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CHAPTER 4

Infectious Disorders of the GI Tract

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GI infections are a major cause of morbidity and mortality worldwide. As the number of transplant patients and those with other immunocompromising conditions increases, and as global urbanization and transcontinental travel become more frequent, the surgical pathologist must be familiar with infectious diseases that were once limited to tropical regions of the world, or the realm of esoterica.

The goal of the surgical pathologist in evaluating GI specimens for infectious colitis is twofold. First, acute self-limited processes and infectious processes must be differentiated from chronic idiopathic inflammatory bowel disease (ulcerative colitis or Crohn's disease). Second, dedicated attempts must be made to identify the specific infecting organisms.[1] In recent years, the surgical pathologist's ability to diagnose infectious processes in tissue sections has grown exponentially with the advent of new histochemical stains, immunohistochemistry, in situ hybridization, and polymerase chain reaction (PCR) analysis. As these techniques have developed, our knowledge of the specific histologic patterns of inflammation related to various organisms has also increased.

Most enteric infections are self-limited. Patients who undergo endoscopic biopsies generally have chronic or debilitating diarrhea or systemic symptoms, or they are immunocompromised. A discussion with the gastroenterologist regarding symptomatology and colonoscopic findings, as well as knowledge of travel history, food intake (such as sushi or poorly cooked beef), sexual practices, and immune status, can aid immeasurably in evaluation of biopsies for infectious diseases.

Viral Infections of the GI Tract

The type of viral infection and the manifestations of disease vary with the site of infection and the immune status of the patient.

CYTOMEGALOVIRUS

Clinical Features

Cytomegalovirus (CMV) infection may develop anywhere in the GI tract, from mouth to anus, in both immunocompromised and immunocompetent persons. CMV is best known as an opportunistic pathogen in patients with a suppressed immune system, including those with AIDS, and after solid organ or bone marrow transplantation.[2] Primary infections in healthy persons are generally self-limited. Symptoms vary with the immune status of the patient and the site of infection. The most common clinical symptoms are diarrhea (either bloody or watery), abdominal pain, fever, and weight loss.[2] A rare, but important, entity associated with pediatric CMV infection is hypertrophic gastropathy and protein-losing enteropathy resembling Ménétrier's disease.

In addition, secondary CMV may be superimposed on chronic GI diseases, such as ulcerative colitis and Crohn's disease. In such cases, CMV superinfection is associated with exacerbations of the underlying disease, steroid-refractory disease, toxic megacolon, and a higher mortality rate. In fact, some authorities recommend immunohistochemical evaluation for CMV as part of the routine evaluation of biopsies in patients with steroid-refractory ulcerative colitis.[3]

Pathologic Features

CMV causes a remarkable variety of gross lesions. Ulceration is the most common. Ulcers may be single or multiple, and either superficial or deep. Segmental ulcerative lesions and linear ulcers may mimic Crohn's disease. Other gross lesions include mucosal hemorrhage, pseudomembranes, and obstructive inflammatory masses.

The histologic spectrum of CMV infection is varied, ranging from minimal inflammation to deep ulcers with prominent granulation tissue and necrosis (Fig. 4-1A). Characteristic "owl's eye" viral inclusions may be seen on routine H&E preparations and can be either intracytoplasmic or intranuclear (see Fig. 1B). Inclusions are

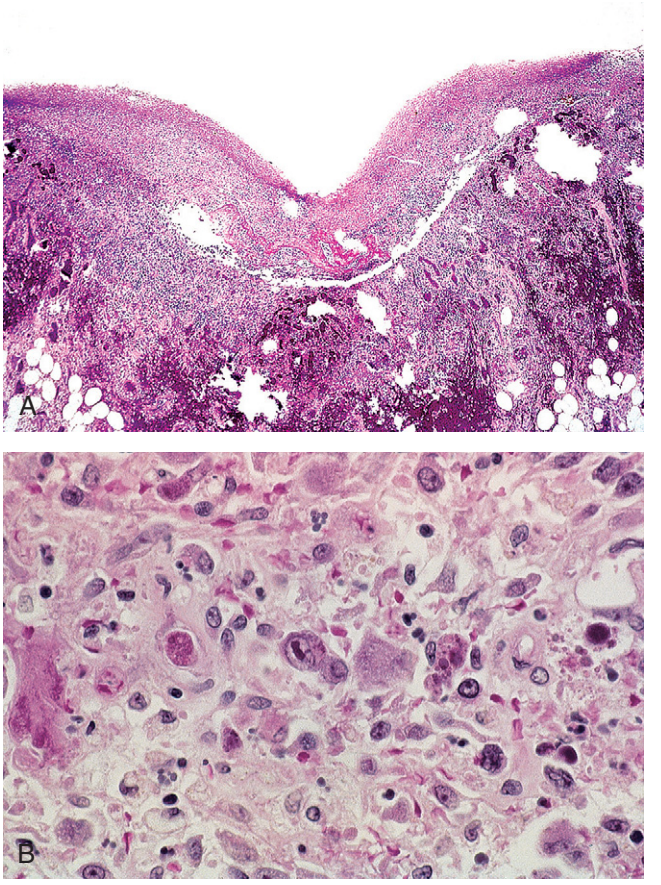

FIGURE 4-1 A, Colonic ulcer caused by cytomegalovirus with granulation tissue and necrosis at the base. **B,** Characteristic "owl's-eye" inclusions are seen in endothelial cells in the ulcer base.

preferentially found in endothelial cells and stromal cells, and only rarely in epithelial cells. Unlike adenovirus and herpes, CMV inclusions are often found deep in ulcer bases rather than at the edges of ulcers or in the superficial mucosa. Adjacent nuclei may be enlarged, appear smudged, or have a ground-glass appearance, but they lack typical inclusions. Associated histologic features include cryptitis, a mixed inflammatory infiltrate usually including numerous neutrophils, and mucosal ulceration.[2] Crypt abscesses, crypt atrophy and loss, and numerous apoptotic enterocytes may be seen as well.[4] Characteristic inclusions, with virtually no associated inflammatory reaction, may occur in immunocompromised patients.

In biopsy specimens, the diagnosis may be easily missed when only rare inclusions are present. Examination of multiple levels, and use of immunohistochemistry, may be invaluable in detecting the rare cells containing an inclusion. Other diagnostic aids include viral culture, PCR assays, in situ hybridization, and serologic studies and antigen tests. Isolation of CMV in culture, however, does not imply active infection, as virus may be excreted for months to years after a primary infection.[2]

Differential Diagnosis

The differential diagnosis of CMV includes primarily other viral infections, particularly adenovirus.[5] Adenovirus inclusions are usually crescent shaped, generally located in surface epithelium, and only intranuclear in location. CMV inclusions have an "owl's eye" morphology, are generally located in endothelial or stromal cells, and exist in either the nucleus or cytoplasm. The ballooning degeneration phase of adenovirus infection, just before cell lysis, most closely resembles CMV.

Distinction between CMV infection and graft-versus-host disease in bone marrow transplant patients may be particularly difficult, because the clinical and histologic features are similar. Immunohistochemistry or in situ hybridization studies should be used to rule out CMV infection in this setting, because failure to identify CMV infection could result in delay of antiviral therapy.[4] Furthermore, these conditions may coexist. Graft-versus-host disease is favored when there is abundant apoptosis associated with crypt necrosis and dropout, in the setting of minimal inflammation. The presence of viable nests of endocrine cells favors graft-versus-host disease.

HERPESVIRUS

Clinical Features

Herpetic infection may occur throughout the GI tract but is most common in the esophagus and anorectum. Although herpes infections of the gut are often seen in immunocompromised patients, they are not limited to this group.

Patients with herpetic esophagitis present with odynophagia, dysphagia, chest pain, nausea, vomiting, fever, and GI bleeding. Many have disseminated herpes infection at the time of diagnosis.[6] Herpetic proctitis is the most common cause of nongonococcal proctitis in homosexual men. Patients generally present with severe anorectal pain, tenesmus, constipation, discharge, hematochezia, and fever. Concomitant neurologic symptoms (difficulty in urination and paresthesias of the buttocks and upper thighs) are also well described, as is inguinal lymphadenopathy.[6]

Pathologic Features

Ulcers are the most common gross finding in the esophagus, and these are usually associated with an exudate. However, many patients have a nonspecific erosive esophagitis. In herpetic proctitis, the presence of perianal vesicles is common. Proctoscopic findings include ulceration and mucosal friability. Vesicles are occasionally seen in the rectum or anal canal.[6,7]

Typical histologic findings, regardless of site, include focal ulceration, neutrophils in the lamina propria, and an inflammatory exudate that often contains sloughed epithelial cells (Fig. 4-2A). In the anorectum, perivascular lymphocytic cuffing and crypt abscesses may be seen as well. Characteristic viral inclusions and multinucleate giant cells are present in only a minority of biopsy specimens (Fig. 4-2B).[7] The best place to search for viral inclusions is in the squamous epithelium at the edges of ulcers and in sloughed cells in the exudate. Viral culture is the most valuable diagnostic aid. Immunohistochemistry and in situ hybridization are also specific.

Differential Diagnosis

The differential diagnosis predominantly includes other viral infections including CMV and varicella-zoster, which may also infect the GI tract.[8] Mixed infections are common in many situations in which herpetic infection is found. In immunocompetent patients, herpetic infection is often self-limited; immunocompromised persons may be at risk for dissemination and life-threatening illness.

ENTERIC VIRUSES

Some common enteric viruses known to cause diarrhea include, but are not limited to, adenovirus, rotavirus, coronavirus, echovirus, enterovirus, astrovirus, and Norwalk virus.[9-11] Many enteric viruses do not cause disease. Others seldom if ever cross the stage of the surgical pathologist, because they are detected in stool samples rather than biopsy specimens. On rare occasions, when the surgical pathologist obtains biopsy from a patient with viral enteritis, nonspecific biopsy findings include villous fusion, epithelial reactive and degenerative changes, and a mononuclear cell infiltrate in the lamina propria (Fig. 4-3).

ADENOVIRUS

Adenovirus infection is second only to rotavirus as a cause of childhood diarrhea. However, it has gained attention in

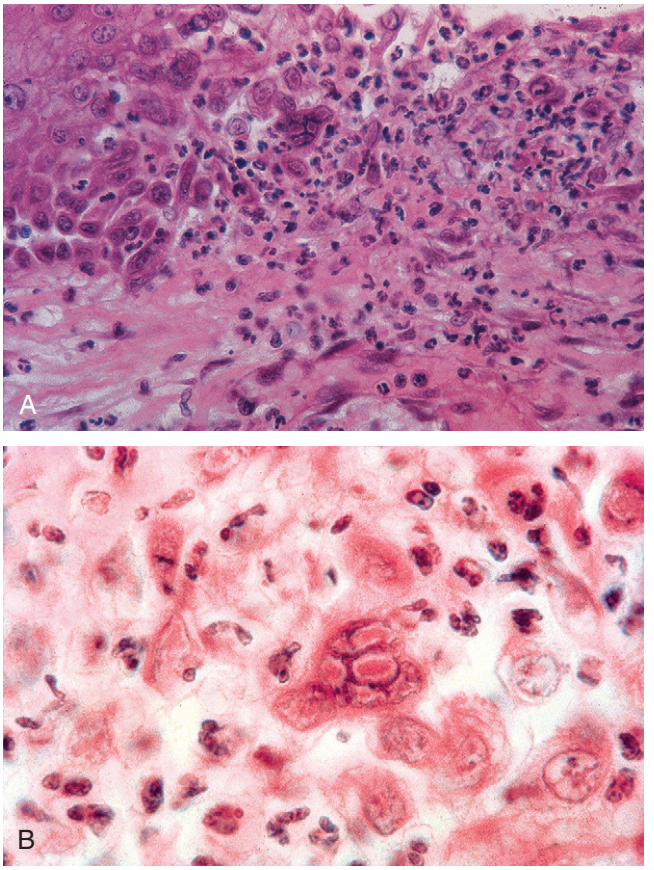

FIGURE 4-2 Typical herpetic inclusions are seen in the squamous epithelium at the edge of an esophageal ulcer.

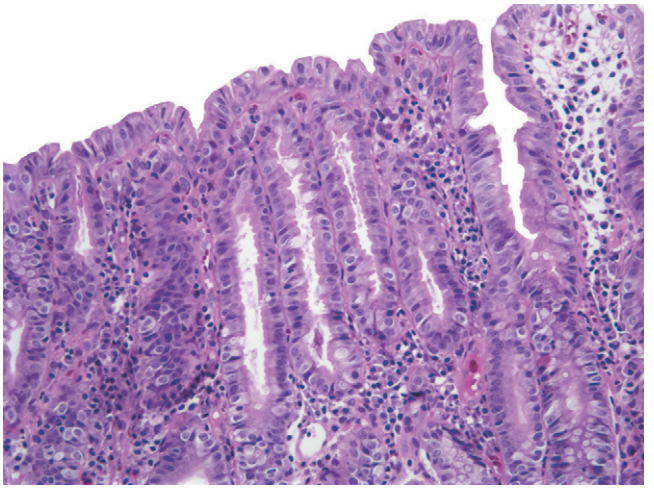

FIGURE 4-3 Villous fusion, surface reactive and degenerative changes, and a mononuclear cell infiltrate are nonspecific features that can be seen in biopsies from patients with gastroenteritis caused by enteric viruses.

recent years as a cause of diarrhea in immunocompromised patients, especially those with AIDS. Virtually all patients present with diarrhea, sometimes accompanied by fever, weight loss, and abdominal pain. Characteristic inclusions may be seen, especially in immunocompromised patients, in the nuclei of surface epithelial cells (particularly goblet cells), sometimes accompanied by epithelial degenerative changes.[5,12] Useful aids to help in the diagnosis of adenovirus infection include immunohistochemistry, stool examination by electron microscopy, and viral culture. This entity is discussed further and illustrated in Chapter 5.

HUMAN PAPILLOMAVIRUSES

HPV has been implicated in the pathogenesis of esophageal papillomas, esophageal squamous cell carcinomas, anal condylomas, and anal squamous cell carcinomas. These entities are discussed in detail in Chapters 16, 20, and 28.

HUMAN IMMUNODEFICIENCY VIRUS

Histologic abnormalities of the bowel mucosa have been noted in HIV-positive patients both with and without diarrhea. These features include crypt hypertrophy, increased numbers of apoptotic enterocytes, and villus atrophy. The changes resemble those seen in mild graft-versus-host disease and chemotherapy-related mucosal injury.[13] Many patients have chronic diarrhea, but some are asymptomatic. Some authors support use of the term *AIDS enteropathy* to describe these morphologic findings, provided that the bowel has been adequately sampled and all other infectious causes have been excluded.[13] Others believe that this is a poorly understood term that does not clearly represent a specific disease entity and thus should be avoided. Chronic idiopathic esophageal ulcers have also been described in association with HIV; this entity is discussed in Chapter 5.

Other viruses that affect the GI tract include measles (rubeola) and varicella-zoster, which may cause ulcerative gastroenteritis. In addition, some DNA viruses have been implicated in the pathogenesis of sporadic chronic idiopathic intestinal pseudo-obstruction.

Bacterial Infections of the GI Tract

Bacterial diarrhea is a worldwide health problem, with *Escherichia coli, Salmonella, Shigella*, and *Campylobacter* being the most common pathogens. Many bacterial infections of the gut are related to ingestion of contaminated water or food, or foreign travel. Although these organisms are usually recovered by culture, surgical pathologists may play a valuable role in diagnosis. Despite the dizzying array of bacterial infections that may affect the GI tract, most of these organisms produce a spectrum of histologic features that may be broadly categorized as follows (Table 4-1):

TABLE 4-1 Classification of Bacterial Infections of the GI Tract by Histologic Pattern

Minimal or No Inflammatory Change	Acute Self-Limited Colitis Pattern	Pseudo-membranous Pattern	Predominantly Granulomatous	Diffuse Histiocytic	Predominantly Lymphohistiocytic	Marked Architectural Distortion	Ischemic Pattern
Vibrio cholerae Enteropathogenic *E. coli* Enteroadherent *E. coli* Spirochetosis *Neisseria* species	*Shigella* *Campylobacter* *Aeromonas* Occasionally *Salmonella* (especially nontyphoid) Occasionally *C. difficile* Syphilis (±increased plasma cells)	Enterohemorrhagic *E. coli* *C. difficile* Occasionally *Shigella*	*Yersinia* *M. tuberculosis* Actinomycosis MAI (immunocompetent patients) Rarely, syphilis	*Rhodococcus equi* Whipple's disease MAI (immunocompromised patients)	LGV *Salmonella typhimurium*	*Salmonella typhimurium* *Shigella*	Enterohemorrhagic *E. coli*

C. difficile, Clostridium difficile; E. coli, Escherichia coli; LGV, lymphogranuloma venereum; MAI, Mycobacterium avium-intracellulare; M. tuberculosis, Mycobacterium tuberculosis.

- Organisms that produce mild or complete absence of histologic changes (e.g., *Vibrio cholerae* and *Neisseria gonorrhoeae*)
- Organisms that produce histologic features of acute infectious self-limited colitis (ASLC) or focal active colitis, such as *Shigella* and *Campylobacter*
- Organisms that produce specific or characteristic histologic features, such as pseudomembranes, granulomas, or viral inclusions

ACUTE SELF-LIMITED COLITIS

The ASLC pattern is the most common pattern in enteric infections. Typical histologic features include neutrophils in the lamina propria, with or without crypt abscesses and cryptitis, preservation of crypt architecture, and lack of basal plasmacytosis.[1,14] The acute inflammatory component is often most prominent in the middle to upper levels of the crypts. Lack of crypt distortion, Paneth cell metaplasia and basal lymphoplasmacytosis help to distinguish ASLC from inflammatory bowel disease. The changes may be focal, as in focal active colitis, or diffuse.

Because most patients do not present at endoscopy until several weeks after the onset of symptoms, pathologists usually are not exposed to the classic histologic features of acute infectious colitis. This is important, as the resolving phase of infectious colitis is more challenging to diagnose. At this stage, only occasional foci of neutrophilic cryptitis and only patchy increases in lamina propria inflammation may be found, and these may, in fact, contain abundant plasma cells and increased intraepithelial lymphocytes. As these features are also seen in Crohn's disease or even lymphocytic colitis, it is important to be aware of the patient's symptoms (particularly acute versus chronic onset), and, ideally, the culture results, because the exact diagnosis may be difficult to resolve on histologic grounds alone. The pathologic details of specific bacterial infections follow.

