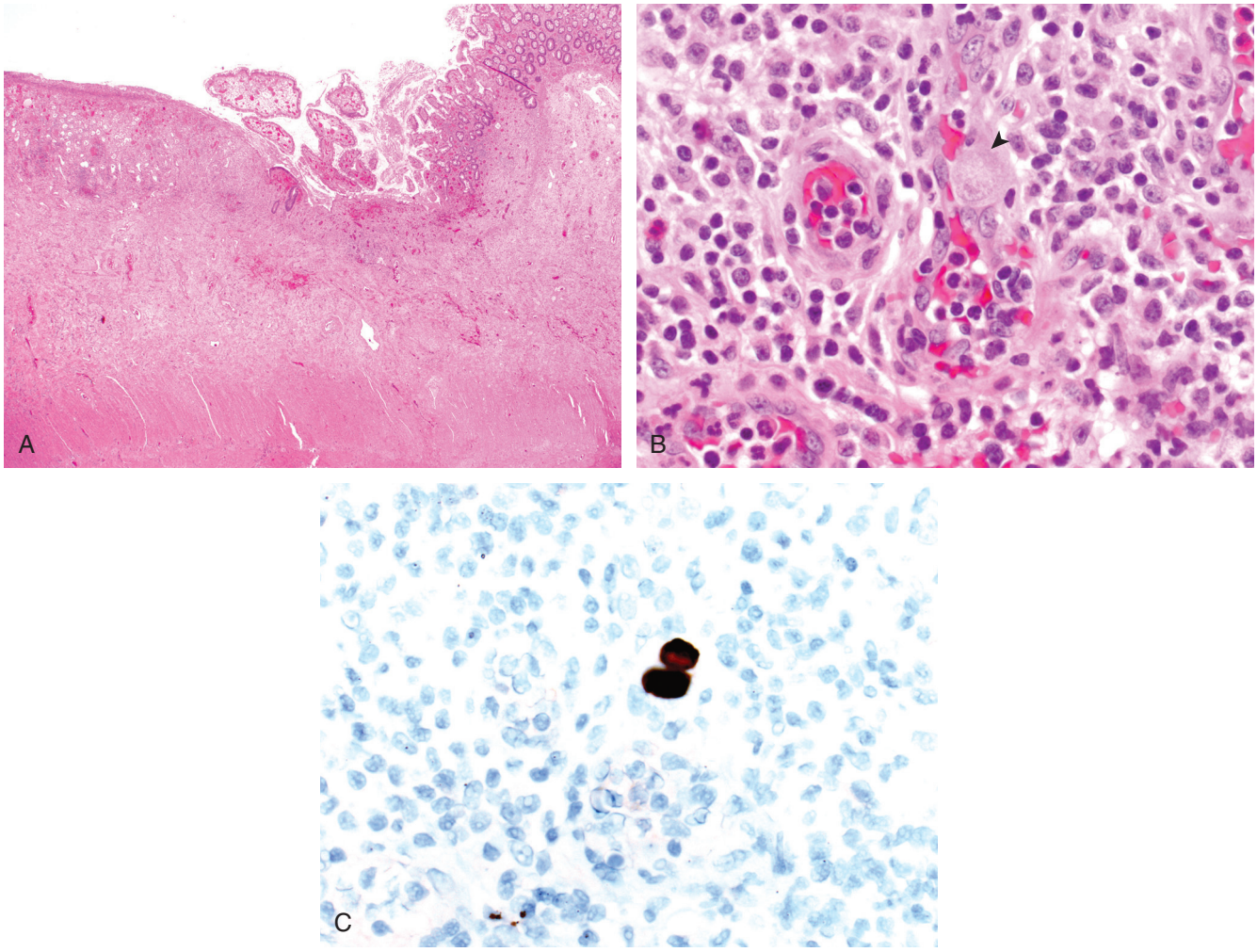

Figure 9-23. *Cytomegalovirus* (CMV) infection superimposed on chronic ischemia of small intestine. The resection specimen of small intestine from a patient with HIV infection who presented with small-bowel obstruction reveals chronic enteritis with ulceration and mural fibrosis (**A**). Proliferating capillaries in the submucosa contain endothelial cells exhibiting atypical CMV cytopathic changes, i.e., cytomegaly with multiple small eosinophilic granules in the cytoplasm (*arrowhead*) (**B**) that react with CMV immunostain (**C**).

supported by the detection of HIV proteins and nuclear acids in various cell types of the intestine (i.e., epithelial cells, lymphocytes, and macrophages). Furthermore, combination antiretroviral therapy has led to improvement of gastrointestinal symptoms in these individuals.[192]

Two competing hypotheses have been advanced to explain the diarrheal disease of mucosal HIV infection. It has been suggested that HIV enteropathy is a pathophysiologic consequence of exposure to gp120, which arises from mononuclear cells of the lamina propria, and therefore is independent of epithelial HIV infection.[193-195] Others have argued that the diarrhea is driven by cytokines (tumor necrosis factor and related moieties) released from infected lymphoid cells that can inhibit mucosal ion flux,[196,197] resulting in malabsorption, diarrhea, and weight loss.[198-200]

Vacuolated enterocytes may show conversion from columnar to cuboidal morphology, with cellular apoptosis, seen in a background of either villus and crypt atrophy or hyperplasia (Fig. 9-24). These epithelial changes are associated with mild mucosal inflammation, intraepithelial lymphocytosis, and dilated lacteals. The histologic changes are often mild and disproportionate to the symptoms.[201,202]

Protozoa

Flagellates

Giardia intestinalis (*Giardia lamblia*) is the most prevalent human protozoan pathogen and the leading cause of waterborne diarrheal outbreaks in North America. *G. intestinalis* infection is associated with a broad spectrum of manifestations. Serious diarrhea illness with intestinal malabsorption and marked weight loss can be seen in young children and in previously unexposed adults, particularly travelers from low- to high-prevalence parts of the world. Infants and young children may suffer impairment of growth and development. However, in the vast majority of individuals world wide, the parasite is apparently carried without significant morbidity.[203]

The life cycle of *Giardia* includes two stages: cyst and trophozoite. The former is the infectious form; it is both relatively inert and environmentally resistant. After ingestion, excystation occurs in the duodenum as a result of exposure to gastric juice and pancreatic enzymes, yielding two trophozoites from each cyst.[204,205] These trophozoites replicate in duodenal crypts and in the upper jejunum, reproducing asexually by binary fission.[203]

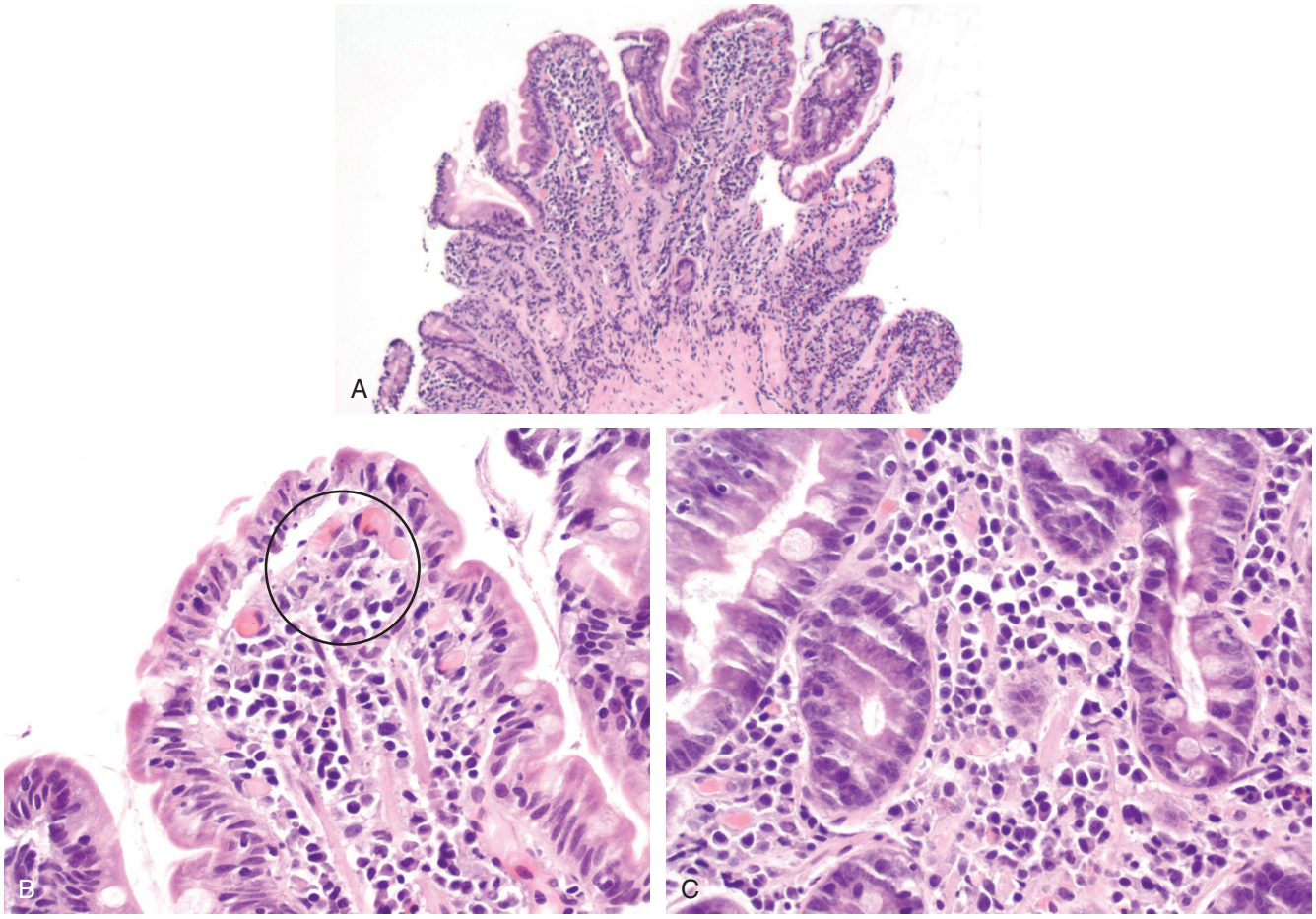

Figure 9-24. Human immunodeficiency virus (HIV) enteropathy. **A,** Small-intestinal mucosa with partial villous blunting demonstrates apoptosis within the epithelium as well as in the lamina propria mononuclear cells. **B,** A region of apoptosis is seen *(within circle)*. **C,** The lamina propria shows increased plasma cells.

