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

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

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

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

Typhoid Fever

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

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

MORPHOLOGY

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

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

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

Yersinia

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

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