MAJOR CAUSES OF BACTERIAL ENTEROCOLITIS

Vibrio cholerae and Related Species

V. cholerae is the causative agent of cholera, an important worldwide cause of watery diarrhea and dysentery that may lead to significant dehydration and death. Despite the severity of the illness, *V. cholerae* is a noninvasive, potent toxin–producing organism that causes minimal or no histologic changes. Rare nonspecific findings such as small bowel mucin depletion and a mild increase in lamina propria mononuclear cells have been reported.[15] Other species, such as *Vibrio hollisae* and *Vibrio parahaemolyticus*, can also cause severe gastroenteritis.

Escherichia coli

E. coli is the most common gram-negative human pathogen. The diarrheogenic *E. coli* are classified into five groups, based primarily on serotyping. If pathogenic *E. coli* are suspected, the clinical laboratory should be notified to search for them specifically, as they may be missed on routine culture.

Enterotoxigenic *E. coli* and enteropathogenic *E. coli*. These noninvasive *E. coli* cause nonbloody diarrhea. Enterotoxigenic *E. coli* is a major cause of traveler's diarrhea, as well as food-borne outbreaks in industrialized nations.[16] Enteropathogenic *E. coli* is predominantly an infection of infants and neonates. The gross and microscopic pathology of neither has been well described in humans.

Enteroinvasive *E. coli*. The pathology of enteroinvasive *E. coli* has not been well described in humans either. These organisms are similar to *Shigella* genetically and in their clinical presentation and pathogenesis, so they may be similar in their pathology as well. Symptoms include diarrhea (generally mucoid and watery but nonbloody), tenesmus, fever, malaise, and abdominal cramps. Enteroinvasive *E. coli* is transmitted via contaminated cheese, water, and person-to-person contact. These organisms are a cause of traveler's diarrhea.[17] They produce a severe dysentery-like illness as well as bacteremia, which can be a particular problem in AIDS patients.

Enteroadherent *E. coli*. These noninvasive *E. coli* are similar to enteropathogenic *E. coli*. Both have been increasingly recognized as causes of chronic diarrhea and wasting in patients with AIDS. Although endoscopic findings are usually unremarkable, right colon biopsies more often yield pathologic findings. Histologic examination shows degenerated surface epithelial cells with associated intraepithelial inflammatory cells. A coating of adherent bacteria on the surface epithelium is the most prominent feature, which may stain gram-negative (Fig. 4-4).[18]

Enterohemorrhagic *E. coli*. The most common strain of enterohemorrhagic *E. coli* is O157:H7. This pathogen gained national attention in 1993 when a massive outbreak in the western United States was linked to contaminated hamburger meat. Although contaminated meat is the most frequent mode of transmission, infection may also occur through contaminated water, milk, produce, and person-to-person contact. Enterohemorrhagic *E. coli* produces a cytotoxin similar to that of *Shigella dysenteriae*; however, there is no tissue invasion. Affected persons may develop hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura. Children and older adults are at particular risk for grave illness.[19]

GI symptoms usually consist of bloody diarrhea with severe abdominal cramps and mild or no fever. Nonbloody, watery diarrhea may occur in some. Only one third of

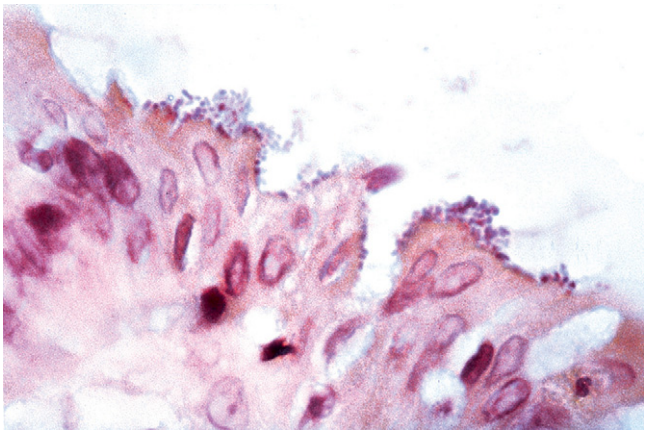

FIGURE 4-4 Enteroadherent *Escherichia coli* in a patient with AIDS. A coating of gram-negative rods with little inflammatory reaction is noted at the surface of the colonic mucosa (Gram). (Courtesy of Dr. Mary Bronner.)

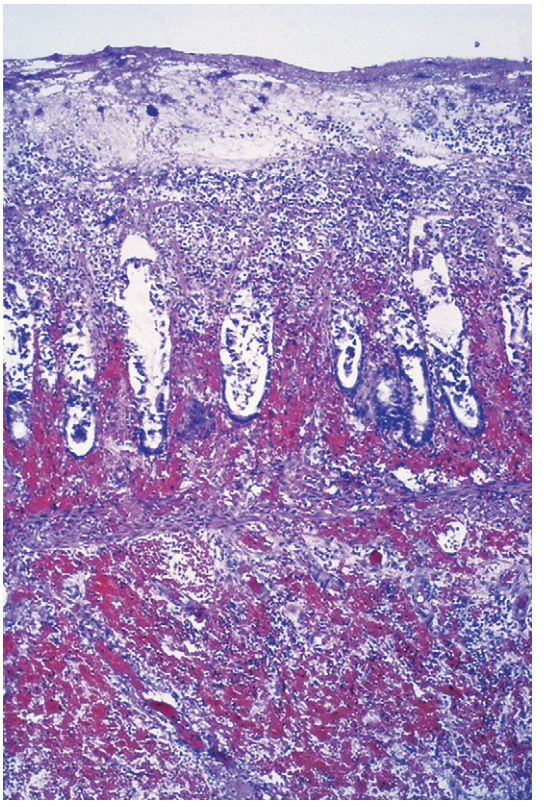

FIGURE 4-5 Enterohemorrhagic *Escherichia coli*. The hemorrhagic necrosis, acute inflammatory exudates, and crypt withering are very similar to the features of ischemic colitis.

patients have fecal leukocytes. Endoscopically, patients may have colonic edema, erosions, ulcers, and hemorrhage, and the right colon is usually more severely affected. The edema may be so marked that it causes obstruction, and surgical resection may be required to relieve this or to control bleeding. The histopathologic features include marked edema and hemorrhage in the lamina propria and submucosa, with associated mucosal acute inflammation and necrosis (Fig. 4-5). Microthrombi may be present in small-caliber blood vessels, and pseudomembranes may occasionally be present as well.[20,21]

Routine stool cultures cannot distinguish O157:H7 from normal intestinal flora, because microbiologic diagnosis requires screening on selective agar. An immunohistochemical stain for this organism has recently been described.

The differential diagnosis includes *Clostridium difficile*–related colitis, idiopathic inflammatory bowel disease, and especially ischemic colitis, from which enterohemorrhagic *E. coli* may be histologically indistinguishable. In cases of the latter, knowledge about the specific clinical situation, age and demographics of the patient, type of onset of illness, and type of diarrhea, along with endoscopic findings, may aid in distinguishing ischemic from *E. coli* infection.

Salmonella

These gram-negative bacilli are transmitted through food and water and are prevalent where sanitation is poor. They are an important cause of both food poisoning and traveler's diarrhea.

Typhoid (enteric) fever *(S. typhimurium)*. Patients with typhoid fever typically present with abdominal pain, headache, a rise in fever over several days, and occasionally constipation. There is often an abdominal rash and leukopenia. Diarrhea, which begins in the second or third week of infection, is initially watery but may progress to severe GI bleeding.[22]

Any level of the alimentary tract may be involved, but the characteristic pathology is most prominent in the ileum, appendix, and colon, and is associated with Peyer's patches. Grossly, the bowel wall is thickened, and raised nodules may be seen corresponding to hyperplastic Peyer's patches. Aphthous ulcers overlying Peyer's patches, linear ulcers, discoid ulcers, or full-thickness ulceration and necrosis are common as the disease progresses. There may be associated suppurative mesenteric lymphadenitis. Perforation and toxic megacolon may complicate typhoid fever.[22-24] Occasionally, the mucosa is grossly normal or only mildly inflamed and edematous.[24,25]

Histiocytes are the predominant inflammatory cell. Following hyperplasia of Peyer's patches, acute inflammation of the overlying epithelium develops. Eventually, macrophages, mixed with occasional lymphocytes and plasma cells, infiltrate and obliterate the lymphoid follicles; neutrophils are not prominent.[23] Necrosis then begins in the Peyer's patch and spreads to the surrounding mucosa, which eventually ulcerates. The ulcers are typically very deep, with the base at the level of the muscularis propria. Typhoid fever occasionally shows features more consistent

with acute self-limited colitis, including prominent neutrophils, cryptitis, crypt abscesses, and overlying fibrinous exudate.[24,25] Granulomas are occasionally seen as well.

Nontyphoid *Salmonella* species. Nontyphoid *Salmonella* species (e.g., *Salmonella enterica* and *Salmonella muenchen*) generally cause self-limited gastroenteritis. Endoscopic findings include mucosal redness, ulceration, and exudates; the pathologic features are those of nonspecific ASLC. Occasionally, significant crypt distortion is seen.[25]

The differential diagnosis of typhoid fever includes yersiniosis and other infectious processes, as well as Crohn's disease, and there may be significant histologic overlap between them (Table 4-2).[23,25] Neutrophils and granulomas are often more prominent in Crohn's disease and in yersiniosis. The differential diagnosis of nontyphoid *Salmonella* includes other causes of acute self-limited infectious colitis, as well as ulcerative colitis.[17] In addition, *Salmonella* infection may complicate preexisting idiopathic inflammatory bowel disease. Although significant crypt distortion has been reported in some cases of salmonellosis, it is generally more pronounced in ulcerative colitis. Clinical presentation and stool cultures may be invaluable in sorting out the differential diagnosis.

Shigella

Shigella are virulent, invasive, gram-negative bacilli that cause severe watery or bloody diarrhea (or both). They are a major cause of infectious diarrhea worldwide. The organism is usually transmitted by water contaminated with feces. It has the highest infectivity rate of all of the enteric gram-negative bacteria, so symptoms may result from ingestion of a very low number of organisms. Infants, young children, and malnourished or debilitated patients are most commonly affected. Symptoms include abdominal pain, fever, and diarrhea that is initially watery but later turns bloody. Chronic disease is rare.

Grossly, the large bowel is typically affected (the left side usually more severely), but the ileum may be involved as well. The mucosa is hemorrhagic, with exudates that may form pseudomembranes. Ulcerations are variably present. Histologically, early disease has the features of acute self-limited colitis with cryptitis, crypt abscesses (often superficial), and ulceration. Pseudomembranes similar to *C. difficile* infection may be seen, as well as aphthous ulcers similar to those seen in Crohn's disease. As the disease continues, there is increased mucosal destruction with many neutrophils and other inflammatory cells in the lamina propria. Marked architectural distortion mimicking idiopathic inflammatory bowel disease is well described.[26]

The differential diagnosis of early shigellosis includes primarily other enteroinvasive infections, particularly those caused by *E. coli* and *C. difficile*. Shigellosis, particularly later in the course of the disease, may be extremely difficult to distinguish from Crohn's disease or ulcerative colitis, both endoscopically and histologically.[1] Stool cultures and clinical presentation may be very helpful.

TABLE 4-2 Infectious Mimics of Chronic Idiopathic Inflammatory Bowel Disease

Mimics of Crohn's Disease
Cytomegalovirus
Salmonella typhimurium
Shigella species
Yersinia species
Mycobacterium tuberculosis
Aeromonas species
Lymphogranuloma venereum
Amebiasis
Mimics of Ulcerative Colitis
Shigella species
Nontyphoid *Salmonella* species
Amebiasis

Campylobacter

These gram-negative organisms are major causes of diarrhea worldwide and are the most common stool isolate in the United States.[27] *Campylobacter* is found in contaminated meat, water, and milk, and it is a common animal pathogen. *Campylobacter jejuni* is most commonly associated with food-borne gastroenteritis. *Campylobacter fetus* and the other less common species are more often seen in immunosuppressed patients and homosexual men.[19] Patients typically have fever, malaise, abdominal pain (often severe), and watery diarrhea, which may contain blood and leukocytes.[28] Most infections are self-limited, especially in healthy patients. Of note, Guillain-Barré syndrome and reactive arthropathy are associated with *Campylobacter* infection.[27]

Endoscopic findings include friable colonic mucosa with associated erythema and hemorrhage. Histologic examination shows features of acute self-limited colitis. Interestingly, *C. jejuni* has been demonstrated by molecular methods in almost 20% of patients who have the focal active colitis pattern of inflammation on colon biopsy.[29] Mild crypt distortion may occasionally be seen, although crypt architecture is normally well preserved.[28]

Yersinia

Yersinia enterocolitica and *Yersinia pseudotuberculosis* are the species that cause human GI disease. *Yersinia* is one of the most common agents of bacterial enteritis in western and northern Europe, and the incidence is rising in both Europe and the United States. These gram-negative

coccobacilli may cause appendicitis, ileitis, colitis, and mesenteric lymphadenitis. Although yersiniosis is usually a self-limited process, chronic infections (including chronic colitis) have been well documented. Immunocompromised and debilitated patients, as well as patients on deferoxamine or with iron overload, are at risk for serious disease.

Yersinia preferentially involves the ileum, right colon, and appendix, and it may cause a pseudoappendicular syndrome. In addition, it is responsible for many isolated cases of granulomatous appendicitis.[30] Grossly, involved bowel has a thickened, edematous wall with nodular inflammatory masses centered on Peyer's patches. Aphthous and linear ulcers may be seen. Involved appendices are enlarged and hyperemic, similar to that seen in suppurative appendicitis; perforation is often seen. Involved lymph nodes may show gross foci of necrosis.

Both suppurative and granulomatous patterns of inflammation are common and are often mixed. *Y. enterocolitica* has not typically been associated with discrete granulomas, but it has been characterized by hyperplastic Peyer's patches with overlying ulceration, acute inflammation, hemorrhagic necrosis, and palisading histiocytes.[31] GI infection with *Y. pseudotuberculosis* has characteristically been described as a granulomatous process with central microabscesses, almost always accompanied by mesenteric adenopathy (Fig. 4-6A).[32] There is significant overlap between the histologic features of *Y. enterocolitica* and *Y. pseudotuberculosis* infection, however, and either species may show epithelioid granulomas with prominent lymphoid cuffing (see Fig. 4-6B), lymphoid hyperplasia, transmural lymphoid aggregates, mucosal ulceration, and lymph node involvement.[30] Gram stains are usually not helpful, but cultures, serologic studies, and PCR assays may be useful in confirming the diagnosis.

The major differential diagnosis includes other infectious processes, particularly those caused by mycobacteria and *Salmonella*. Acid-fast stains and culture results help distinguish mycobacterial infection. The specific clinical features, and the presence of greater numbers of neutrophils, microabscesses, and granulomas may help to distinguish yersiniosis from salmonellosis.

Crohn's disease and yersiniosis may be very difficult to distinguish from one another, and, in fact, have a long and complicated relationship. Both disorders may show similar histologic features, including transmural lymphoid aggregates, skip lesions, and fissuring ulcers. In fact, isolated granulomatous appendicitis has frequently been interpreted as representing primary Crohn's disease of the appendix (see Chapter 15). However, patients with granulomatous inflammation confined to the appendix rarely develop generalized inflammatory bowel disease.[33] Features that favor a diagnosis of Crohn's disease include cobblestoning of mucosa, presence of creeping fat, and histologic changes of chronicity including crypt distortion, thickening of the muscularis mucosa, and prominent neural hyperplasia. However, some cases are simply indistinguishable on histologic grounds alone.

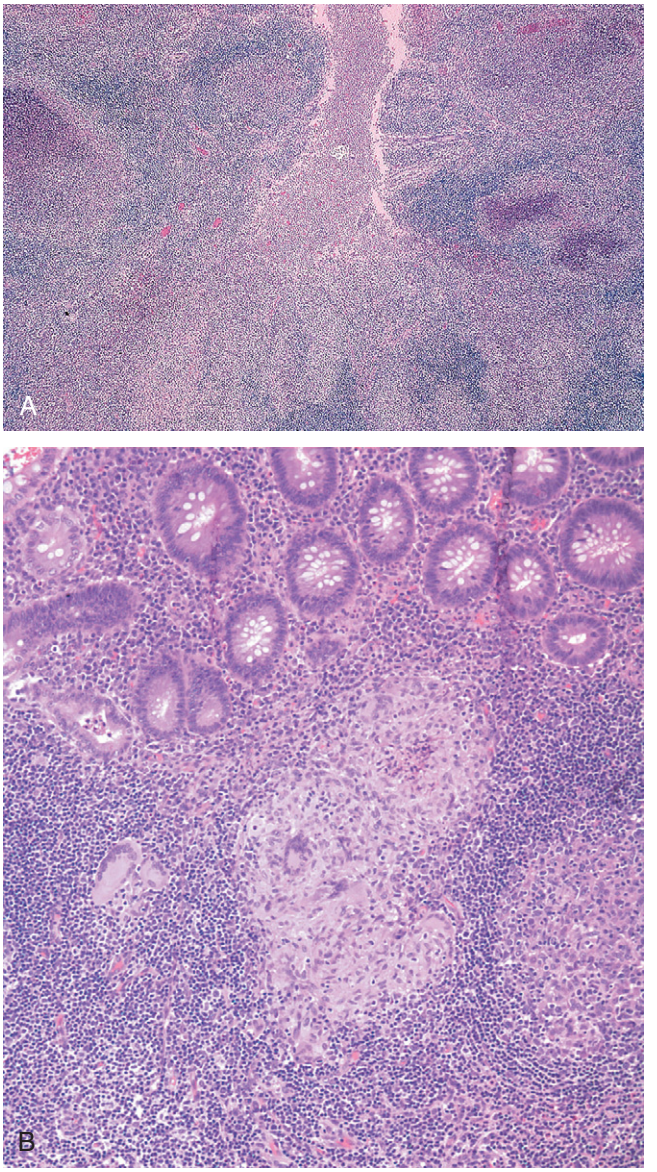

FIGURE 4-6 A, Lymphoid hyperplasia with necrotizing granulomatous inflammation and prominent microabscess formation in appendicitis caused by *Yersinia pseudotuberculosis*. **B,** Epithelioid granulomas with prominent lymphoid cuffs in *Yersinia enterocolitica* infection.