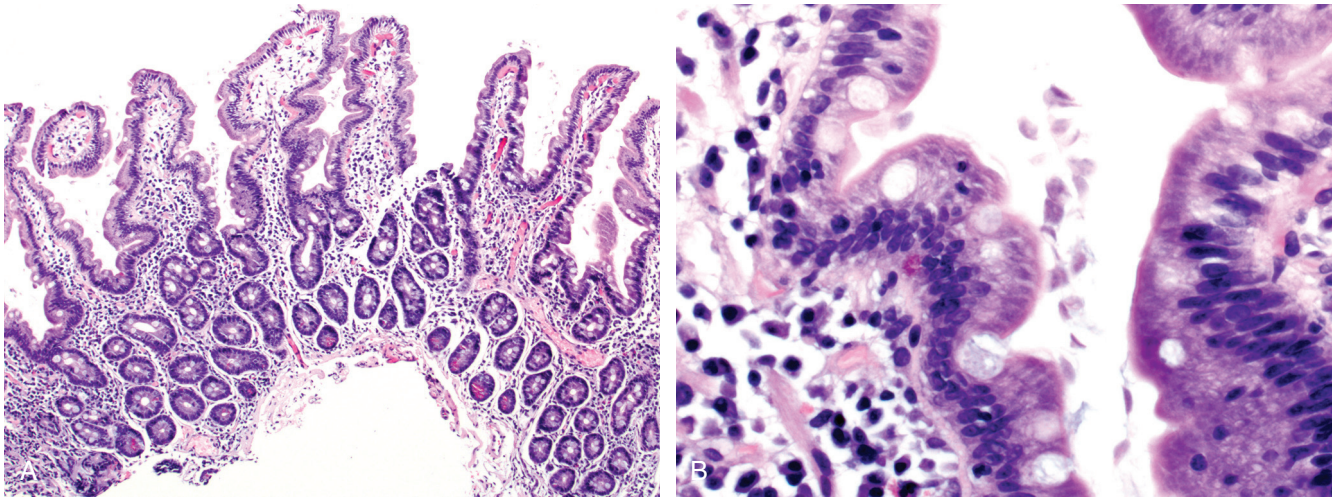

Figure 9-25. *Giardia* infection of duodenum in a patient who presented with acute onset of diarrhea after a camping trip. **A,** At low power, the duodenal mucosa is unremarkable and without significant inflammation or villous architectural distortion. **B,** High power reveals characteristic teardrop-shaped trophozoites between villi.

The cysts may be round or oval and measure 11 × 10 μm. They each have four nuclei, axonemes, and two median bodies. The trophozoites are 10 to 20 μm in length and 5 to 15 μm in width and have the shape of a teardrop when viewed from the dorsal or ventral aspect. They exhibit two identical nuclei and a ventral concave sucking disk with four pairs of flagella, two axonemes, and two median bodies.[203] Disruption and distortion of the intestinal microvilli occurs at the site where the ventral disk interfaces with the microvillus membrane.[206]

The duodenal and/or jejunal biopsies from infected patients with normal absorption demonstrate preserved villous architecture with or without signs of epithelial damage, and intraepithelial lymphocytes are not increased (Fig. 9-25). Conversely, infected patients with proven intestinal malabsorption are likely to show mild to marked villous blunting, inflammatory expansion of the lamina propria, and increased intraepithelial lymphocytes.[207-210] A flattened mucosa is rarely seen. Even without apparent histologic abnormalities, trophozoites are usually found if at least two biopsy specimens are obtained from the duodenum.[207] The organisms can be detected in gastric or ileal biopsies, and rarely in the colonic biopsies as well.[208] Nodular lymphoid hyperplasia of the small intestine may also be seen.[207] Patients whose biopsies lack lamina propria plasma cells usually have coexisting hypogammaglobulinemia.

If normal or relatively preserved villous architecture is present, the differential diagnosis includes celiac sprue (Marsh I classification), other infectious agents (e.g., postviral enteritis, cryptosporidia, bacterial overgrowth), non-gluten food sensitivity (especially in children), use of nonsteroidal anti-inflammatory drugs (NSAIDs), autoimmune disorders, immunodeficiency, and inflammatory bowel disease, among others. If the mucosa is flat, the most important differential diagnosis is celiac sprue (Marsh III), given that both conditions are often associated with intestinal malabsorption. Other diseases to consider would include tropical sprue, autoimmune enteropathy, immunodeficiency, non-gluten food sensitivity, and infectious enteritis or protracted infection of the small intestine. However, with careful review of the small-intestinal biopsies, the offending trophozoites can usually be identified.

Table 9-6 Comparison of Coccidians

Coccidians	Morphology
Cryptosporidium parvum	2-5 μm basophilic spherical bodies protruding from the apex of the enterocytes GMS negative
Cyclospora cayetanensis	8-10 μm crescent or ovoid microorganisms normally located in enterocytes but can be present at the cell surface At some stages of infection, surrounded by a parasitophorous vacuole (EM) GMS negative
Isospora belli	20-μm oval, blue enterocyte inclusions, both perinuclear and subnuclear Rarely present in the lamina propria or in macrophages At some stages of infection, surrounded by a parasitophorous vacuole (EM)
Microsporidia (*Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*)	Difficult to detect in H&E-stained sections 2-3 μm apical inclusions in the enterocytes

EM, electron microscopy; GMS, Grocott methenamine silver stain; H&E, hematoxylin and eosin stain.

Coccidians

Cryptosporidium, Microsporidium, Isospora, and *Cyclospora* have all been identified in the small intestine of AIDS patients but are also important pathogens in otherwise healthy persons, including infants and children in developing countries (Table 9-6).[211,212] Of these, microsporidia are single-celled, obligate intracellular parasites that have recently been reclassified from protozoa to fungi but will nevertheless be discussed in this

section.[213] Transmission is via the fecal-oral route, either by direct contact or through contaminated water or food.[212]

In immunocompetent individuals, infection is usually self-limited and typically lasts for a few days but may persist for up to 4 weeks. Symptoms often consist of diarrhea, abdominal pain, and malaise. Nausea, vomiting, and fever may be reported. Conversely, immunocompromised patients are at risk for severe and chronic diarrhea that may be life-threatening. Weight loss and cramping abdominal pain are proportional to the severity of the diarrhea.

Other enteric opportunistic pathogens may infect profoundly immunocompromised patients.[212] Patients with isosporiasis are likely to have peripheral eosinophilia. Endoscopic examination often shows normal intestinal mucosa or mild erythema, mucosal granularity, atrophy, and superficial erosions. Although all four coccidians primarily involve the mucosa of the small intestine, especially in the distal segment, the colonic mucosa and biliary tract can also be involved in the setting of heavy infection.[212]

Diagnosis is usually based on the examination of stool specimens. Less frequently, examination of duodenal/jejunal aspirates with special stains can establish the diagnosis. Evaluation of small bowel biopsy specimens by electron microscopy may be more sensitive than stool examination for the diagnosis of intestinal microsporidiosis (Figs. 9-26 and 9-27).[214,215] With the development of sensitive diagnostic tests (e.g., ELISA), immunohistochemistry, and PCR,[58] it is likely that low-intensity infections will be more frequently identified, with some probably of little clinical significance.[212]

In all coccidial infections, the small-intestinal mucosa shows nonspecific findings, including normal intestinal mucosa in low-density infections or intraepithelial lymphocytosis, various degrees of villous atrophy, crypt hyperplasia, and mixed inflammation in the lamina propria if the organism burden is high.[216,217] The diagnosis is based on organism morphology by light microscopy and/or ultrastructural examination of biopsy specimens. Microsporidia are difficult to detect in H&E-stained sections, but special stains such as GMS, PAS, modified acid-fast, modified trichrome, auramine, Warthin-Starry, and Brown-Brenn stains can aid greatly in the diagnosis (see Table 9-6).

Helminths

The conventional method used to diagnose gastrointestinal helminth infections is examination of stool for ova and parasites, but pathologists may at times encounter these organisms in endoscopic biopsies or in resection specimens. In this section, helminths that can affect the small intestine are briefly described.

Enterobius vermicularis (Pinworm)

Pinworms are one of the most common human parasites and tend to infest young children. They have a worldwide distribution, but they are more commonly seen in cold or temperate climates and in developed countries. The worms live and reproduce in the ileum, cecum, proximal colon, and appendix; however, pathologists are most likely to encounter them in colonic specimens, usually as an incidental finding in the appendix.

