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

Pseudomembranous Colitis

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

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

MORPHOLOGY

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

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

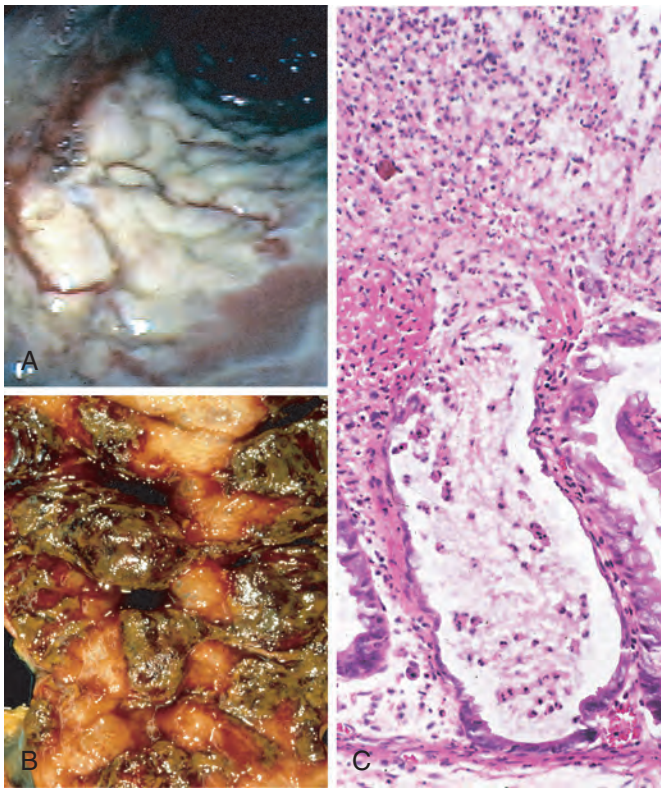

Figure 17-29 *Clostridium difficile* colitis. **A,** The colon is coated by tan pseudomembranes composed of neutrophils, dead epithelial cells, and inflammatory debris (endoscopic view). **B,** Pseudomembranes are easily appreciated on gross examination. **C,** Typical pattern of neutrophils emanating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

Whipple Disease

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

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