Aeromonas

Aeromonas species, initially thought to be nonpathogenic gram-negative bacteria, are increasingly recognized as causes of gastroenteritis in both children and adults. The motile *Aeromonas hydrophila* and *Aeromonas sobria* most often cause GI disease in humans. The typical presentation is bloody diarrhea, sometimes chronic, accompanied by nausea, vomiting, and cramping pain. The diarrhea may

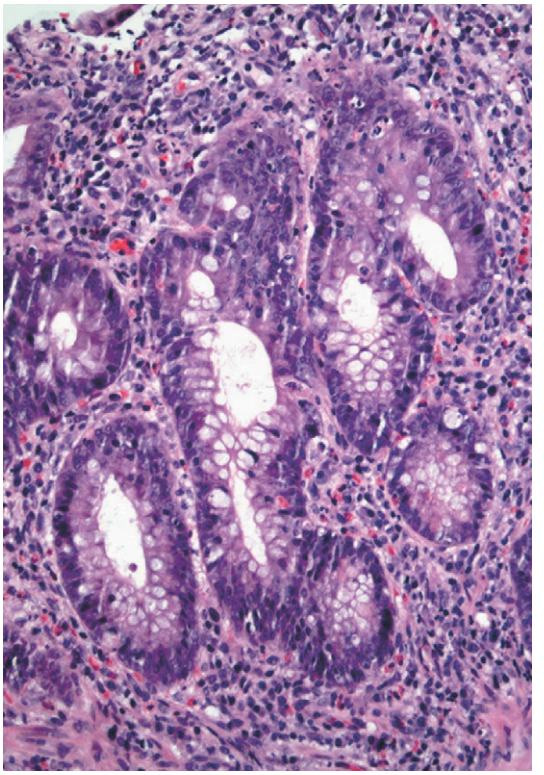

FIGURE 4-7 Focal cryptitis and architectural distortion from a right colon biopsy in a case of culture-proven *Aeromonas* infection.

contain mucus as well as blood. The duration of illness varies widely, ranging from a few days to several years, indicating that *Aeromonas* infection can cause chronic colitis.[34-38]

Endoscopically, signs of colitis, including edema, friability, erosions, exudates, and loss of vascular pattern, may be seen. The features are often segmental and may mimic ischemic colitis or Crohn's disease.[34] Pancolitis mimicking ulcerative colitis has also been described. The histologic features are usually those of acute self-limited colitis. However, ulceration and focal architectural distortion may be seen in some instances (Fig. 4-7).[34-38]

Stool cultures are critical to diagnosis. The differential diagnosis includes other infectious processes, ischemic colitis, and chronic idiopathic inflammatory bowel disease. Culture helps to exclude other infections, but when architectural distortion is present in a patient with chronic symptoms, it may be difficult to distinguish between *Aeromonas* infection, Crohn's disease, and ulcerative colitis. In fact, some authorities recommend culturing for *Aeromonas* in all patients with refractory chronic inflammatory bowel disease.

CLOSTRIDIAL DISEASES OF THE GUT

Clostridial organisms are some of the most potent toxigenic bacteria in existence and are very important gut pathogens. This group of bacteria is responsible for pseudomembranous/antibiotic-associated colitis (usually *C. difficile*), necrotizing jejunitis or pig-bel (usually *Clostridium perfringens* [*welchii*]), neutropenic enterocolitis (often *Clostridium septicum*), and botulism (*Clostridium botulinum*).[39]

C. difficile–related colitis. *C. difficile* infection is most commonly related to prior antibiotic exposure (especially orally administered), because the organisms cannot infect in the presence of normal flora.[39] It is the most common nosocomial GI pathogen. The majority of patients are older adults, although infection is certainly not limited to this patient group. In addition, *C. difficile* infection has increased significantly in patients with chronic idiopathic inflammatory bowel disease, and it negatively affects clinical outcome in terms of hospitalization and need for colectomy.[40,41]

The range of disease is variable, from mild diarrhea to fully developed pseudomembranous colitis to fulminant disease with perforation or toxic megacolon.[42,43] Watery diarrhea is almost always present initially and may be accompanied by abdominal pain, cramping, fever, and leukocytosis. Bloody diarrhea is sometimes seen. Symptoms can occur up to several weeks after discontinuation of antibiotic therapy.[42]

Endoscopically, classic pseudomembranous colitis shows yellow-white pseudomembranes, most commonly in the left colon, that bleed when scraped. The distribution is often patchy, and the rectum may be spared.[42] Atypical findings include mucosal erythema and friability without pseudomembranes. Typical histologic findings may be seen, however, in the absence of gross pseudomembranes. Histologically, the classic features of pseudomembranous colitis—"volcano" lesions with intercrypt necrosis and ballooned crypts—give rise to the laminated pseudomembrane composed of fibrin, mucin, and neutrophils (Fig. 4-8A-C). The ballooned glands are filled with neutrophils and mucin, and they often lose the superficial epithelial cells.[43] The degenerated goblet cells often spill into the lumen of degenerated and necrotic crypts, and they mimic signet ring cell carcinoma. In fact, this feature is helpful to distinguish the condition from ischemic colitis, as the latter does not normally show this feature. More severe and prolonged pseudomembranous colitis may lead to full-thickness mucosal necrosis. Less characteristic lesions, usually focal active colitis with occasional crypt abscesses but lacking pseudomembranous features, have been well described in association with a positive *C. difficile* toxin assay.[43]

It is important to note that *pseudomembranous colitis* is a descriptive diagnosis, not a specific diagnosis. Although most cases of pseudomembranous colitis are related to *C. difficile*, other infectious entities, as well as ischemic colitis, may have a similar endoscopic and histologic appearance. A hyalinized lamina propria favors the diagnosis of ischemia; other features, such as crypt withering, pseudomembranes, and mucosal necrosis, may be seen in either

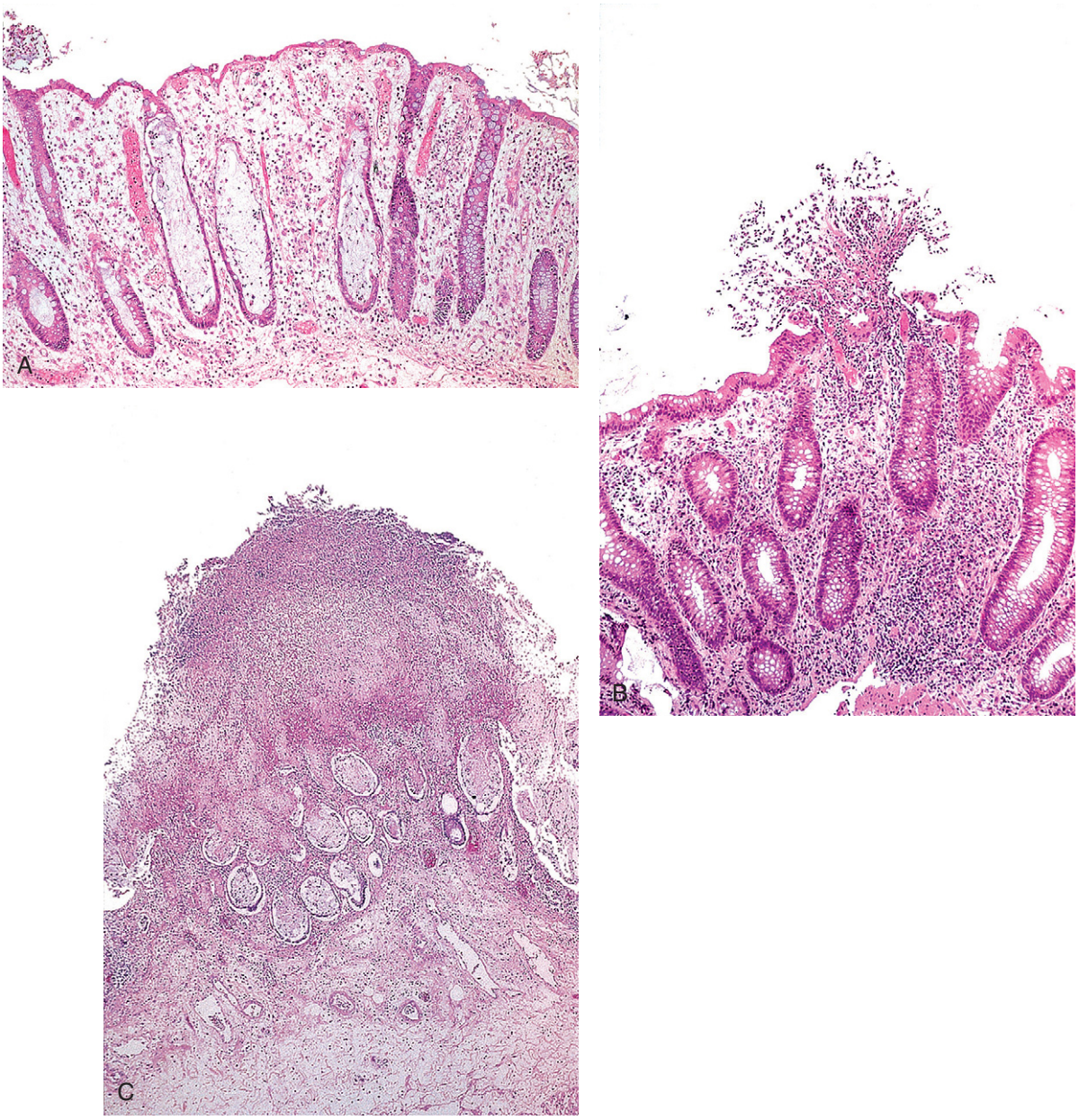

FIGURE 4-8 A, Early pseudomembranous colitis with ballooned crypts containing neutrophils and intercrypt necrosis but no pseudomembrane. **B,** Intercrypt necrosis giving rise to early "volcano" lesion. **C,** Classic "volcano" lesion with laminated pseudomembrane composed of fibrin, mucin, and neutrophils.

entity.[44] Endoscopically, pseudomembrane formation is more frequent in pseudomembranous colitis, although it can be seen in ischemia as well. History of antibiotic use and stool assay for *C. difficile* toxin may be invaluable in resolving the differential diagnosis.

C. perfringens (welchii). *C. perfringens* causes diarrhea related to food poisoning and is also a cause of antibiotic-associated and nosocomial diarrhea. The notorious pig-bel (segmental necrotizing enterocolitis) is caused by *C. perfringens* type C; it usually follows a meal rich in infected meat. It is most common in Southeast Asia and New Guinea, where it was initially described following ritual pork feasting. Similar cases have been described after eating binges in Western countries. Symptoms include abdominal pain, bloody diarrhea, and vomiting, often with abdominal distension. Complications include perforation, obstruction, bowel gangrene, and septicemia with shock and rapid death. Mild or subacute forms have also been described.[45]

Involvement is predominantly seen in, but is not limited to, the jejunum. The bowel is often dusky gray-green, similar in appearance to ischemia. The necrotic areas may be segmental and focal, with intervening areas of normal

mucosa. The mucosal exudate may be similar to that seen in pseudomembranous colitis, but inflammation and necrosis often become transmural and lead to perforation. Histologically, the mucosa is edematous, necrotic, and ulcerated, with a heavy acute inflammatory infiltrate at the edges of ulcers. Pneumatosis may be present in severe cases, particularly in the mucosa and submucosa. Small vessel vasculitis and microthrombi may be seen.[45] Gram-positive bacilli typical of clostridia can be found in the necrotic exudate.

C. septicum. Neutropenic enterocolitis (typhlitis) is a serious complication of both chemotherapy-related and primary neutropenia. Most patients have received chemotherapy within the previous month before the onset of colitis. *C. septicum* has been frequently reported as a causative agent, especially in adults; other commonly implicated bacteria include other clostridial species, *E. coli*, *Pseudomonas*, and *Enterococcus*.[46,47] An association with CMV has also been noted. Patients usually present with GI hemorrhage, fever, abdominal pain and distension, and diarrhea.[46] Perforation is a well-described complication.

The right colon is preferentially involved, although the ileum and other sites in the colon may be affected as well. Gross findings include diffuse dilation and marked edema of the bowel, with varying severity of ulceration and hemorrhage.[46] Exudates and pseudomembranes resembling *C. difficile* colitis are common. Microscopically, changes range from mild hemorrhage to prominent submucosal edema, ulceration, marked hemorrhage, and necrosis, typically with a striking absence of inflammatory cells (Fig. 4-9). Pneumatosis may occur rarely if the inciting organism is gas producing. However, a few neutrophils may sometimes be found despite peripheral neutropenia. Occasionally, organisms can be detected in the wall of the bowel or in mucosal or submucosal blood vessels on Gram stain.

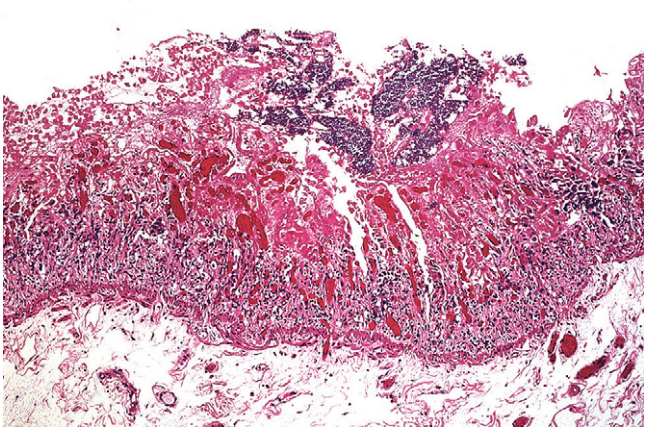

FIGURE 4-9 Typhlitis (neutropenic enterocolitis) in a chemotherapy patient. Ulceration with hemorrhage, prominent submucosal edema, mucosal ulceration and necrosis, and an exudate containing numerous bacteria and yeast are typical features. Neutrophils are scarce.

The differential diagnosis includes ischemic colitis and pseudomembranous colitis. The appropriate clinical setting and dearth of inflammatory cells favor a diagnosis of necrotizing enterocolitis.

MYCOBACTERIAL INFECTIONS OF THE GI TRACT

Mycobacterium tuberculosis. This organism remains common in developing countries and immigrant populations. There has also been a remarkable resurgence of tuberculosis in Western countries, due in large part to AIDS but also caused by institutional overcrowding and immigrant populations. GI symptoms (rather than pulmonary) may be the initial presentation. In fact, primary GI tuberculosis has been well documented. Symptoms and signs are nonspecific and include weight loss, fever, abdominal pain, diarrhea, and a palpable abdominal mass.[48,49] Mesenteric adenopathy is common.

Grossly, the ileocecal and jejunoileal areas are most commonly involved, followed by the appendix and ascending colon[48,49]; the ileocecal valve is often deformed and gaping. Rectal, anal, duodenal, and gastroesophageal involvement are much less frequent but are well described. Strictures and ulcers (often occurring together) are the most common endoscopic findings, along with thickened mucosal folds and inflammatory nodules. The ulcers are often circumferential and transverse. Multiple and segmental lesions with skip areas are common. Large inflammatory masses, usually involving the ileocecum, may be seen, and well-described complications include obstruction, perforation, and hemorrhage.[48-50] Anal and perianal disease have also been reported, but rarely.[51]

The characteristic histologic lesion consists of caseating, often confluent, granulomas, present at any level of the gut wall (Fig. 4-10A); a rim of lymphocytes may be present at the periphery of the granulomas. Granulomas may be rare, or remote, with hyalinization and calcification. Aphthous ulcers, as well as inflammation of submucosal vessels, may be present. Acid-fast stains sometimes demonstrate organisms in granulomas or necrotic areas (see Fig. 4-10B), but culture is usually required for definitive diagnosis. In addition, PCR assays are available. Skin tests with purified protein derivative are unreliable in immunocompromised or debilitated patients.

The differential diagnosis includes other granulomatous infectious processes, especially yersiniosis and fungal disease (Table 4-3).[30,52-54] The granulomas of yersiniosis are typically noncaseating, with striking lymphoid cuffs, but there may be considerable histologic overlap. Crohn's disease may be very difficult to distinguish from tuberculosis. Features favoring Crohn's disease are the presence of linear rather than circumferential ulcers, transmural lymphoid aggregates, deep fistulas and fissures, and mucosal

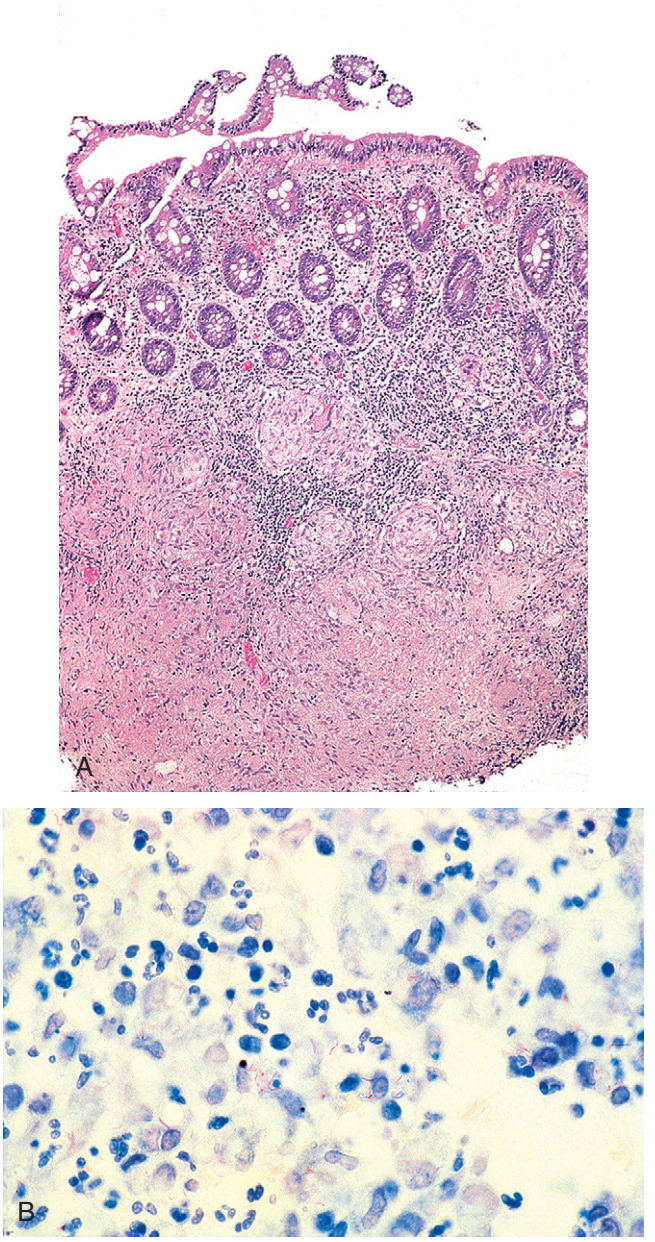

FIGURE 4-10 **A,** Colonic *Mycobacterium tuberculosis* with mucosal and submucosal confluent, caseating granulomas. **B,** Rare acid-fast organisms are seen in the necroinflammatory infiltrate (Ziehl-Neelsen).

changes of chronicity that are present away from areas of granulomatous inflammation.[52] Tuberculosis also commonly lacks mucosal cobblestoning. Atypical mycobacteria, such as *Mycobacterium kansasii* and *Mycobacterium bovis*, may cause a similar pathologic picture.