Ascaris lumbricoides

The distribution of ascariasis is worldwide, with the greatest frequency being in moist tropical climates. The mode of infection is fecal contamination of toys, soil, and fingers; contaminated raw vegetables; and drinking water. Usually. children are more vulnerable than adults to *Ascaris* infection. Patients may be asymptomatic, or they may complain of vague abdominal pain. However, massive infection with obstruction, perforation with peritonitis, appendicitis, and pancreatobiliary obstruction does occur.[218-220]

Tissue damage may be seen primarily at the sites of attachment, but adult *A. lumbricoides* in the small intestine usually produces no diagnostic lesions.[218-220] This nematode (round worm) is characterized by its large size, even in its larval form. The female worms reach lengths of greater than 30 cm; males

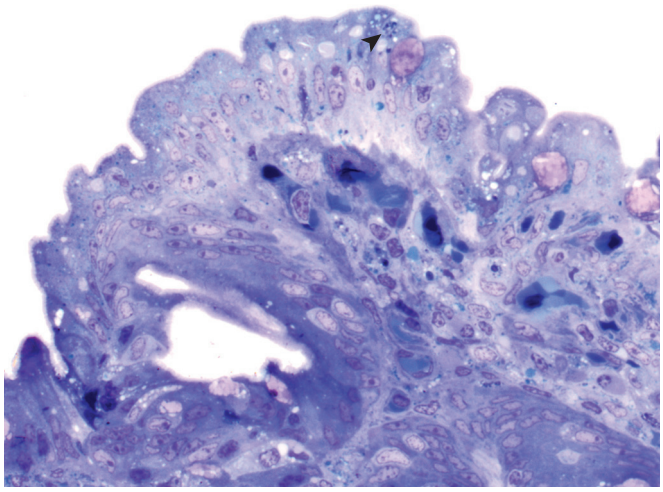

Figure 9-26. *Enterocytozoon bieneusi* infection of duodenum. A mucosal biopsy shows partial villous blunting, with the enterocytes infected with microsporidia spores *(arrowhead)* (toluidine blue stain).

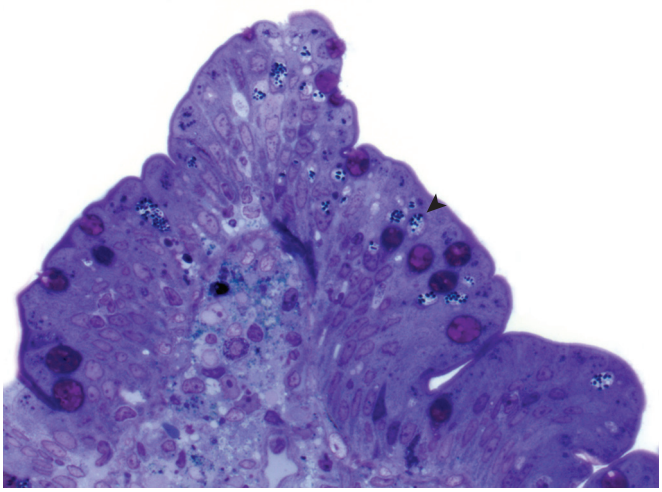

Figure 9-27. *Microspora septata intestinale* infection of duodenum. Spores are grouped in supranuclear vacuoles of enterocytes *(arrowhead)* (toluidine blue stain).

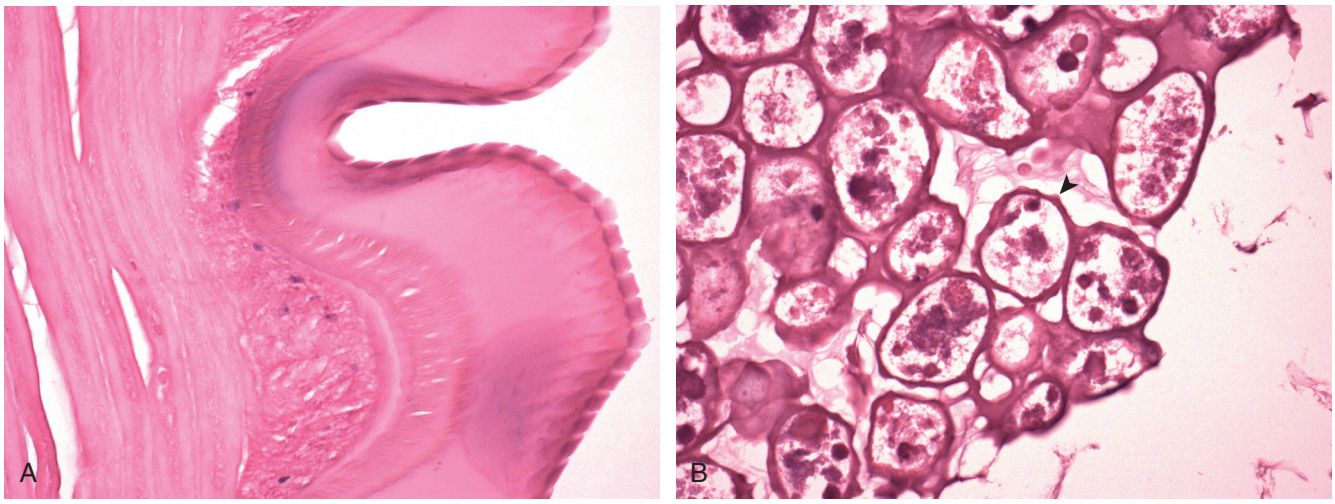

Figure 9-28. A, *Ascaris lumbricoides* with thick annulate cuticle and hypodermis. **B,** The mature ova of *Ascaris* exhibit prominent mamillations *(arrowhead).*

are somewhat smaller. The helminth displays an annulate, multilayered cuticle with prominent hypodermis and conspicuous lateral cords. The female pseudocoelem includes paired genital tubes that contain innumerable ova which, when mature, exhibit prominent mamillations (Fig. 9-28). Even if the organism is no longer viable, it can be readily identified by virtue of its size.

Ancylostomiasis (Hookworm)

The distribution of hookworm (*Necator americanus* and *Ancylostoma duodenale*) is worldwide, with particular prevalence in rural areas of the moist tropics where there is inadequate sanitation and people walk barefoot. The filariform larvae penetrate the skin of the feet or hands, enter venules, and are carried to the capillaries of the lung, where they break through the capillaries into alveolar sacs. They subsequently migrate through proximal airways to the gastrointestinal tract. Adult hookworms are creamy white, cylindrical nematodes with a large buccal capsule that includes teeth or cutting plates.[219,221,222]

The patients are usually asymptomatic, but dyspepsia, nausea, and epigastric discomfort may occur. In addition, because the worms attach to the intestinal mucosa and withdraw blood from villous capillaries, anemia may ensue if the infestation is left untreated.

Mucosal damage is usually minor, but dense eosinophilic infiltrate extending into the submucosa or villous blunting may be seen. Biopsy specimens may occasionally reveal intestinal mucosa in the buccal cavity of the worm.[219,221,222]

Strongyloides stercoralis

The distribution of *S. stercoralis* is worldwide, with the greatest prevalence in warm and wet regions. Adults, especially old, hospitalized, institutionalized, or immunocompromised individuals, are more prone than others to be infected by *Strongyloides.*

Filariform larvae penetrate the skin, enter the venous system, travel to the lung, and migrate up the proximal airways and down into the esophagus, eventually reaching the small intestine. Adult female worms parasitizing human small intestine lay eggs in the intestinal mucosa that hatch into rhabditiform larvae, which are shed in the stool. In an unfavorable environment, rhabditiform larvae transform into filariform larvae (parasitic phase). In the autoinfection cycle, rhabditiform larvae change into infective filiform larvae in the intestine or on the perianal skin and directly invade the host. This autoinfective capability leads to prolonged illness. Disseminated infection (i.e., migration of larvae to organs beyond the range of the autoinfective cycle) can occur in immunocompromised hosts and results in severe, life-threatening illness.[218,219,223-230] Systemic parasitic infection predisposes to gram-negative sepsis.

Adult female worms are 2 to 3 mm in length, with 1- to 2-μm thick cuticles and fine transverse striations. Eggs are 50 to 60 μm, oval, thin shelled, and embryonated when they exit the female. Rhabditiform larvae are 200 to 300 μm, and filariform larvae are 300 to 600 μm.[218,219,223-230]

Many patients are asymptomatic carriers, but abdominal pain, diarrhea, nausea, vomiting, anorexia, weight loss, and gastrointestinal bleeding, in any order or combination, have been reported. Ileus, small-bowel obstruction, and malnutrition also occur. Computed tomography scans occasionally reveal intra-abdominal lymphadenopathy. Gastrointestinal manifestations can be accompanied by pruritus, rash, eosinophilia, and pulmonary symptoms.[218,219,223-230]

Mucosal lesions may lead to esophagitis and gastritis in addition to duodenitis, jejunitis, ileitis, and colitis with pseudomembranous colitis. Mucosal ulceration is the most common finding in the small intestine, but it can occur at any level of the gastrointestinal tract. Histologically, the crypts are often distended by numerous larvae and adult worms (Fig. 9-29), but the organisms may be difficult to detect due to their patchy distribution. Other histologic features include villous blunting, ulcers and necrosis, edema, and a dense eosinophilic infiltrate of the lamina propria. Granulomas may also be seen.[218,219,223-230]

Capillaria philippinensis (Intestinal Capillariasis)

Although endemic in the Philippines and Thailand, cases of *C. philippinensis* have been reported in nonendemic areas.

