system (CNS) and cardiac problems; it is caused by the bacterium *Tropheryma whipplei.* Until the identification of *T. whipplei* by polymerase chain reaction, the hallmark of Whipple's disease had been the presence of PAS-positive macrophages in the small intestine (Fig. 349-4*E*) and other organs with evidence of disease.

Etiology *T. whipplei*, a small (50–500 nm) gram-positive bacillus in the group Actinobacteria, has low virulence but high infectivity. Symptoms of Whipple's disease are relatively minimal compared to the bacterial burden in multiple tissues.

Clinical presentation The onset of Whipple's disease is insidious and is characterized by diarrhea, steatorrhea, abdominal pain, weight loss, migratory large-joint arthropathy, and fever as well as ophthalmologic and CNS symptoms. Dementia is a relatively late symptom and an extremely poor prognostic sign, especially in patients who experience relapse after the induction of a remission with antibiotics. For unexplained reasons, the disease occurs primarily in middle-aged white men. The steatorrhea in these patients is generally believed to be secondary to both small-intestinal mucosal injury and lymphatic obstruction due to the increased number of PAS-positive macrophages in the lamina propria of the small intestine.

Diagnosis The diagnosis of Whipple's disease is suggested by a multisystemic disease in a patient with diarrhea and steatorrhea. Tissue biopsy of the small intestine and/or other organs that may be involved (e.g., liver, lymph nodes, heart, eyes, CNS, or synovial membranes), given the patient's symptoms, is the primary approach. The presence of PAS-positive macrophages containing the characteristic small bacilli is suggestive of this diagnosis. However, *T. whipplei*–containing macrophages can be confused with PAS-positive macrophages containing *M. avium* complex, which may be a cause of diarrhea in AIDS. The presence of the *T. whipplei* bacillus outside of macrophages is a more important indicator of active disease than is their presence within the macrophages. *T. whipplei* has now been successfully grown in culture.

TREATMENT WHIPPLE'S DISEASE

The treatment for Whipple's disease is prolonged use of antibiotics. The current regimen of choice is double-strength trimethoprim-sulfamethoxazole for ~1 year. PAS-positive macrophages can persist after successful treatment, and the presence of bacilli outside of macrophages is indicative of persistent infection or an early sign of recurrence. Recurrence of disease activity, especially with dementia, is an extremely poor prognostic sign and requires an antibiotic that crosses the blood-brain barrier. If trimethoprim-sulfamethoxazole is not tolerated, chloramphenicol is an appropriate second choice.

PROTEIN-LOSING ENTEROPATHY

Protein-losing enteropathy is not a specific disease but rather a group of gastrointestinal and nongastrointestinal disorders with hypoproteinemia and edema in the absence of either proteinuria or defects in protein synthesis (e.g., chronic liver disease). These diseases are characterized by excess protein loss into the gastrointestinal tract. Normally, ~10% of total protein catabolism occurs via the gastrointestinal tract. Evidence of increased protein loss into the gastrointestinal tract is found in more than 65 different diseases, which can be classified into three groups: (1) mucosal ulceration, such that the protein loss primarily represents exudation across damaged mucosa (e.g., ulcerative colitis, gastrointestinal carcinomas, and peptic ulcer); (2) nonulcerated mucosa, but with evidence of mucosal damage so that the protein loss represents loss across epithelia with altered permeability (e.g., celiac disease and Ménétrier's disease in the small intestine and stomach, respectively); and (3) lymphatic dysfunction, representing either primary lymphatic disease or lymphatic disease secondary to partial lymphatic obstruction that may occur as a result of enlarged lymph nodes or cardiac disease.

Diagnosis The diagnosis of protein-losing enteropathy is suggested by peripheral edema and low serum albumin and globulin levels in the absence of renal and hepatic disease. An individual with protein-losing enteropathy only rarely has selective loss of *only* albumin or *only* globulins. Therefore, marked reduction of serum albumin with normal serum globulins should not initiate an evaluation for protein-losing enteropathy but should suggest renal and/or hepatic disease. Likewise, reduced serum globulins with normal serum albumin levels are more likely a result of reduced globulin synthesis rather than enhanced globulin loss into the intestine. An increase in protein loss into the gastrointestinal tract has been documented by the administration of one of several radiolabeled proteins and its quantitation in stool during a 24- or 48-h period. Unfortunately, none of these radiolabeled proteins is available for routine clinical use. α_1-Antitrypsin, a protein that accounts for ~4% of total serum proteins and is resistant to proteolysis, can be used to detect enhanced rates of serum protein loss into the intestinal tract but cannot be used to assess gastric protein loss because of its degradation in an acid milieu. α_1-Antitrypsin clearance is measured by determining stool volume as well as both stool and plasma α_1-antitrypsin concentrations. In addition to the loss of protein via abnormal and distended lymphatics, peripheral lymphocytes may be lost via lymphatics, with consequent relative lymphopenia. Thus, lymphopenia in a patient with hypoproteinemia indicates increased loss of protein into the gastrointestinal tract.

Patients with increased protein loss into the gastrointestinal tract from lymphatic obstruction often have steatorrhea and diarrhea. The steatorrhea is a result of altered lymphatic flow as lipid-containing chylomicrons exit from intestinal epithelial cells via intestinal lymphatics (Table 349-4; Fig. 349-4). In the absence of mechanical or anatomic lymphatic obstruction, intrinsic intestinal lymphatic dysfunction—with or without lymphatic dysfunction in the peripheral extremities—has been designated *intestinal lymphangiectasia.* Similarly, ~50% of individuals with intrinsic peripheral lymphatic disease (Milroy's disease) also have intestinal lymphangiectasia and hypoproteinemia. Other than steatorrhea and enhanced protein loss into the gastrointestinal tract, all other aspects of intestinal absorptive function are normal in intestinal lymphangiectasia.

Other Causes Patients who appear to have idiopathic protein-losing enteropathy without evidence of gastrointestinal disease should be examined for cardiac disease—especially right-sided valvular disease and chronic pericarditis (Chaps. 284 and 288). On occasion, hypoproteinemia can be the only presenting manifestation in these two types of heart disease. Ménétrier's disease (also called *hypertrophic gastropathy*) is an uncommon entity that involves the body and fundus of the stomach and is characterized by large gastric folds, reduced gastric acid secretion, and, at times, enhanced protein loss into the stomach.

TREATMENT PROTEIN-LOSING ENTEROPATHY

As excess protein loss into the gastrointestinal tract is most often secondary to a specific disease, treatment should be directed primarily to the underlying disease process and not to the hypoproteinemia. For example, if significant hypoproteinemia with resulting peripheral edema is secondary to celiac disease or ulcerative colitis, a gluten-free diet and mesalamine, respectively, would be the initial therapy. When enhanced protein loss is secondary to lymphatic obstruction, it is critical to establish the nature of this obstruction. Identification of mesenteric nodes or lymphoma may be possible by imaging studies. Similarly, it is important to exclude cardiac disease as a cause of protein-losing enteropathy, either by echosonography or, on occasion, by a right-heart catheterization.

The increased protein loss that occurs in intestinal lymphangiectasia is a result of distended lymphatics associated with lipid malabsorption. The hypoproteinemia is treated with a low-fat diet and the administration of MCTs (Table 349-3), which do not exit from the intestinal epithelial cells via lymphatics but are delivered to the body via the portal vein.