Mycobacterium avium-intracellulare complex. This is the most common mycobacterium isolated from the GI tract. Symptoms include diarrhea, abdominal pain, fever, and weight loss, and often reflect systemic infection. Endoscopy is usually normal, although white nodules, small ulcers, or

TABLE 4-3 Features Useful in Diagnosing *Mycobacterium tuberculosis*, *Yersinia*, and Crohn's Disease

	M. tuberculosis	*Yersinia*	Crohn's Disease
Caseating granulomas	Frequent	Rare	Absent
Confluent granulomas	Frequent	Frequent	Absent
Few granulomas	Rare	Rare	Common
Prominent lymphoid cuff	Frequent	Frequent	Uncommon
Ulcers (both aphthous and deep)	Common	Common	Common
Architectural distortion	Common	Common	Common
Changes of chronicity unassociated with sites of granulomatous inflammation	Absent	Absent	Common
Multiple sites of involvement	Common	Rare	Common

hemorrhages may be seen. The small bowel is preferentially involved, but colonic and gastroesophageal involvement may be present, as well as mesenteric adenopathy.[55,56]

Immunocompetent patients typically manifest a granulomatous response, with or without necrosis. Immunocompromised patients generally have villi distended by a diffuse infiltration of histiocytes containing bacilli (Fig. 4-11A), with little inflammatory response other than occasional poorly formed granulomas.[55] The bacilli stain with acid-fast stains, as well as periodic acid–Schiff (PAS) and Gomori's methenamine silver (GMS). Culture and PCR assays may also be helpful. Organisms are generally abundant in the immunocompromised host (see Fig. 4-11B) but may be hard to detect in healthy patients. The differential diagnosis includes Whipple's disease and other infectious processes.

SPIROCHETAL INFECTIONS OF THE GI TRACT

Syphilis *(Treponema pallidum)*. GI syphilis predominantly involves the anorectum, although other sites may be infected as well, particularly the stomach.[56,57] Patients are often asymptomatic,[56-58] but pain, constipation, bleeding, and discharge may be present.

Gross findings in primary syphilis include anal chancres and an associated mild proctitis. Signs of secondary

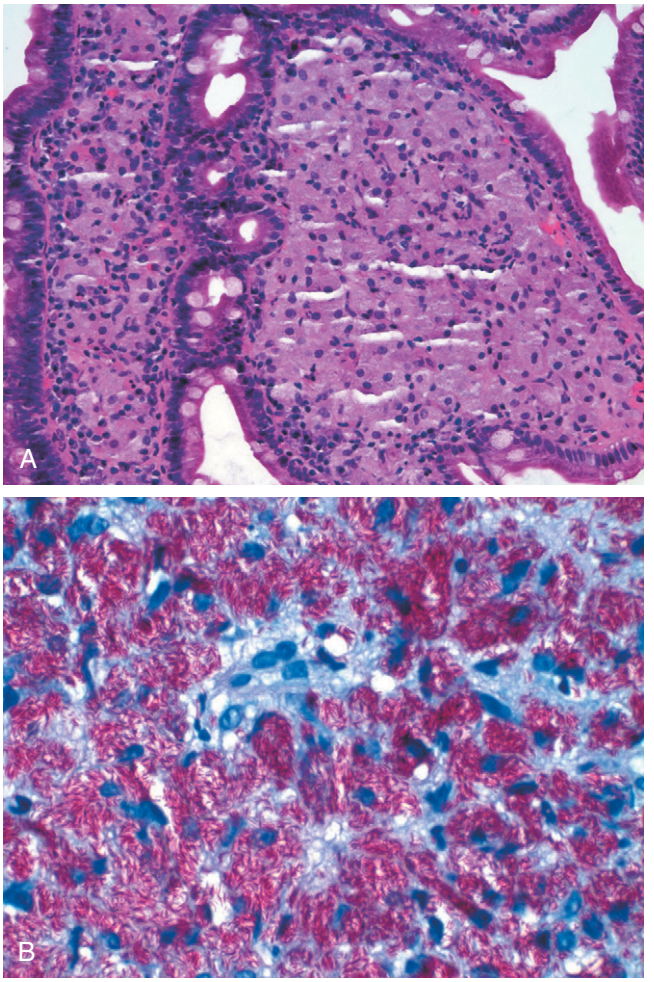

FIGURE 4-11 A, Small bowel villi are distended by clusters of histiocytes containing *Mycobacterium avium-intracellulare*, with little associated inflammatory response. (Courtesy of Dr. Jesse McKenney.) **B,** The histiocytes are packed with numerous acid-fast organisms typical of *M. avium-intracellulare* (Ziehl-Neelsen). (Courtesy of Dr. Jesse McKenney.)

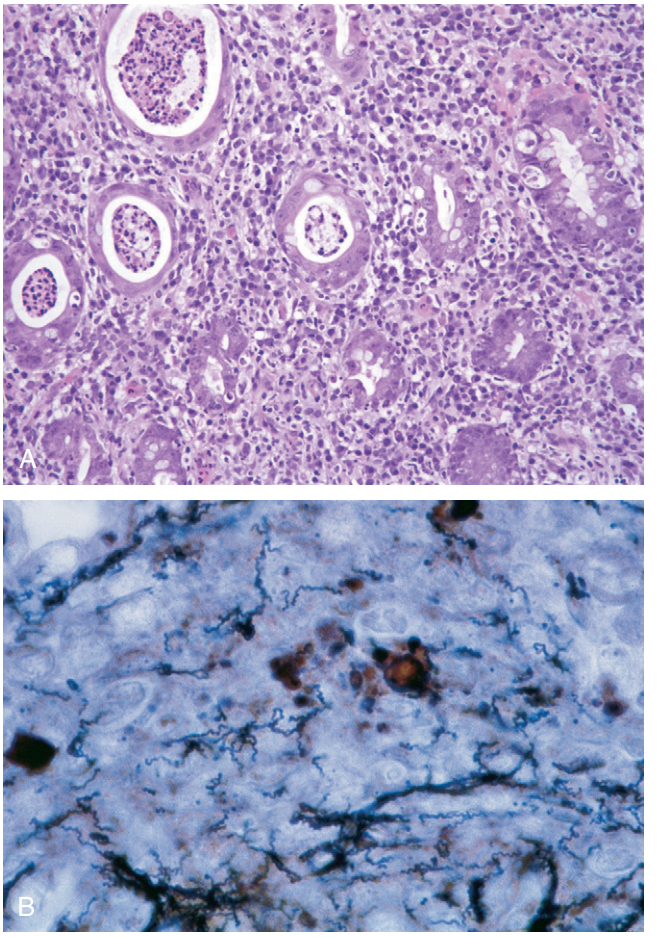

FIGURE 4-12 A, Syphilitic proctitis featuring neutrophilic cryptitis, crypt abscesses, and a striking plasmacytic infiltrate in the lamina propria. (Courtesy of Dr. Amy Hudson.) **B,** Numerous spirochetes are seen with silver impregnation staining (Warthin-Starry). (Courtesy of Drs. Rodger Haggitt and Mary Bronner.)

syphilis typically appear 6 to 8 weeks later and include masses, a mucocutaneous rash, or condyloma lata (raised, moist, smooth warts that secrete mucus and are associated with itching and a foul odor).[56,58] Inguinal adenopathy is typical. The gross signs of primary and secondary infection sometimes coexist.

Gastric involvement may be either an early or a late manifestation of syphilis. The most common presenting sign is upper GI bleeding, and patients typically have antral erosions, ulcers, or features of gastritis endoscopically.[57] Ulcers may have irregular, heaped-up edges that mimic malignancy.

Histologically, syphilitic chancres typically contain a dense mononuclear cell infiltrate with prominent plasma cells. Syphilitic proctitis is very nonspecific, often showing features of acute self-limited or focal active colitis, with or without an increase in plasma cells (Fig. 4-12A). Syphilitic gastritis more often features a dense plasmacytic infiltrate.[57] However, the glands may be relatively spared by inflammation. Granulomas have been reported, and occasionally prominent, proliferative capillary endothelial cells are noted.[59,60] Darkfield examination, silver impregnation stains (see Fig. 4-12B), serologic studies, and immunohistochemistry may be helpful diagnostic aids.

The gross differential diagnosis of chancre includes anal fissures, fistulas, or traumatic lesions. In general, condyloma acuminata are more dry and keratinized than condyloma lata. The histologic differential diagnosis primarily includes other infectious processes, including *Helicobacter pylori* infection in the stomach. If the plasma cell infiltrate is very prominent and monomorphic, plasmacytoma should also be considered.

Intestinal spirochetosis. Intestinal spirochetosis is usually seen in homosexual men, although it has been described in a wide variety of conditions including diverticular disease and ulcerative colitis, and in patients with adeno-

mas. It probably represents infection by a group of related organisms.[61] Patients with this histologic finding often have symptoms such as diarrhea or anal pain and discharge, but it is not clear that spirochetosis causes these symptoms, and many immunocompromised patients have other infections (especially gonorrhea) that complicate the clinical picture. However, symptomatic patients do appear to respond to antimicrobial therapy.[61-63] Any level of the colon may be involved, even the appendix. Typically, endoscopic abnormalities are either mild or completely absent.

On H&E, spirochetosis resembles a fuzzy, "fringed" blue line at the luminal border of the colonic mucosa (Fig. 4-13A). Tissue invasion by organisms is not seen, and the changes can be very focal. Most cases show no associated inflammatory infiltrate, although occasionally an associated cryptitis is present. The organisms stain intensely with Warthin-Starry or similar silver stains (see Fig. 4-13B). They also stain with alcian blue (pH 2.5) and PAS.[64]

The differential diagnosis primarily consists of other organisms with a prominent glycocalyx, which does not stain with silver impregnation stains. Occasionally, enteroadherent *E. coli* can induce a similar histologic appearance, but *E. coli* are gram-negative and lack spirillar morphology.

OTHER CAUSES OF SEXUALLY TRANSMITTED BACTERIAL PROCTOCOLITIS

Although herpes simplex virus is the most common etiologic agent of infectious proctocolitis among homosexual men, *N. gonorrhoeae, T. pallidum*, and *Chlamydia* are also frequent causes. Patients generally present with anal discharge, pain, diarrhea, constipation, bloody stools, and tenesmus. Proctoscopic findings range from normal to erythema, mucosal friability, and surface erosions.[58]

Chlamydia trachomatis. Serotypes L1, L2, and L3 cause lymphogranuloma venereum (LGV). Anal pain is usually severe and accompanied by bloody discharge and tenesmus.[59-65] The anorectum is the most common site, but LGV has been described in the ileum and colon as well.[65] The inflammatory infiltrate is variable; most patients have a lymphoplasmacytic infiltrate in the mucosa and submucosa, but neutrophils may be prominent as well. Granulomatous inflammation is sometimes present. Histologic features mimicking Crohn's disease have been described.[65,66] In addition, LGV may produce a striking "follicular" proctitis.[65] Culture, direct immunofluorescence studies, and immunohistochemistry may serve as valuable diagnostic aids.

Granuloma inguinale. *Calymmatobacterium granulomatis* (recently reclassified as *Klebsiella granulomatis*) causes anal and perianal disease that may resemble LGV, although

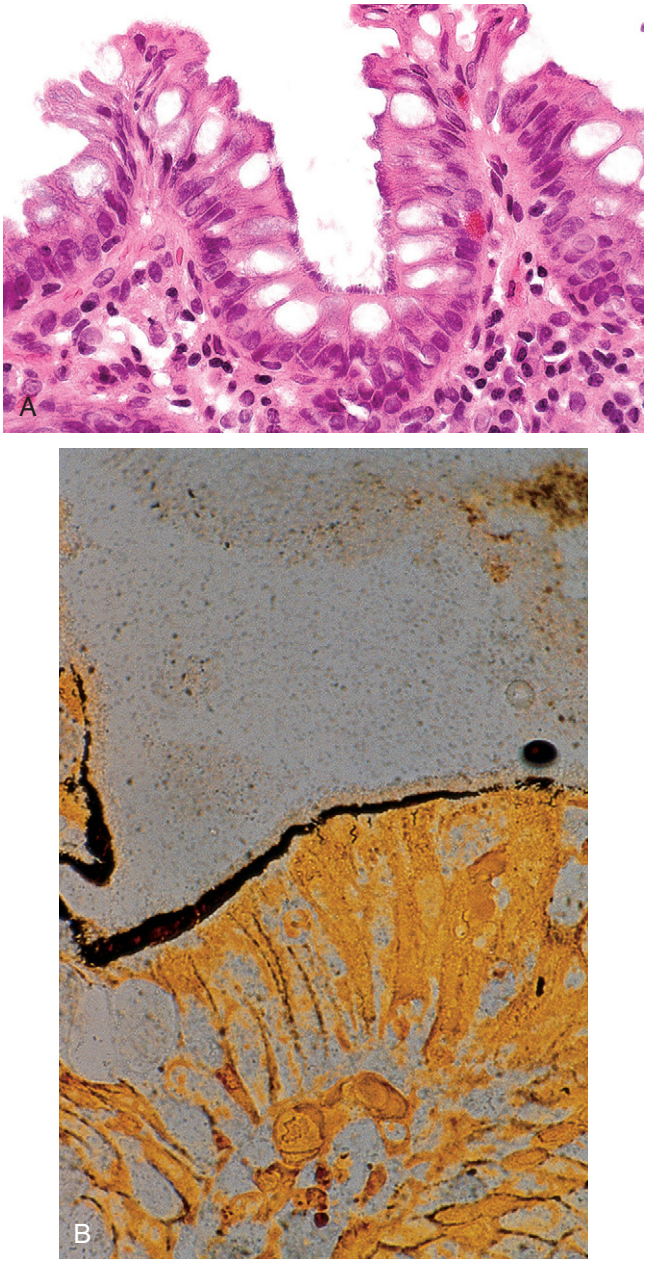

FIGURE 4-13 A, Spirochetosis characterized by a fuzzy, "fringed" blue line at the luminal border of the colonic mucosa. **B,** Organisms stain intensely with silver impregnation staining (Warthin-Starry).

extension into the rectum favors a diagnosis of LGV.[66] Warthin-Starry or Giemsa stain aids in visualizing the Donovan bodies typical of granuloma inguinale.

Neisseria gonorrhoeae. Gonorrhea has been reported in up to 20% of homosexual men and is frequently asymptomatic. The anorectum (alone or in combination with the pharynx and urethra) is a common site of infection. *Neisseria meningitidis* has also been isolated from the anorectum of homosexual men. Proctoscopic examination is usually unremarkable. Most biopsies in rectal gonorrhea are normal; some reveal a mild increase in neutrophils and

mononuclear cells, or focal cryptitis.[67] Gram-negative cocci are occasionally seen on a Gram stain of anal discharge, and culture can be a valuable diagnostic aid.

MISCELLANEOUS BACTERIAL INFECTIONS

Bacterial esophagitis. Bacterial esophagitis is rare, usually found in immunocompromised or debilitated patients. Implicated bacteria include *Staphylococcus aureus, Lactobacillus acidophilus*, and *Klebsiella pneumoniae*. Endoscopic findings include ulceration, pseudomembrane formation, and hemorrhage. Histologic findings include acute inflammation and necrosis, with bacteria demonstrable in the wall of the esophagus.[68]

Phlegmonous gastritis and enteritis. Phlegmonous enteritis, gastritis, and esophagitis have all been well documented. This is a suppurative, primarily submucosal inflammatory process, characterized by marked edema. The causative organisms vary and include *E. coli*, clostridial organisms, *Proteus*, staphylococci, and group A streptococci.[69,70] Most patients are debilitated, and many have cirrhosis or alcoholic liver disease.[70] Affected patients may have nonspecific GI or systemic symptoms, or phlegmonous disease may be found incidentally at autopsy. Patients typically develop an acute abdomen, sometimes complicated by hematemesis or vomiting of purulent material.

Any portion of the alimentary tract may be involved. Typically, the gut wall is markedly thick and edematous. Occasionally, gas-producing organisms such as *C. perfringens* may lead to the formation of gas bubbles in the submucosa ("emphysematous" changes) (Fig. 4-14). Although the mucosa may be red and friable, discrete ulceration is rarely present. Histologically, there is intense edema and acute inflammation located predominantly in the submucosa, and there may be transmural involvement as well.[70] The mucosa may be spared or sloughed entirely, especially in the stomach. Venous thrombosis may complicate the picture, causing ischemic changes. Gram stain may show organisms in the bowel wall, which is diagnostic.

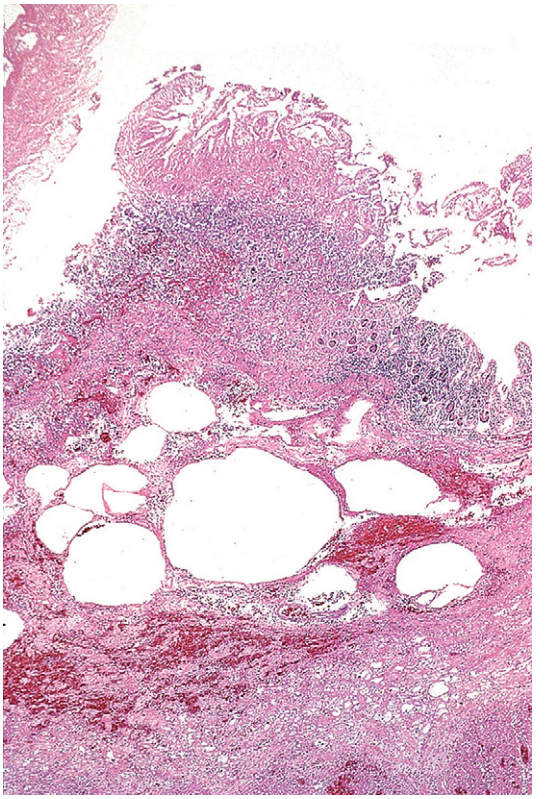

FIGURE 4-14 Emphysematous enteritis caused by *Clostridium perfringens*. Note transmural necrosis and mucosal sloughing with associated gas bubbles in the gut wall. (Courtesy of Dr. David Owen.)