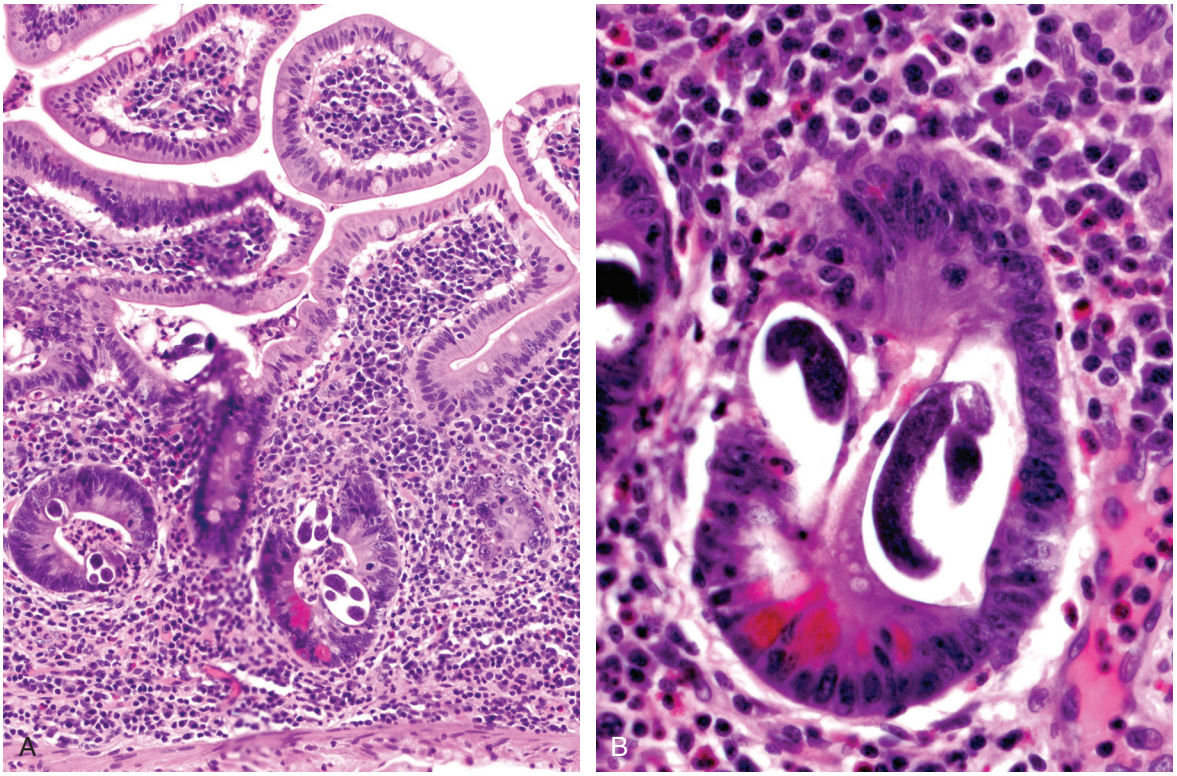

Figure 9-29. Ileum of a patient infected with the adult *Strongyloides stercoralis* **(A)** and rhabditiform larvae **(B)** in crypts.

Transmission to humans is through ingestion of freshwater fish infected by larvae. The worms inhabit both the small and large intestine. At autopsy, as many as 200,000 worms can be recovered from a liter of intestinal contents. Autoinfection is attributed to the huge numbers of the organisms.[219,221,231,232]

The female worms range in size from 2.5 to 4.3 mm, and the male worms are slightly smaller. *C. philippinensis* eggs, 36 to 45 µm long, are barrel shaped with flattened bipolar plugs. *C. philippinensis* resembles *Trichuris* and *Trichinella* species but is distinguished from them by its characteristic ova. The symptoms of infection are nonspecific and include dull gastric pain or generalized abdominal pain, as well as watery and voluminous diarrhea with an increased amount of fat. Intractable diarrhea can lead to ascites and weight loss, followed by cachexia and death. The natural course of the disease is relatively rapid, and the period between onset of symptoms and death is as short as 2 to 3 months.[219,221,231,232]

Grossly, the small intestine is thickened, congested, and distended with fluid. An extremely large number of adult worms, larvae, and ova may be seen within the jejunum, the proximal portion of the ileum, and occasionally the duodenum. Worms are most commonly found in the crypts of the small intestine, but they may also invade the lamina propria. The intestinal villi tend to exhibit secondary changes such as villous atrophy and epithelial sloughing (Fig. 9-30).[219,221,231,232]

Trematodes

Schistosomiasis is the most common disease caused by trematodes worldwide. All *Schistosoma* species cause disease, and any level of the gastrointestinal tract may be affected. However, pathologists are most likely to encounter the organisms in colonic specimens.

Fasciolopsis buski (Intestinal Fluke)

Fasciolopsis buski infection is prevalent in countries of eastern Asia and the southwest Pacific, and the highest incidence is reported in eastern China. Transmission of the fluke to humans is via ingestion of aquatic plants, such as water chestnuts, containing infective metacercariae. These encyst in the duodenum, attach to the mucosa, and mature into adult worms in about 3 months.[218,233-237]

The adult is a flat, fleshy, ovate trematode that is 2 to 7.5 cm in length (Fig. 9-31). Eggs measure 130 to 140 µm in length and are ellipsoid, with a small operculum at one end.[218,233-237] The majority of infections remain asymptomatic; however, in cases of heavy infection, patients may develop diarrhea, often alternating with constipation, epigastric pain, nausea and vomiting, and hemorrhage, secondary to intestinal obstruction and mucosal injury. Also, the absorption of parasitic metabolites can cause generalized edema, which is most striking in the face. The duodenum and jejunum are most severely affected, with the large adult worms attaching to the mucosa and inducing an intense inflammation with possible ulceration and abscess formation. Leukocytosis and peripheral eosinophilia are also frequently associated with fasciolopsiasis.[218,233-237]

Cestodes

Adult *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), and *Diphyllobothrium latum* (fish tapeworm) are

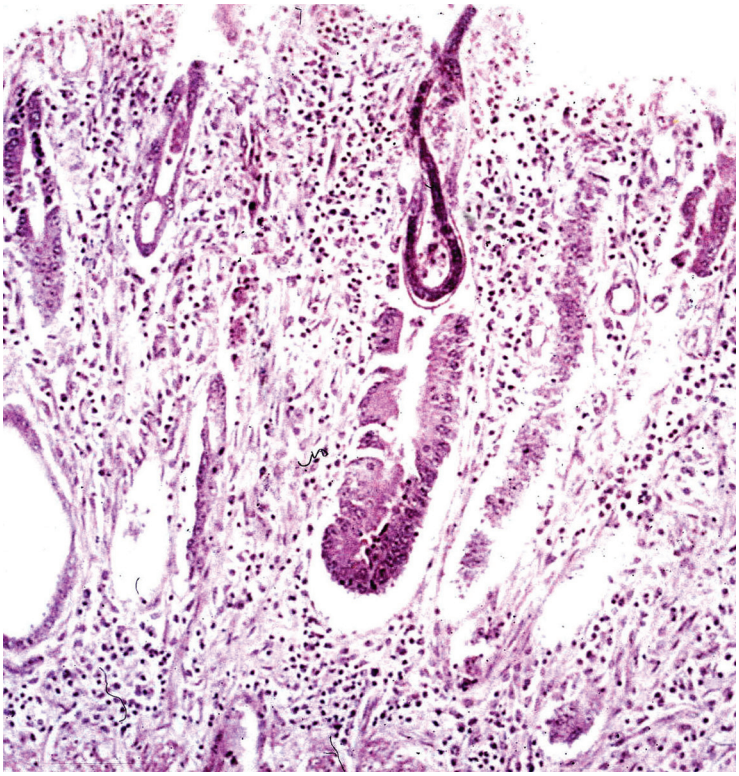

Figure 9-30. *Capillaria philippinensis.* The involved ileum exhibits villous atrophy, epithelial sloughing, and a helminth in a crypt.

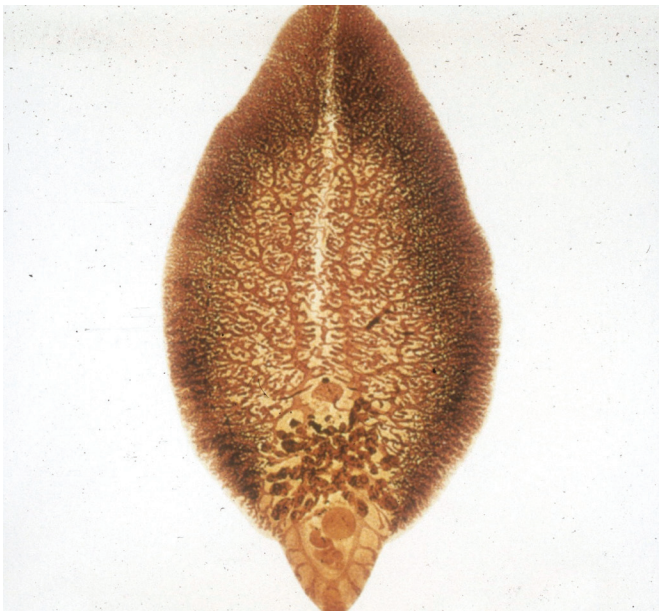

Figure 9-31. *Fasciolopsis buski* (130 to 140 μm in length).

among the largest parasites that infect humans, and they occasionally cause gastrointestinal disease. About 40% of patients with *Hymenolepis nana* (dwarf tapeworm) infection have low vitamin B_{12} levels, because the tapeworm competes with the host for the vitamin.[218,238,239]

Infectious Colitis

Although there is worldwide variation in the most common intestinal infectious agents, diseases that were once considered "tropical" are no longer diagnosed only in distant exotic places but may be encountered anywhere, as a result of international travel and migratory populations. In the West, breakdown in sanitary handling of food and contamination of poultry flocks, as well as the use of raw or partially cooked foods, have led to epidemics of infectious colitis.[240]

Infectious colitis manifests as an acute diarrheal disease frequently associated with hematochezia or microscopic evidence of blood loss. In North America, the diarrheas, commonly of bacterial etiology, are usually self-limited and are commonly referred to as "acute self-limited colitis." However, in immunodeficient patients, presentations may be severe and a benign clinical outcome less certain.

Bacteria

Common Histologic Features of Bacterial (Invasive) Colitis

In response to infection, the colonic mucosa shows remarkable histologic variability. In practice, the dilemma is to distinguish between infectious colitis and the early manifestations of chronic inflammatory bowel disease. Early in the course of infectious colitis, edema of the lamina propria with clusters of neutrophils and ectatic capillaries are the dominant findings. Established crypt abscesses are rare. Commonly, the changes are patchy, and the overall mucosal architecture is preserved. Minimal degenerative changes, limited to the upper half of the mucosa, can be

seen. These include mucin depletion and epithelial damage with flattened cytoplasm associated with cryptic dilatation. Concurrently, the inflammatory infiltrate of the lamina propria is mixed, characteristically with more neutrophils than lymphocytes and plasma cells. Microthrombi can plug dilated capillaries and can account for the focal hemorrhage of the lamina propria.

