TABLE 349-6 DISEASES THAT CAN BE DIAGNOSED BY SMALL-INTESTINAL MUCOSAL BIOPSIES

Lesions	Pathologic Findings
Diffuse, Specific	
Whipple's disease	Lamina propria includes macrophages containing material positive on periodic acid–Schiff staining
Agammaglobulinemia	No plasma cells; either normal or absent villi ("flat mucosa")
Abetalipoproteinemia	Normal villi; epithelial cells vacuolated with fat postprandially
Patchy, Specific	
Intestinal lymphoma	Malignant cells in lamina propria and submucosa
Intestinal lymphangiectasia	Dilated lymphatics; clubbed villi
Eosinophilic gastroenteritis	Eosinophil infiltration of lamina propria and mucosa
Amyloidosis	Amyloid deposits
Crohn's disease	Noncaseating granulomas
Infection by one or more microorganisms (see text)	Specific organisms
Mastocytosis	Mast cell infiltration of lamina propria
Diffuse, Nonspecific	
Celiac disease	Short or absent villi; mononuclear infiltrate; epithelial cell damage; hypertrophy of crypts
Tropical sprue	Similar to celiac disease
Bacterial overgrowth	Patchy damage to villi; lymphocyte infiltration
Folate deficiency	Short villi; decreased mitosis in crypts; megalocytosis
Vitamin B_{12} deficiency	Similar to folate deficiency
Radiation enteritis	Similar to folate deficiency
Zollinger-Ellison syndrome	Mucosal ulceration and erosion from acid
Protein-calorie malnutrition	Villous atrophy; secondary bacterial overgrowth
Drug-induced enteritis	Variable histology

Several microorganisms can be identified in small-intestinal biopsy samples, establishing a correct diagnosis. At times, the biopsy is performed specifically to diagnose infection (e.g., Whipple's disease or giardiasis). In most other instances, the infection is detected incidentally during the workup for diarrhea or other abdominal symptoms. Many of these infections occur in immunocompromised patients with diarrhea; the etiologic agents include *Cryptosporidium, Isospora belli,* microsporidia, *Cyclospora, Toxoplasma*, cytomegalovirus, adenovirus, *Mycobacterium avium-intracellulare*, and *G. lamblia.* In immunocompromised patients, when *Candida, Aspergillus, Cryptococcus*, or *Histoplasma* organisms are seen on duodenal biopsy, their presence generally reflects systemic infection. Apart from Whipple's disease and infections in the immunocompromised host, small-bowel biopsy is seldom used as the primary mode of diagnosis of infection. Even giardiasis is more easily diagnosed by stool antigen studies and/or duodenal aspiration than by duodenal biopsy.

Patients with steatorrhea require assessment of *pancreatic exocrine function*, which is often abnormal in chronic pancreatitis. The secretin test that collects pancreatic secretions by duodenal intubation following intravenous administration of secretin is the only test that directly measures pancreatic exocrine function but is available only at a few specialized centers. Endoscopic approaches (endoscopic retrograde cholangiopancreatography, endoscopic ultrasound) provide an excellent assessment of pancreatic duct anatomy but do *not* assess exocrine function (Chap. 370).

Table 349-7 summarizes the results of the D-xylose test, the Schilling test, and small-intestinal mucosal biopsy in patients with steatorrhea of various etiologies.

SPECIFIC DISEASE ENTITIES

CELIAC DISEASE

Celiac disease is a common cause of malabsorption of one or more nutrients. Although celiac disease was originally considered largely a disease of white individuals, especially persons of European descent, recent observations have established that it is a common disease with protean manifestations, a worldwide distribution, and an estimated incidence in the United States that is as high as 1 in 113 people. Its incidence has increased over the past 50 years. Celiac disease has had several other names, including nontropical sprue, celiac sprue, adult celiac disease, and gluten-sensitive enteropathy. The etiology of celiac disease is not known, but environmental, immunologic, and genetic factors are important. Celiac disease is considered an "iceberg" disease. A small number of individuals have classical symptoms and manifestations related to nutrient malabsorption along with a varied natural history; the onset of symptoms can occur at all points from the first year of life through the eighth decade. A much larger number of individuals have "atypical celiac disease", with manifestations that are not obviously related to intestinal malabsorption (e.g., anemia, osteopenia, infertility, and neurologic symptoms). Finally, an even larger number of persons have "silent celiac disease"; they are essentially asymptomatic despite abnormal small-intestinal histopathology and serologies (see below).

The hallmark of celiac disease is an abnormal small-intestinal biopsy (Fig. 349-4) and the response of the condition (including symptoms and histologic changes on small-intestinal biopsy) to the elimination of gluten from the diet. The histologic changes have a proximal-to-distal intestinal distribution of severity, which probably reflects the exposure of the intestinal mucosa to varied amounts of dietary gluten. The symptoms do not necessarily correlate with histologic changes, especially as many newly diagnosed patients with celiac disease may be asymptomatic or only minimally symptomatic (often with no gastrointestinal symptoms).

The symptoms of celiac disease may appear with the introduction of cereals into an infant's diet, although spontaneous remissions often occur during the second decade of life that may be either permanent or followed by the reappearance of symptoms over several years. Alternatively, the symptoms of celiac disease may first become evident at almost any age throughout adulthood. In many patients, frequent spontaneous remissions and exacerbations occur. The symptoms range from significant malabsorption of multiple nutrients, with diarrhea, steatorrhea, weight loss, and the consequences of nutrient depletion (i.e., anemia and metabolic bone disease), to the absence of gastrointestinal symptoms despite evidence of the depletion of a single nutrient (e.g., iron or folate deficiency, osteomalacia, edema from protein loss). Asymptomatic relatives of patients with celiac disease have been identified as having this disease either by small-intestinal biopsy or by serologic studies (e.g., antiendomysial antibodies, tissue transglutaminase [tTG], deamidated gliadin peptide). The availability of these "celiac serologies" has led to a substantial increase in the frequency of diagnosis of celiac disease, and the diagnosis is now being made primarily in patients without "classic" symptoms but with atypical and subclinical presentations.

Etiology The etiology of celiac disease is not known, but environmental, immunologic, and genetic factors all appear to contribute to the disease. One *environmental* factor is the clear association of the disease with gliadin, a component of gluten that is present in wheat, barley, and rye. In addition to the role of gluten restriction in treatment, the instillation of gluten into both the normal-appearing rectum and the distal ileum of patients with celiac disease results in morphologic changes within hours.

An *immunologic* component in the pathogenesis of celiac disease is critical and involves both adaptive and innate immune responses. Serum