Actinomycosis *(Actinomyces israelii)*. This filamentous anaerobic gram-positive bacterium is a normal inhabitant of the oral cavity and the upper GI tract. Rarely, it produces a chronic, nonopportunistic GI infection.[71] Infection is usually in a solitary site, and it may occur at any level of the GI tract. Symptoms include fever, weight loss, abdominal pain, and, occasionally, a palpable mass. Perianal fistulas and chronic (often granulomatous) appendicitis have both been described. In fact, sometimes actinomycosis is associated with diverticular disease. Grossly, inflammation may produce a large, solitary mass, with or without ulceration, and infiltration into surrounding structures.[72]

The organism typically produces actinomycotic ("sulfur") granules, consisting of irregular round clusters of bacteria rimmed by eosinophilic, clublike projections (Splendore-Hoeppli material). The inflammatory reaction is predominantly neutrophilic, with occasional abscess formation (Fig. 4-15). Palisading histiocytes and giant cells, as well as frank granulomas, often surround the neutrophilic inflammation. There may be an associated fibrotic response. Gram stain reveals the filamentous, gram-positive organisms. GMS and Warthin-Starry stains are also used to show these organisms.

The gross differential diagnosis includes peptic ulcer, lymphoma, and carcinoma. The histologic differential diagnosis includes primarily other infectious agents, particularly *Nocardia*. Unlike *Nocardia*, all actinomycetes are not acid-fast. Care should also be taken not to confuse actinomycosis with fungi, or other bacteria, that form clusters and chains but are not truly filamentous, such as *Pseudomonas* and *E. coli*.

Whipple's disease *(Tropheryma whippelii)*. Whipple's disease typically presents in middle-aged white men with chronic weight loss, arthritis, malabsorption, and lymphadenopathy. Many patients also have significant neuropsychiatric manifestations.[73]

The small bowel is most often affected, although colonic and appendiceal involvement may be seen as well. Endoscopically, mucosal folds are thickened and coated with

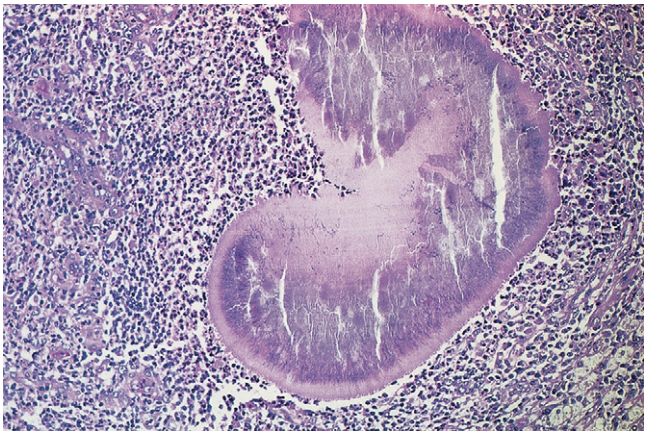

FIGURE 4-15 Actinomycotic ("sulfur") granule consisting of irregularly rounded clusters of bacteria bordered by Splendore-Hoeppli material and an acute inflammatory exudate. (Courtesy of Dr. George F. Gray, Jr.)

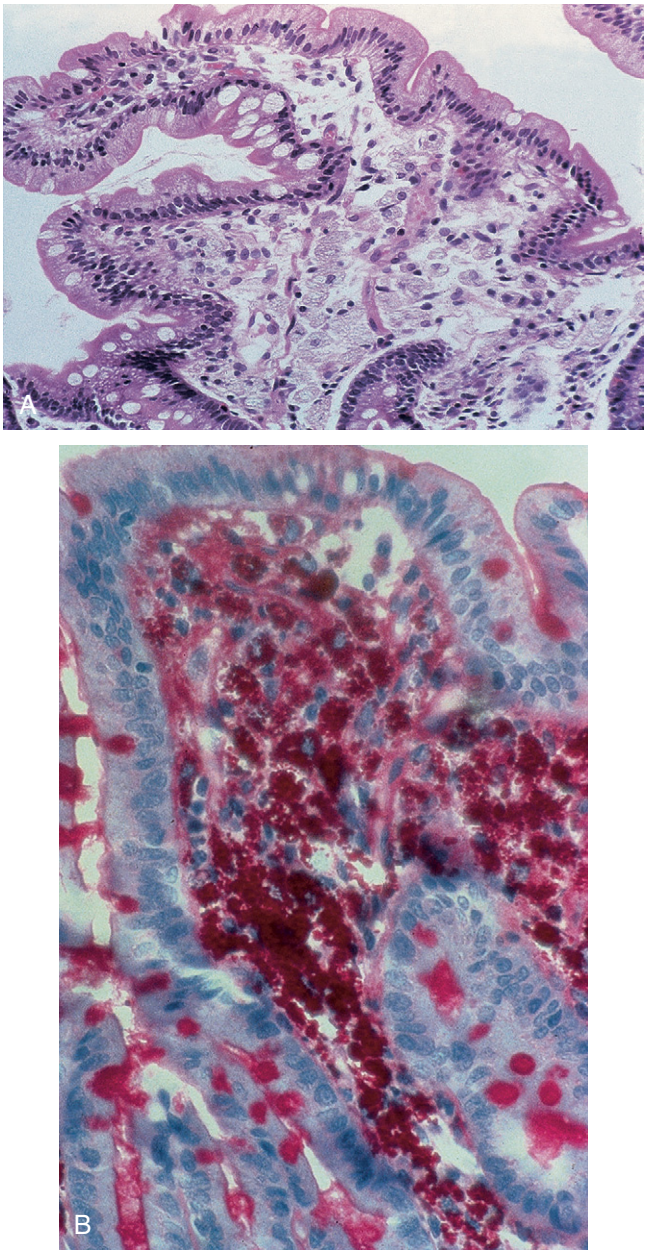

FIGURE 4-16 Whipple's disease. **A,** Villi are distended by an infiltrate of foamy macrophages. **B,** The Whipple bacillus stains intensely with periodic acid–Schiff. (**A** and **B** courtesy of Dr. George F. Gray, Jr.)

yellow-white plaques, often with surrounding erythema and friability. Histologically, the characteristic lesion results from massive infiltration of the lamina propria and submucosa with foamy macrophages (Fig. 4-16A). The infiltrate often blunts and distends villi. Involvement may be diffuse or patchy. There is usually no associated mononuclear inflammatory infiltrate, but varying numbers of neutrophils may be present. The lamina propria may contain small foci of fat, and overlying vacuolization of enterocytes may occur as well.[74]

Whipple's bacillus was identified as *T. whippelii*, an actinobacterium, 84 years after Whipple initially reported this disease. This bacillus is strongly PAS positive (see Fig. 4-16B); electron microscopy and PCR assays may be diagnostic as well. The differential diagnosis includes, predominantly, *M. avium-intracellulare* infection. However, rarely, other intracellular organisms such as *Histoplasma* and *Rhodococcus* may simulate Whipple's disease.

Rhodococcus equi. These gram-positive coccobacilli may, occasionally, infect humans, particularly the immunocompromised. GI infection presents as chronic (often bloody) diarrhea and is generally a manifestation of systemic involvement. *R. equi* produces inflammatory polyps, sometimes with associated mesenteric adenitis. Histologically, polyps consist of organism-laden macrophages that pack the mucosa and submucosa, often with an associated granulomatous response. Organisms stain with PAS and Gram stains, and they may be partially acid-fast. The histologic features may mimic infection with *M. avium-intracellulare* or Whipple's disease.[75]

Rocky Mountain spotted fever *(Rickettsia rickettsii).* This disease is transmitted by bites of the common wood or dog tick. Many patients have significant GI findings, including nausea, vomiting, diarrhea, pain, and GI bleeding. These manifestations may precede the rash. Involvement of every portion of the GI tract has been documented.[76] Typical histologic findings include vasculitis, often with accompanying nonocclusive microthrombi, and hemorrhage. The inflammatory infiltrate is composed of mononuclear cells with occasional lymphocytes, macrophages, and neutrophils. Immunofluorescence staining demonstrates the organism, and serologic studies may also be of use.

Malakoplakia. This rare disorder may affect any portion of the GI tract. It consists of soft, yellow plaques containing a

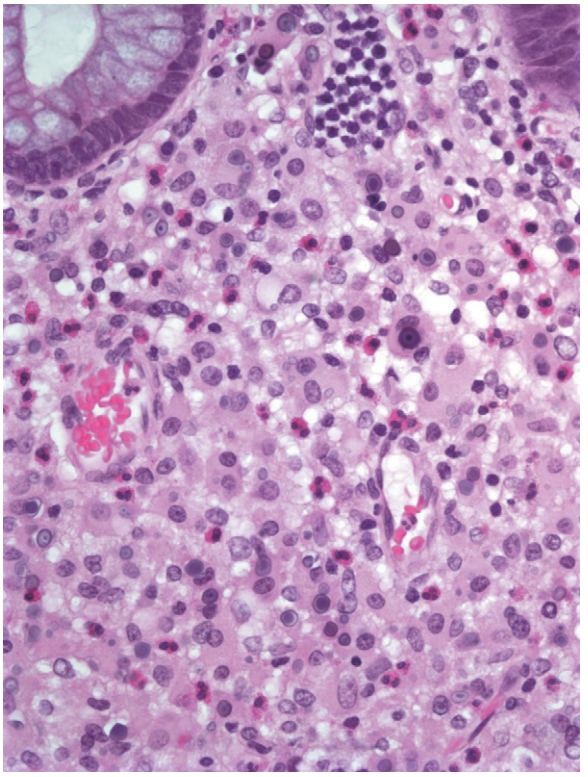

FIGURE 4-17 This colon resection shows multiple nodules of malakoplakia characterized by a macrophage infiltrate and numerous Michaelis-Gutmann bodies. (Courtesy of Dr. Joel K. Greenson.)

dense histiocytic infiltrate with characteristic Michaelis-Gutmann bodies (Fig. 4-17). The majority of cases are associated with colorectal adenocarcinoma or some other immunocompromising condition. Numerous bacteria have been associated with GI malakoplakia, including *E. coli, Klebsiella, Yersinia*, mycobacterial organisms, and *R. equi*.

Bacillary angiomatosis. These pyogenic granuloma-like lesions occur in immunocompromised patients and mimic Kaposi's sarcoma. They are usually associated with *Bartonella quintana*.

Helicobacter pylori and *Helicobacter heilmannii*. These bacteria are discussed in detail in Chapter 12.

Fungal Infections of the GI Tract

The importance of fungal infections of the GI tract has increased as the numbers of patients with organ transplants, AIDS, and other immunodeficiency states have risen. GI fungal infections occur mainly in immunocompromised patients, but virtually all have been described in immunocompetent persons as well. Signs and symptoms of GI fungal infections are, in general, similar, regardless of the type of fungus, and they include diarrhea, vomiting, melena, frank GI bleeding, abdominal pain, and fever. Esophageal fungal infections usually present with odynophagia and dysphagia. Fungal infections of the GI tract are often a part of a disseminated disease process, but GI symptoms and signs may be the presenting manifestations.

Other fungal infections that occasionally involve the GI tract, but are not discussed here, include *Blastomycosis dermatitidis, Paracoccidioides brasiliensis* (South American blastomycosis), and *Fusarium*.

Candida species. *Candida* is the most common infection of the esophagus, but it may infect any level of the GI tract. The GI tract is a major portal for disseminated candidiasis, as *Candida* often superinfects ulcers that develop from other causes. *Candida albicans* is most common, but *Candida tropicalis* and *Candida (Torulopsis) glabrata* may produce similar manifestations.[77]

Grossly, the esophagus typically contains white plaques that can be readily scraped off to reveal ulcerated mucosa underneath. The gross features of candidiasis in the remainder of the GI tract are variable and include ulceration, pseudomembrane formation, and inflammatory masses (Fig. 4-18A). If vascular invasion is prominent, the bowel may appear infarcted.[78] Involvement may be diffuse or segmental.

The associated inflammatory response ranges from minimal (especially in immunocompromised patients) to marked with prominent neutrophilic infiltrates, abscess formation, erosion or ulceration, and necrosis. Granulomas are occasionally present as well. Fungi may invade any level of the gut wall. Invasion of mucosal and submucosal blood vessels is sometimes a prominent feature in invasive *Candida* infection.[77,78] *C. albicans* and *C. tropicalis* produce a mixture of budding yeast forms, hyphae, and pseudohyphae (see Fig. 4-18). *C. glabrata* features tiny budding yeast forms (similar to those of *Histoplasma*) but does not produce hyphae or pseudohyphae.[79]

Aspergillus species. *Aspergillus* infection of the GI tract occurs almost exclusively in immunocompromised patients and is much less frequently seen in the esophagus than is candidiasis. Gross findings are similar to those seen with *Candida* infection.[78] The majority of patients with aspergillosis have coexistent lung lesions.

The characteristic histologic lesion of aspergillosis is a nodular infarction consisting of a zone of ischemic necrosis centered on blood vessels containing fungal organisms (Figs. 4-19 and 4-20). Fungal hyphae often extend outward from the infarct, in parallel or radial arrays. The inflammatory response ranges from minimal to marked, with a prominent neutrophilic infiltrate, and granulomatous inflammation may develop as well.[79] Transmural infarction of the bowel wall is common. The typical hyphae of *Aspergillus* are septate, and they branch at acute angles.

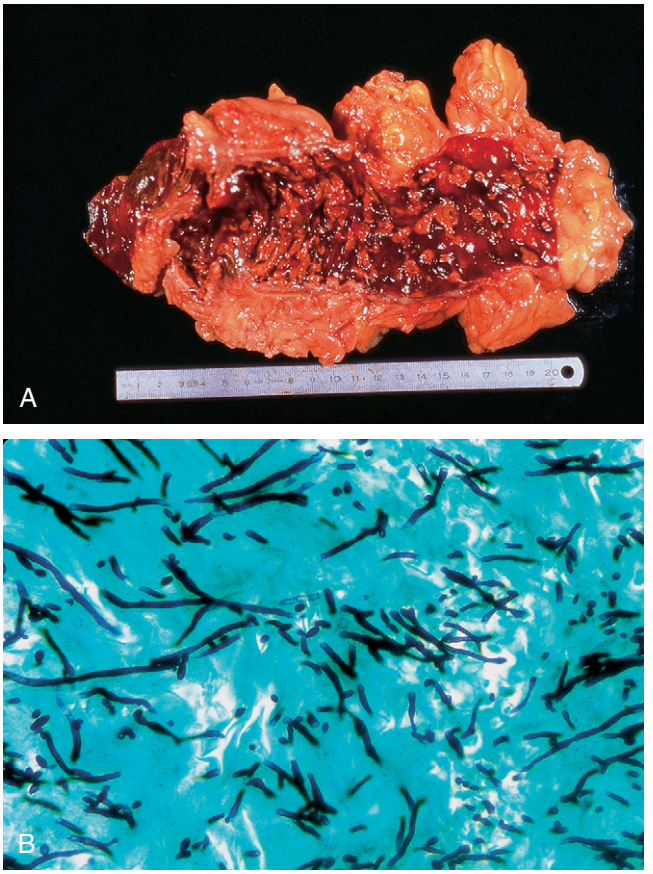

FIGURE 4-18 A, Colonic candidiasis featuring yellow-white plaques with associated marked mucosal ulceration. (Courtesy of Dr. Cole Elliott.) **B,** Gomori's methenamine silver staining shows the mixture of budding yeast and pseudohyphae typical of *Candida* species.

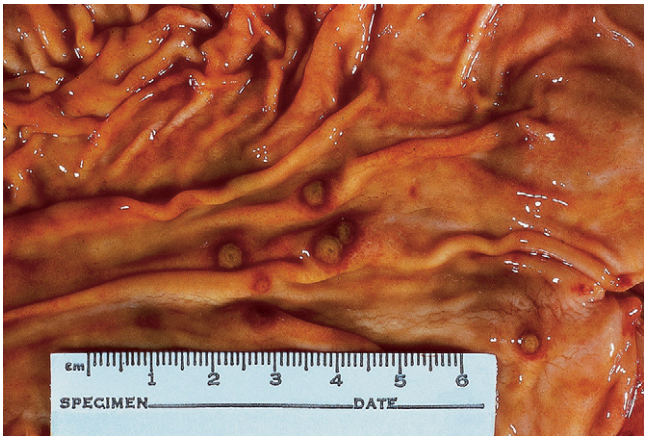

FIGURE 4-19 Typical "target lesion" of aspergillosis, shown in the stomach, consisting of hemorrhagic infarction and necrosis centered on a blood vessel.

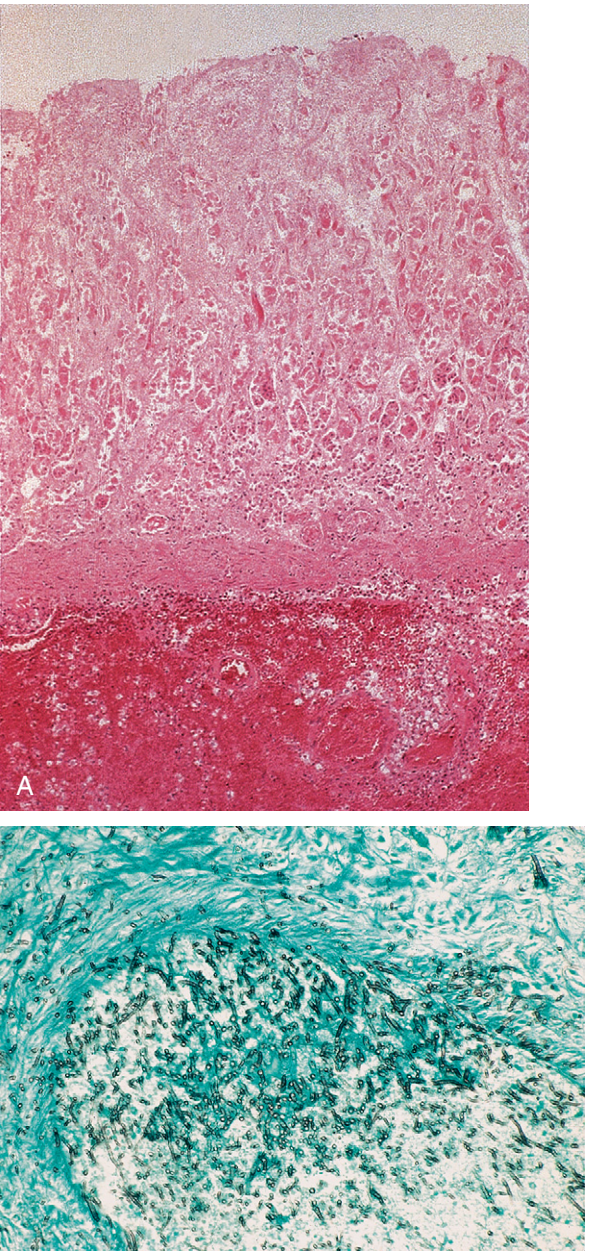

FIGURE 4-20 A, Ischemic necrosis of the mucosa and submucosa in a case of gastric aspergillosis. **B,** *Aspergillus* organisms fill and penetrate a vessel in the submucosa (Gomori's methenamine silver).