Later in the course of the infection, biopsies may show scattered neutrophils, inflammation with slightly decreased goblet cells, mucin depletion, and cellular degeneration, sometimes with vacuolization. Commonly, a mild increase in plasma cells is noted in the lamina propria, sometimes in association with lymphoid aggregates. However, a well-established dense basal lymphoplasmacytic infiltrate is uncommon. These changes habitually resolve in 2 to 3 weeks, or certainly within a trimester.[241-243]

Histologic Features Associated with Bacterial Infection

Escherichia coli

E. coli is the most prevalent aerobic bacterium of the gut. Five variants are responsible for most common diarrheal illnesses (ETEC, EPEC, EIEC, EHEC, and EAEC species).[244] The ETEC species include O157:H7, which produces a verotoxin and results in a hemorrhagic colitis with features similar to those of ischemic colitis. The diarrheogenic *E. coli* (ETEC, EAggEC, and EIEC *E. coli*) account for more than 50% of traveler's diarrhea.[245]

In North America, *E. coli* O157:H7 is the strain most commonly associated with the hemolytic and uremic syndrome. Its pathogenicity is attributable to two Shiga-like toxins (I and II). These toxins interact with a mucosal receptor in Peyer patches. Eventually, the absorbed toxins cause epithelial and endothelial damage of not only the colon but also the kidneys.[246-248] Incubation takes about 4 days, and the illness lasts about 1 week. In many cases, the disease is self-limited, with minimal or even no diarrhea.

Those who develop a colitis may show various endoscopic appearances, ranging from normal mucosa to edema, erosion, and pseudomembranes. The histologic findings include overlapping features of both ischemic colitis and infectious colitis. Submucosal edema, hemorrhage, pseudomembranes, and withering crypts are seen, along with marked inflammatory infiltrate and cryptitis (Fig. 9-32).[249,250]

Aeromonas

Members of the bacterial genus *Aeromonas* produce a wide area of virulence factors and have been associated with cases of gastroenteritis, particularly in young children. Chronic symptoms also have been reported.[251]

Campylobacter

Campylobacter bacteria rank among the most common causes of infectious diarrhea. Most infections are self-limited cases of simple diarrhea, occasionally associated with systemic symptoms, but severe infections can occur. Domestic animals, particularly poultry, are reservoirs of infection, and the organism is primarily transmitted by the fecal-oral route. Infections peak in summer and early fall and generally result from ingestion of contaminated food or water.

Campylobacter jejuni, the most important species, produces typical infectious colitis that lasts from 1 to 7 days. The symptoms usually begin with a prodrome of fever, headache, and myalgias 12 to 24 hours before the onset of gastrointestinal symptoms. Colitis is reported in up to 80% of infections. Colonoscopic findings are nonspecific and range from segmental ulceration to diffuse colitis.[252] Organisms may be seen in the lamina propria by ultrastructural analysis, and granulomatous changes with giant cells may also occur. On biopsy, a focal active colitis is observed.[253] Rare cases produce changes mimicking ulcerative colitis.[252] Complications include toxic megacolon and the development of Guillain-Barré syndrome.[254,255]

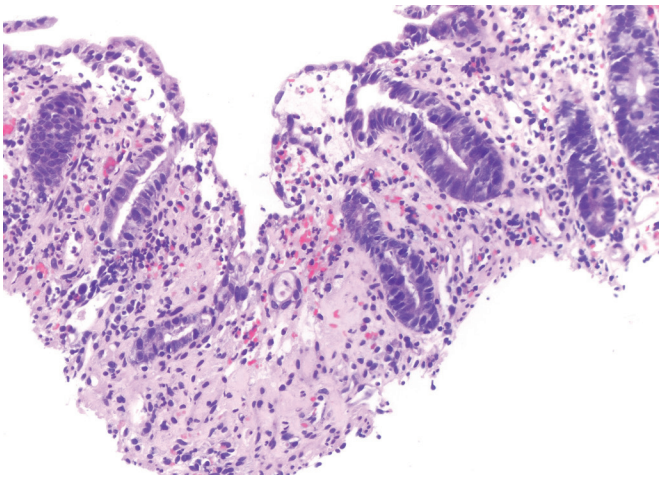

Figure 9-32. Colitis associated with *Escherichia coli* O157:H7 infection. The histology shows evidence of ischemic colitis with hyalinized stroma and withering crypts.

Shigella

The enteroinvasive *Shigella* bacteria cause mucosal changes resembling those of chronic inflammatory bowel disease.

Salmonella

Salmonella species are associated with a common form of infectious diarrhea. Classic typhoid fever due to *S. typhi* is primarily an ileal disease (see earlier discussion). However, nontyphoid salmonellosis may involve the colon as well.

At endoscopy, a wide range of nonspecific changes are seen. These include mild edema with petechial hemorrhage and, in severe cases, friability and ulceration. The histologic changes are indistinguishable from other types of bacterial diarrhea and some inflammatory bowel diseases, especially if the specimens were obtained early in the course of inflammatory bowel disease. Complications include the occasional development of toxic megacolon (Fig. 9-33).

Clostridium difficile

C. difficile is a gram-positive bacillus that produces two principal toxins that play a role in pathogenesis of disease. Toxin A is an enterotoxin responsible for food accumulation in the gut and for damage to the enterocolonic mucosa; toxin B is a labile motility-altering cytotoxin that leads to food accumulation.

The spectrum of *C. difficile* colitis ranges from asymptomatic carriage to fulminant colitis. The presence of *C. difficile*

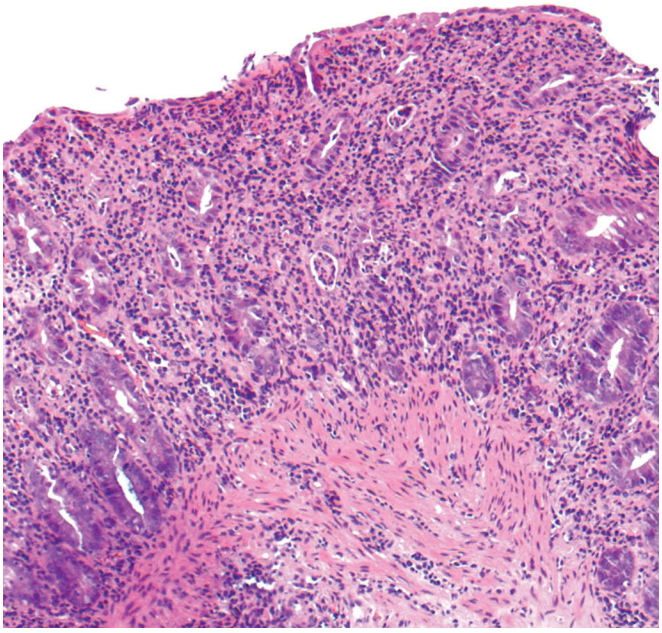

Figure 9-33. Colitis associated with *Salmonella typhi* infection. The lamina propria is moderately expanded by mixed lymphoplasmacytic infiltrate, as well as scattered neutrophils. Cryptitis is present as well. The morphologic features are not specific.

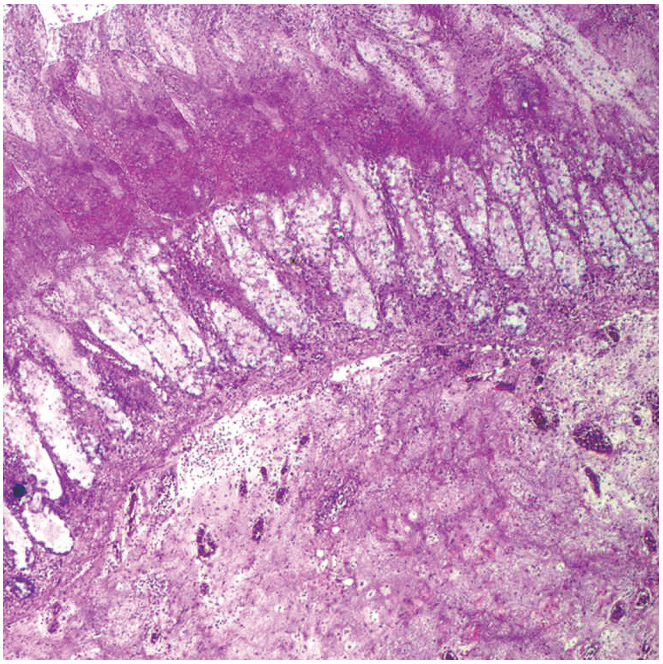

Figure 9-34. Low-power view of specimen from a patient with *Clostridium difficile*–associated pseudomembranous colitis characterized by edema of the submucosa and destructive changes of the mucosa.

infection has been steadily increasing in recent years, particularly among institutionalized patients, and it currently represents a major cause of hospital-acquired diarrhea. *C. difficile* infection is also prevalent in patients with inflammatory bowel disease (particularly ulcerative colitis) who are receiving maintenance immunomodulation therapy, and it is associated with exacerbation of the disease. It appears to play a minor role in sporadic diarrhea. It is well established that *C. difficile* infection follows exposures to antibiotics targeting gut anaerobes, and transmission occurs nosocomially from one host to another.

Toxigenic *C. difficile* is responsible for more than 90% of cases of pseudomembranous colitis and 30% to 40% of cases of antibiotic-associated colitis. The diarrhea usually begins within a few days after antibiotics are started. Some patients develop pseudomembranous colitis, whereas others suffer only mild diarrhea.

