rologic disorders, such as ataxia, autism, depression, epilepsy, Down syndrome, and Turner syndrome.

MORPHOLOGY

Biopsy specimens from the second portion of the duodenum or proximal jejunum, which are exposed to the highest concentrations of dietary gluten, are generally diagnostic in celiac disease. The histopathology is characterized by increased numbers of intraepithelial CD8+ T lymphocytes (intraepithelial lymphocytosis), crypt hyperplasia, and villous atrophy (Fig. 17-26). This loss of mucosal and brush-border surface area probably accounts for the malabsorption. In addition, increased rates of epithelial turnover, reflected in increased crypt mitotic activity, may limit the ability of absorptive enterocytes to fully differentiate and express proteins necessary for terminal digestion and transepithelial transport. Other features of fully developed celiac disease include increased numbers of plasma cells, mast cells, and eosinophils, especially within the upper part of the lamina propria. With increased frequency of serologic screening and early detection of disease-associated antibodies, it is now appreciated that an increase in the number of intraepithelial lymphocytes, particularly within the villus, is a sensitive marker of celiac disease, even in the absence of epithelial damage and villous atrophy. However, intraepithelial lymphocytosis and villous atrophy are not specific for celiac disease and can be present in other diseases, including viral enteritis. The combination of histology and serology, therefore, is most specific for diagnosis of celiac disease.

Adherence to a gluten-free diet typically results in resolution of symptoms, decreasing titers of anti-tissue transglutaminase or other celiac disease-associated antibodies, and restoration of normal or near normal mucosal histology within 6 to 24 months.

Clinical Features. In adults, celiac disease presents most commonly between the ages of 30 and 60. Many cases of celiac disease escape clinical attention for extended periods because of atypical presentations. Other patients may have silent celiac disease, defined as positive serology and villous atrophy without symptoms, or latent celiac disease, in which positive serology is not accompanied by villous atrophy. Celiac disease may be associated with chronic diarrhea, bloating, or chronic fatigue, but is often asymptomatic. These cases may present with anemia due to chronic iron and vitamin malabsorption. In adults, celiac disease is detected twice as frequently in women, perhaps because monthly menstrual bleeding accentuates the effects of impaired absorption.

Pediatric celiac disease, which affects males and females equally, may present with malabsorption or atypical symptoms affecting almost any organ. In those with classic symptoms, disease typically begins after introduction of gluten to the diet, between ages of 6 and 24 months, and manifests as irritability, abdominal distention, anorexia, chronic diarrhea, failure to thrive, weight loss, or muscle wasting. Children with nonclassic symptoms tend to present at older ages with complaints of abdominal pain, nausea, vomiting, bloating, or constipation. Common extraintestinal complaints include arthritis or joint pain, aphthous stomatitis, iron deficiency anemia, delayed puberty, and short stature.

A characteristic itchy, blistering skin lesion, dermatitis herpetiformis (Chapter 25), can be present in as many as 10% of patients. Unfortunately, the only treatment currently available for celiac disease is a gluten-free diet. While adhering to this diet can be challenging, it does result in symptomatic improvement for most patients. A gluten-free diet may also reduce the risk of long-term complications including anemia, female infertility, osteoporosis, and cancer (discussed bellow).

Noninvasive serologic tests are generally performed prior to biopsy. The most sensitive tests are the measurement of IgA antibodies against tissue transglutaminase. IgA anti-endomysial antibodies can also be present. IgG anti-tissue transglutaminase antibodies may be detected in patients with IgA deficiency. The absence of HLA-DQ2 and HLA-DQ8 is useful for its high negative predictive value, but the presence of these alleles is not helpful in confirming the diagnosis.

Individuals with celiac disease have a higher than normal rate of malignancy. The most common celiac disease-associated cancer is enteropathy-associated T-cell lymphoma, an aggressive lymphoma of intraepithelial T lymphocytes. Small intestinal adenocarcinoma is also more frequent in individuals with celiac disease. Thus, when symptoms such as abdominal pain, diarrhea, and weight loss develop despite a strict gluten-free diet, cancer or refractory sprue, in which the response to a gluten-free diet is lost, must be considered.

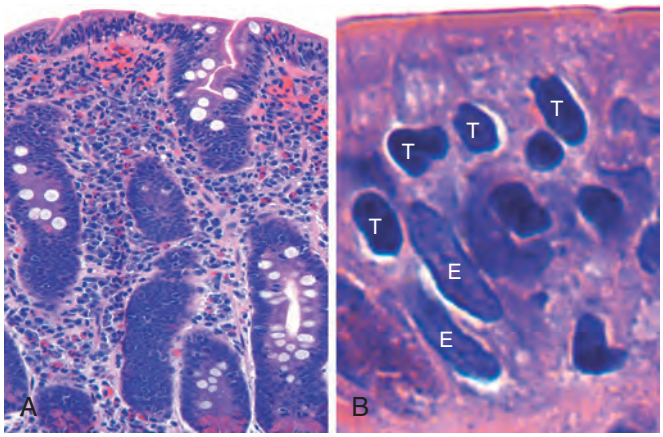

Figure 17-26 Celiac disease. **A,** Advanced cases of celiac disease show complete loss of villi, or total villous atrophy. Note the dense plasma cell infiltrates in the lamina propria. **B,** Infiltration of the surface epithelium by T lymphocytes, which can be recognized by their densely stained nuclei (labelled **T**). Compare to elongated, pale-staining epithelial nuclei (labeled **E**).

Environmental Enteropathy

Environmental enteropathy, which has also been referred to as *tropical enteropathy* or *tropical sprue*, is a disorder prevalent in areas and populations with poor sanitation and hygiene, such as those in developing countries, including many parts of sub-Saharan Africa, such as Gambia; aboriginal populations within northern Australia; and some groups within South America and Asia, such as residents of impoverished communities within Brazil, Guatemala, India, and Pakistan. Affected individuals often suffer from malabsorption and malnutrition, stunted growth, and