Mucormycosis and related zygomycoses. The histologic lesions of mucormycosis and related zygomycoses are remarkably similar to those seen in aspergillosis. In contrast to *Aspergillus*, these organisms have broad, ribbon-like, pauciseptate hyphae that branch randomly at various angles.[79] Ulcers are the most common gross manifestation, often large with rolled, irregular edges that may mimic malignancy. These fungi may also superinfect previously ulcerated tissues. Patients with diabetes, or with other causes of systemic acidosis, are at increased risk for developing zygomycosis.[80]

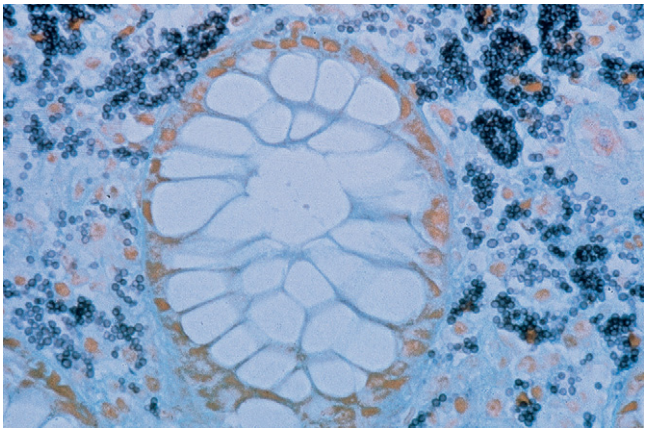

FIGURE 4-21 Numerous *Histoplasma* organisms are seen distending histiocytes in the lamina propria on this Gomori's methenamine silver stain. (Courtesy of Dr. Patrick J. Dean.)

Histoplasmosis. *Histoplasma capsulatum* is endemic to the central United States but has been described in many nonendemic areas as well. GI involvement occurs in more than 80% of patients with disseminated infection. Patients often present initially with signs and symptoms of GI illness, but they do not always have concomitant pulmonary involvement.[81]

The ileum is the most common site, but any portion of the GI tract may be involved. Gross lesions range from normal to ulcers, nodules, and obstructive masses. Often, a combination of these lesions is present. Histologic findings include diffuse lymphohistiocytic infiltrates and nodules, usually involving the mucosa and submucosa, with associated ulceration (Fig. 4-21). These lesions are usually located over Peyer's patches. Discrete granulomas, and giant cells, are present in only a minority of cases. In immunocompromised patients, large numbers of organisms may be seen with virtually no tissue reaction.[81] *Histoplasma* organisms are small, ovoid, usually intracellular yeast forms with small buds at the more pointed pole.

Cryptococcus neoformans. This fungus is an unusual but important cause of GI infection. Virtually all patients with GI cryptococcosis have hematogenously disseminated disease with multisystem organ involvement, and most have associated pulmonary and meningeal disease.[82]

Grossly, cryptococcal infection may be located anywhere in the GI tract. Endoscopic lesions include nodules and ulcers, sometimes associated with a thick white exudate. However, the mucosa is normal in many cases.[82]

Histologic features include typical round-to-oval yeast forms with narrow-based budding; and cryptococci may show considerable variation in size. Occasionally, they produce hyphae and pseudohyphae. Often a halo effect can be seen with H&E staining, representing the capsule of the organism. Both superficial and deep involvement may occur, and lymphatic involvement is not uncommon. The

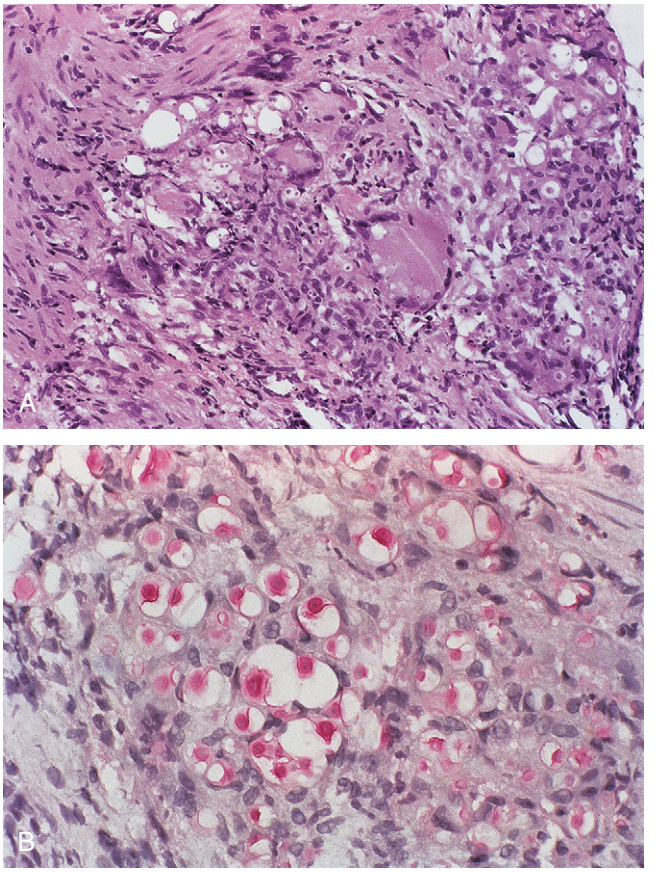

FIGURE 4-22 This case of gastric cryptococcosis features a granulomatous reaction with associated giant cells and acute inflammation. **A,** A halo effect can be seen around the organisms. **B,** The round to oval yeast forms have a mucopolysaccharide capsule that stains with mucicarmine. (Courtesy of Dr. Kay Washington.)

inflammatory reaction is variable and depends on the immune status of the host, ranging from a suppurative, necrotizing inflammatory reaction, often with granulomatous features (Fig. 4-22A), to virtually no reaction such as in anergic hosts.[79,82] The mucopolysaccharide capsule stains with alcian blue, mucicarmine (see Fig. 4-22B), and colloidal iron; GMS stains are positive as well. Unfortunately, capsule-deficient cryptococci can pose a diagnostic challenge, but most have sufficient capsular material left to be seen with mucin stains.[79,82]

Pneumocystis carinii. Although the life cycle of this organism more closely resembles that of a protozoan, there is convincing molecular evidence indicating that *P. carinii* has greater homology with fungi. *P. carinii* pneumonia is a major cause of morbidity in the AIDS population, and extrapulmonary (including GI) involvement is not uncommon.[83]

Endoscopically, *P. carinii* infection resembles a nonspecific, often erosive, esophagogastritis or colitis, sometimes with small polypoid nodules. Microscopically, granular,

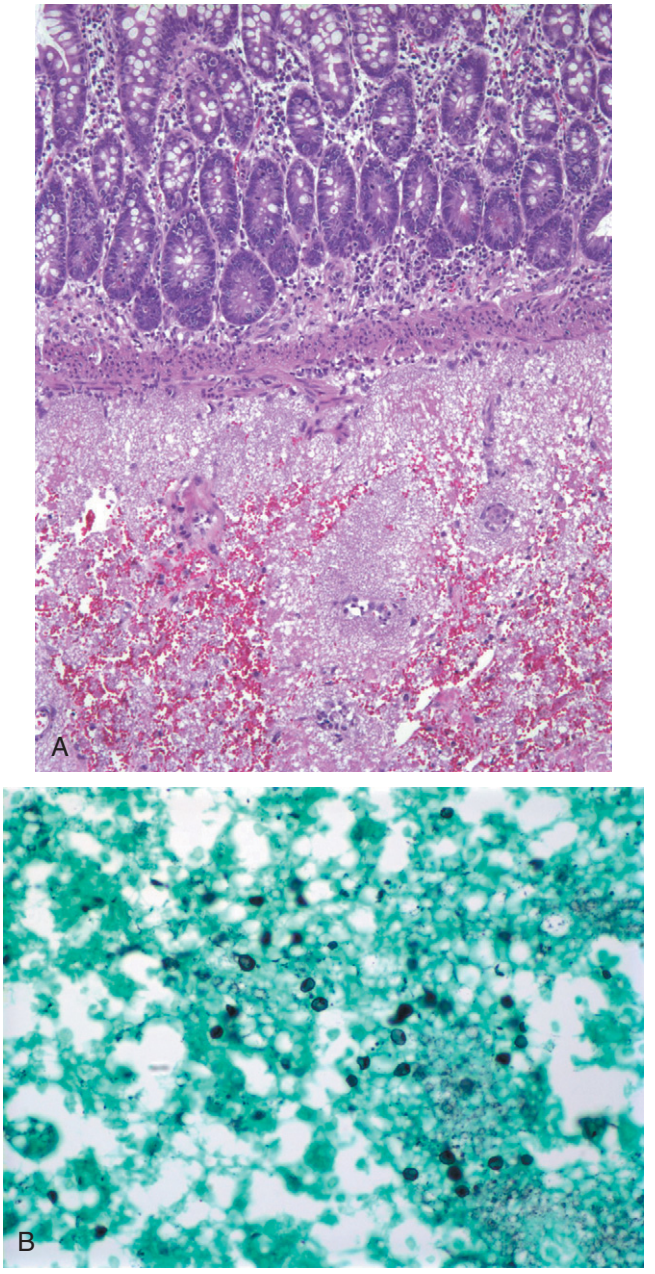

FIGURE 4-23 A, Small bowel resection showing the characteristic foamy casts of *Pneumocystis carinii* in the submucosa. **B,** Gomori's methenamine silver stain highlights numerous cyst forms with central enhanced staining. (Courtesy of Dr. Henry Appelman.)

foamy eosinophilic casts common to pulmonary infection may be seen in mucosal vessels or in the lamina propria (Fig. 4-23).[83] As in the lung, a wide variety of inflammatory responses may occur, including granulomatous inflammation, prominent macrophage infiltrates, and necrosis.

The fungi can usually be correctly identified in tissue sections on the basis of morphologic criteria (Table 4-4). Although organisms may be identifiable on H&E sections in heavy infections, GMS and PAS stains remain valuable diagnostic aids. However, culture is ultimately the gold standard for speciation. In fact, antifungal therapy may vary according to the specific type of fungus involved. Furthermore, fungi exposed to antifungal therapy or ambient air may produce bizarre and unusual forms. Helpful diagnostic aids, in addition to culture, include serologic assays, antigen tests, and immunohistochemistry.

The differential diagnosis of fungal infections includes other infectious processes, and occasionally Crohn's disease, ulcerative colitis, sarcoidosis, and ischemic colitis.

Parasitic Infections of the GI Tract

PROTOZOAL INFECTIONS

Protozoa are prevalent pathogens in tropical and subtropical countries, but they cause some of the most common intestinal infections in North America and Europe as well. Immigration, increasing numbers of immunocompromised patients, use of institutional child-care facilities, and the development of improved diagnostic techniques have enhanced our understanding and recognition of these protozoa.[84,85] Many protozoal illnesses are diagnosed by examination of stool samples, but they are also important to the surgical pathologist.

Entamoeba histolytica

Approximately 10% of the world's population is infected with the *E. histolytica* parasite, predominantly in tropical and subtropical regions. Male homosexuals in Western countries also commonly harbor this pathogen. Although some patients suffer a severe, dysentery-like, fulminant colitis, many others are asymptomatic or show only vague GI symptoms.[86] Complications include bleeding and dissemination to other sites, particularly the liver. Rarely, large inflammatory masses (amebomas) may form.

Grossly, small ulcers are initially seen, but these may coalesce to form large, irregular, geographic or serpiginous ulcers. Ulcers may undermine adjacent mucosa to produce classic "flask-shaped" lesions (Fig. 4-24A), and there may be associated inflammation or inflammatory polyps as well. The intervening mucosa is often normal. The cecum is the most common site of involvement, but any portion of the large bowel or appendix may be infected. Fulminant colitis, resembling ulcerative colitis; pseudomembranous colitis, resembling that caused by *C. difficile*; and toxic megacolon have all been described in association with *E. histolytica* infection.[87] Colonoscopy may be normal in asymptomatic patients or in those with mild disease.[86]

Histologically, early lesions show a mild neutrophilic infiltrate. In more advanced disease, ulcers are often deep, extending into the submucosa, with undermining of adjacent normal mucosa (see Fig. 4-24A). There is usually abundant necroinflammatory debris. The organisms are generally found in the purulent material. Invasive amebae are also occasionally present in the bowel wall. Adjacent

TABLE 4-4 Morphologic Features of Fungi Seen in the GI Tract

Organism	Morphologic Features	Host Reaction	Major Differential Diagnoses
Aspergillus species	Hyphae: septate, uniform width Branching: regular, acute angles Conidial head formation in cavitary lesions	Ischemic necrosis with angioinvasion Acute inflammation Occasionally granulomatous	Zygomycetes *Fusarium* *Pseudallescheria boydii*
Zygomycetes	Hyphae: pauciseptate, ribbon-like, thin walls Branching: haphazard	Similar to *Aspergillus*	Similar to *Aspergillus*
Candida albicans *Candida tropicalis*	Mixture of budding yeast and pseudohyphae; occasional septate hyphae	Usually suppurative May be necrotic and ulcerative Occasionally granulomatous Occasional angioinvasion	*Trichosporon*
Candida glabrata	Budding yeast No hyphae No halo effect	Similar to other *Candida* species	*Histoplasma* *Cryptococcus*
Cryptococcus neoformans	Pleomorphic Narrow-based buds Usually mucicarmine positive	Usually suppurative May have extensive necrosis Sometimes granulomatous	Histoplasmosis Blastomycosis *C. glabrata*
Histoplasma capsulatum	Ovoid, narrow-based buds Intracellular Halo effect around organism on H&E	Lymphohistiocytic infiltrate with parasitized histiocytes Occasional granulomas	*Cryptococcus* *Penicillium marneffei* *C. glabrata* Intracellular parasites *Pneumocystis carinii*
Pneumocystis carinii	Ovoid Central enhanced staining Foamy casts	Ranges from suppurative to granulomatous	Histoplasmosis Small parasites

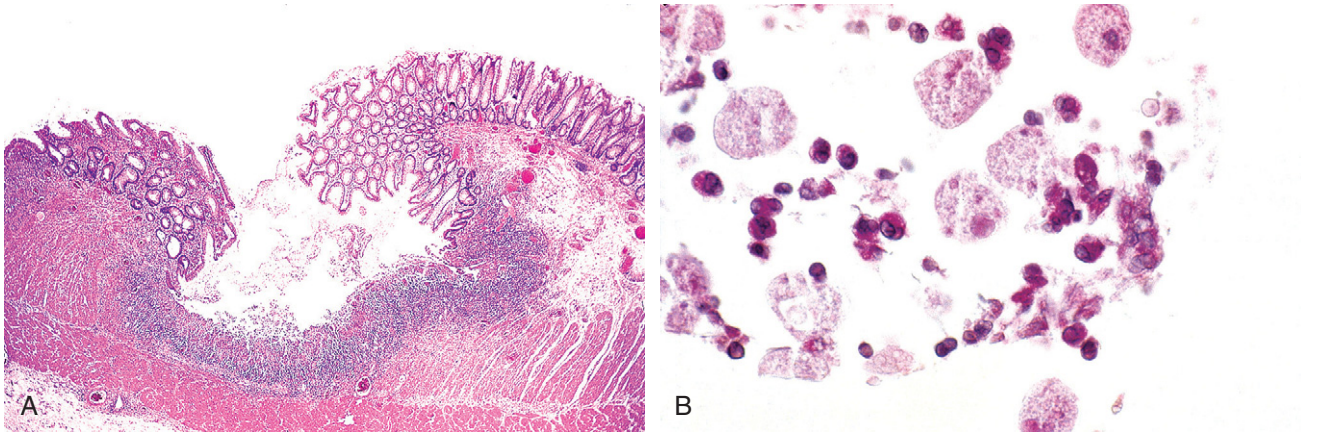

FIGURE 4-24 A, This entamebic ulcer is deep and flask-shaped, undermining adjacent normal mucosa. **B,** *Entamoeba histolytica* in the inflammatory exudates, containing ingested erythrocytes.

mucosa is usually normal but may show gland distortion and inflammation. The organisms may be few in number. They resemble macrophages, with foamy cytoplasm and round, eccentric nuclei. The presence of ingested red blood cells (see Fig. 4-24B) is pathognomonic of *E. histolytica*.[87] In asymptomatic patients or those with only mild symptoms, histologic changes may range from normal to a heavy mixed inflammatory infiltrate. Organisms may be particularly difficult (if not impossible) to detect in these patients. Invasive amebiasis does not generally occur in patients who have only mild, or absent, symptoms.[86]

Distinction of amebae from macrophages in inflammatory exudates may be difficult. However, amebae are trichrome and PAS positive. In addition, their nuclei are

usually more rounded and paler, and have a more open nuclear chromatin pattern (see Fig. 4-24B). Macrophages stain with alpha-1-antitrypsin and chymotrypsin, whereas amebae do not. The differential diagnosis of amebiasis also includes Crohn's disease, ulcerative colitis, and other types of infectious colitis. Although some features of amebiasis may mimic idiopathic inflammatory bowel disease, many of the other diagnostic features of Crohn's disease (e.g., transmural lymphoid aggregates, mural fibrosis, granulomas, neural hyperplasia) and ulcerative colitis (e.g., basal lymphoplasmacytosis, diffuse architectural distortion, pancolitis) are not typically present in amebiasis.

Flagellates

Giardia lamblia. Giardiasis is the leading GI protozoal disease in the United States. The overall prevalence rate is 2% to 7%, but it is up to 35% in day care centers. Patients often present with explosive, foul-smelling, watery diarrhea, abdominal pain and distension, nausea, vomiting, malabsorption, and weight loss. The infection may resolve spontaneously but often persists for weeks or months if left untreated.[88,89] The cyst, which is the infective form, is extremely hardy, is chlorine resistant, and may survive in water for several months. However, the mechanism by which these organisms cause GI illness is poorly understood.