Pseudomembranous colitis due to *C. difficile* shows a spectrum of histologic changes, beginning with mild lesions that exhibit a luminal spray of mucus and neutrophils above a background mucosa with minimal inflammation. More advanced disease shows marked inflammatory erosion of the lamina propria covered by a fibrinopurulent cap and cystification of crypts. Finally, mucosal inflammation and erosion extends to form confluent pseudomembranes. In some patients, toxic megacolon ensues.[256] In this setting, the finding of signet-ring cells should not be mistaken as indicating a carcinoma (Figs. 9-34 through 9-36).[257] The standard for diagnosis of *C. difficile* is a toxin test that is positive in more than 90% of patients with classic histologic changes of pseudomembranous colitis.

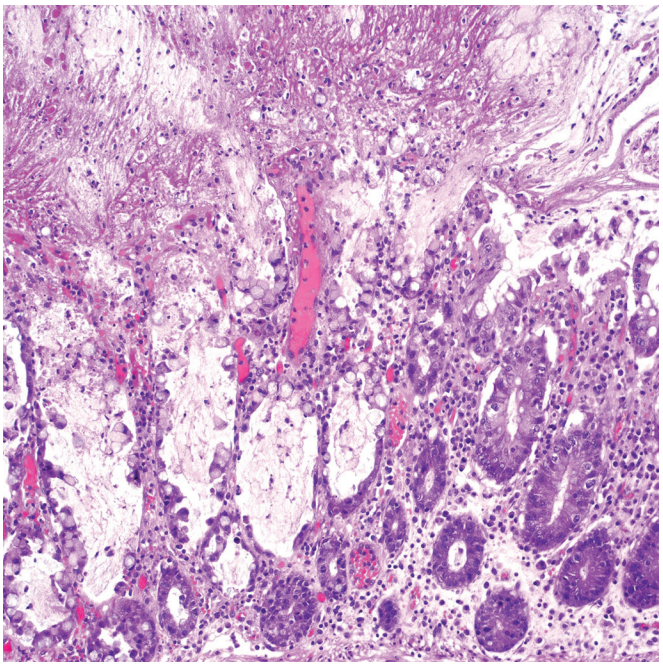

Figure 9-35. At higher power, *Clostridium difficile* pseudomembranous colitis is characterized by sloughing off of superficial epithelial cells. The coating of fibrinopurulent material creates a pseudomembrane.

Yersinia

Y. enterocolitica and *Y. pseudotuberculosis* are gram-negative aerobic coccobacilli. The latter species causes colitis that usually involves the terminal ileum and mesenteric lymph nodes (see earlier discussion). In *Y. enterocolitica*–associated acute colitis, the mucosa is erythematous and friable, with tiny superficial ulcerations. Granulomas are absent, but aggregates of histiocytes are frequently seen.

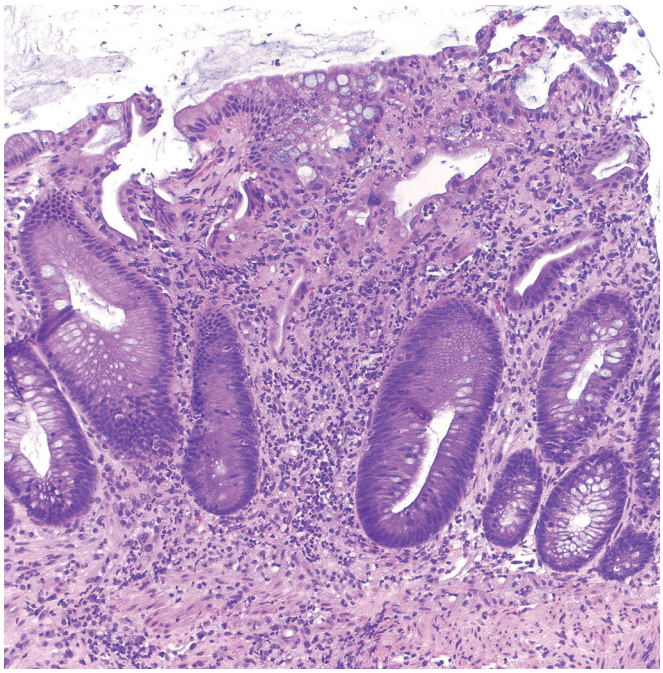

Figure 9-36. Colitis in a patient with a positive toxin test for *Clostridium difficile* colitis but no evidence of pseudomembrane formation. Nonspecific degenerative changes of the surface epithelium, neutrophils, and mild expansion of the lamina propria are present.

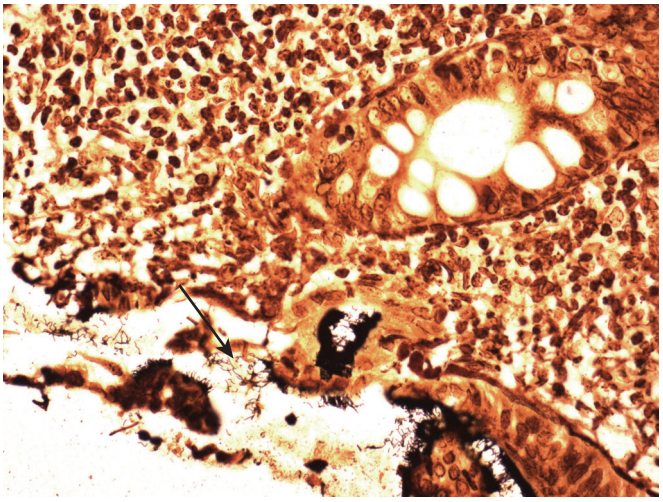

Figure 9-37. Intestinal spirochetosis. With Warthin-Starry stain, numerous tangled spirochetes are seen distributed along the apical surfaces of the mucosa *(arrow)*.

Mycobacterium tuberculosis

Tuberculosis of the colon, which is increasing in prevalence due to global travel, is essentially limited to the ileocecal region. Most patients have concomitant pulmonary tuberculosis. The tubercle bacillus can reach the gastrointestinal tract by several routes, including swallowed sputum, infected food, adjacent tissues, lymphatic spread, and via the bloodstream. Colonoscopy can be challenging, given the presence of ulceration and hypertrophic polypoid masses. Ulcerative, hyperplastic, and sclerotic variants may be seen. The differential diagnosis includes ileocecal Crohn disease and carcinoma.[258]

Biopsies reveal mucosal ulceration, granulation tissue, and microabscesses. Characteristic necrotizing granulomas are usually seen in the ulcer bed. The granulomas in tuberculosis are much larger than those seen in Crohn disease. They are confluent, and caseation is a common feature. AFB are demonstrated in 35% to 60% of cases. If *M. tuberculosis* is suspected, acid-fast staining of tissues and cultures is required to establish the diagnosis, and the recent development of PCR technology can increase the diagnostic yield.

Intestinal Spirochetosis

The prevalence of intestinal spirochetosis in rectal biopsies is between 2% and 7% in the West but between 11% and 34% in developing countries. Homosexual men and HIV-infected patients are reported to have the highest prevalence (up to 54%).

Whether the organism is of clinical significance or is a commensal bacterium has been debated. Colonoscopy reveals mucosal erosions and hyperemia. Histologically, the irregular luminal aspect of the surface epithelium seen on H&E-stained sections is emphasized by PAS or Warthin-Starry stains. Ultrastructural analysis also identifies the spirochetes. The disorder is most frequently seen in the right colon.[259] The spirochetes or brachyspira, *Brachyspira aalborgi* and *Brachyspira pilosicoli*, are found between and parallel to the microvilli and do not penetrate the cytoplasm in most cases (Fig. 9-37). Mild inflammation may be seen in colonic biopsies. Improvement of symptoms and decrease in immunoglobulin E plasma cells within the lamina propria has been observed after treatment with metronidazole. Cases of severe colitis are rare but have been reported.[260,261]

Viruses

Many viruses, including rotavirus, enteric adenovirus, calicivirus, astrovirus, CMV, herpesvirus, and adenovirus can produce colitis. CMV, adenovirus, and HSV are considered here, as the only ones that are likely to be identified on endoscopic biopsies. A wide array of changes, from normal or edematous mucosa to ulcerative colitis, may be seen (Fig. 9-38).

Although CMV infection is usually subclinical, symptoms are common in immunologically suppressed patients, such as patients with AIDS, cancer patients undergoing chemotherapy, transplant recipients, and patients with inflammatory bowel disease.[262,263] CMV colitis can be recognized by the presence of ulceration with or without colitis. The diagnosis of CMV infection depends on the identification of characteristic intranuclear inclusions. Typically, infected cells show endothelial, stromal, or epithelial nuclear and cytoplasmic enlargement with a single, dark red, amphophilic nuclear "bull's-eye" inclusion. However, it is not uncommon for infected cells to show indistinct, smudged, hematophilic nuclei. The cytoplasm of the infected cells can show either granular inclusion or a foamy appearance. The diagnosis can be rendered difficult by granulation tissue arising secondary to the ulceration and the reactive stromal cells. Immunohistochemistry allows a diagnosis to be made in atypical cases.[264]

HSV is a common cause of proctitis in male homosexual patients, in AIDS patients, and in other immunosuppressed indi-

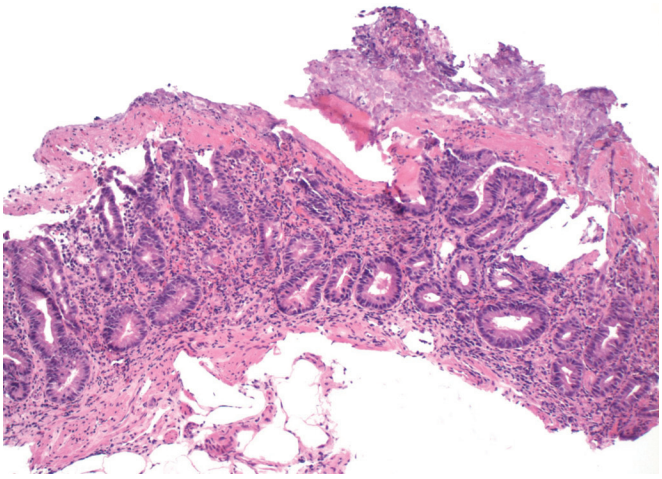

Figure 9-38. Amebiasis of the rectum. The colonic mucosa is moderately inflamed and shows a surface erosion with fibrinopurulent material.