Endoscopic examination is generally unremarkable, and small intestinal biopsies are often normal in appearance. However, rarely, biopsies may show mild to moderate villous blunting and increased lamina propria inflammatory cells including neutrophils, plasma cells, and lymphocytes. *Giardia* trophozoites resemble pears that are cut lengthwise and contain two ovoid nuclei with a central karyosome at the luminal surface (Fig. 4-25).[88] Tissue invasion is not a feature of this infection. Although *Giardia* is characteristically described as a small bowel inhabitant, colonization of the stomach and colon has also been reported.[88] Absence or a marked decrease of plasma cells in the lamina propria in a patient with giardiasis should alert the pathologist to the possibility of an underlying immunodeficiency disorder (see Chapter 5).

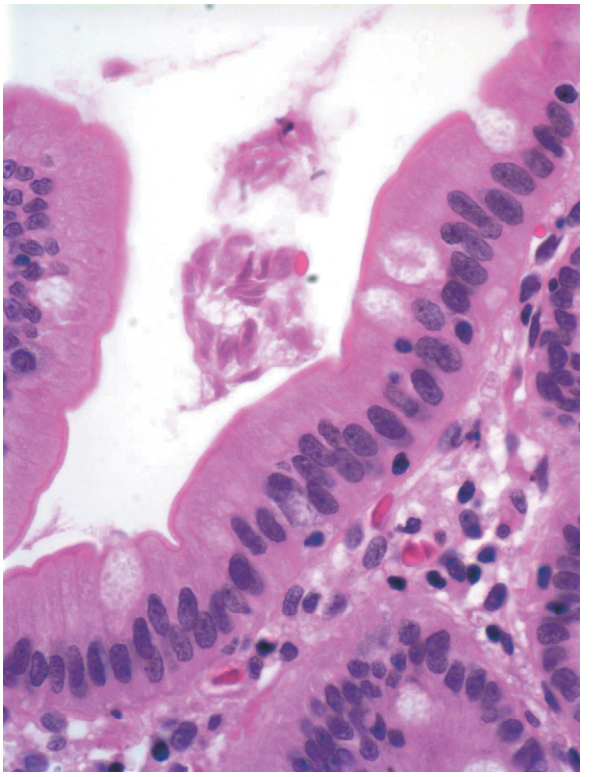

FIGURE 4-25 Duodenal mucosa with numerous *Giardia* trophozoites at the luminal surface, without significant mucosal inflammation. (Courtesy of Dr. Rodger Haggitt.)

Leishmania donovani and related species. Leishmaniasis is endemic in over 80 countries in Africa, Asia, South and Central America, and Europe.[90] GI signs and symptoms include fever, abdominal pain, diarrhea, dysphagia, malabsorption, and weight loss. In fact, GI involvement is generally part of widely disseminated disease. Leishmaniae may be found at any level of the alimentary tract. The spectrum of endoscopic findings includes normal mucosa, focal ulceration, and changes of enteritis.[91]

Histologically, amastigote-containing macrophages are present in the lamina propria. In large numbers, macrophages may distend and blunt intestinal villi. An associated inflammatory infiltrate is normally absent. Amastigotes are round to oval, tiny organisms with a nucleus and kinetoplast in a "double-knot" configuration; they do not have typical flagella. They are highlighted by Giemsa staining. The differential diagnosis primarily includes other parasitic and fungal infections. *Leishmania* may be confused with organisms such as *Histoplasma* and *Trypanosoma cruzi*. Leishmaniae are GMS negative, and they affect the lamina propria rather than the myenteric plexus.[90,91] Serologic studies and immunohistochemistry may aid in the diagnosis.

Trypanosoma cruzi (Chagas' disease). Chagas' disease is one of the most serious public health problems in South America. Parasitic involvement of the enteric nervous system is common in this disease, and an achalasia-like megaesophagus and megacolon are the most frequent manifestations.[92] Histologically, there is inflammatory destruction of the myenteric plexus, with loss of up to 95% of neurons. However, the parasite is rarely visible in myenteric plexuses.[93] The differential diagnosis includes idiopathic primary achalasia as well as other visceral neuropathies. However, many of these latter disorders lack inflammation of the myenteric plexus. Unlike primary achalasia, Chagas' disease usually involves other organ systems (especially the heart) or other areas of the GI tract. Nevertheless, often the differential is resolved only clinically.

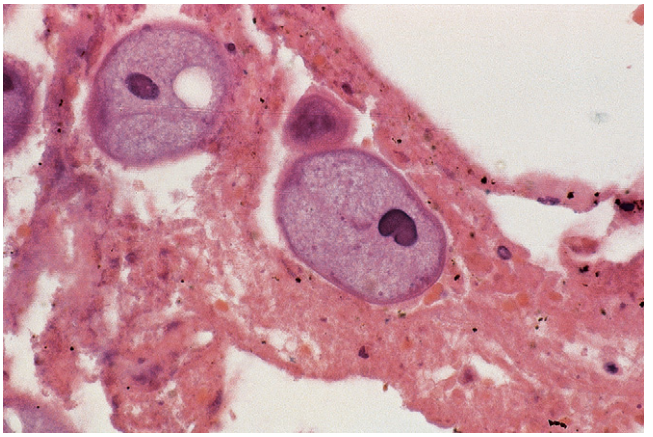

FIGURE 4-26 *Balantidium coli* in the bowel wall. Note the large size, the kidney bean–shaped nucleus, and cilia. (Courtesy of Dr. David Owen.)

Ciliates

Balantidium coli. This ciliate may produce a spectrum of clinical and pathologic changes similar to those produced by *E. histolytica*. *B. coli* cells are distinguished from amebae by their larger size, kidney bean–shaped nucleus, and, of course, the presence of cilia (Fig. 4-26).[94]

Coccidians

Coccidial infection is particularly important when considering the differential diagnosis of diarrhea in patients with AIDS, but it is also seen in healthy persons, including infants and children, in developing countries.[95] Transmission is normally via the fecal-oral route, either directly or via contaminated food and water.[96] All coccidians, except microsporidia (which is thought to be limited to immunocompromised patients) can cause diarrhea (often prolonged) in healthy patients, especially infants and children, travelers, and individuals who are institutionalized. Diarrhea may be accompanied by fever, weight loss, abdominal pain, and malaise. Stool does not usually contain red blood cells or leukocytes. In immunocompetent persons, infection is usually self-limited, but immunocompromised patients are at risk for chronic, severe diarrhea, with malabsorption, dehydration, and death.[96] Many coccidial infections are asymptomatic. Endoscopic findings are usually absent or mild and include mild erythema, mucosal granularity, mucosal atrophy, and superficial erosions.

Although electron microscopy was once considered the gold standard for diagnosis, it is expensive and not widely used. Examination of stool specimens may be very helpful (particularly with special stains), but analysis of mucosal biopsy specimens is more sensitive. Enzyme-linked immunosorbent assay (ELISA) techniques, immunohistochemistry, and PCR studies are also available for diagnosis of these parasites.[95]

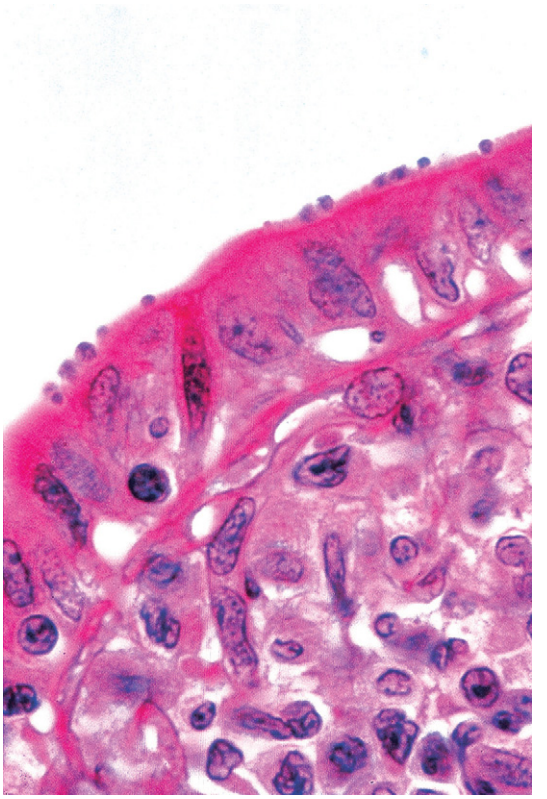

FIGURE 4-27 *Cryptosporidium parvum*. The 2- to 5-mμ basophilic spherical bodies protrude from the apex of the enterocytes. (Courtesy of Drs. Mary Bronner and Rodger Haggitt.)

Cryptosporidium parvum. This organism is most common in the small bowel, but it may infect any segment of the GI tract. The characteristic biopsy appearance is that of a 2- to 5-μm basophilic spherical body that protrudes from the apex of the enterocyte (Fig. 4-27).[97] The organisms are found in the crypts or in the surface epithelium. Associated mucosal changes include villous atrophy (occasionally severe), crypt hyperplasia, mixed inflammation, and crypt abscesses. Giemsa stain may aid in diagnosis, and immunohistochemical antibodies are available. *Cryptosporidium* may be distinguished from most other coccidians by their size and unique apical location. Although *Cyclospora* is similar in appearance, it is much larger (8 to 10 μm).

Cyclospora cayetanensis. This organism most commonly infects the small bowel. Histologic changes in mucosal biopsies are similar to other coccidians.[98] This 8- to 10-μm parasite is normally located in enterocytes but, like *Cryptosporidium*, can be present in the cell surface. There are few detailed light microscopic descriptions of this parasite, and there is disagreement about their features in tissue sections. They may be either crescent or ovoid in shape, and they are sometimes located in a parasitophorous vacuole.[99] The organisms are acid-fast with modified Kinyoun or similar stains, and they are positive with aura-

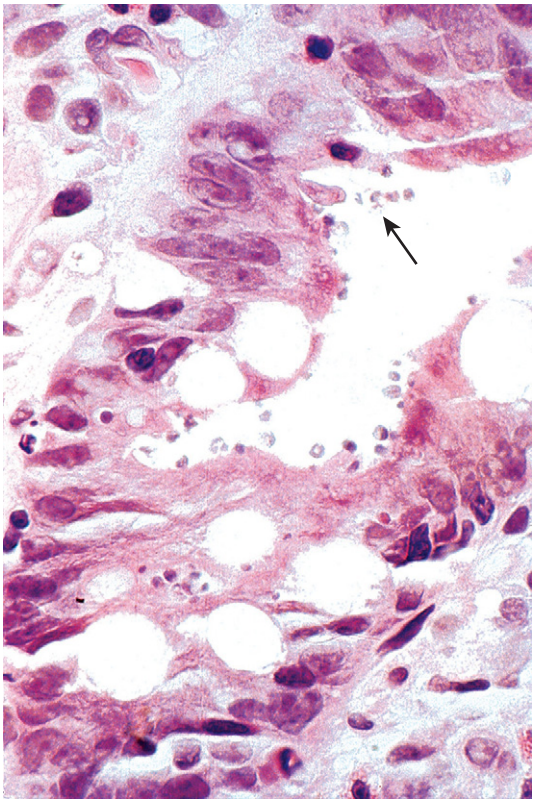

FIGURE 4-28 This patient with AIDS has both *Cryptosporidium* and *Cyclospora* infections. Cryptosporidia are 2 to 5 mμ in size and are located at the apex of the enterocytes *(arrow)*. The round to ovoid *Cyclospora* is similar in appearance but much larger (8 to 10 mμ).

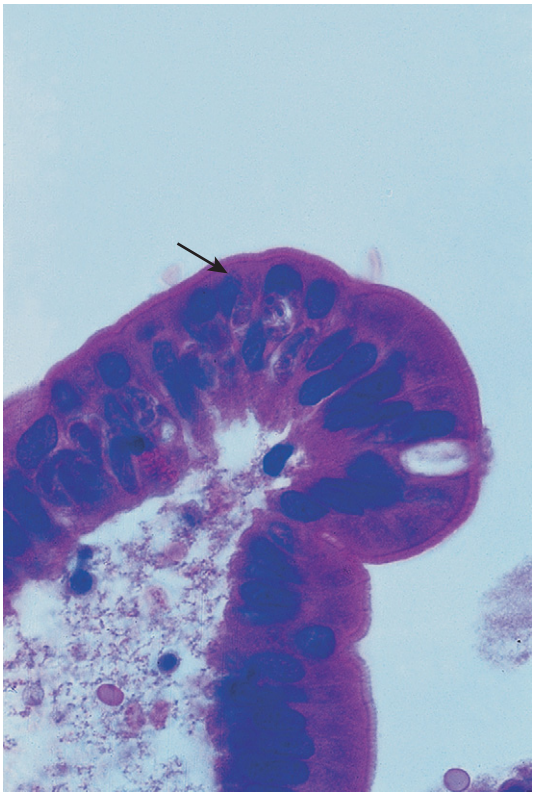

FIGURE 4-29 *Isospora belli*. Banana-shaped intraepithelial inclusions *(arrow)* are seen in apical enterocytes. (Courtesy of Dr. Audrey Lazenby.)

mine. However, they are GMS negative. The major differential diagnosis is with *Cryptosporidium*, but *Cyclospora* organisms are much larger (Fig. 4-28), and they exhibit autofluorescence under epifluorescent light.[98] When crescent-shaped, the organisms may be confused with *Isospora*, which is generally larger.

Isospora belli and related species. The small bowel is the most common site of *Isospora* infection, but the colon may also be involved. *Isospora* may also disseminate widely. Histologic changes include villous blunting, which may be severe, crypt hyperplasia, mixed inflammation, often with prominent eosinophils, and, in chronic infections, fibrosis of the lamina propria. Intraepithelial inclusions, both perinuclear and subnuclear, may be present at all stages of infection. Rarely, organisms are also present in the lamina propria or in macrophages.[100,101] When motile, these parasites are large and banana-shaped, but (Fig. 4-29) as trophozoites they are round with a prominent nucleus. At some stages of infection, the parasites are surrounded by a parasitophorous vacuole. GMS and Giemsa stains are useful to highlight the organism. *Isospora* species are PAS positive but may be easily confused with goblet cells. They are differentiated from other coccidia by their large size and intracellular location. Also, patients with isosporiasis are more likely to have peripheral eosinophilia.

Microsporidia. *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common human pathogens in this group. They are usually present in the small bowel, but any level of the GI tract may be affected. Microsporidia are difficult to detect in H&E-stained sections. The histologic features include patchy villous blunting, vacuolization of the surface epithelium, and patchy lymphoplasmacytic infiltrates in the lamina propria.[102,103] A modified trichrome stain can aid greatly in the diagnosis (Fig. 4-30), and the organisms also stain with Warthin-Starry and Brown-Brenn stains. Occasionally, microsporidial organisms in biopsy specimens demonstrate birefringence under polarized light because of their chitin-rich internal polar filament. However, this method is unreliable because spore birefringence is unpredictable and because microscopes and light sources vary.

Toxoplasma gondii. GI toxoplasmosis is primarily a disease of immunocompromised hosts. Ulcers have been described and organisms are usually located in the ulcer base. Both crescent-shaped tachyzoites and tissue cysts containing

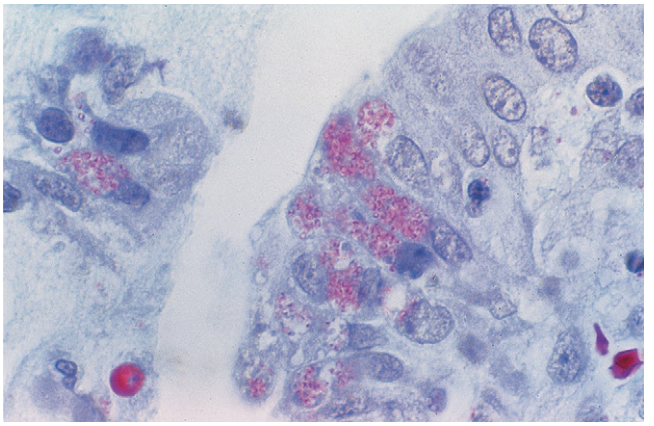

FIGURE 4-30 Tiny microsporidial organisms in enterocytes (modified trichrome).

bradyzoites may be present in tissue sections. Immunohistochemistry and PCR assays, as well as serologic tests, are useful diagnostic aids.[104]

Miscellaneous Protozoal Infections

Dientamoeba fragilis is an ameba of low pathogenicity that occasionally causes diarrhea in affected patients.[105,106] A variety of other amebae are also, occasionally, associated with mild GI disease, including *Entamoeba hartmanni, Entamoeba coli, Entamoeba polecki, Iodamoeba buetschlii*, and *Endolimax nana*. *Blastocystis hominis*, another protozoan of low pathogenicity, may cause enteric disease when present in large numbers.[107,108] However, these organisms are only rarely seen in tissue sections. Indeed, when protozoa of low pathogenicity are identified in tissue sections, symptomatic patients should be evaluated for alternative causes of GI disease.

HELMINTHIC INFECTIONS

Although the most common method of diagnosing GI helminth infections is examination of stool for ova and parasites, these organisms are occasionally detected in biopsy or resection specimens. Hookworms, roundworms (both *Ascaris* and *Enterobius*), and whipworms are the most common helminthic infections in man.[109] GI helminths have a worldwide distribution, but their clinical importance varies with the geographic region. They are more often a cause of serious disease in nations with deficient sanitation systems, poor socioeconomic status, and hot, humid climates. However, helminthic infections are seen in immigrants and in patients who travel to endemic areas, and they are an increasingly important problem in immunocompromised hosts. Nutritional problems caused by helminths can be severe and even life-threatening, especially in children.[109] The most common site of anatomic infection is the small bowel, although the stomach and large bowel may also be involved.[110]

Nematodes

Enterobius vermicularis. Pinworms are one of the most common human parasites. They have a worldwide distribution but are more common in cold or temperate climates and in developed countries. They are extremely common in the United States and northwestern Europe. The infective egg resides in dust and soil, and transmission is believed to be by the fecal-oral route. The worms live and reproduce in the ileum, cecum, proximal colon, and appendix, and then the female migrates to the anus to lay eggs and die. The eggs and worms produce symptoms of pruritus ani. Although many infections are asymptomatic, appendicitis, vulvovaginitis, colitis, and peritoneal involvement have all been described.[110,111] Heavy infections may cause abdominal pain, nausea, and vomiting.

The etiologic role of *Enterobius* in appendicitis and colitis is controversial. Although pinworms are detected in approximately 0.6% to 13% of resected appendices, their ability to cause mucosal damage has been a subject of debate.[112] Some believe that the lack of inflammation surrounding invasive pinworms indicates that the organism invades only after the appendix has been removed, thus to escape the decrease in oxygen tension.[111] However, *Enterobius* organisms are, in fact, capable of mucosal invasion,[111] and, like fecaliths, they can obstruct the appendiceal lumen and cause inflammation.

The worms are 2 to 5 mm in length and thus may be seen with the naked eye (Fig. 4-31). Although the mucosa of the GI tract often appears normal on examination, hemorrhage and ulceration may occur with tissue invasion.

Invasive pinworms incite little or no inflammatory reaction, but an inflammatory infiltrate composed of neutrophils and eosinophils may occur uncommonly. Granulomas, sometimes with necrosis, may develop as a reaction to degenerating worms or eggs. These have been described in the omentum and peritoneum, as well as in the appendix, anus, and colon in rare cases.[111] Primary *Enterobius* infection may be difficult to distinguish from infection complicating a preexisting inflammatory disorder, such as an inflamed anal fissure.

Ascaris lumbricoides (roundworm). *Ascaris* is one of the most common parasites in humans. It has a worldwide distribution but is most common in tropical regions of the world. The worms are ingested from soil contaminated with feces. Clinical findings are variable and include appendicitis, massive infection with obstruction and perforation, childhood growth retardation, and pancreaticobiliary obstruction. Giant worms (up to 20 cm in length) may be identified endoscopically or in resection specimens (Fig. 4-32). Tissue damage occurs primarily at the anatomic sites of attachment.[110]

Ancylostomiasis (hookworm). Hookworm (*Necator americanus* and *Ancylostoma duodenale*) is a common parasite in all tropical and subtropical countries. The worms attach

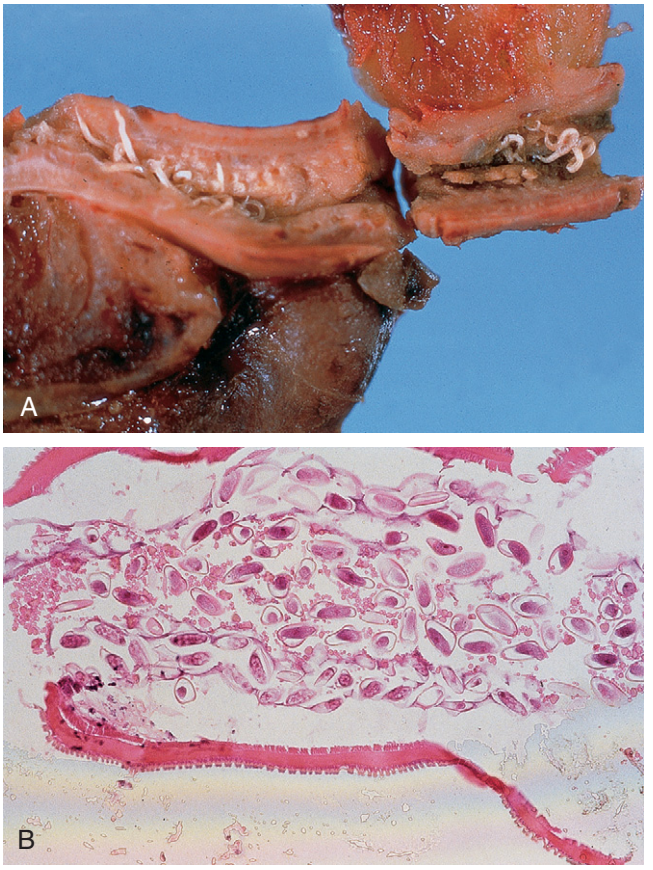

FIGURE 4-31 **A,** Appendix containing numerous pinworms. (Courtesy of Dr. George F. Gray, Jr.) **B,** Section of worm showing cuticle and numerous eggs characteristic of *Enterobius vermicularis*.

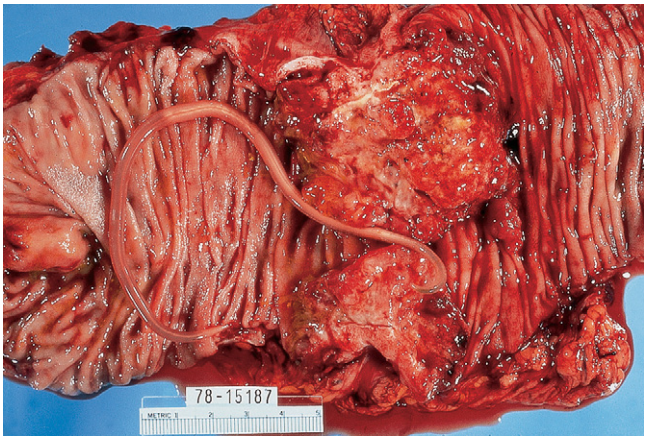

FIGURE 4-32 *Ascaris* atop colon cancer at resection. (Courtesy of Dr. George F. Gray, Jr.)

to the intestinal wall and withdraw blood from villous capillaries, which results in anemia. Other clinical symptoms include abdominal pain, diarrhea, hypoproteinemia, and cough with eosinophilia when the worms migrate.[109] Any level of the GI tract may be involved. Endoscopically, the worms (which measure about 1 cm in length) are visible to the naked eye. Histologic changes are often minimal but may include villous blunting and eosinophilic infiltration.[110] Pieces of worm are occasionally detected in biopsy specimens.

Trichuris trichiura (whipworm). Whipworm is a soil helminth with a worldwide distribution. Although most infections are asymptomatic, some patients develop diarrhea, GI bleeding, malabsorption, anemia, and appendicitis. An ulcerative inflammatory process similar to Crohn's disease and rectal prolapse have also been described.[109,110] The worms live in the small and large intestines, primarily the right colon and ileum. They may cause mucosal hemorrhage and ulceration. The worms are 3 to 5 mm in length and have a characteristic whiplike tail. They may be seen endoscopically. Histologically, the worms thread their anterior end under epithelium, which may produce enterocyte atrophy and an associated mixed inflammatory infiltrate. Crypt abscesses may also be present.[110,113]

Strongyloides stercoralis. *S. stercoralis* is a nematode with a worldwide distribution. In the United States, it is endemic in southeastern urban areas with large immigrant populations, and in mental institutions. *Strongyloides* occurs primarily in adults, many of whom are hospitalized, suffer from chronic illnesses, or are immunocompromised.[114,115] Steroids and human T lymphotropic virus type-1 infection are also associated with strongyloidiasis.[116] Symptoms and signs include diarrhea, abdominal pain and tenderness, nausea, vomiting, weight loss, malabsorption, and GI bleeding. Mesenteric lymphadenopathy may also occur.[117] GI manifestations may be accompanied by rash, eosinophilia, urticaria, pruritus, and pulmonary symptoms.[110,114] However, many patients are asymptomatic.

The *S. stercoralis* worm penetrates the skin, enters the venous system, travels to the lungs, and then migrates up the respiratory tree and down the esophagus to eventually reach the small intestine. The female lives and lays eggs in the small intestine, thus perpetuating the organism's life cycle. This autoinfective capability allows the organism to reside in the host and produce illness for a long time, upward of 30 years. In addition, widespread dissemination may occur in immunocompromised patients, causing severe and even fatal illness.[110,114]

Lesions may be seen in the stomach, as well as in the small and large intestine. Endoscopic findings include hypertrophic mucosal folds and ulcers. However, features typical of pseudomembranous colitis have also been reported. Histologically, both adult worms and larvae may be found in the crypts, but they may be difficult to detect. Adult worms typically have sharply pointed tails that may be curved (Fig. 4-33). Other histologic features include villous blunting, ulcers (which may be fissuring), edema, and a dense eosinophilic and neutrophilic infiltrate. Granulomas are occasionally present as well.[110,114]

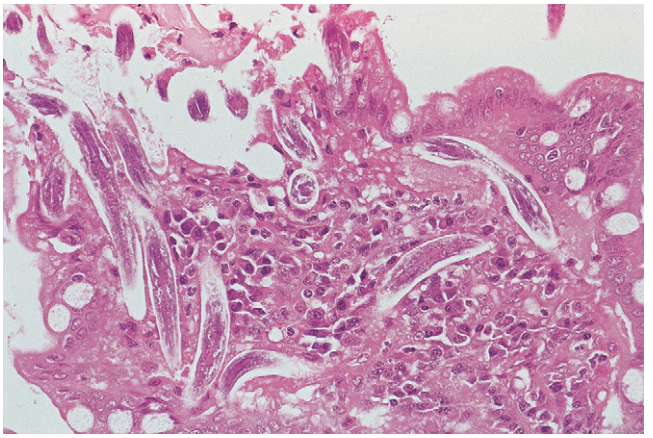

FIGURE 4-33 *Strongyloides stercoralis* infection in the small bowel. Typical worms with curved, sharply pointed tails are present in crypts and lamina propria, accompanied by a neutrophilic infiltrate. (Courtesy of Dr. James A. Waldron.)

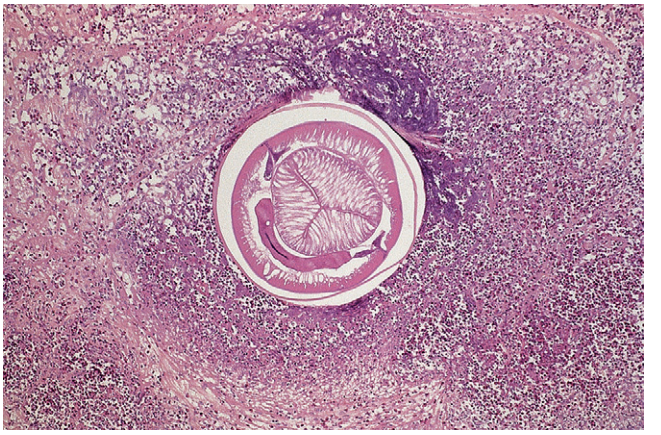

FIGURE 4-34 Gastric anisakiasis. Large *Anisakis* worm in the center of a submucosal eosinophilic and neutrophilic abscess. (Courtesy of Dr. David Owen.)

Anisakis simplex (anisakiasis) and related species. These nematodes parasitize fish and sea mammals, so humans ingest them by eating raw or pickled fish. The most common clinical manifestations are those of acute gastric anisakiasis, characterized by epigastric pain, nausea, and vomiting within 12 hours of ingestion of parasitized food. The symptoms may mimic peptic ulcer disease.[110,118] The allergenic potential of *Anisakis* species has also been recognized, and some patients with gastroallergic anisakiasis manifest both GI and hypersensitivity symptoms such as urticaria, angioedema, eosinophilia, and anaphylaxis.[118]

The stomach is the most frequent site of involvement, although the small bowel, colon, and appendix may also be involved. Endoscopic findings include mucosal edema, hemorrhage, erosions, ulcers, and thickened mucosal folds. Occasionally, larvae may be identified, and removed, endoscopically. Histologic findings include an inflammatory infiltrate rich in eosinophils, which may extend transmurally into serosal and mesenteric tissues (Fig. 4-34). Eosinophilic microabscesses, granulomas, and giant cells may also develop. Inflammatory changes usually surround worms. Larvae (from 0.5 to 3.0 cm in length) are occasionally seen in tissue sections, but very rarely in stool samples.[119,120]

Capillaria species (intestinal capillariasis). *Capillaria* infection is most common in the Philippines, Thailand, and other parts of Asia, although cases have been reported in nonendemic areas. The worms are ingested by eating infected raw fish. Clinical signs and symptoms include malabsorption accompanied by diarrhea and abdominal pain. The worms measure 2 to 4 cm in length and are most commonly found in the crypts of the small bowel, although they may also invade the lamina propria. Although there is usually an absence of an inflammatory reaction, villous blunting, mucosal sloughing, and mild inflammatory changes have been described.[109,121]

Trematodes

Schistosomiasis. All *Schistosoma* species have the capability to cause significant GI disease. Patients generally present with diarrhea (often bloody), accompanied by anemia, weight loss, and protein-losing enteropathy. More dramatic GI presentations have also been described, such as profound dysentery-like illness, obstruction, perforation, intussusception, rectal prolapse, fistulae, and perianal abscesses.[110,122] Any level of the GI tract may be affected. Endoscopically, *Schistosoma* can be seen to cause inflammatory polyposis (particularly in the distal colon) with associated mucosal granularity, friability, punctate ulcers, and hemorrhages. Histologically, inflammatory polyps and mucosal ulcers, with associated granulomatous inflammation and an eosinophilic infiltrate, are typical. Eggs may be detected in histologic specimens and are sometimes calcified.[110,123] In fact, worms are occasionally seen in veins (Fig. 4-35).

Intestinal flukes (*Fasciolopsis buski* and related species). Over 50 species of intestinal flukes have been described in humans, but most clinically significant infections are caused by *F. buski, Echinostoma* species, and *Heterophyes* species.[124-126] These flukes are most common in Asia. They are ingested with aquatic plants, and after maturation, the adult worm attaches to the proximal small bowel mucosa.[110,124] The majority of infections are asymptomatic. Symptoms, which usually occur as a result of heavy infection, include diarrhea, often alternating with constipation; abdominal pain; anorexia; nausea and vomiting; and malabsorption. Ileus, obstruction, and GI bleeding have also been described. The large worms (2 to 7.5 cm) may be seen endoscopically, and mucosal ulceration, inflammation, and abscess formation may occur at sites of tissue attachment.

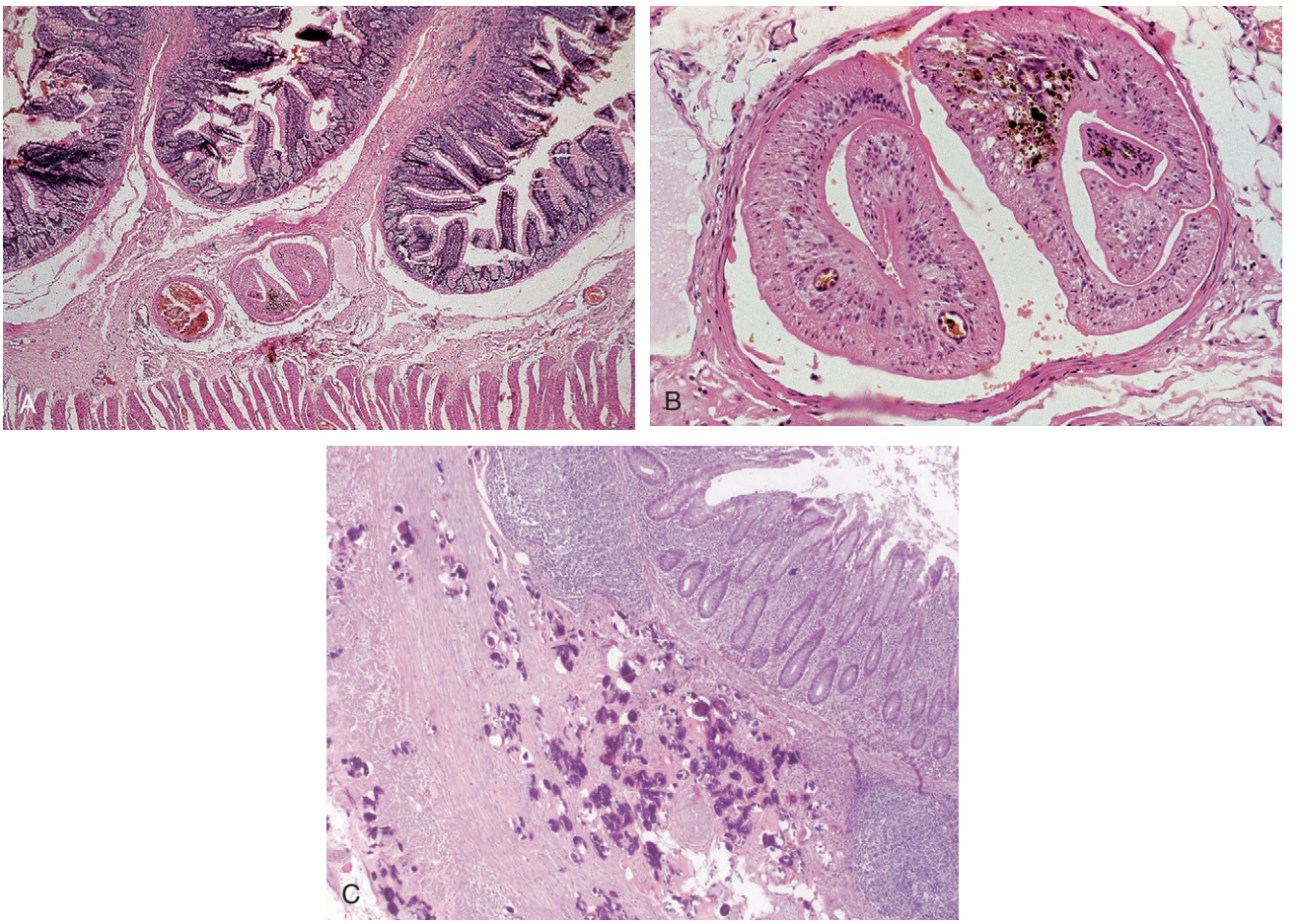

FIGURE 4-35 **A** and **B,** *Schistosoma* worm in a vein in the submucosa of the small bowel. **C,** Calcified eggs in the appendiceal wall in a case of remote schistosomiasis. (Courtesy of Dr. Joe Misdraji.)

Cestodes

Taenia saginata (beef tapeworm), *Taenia solium* (pork tapeworm), and *Hymenolepis nana* (dwarf tapeworm) may occasionally cause GI disease. *Diphyllobothrium latum* (fish tapeworm) is a rare cause of vitamin B_{12} deficiency.[110,120]

Other Helminthic Infections

The Central American nematode, *Angiostrongylus costaricensis* may cause dramatic, even fatal, ileocecal infection characterized by the presence of large obstructive inflammatory masses with perforation and mesenteric vessel thrombosis.[110] *Trichinella spiralis* is a rare cause of diarrhea.[110] Esophagostomiasis, a parasitic disease generally seen in nonhuman primates, may form deep inflammatory masses, predominantly in the right colon and appendix.[110]

The differential diagnosis of helminthic infections usually involves differentiation between the various types of worms. However, other entities to be considered include causes of ulcerative inflammation, eosinophilic infiltration, and granulomatous inflammation, such as tuberculosis, amebiasis, allergic enteritis, and Crohn's disease.

REFERENCES

References, with PubMed access, are available in the online edition through Expert Consult.