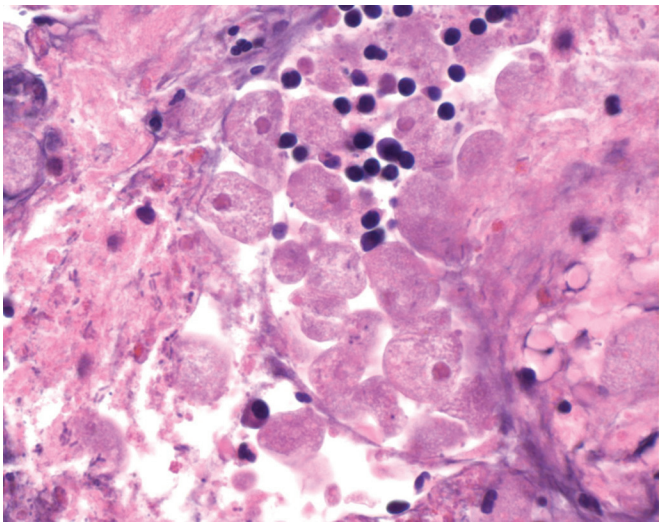

Figure 9-39. Amebiasis of the rectum. Higher magnification shows numerous *Entamoeba histolytica* distributed along the surface epithelium.

viduals. The ulcerations commonly demonstrate peripheral giant cells. Nonspecific cases of severe acute colitis with widespread ulceration have been reported.[265]

Adenovirus is believed to be a common cause of diarrhea in children and patients with HIV infection. Infected vacuolated epithelial cells are found close to the mucosal surface, with amphophilic nuclei that can be either enlarged or crescent-shaped, and the presence of virus can be confirmed by immunocytochemistry. Small intranuclear inclusions are also visible.

Protozoa

The diagnostic identification of protozoa is best done by examination of fresh stool. There is no characteristic histologic pattern on biopsy, and the organisms are usually overlooked on sections unless a careful inspection is made.

Amebiasis

Entamoeba histolytica is found in all climates. Infection is acquired via fecal contamination and ingestion of cysts. In the West, a history of foreign travel to areas of poor sanitation is common, although sexually transmitted cases have been recognized. Infected individuals may present with various symptoms, including toxic megacolon. The range of symptoms is explained in part by the existence of 22 different zymodemes.

Early in infection, edema and nonspecific inflammation with clusters of neutrophils are seen in the lamina propria and surface epithelium. The amebas may be present on the surface, usually in the overlying inflammatory exudate. With time, a large, flask-shaped ulceration may develop. The epithelium shows goblet cell depletion and microulceration with organisms in the exudate overlying the denuded lamina propria (Fig. 9-38). Although there are numerous neutrophils in the lamina propria, crypt abscesses are not conspicuous, and tissue eosinophilia is not a feature.

Deep necrosis with ulceration extending to the submucosa can be seen in severe cases. The mucosa is replaced by a thick, amorphous inflammatory fibrinoid material with abundant organisms and scattered inflammatory cells. The infective trophozoites are at times substantially larger (10-60 μm) than macrophages, display foamy amphophilic cytoplasm with ingested erythrocytes, and sport a punctate central karyosome (Fig. 9-39). The PAS stain aids in recognition of the amebas but obscures the presence of the diagnostic karyosome and ingested erythrocytes. Of note, antidiarrheal preparations can destroy the protozoa and should be avoided before biopsy. Current diagnostic tools include antigen detection in stool and PCR (Fig. 9-39; see Fig. 9-38).[266]

Coccidia

Coccidia is a collective name for the suborder that includes other human pathogens such as *Isospora*, *Sarcocystis*, and *Toxoplasma*. The diagnosis of these intracellular pathogens is difficult to evaluate on colorectal biopsy. *Cryptosporidium parvum* can be seen in immunocompromised as well as normal subjects, but with a markedly different clinical presentation. The former may present with severe diarrhea, sometimes with toxic megacolon. In the setting of AIDS, several other microorganisms are frequently associated. In immunocompetent individuals, *C. parvum* infection usually manifests as a self-limited, flu-like gastroenteritis; it has also been noted as a cause of traveler's diarrhea.

On biopsy, a nonspecific inflammatory infiltrate and rare ulceration are seen. Cryptosporidia are observed as clusters of tiny hematoxylin dots on the epithelial surface or within the crypt. PAS, silver, or Giemsa stain is also helpful in highlighting the organisms (Fig. 9-40).

Other Protozoan Infections

Giardiasis is more commonly recognized in the small bowel, but rare cases of colonic infection have been documented.

Balantidium coli is a ciliated protozoan. Patients are infected through contact with pigs or rats under conditions of poor

personal hygiene. After ingestion of cysts, the trophozoite resides predominantly in the colon. The mucosal lesions are similar to those of amebiasis. Symptoms may include acute diarrhea, fulminant colitis, and perforation. Asymptomatic carriers are recognized.[267]

Helminths

Three classes of helminths can lead to human infection: trematodes (flukes), nematodes (roundworms), and cestodes (tapeworms). Only schistosomiasis leads to colorectal infestation.

Schistosoma mansoni and *Schistosoma japonicum* are the two common trematode worms affecting the colon. The adults reside in the major mesenteric veins, and the disease is caused primarily by an inflammatory reaction to the eggs. The rectal mucosa and submucosa are a good location for identification of *S. mansoni* eggs, whereas those of *S. japonicum* are generally seen in the right colon. The presence of miracidial nuclei indicates that organisms are viable. The ova of *S. mansoni* are characterized by subterminal spines, whereas the eggs of *S. japonicum* have ill-defined subterminal knobs. The eggs are usually surrounded by inflammatory infiltrate in which eosinophils predominate. A granulomatous reaction may develop. In some cases, the eggs are surrounded by an eosinophilic zone of fibrin material, representing an antigen-antibody complex. With time, fibrosis develops around the calcified ova. The lateral spine of *S. mansoni* and the cortical shell stain variably with modified AFB stain; unlike paragonimiasis, the ova are nonrefractile. In countries with endemic infection, the entire colon may become fibrotic, studded with polyps and ulcers. There is an increased incidence of adenocarcinoma in these patients (Figs. 9-41 and 9-42).[268,269]

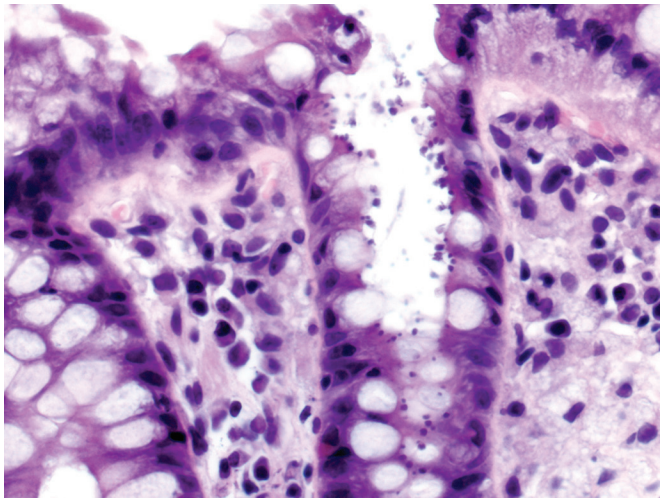

Figure 9-40. *Cryptosporidia parvum* infection in an immunosuppressed patient. The organisms coat the surface epithelium and should not be mistaken for extruded mucin globules.

Strongyloidiasis, trichuriasis, and oxyuriasis are common nematode infestations of the lower gastrointestinal tract. Although *S. stercoralis* is usually restricted to the small intestine, migratory larvae can implant in the colonic mucosa, leading to autoinfection, particularly in the setting of massive infestation. The parasites are found in crypts and superficial mucosae, usually surrounded by transmural eosinophilic inflammation.[270]

Trichuris trichiura (whipworm) preferentially infests the cecum. The body structure of the worm is unique. The anterior three fifths of the worm is threadlike and embeds into the mucosa, whereas the remainder of the organism floats within the lumen. The esophagus shows a characteristic stichosome, and the anterior wall shows characteristic bacillary bands. The posterior part of the worm exhibits the reproductive organs (Fig. 9-43). *Trichuris* causes chronic dysentery. On biopsy, the worm is usually surrounded by an intense focal eosinophilic infiltrate.

Oxyuriasis, or *Enterobius vermicularis*, is the most prevalent parasitic helminth recognized in the West. The adult pinworm attaches to the cecal mucosa, and the worm is commonly

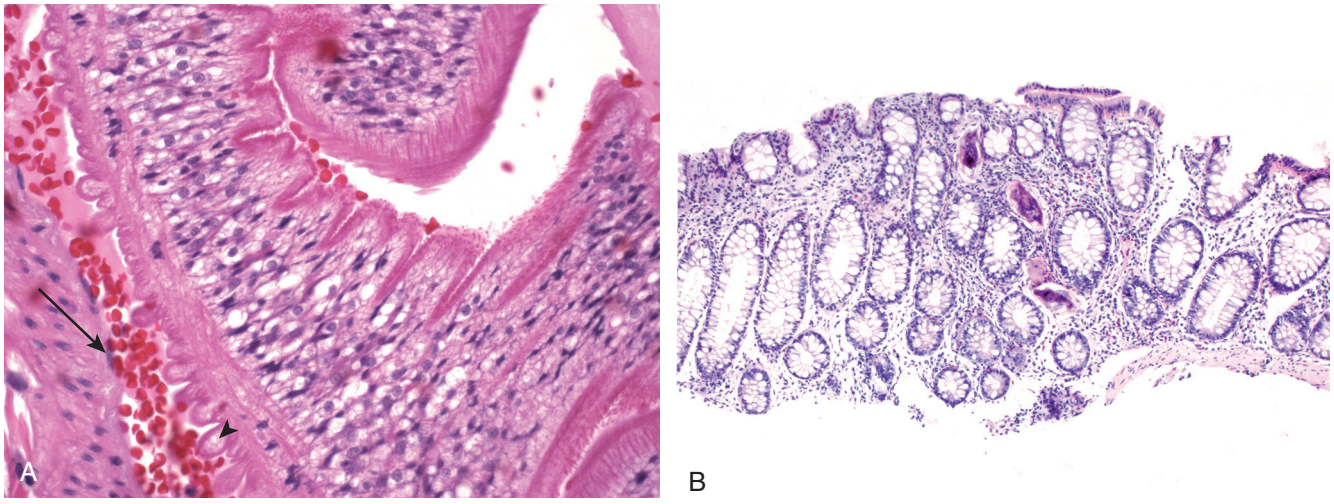

Figure 9-41. A, The tuberculated tegument *(arrowhead)* of an adult male *Schistosoma mansoni* lodged within a mesenteric vein *(arrow).* **B,** Low-power magnification demonstrates degenerating ova within the rectal mucosa.

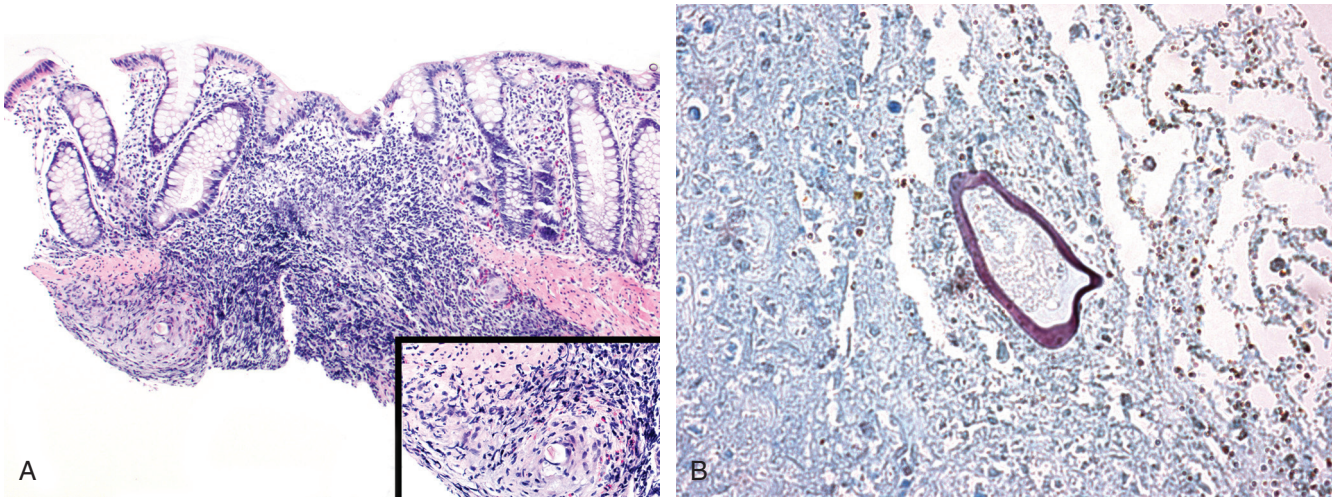

Figure 9-42. A, Colonic schistosomiasis characterized by an ill-formed submucosal granuloma. The inset demonstrates the terminal spine with surrounding ill-formed granulomatous reaction. **B,** A Fite stain highlights the cortex and lateral spine of *Schistosoma mansoni*.

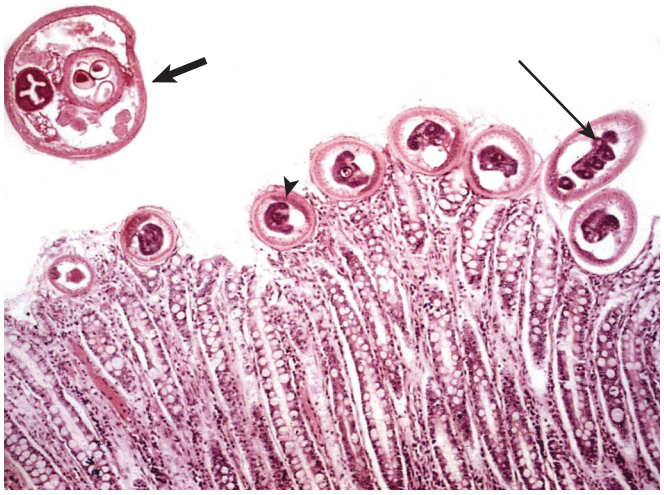

Figure 9-43. *Trichuris trichiura*. The anterior portion of the nematode with stichosome *(arrow)* and bacillary band *(arrowhead)* is embedded in the superficial mucosa, while the posterior two thirds of the helminth containing the sexual organs projects into the bowel lumen *(broad arrow)*.

observed in the lumen of the appendix. Symptoms result from the nocturnal migration of the adult female; she lays eggs on the perianal skin, causing intense pruritus. Diagnosis is classically established by adhering the deposited ova to cellophane tape and examining them under the microscope. Refractile ova are characteristically flattened on one side. The helminth is small, shows a muscular wall, and exhibits prominent lateral alae projecting from the cuticle throughout its length. The central oviducts contain the characteristic flattened eggs. The surrounding mucosa is generally inflamed, and tissue eosinophilia may be present (Fig. 9-44). Inflammatory reaction may produce a presenting polyp or even a mass, sometimes mistaken for a carcinoma.[271] Aberrant migration can lead to similar lesions in the vagina and bladder.

Fungi

Fungal infections of the large bowel are rare. They are commonly opportunistic infections of immunocompromised hosts, although in some regions, histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis are endemic. *Histoplasma* is the organism most likely to involve the gut, and the diagnosis depends on identification of the fungus on biopsy. This is best achieved with silver stains. The dimorphic fungus is most often represented in its yeast form, but mycelial growth may be present. The mass mimics carcinoma, from which it must be distinguished.

Sexually Transmitted Diseases

Proctitis is common in homosexual men and is frequently related to infection by *Neisseria gonorrhoeae*, *Treponema pallidum*, chlamydia, or HSV.[272] The symptoms of gonorrhea, caused by the gram-negative diplococcus *N. gonorrhoeae,* vary from pruritus to severe proctitis and diarrhea. Biopsies frequently are not diagnostic and show either normal mucosa or nonspecific inflammatory change. Fewer than 5% of patients show infectious proctitis.[273]

Secondary syphilis can manifest as proctitis. The changes include marked inflammation, in which small granulomas with giant cells are usually prominent.[272] *Chlamydia trachomatis* is an obligate intracellular bacterium that ranks among the most common causes of sexually transmitted clinical proctitis.[272]

Lymphogranuloma Venereum

In acute cases of lymphogranuloma venereum, the mucosa shows a mixed inflammatory infiltrate. Giant cell granuloma can be seen in association with disrupted crypts. A common differential diagnosis is ulcerative colitis, and the diagnosis is confirmed by immunofluorescent methods. The inflammatory infiltrate may be transmural or may give a pattern of follicular proctitis. Strictures and adenocarcinoma have been reported in chronic infection.

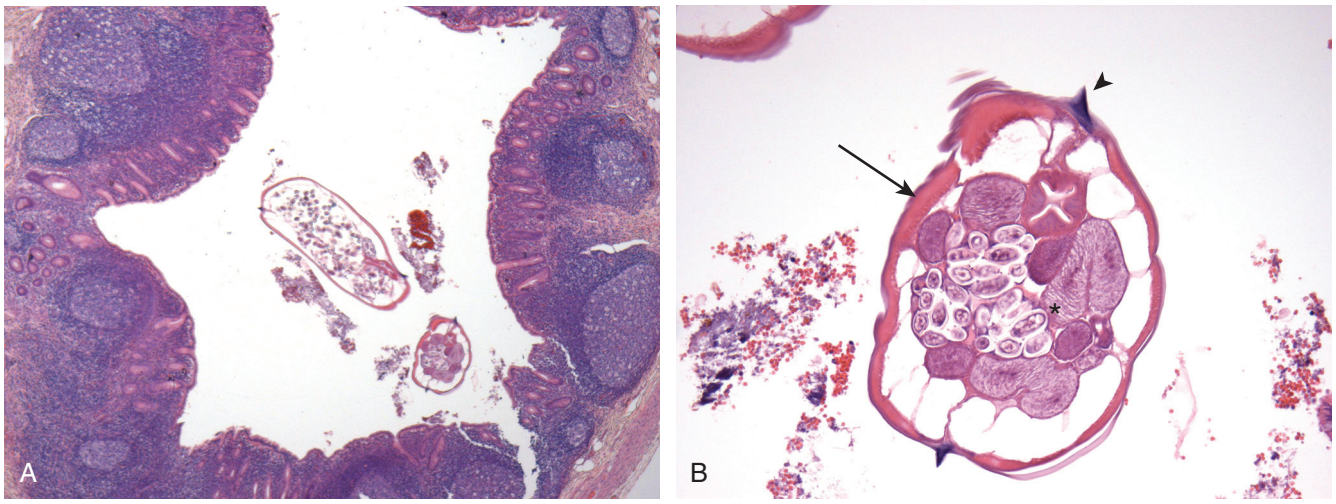

Figure 9-44. A, *Enterobius vermicularis* within the appendiceal lumen. **B,** The helminth shows prominent lateral alae *(arrowhead)*, platymyarian muscle *(arrow)*, and flattened refractile ova *(asterisk)*.

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