Asians) and is 10% among first-degree relatives of celiac disease patients. However, serologic studies provide clear evidence that celiac disease is present worldwide. Furthermore, all patients with celiac disease express the HLA-DQ2 or HLA-DQ8 allele, although only a minority of people expressing DQ2/DQ8 have celiac disease. Absence of DQ2/DQ8 excludes the diagnosis of celiac disease.

Diagnosis A small-intestinal biopsy is required to establish a diagnosis of celiac disease (Fig. 349-4). A biopsy should be performed when patients have symptoms and laboratory findings suggestive of nutrient malabsorption and/or deficiency as well as a positive tTG antibody test. Since the presentation of celiac disease is often subtle, without overt evidence of malabsorption or nutrient deficiency, a relatively low threshold for biopsy performance is important. It is more prudent to perform a biopsy than another test of intestinal absorption that can never completely exclude or establish this diagnosis.

The diagnosis of celiac disease requires the detection of characteristic histologic changes on small-intestinal biopsy together with a prompt clinical and histologic response after the institution of a gluten-free diet. If IgA antiendomysial or tTG antibodies have been detected in serologic studies, they too should disappear after a gluten-free diet is started. With the increase in the number of patients diagnosed with celiac disease (mostly by serologic studies), the spectrum of histologic changes seen on duodenal biopsy has increased and includes findings that are not as severe as the classic changes shown in Fig. 349-4. The classic changes seen on duodenal/jejunal biopsy are restricted to the mucosa and include (1) an increase in the number of intraepithelial lymphocytes; (2) absence or a reduced height of villi, which causes a flat appearance with increased crypt cell proliferation resulting in crypt hyperplasia and loss of villous structure, with consequent villous, but not mucosal, atrophy; (3) a cuboidal appearance and nuclei that are no longer oriented basally in surface epithelial cells; and (4) increased numbers of lymphocytes and plasma cells in the lamina propria (Fig. 349-4*B*). Although these features are characteristic of celiac disease, they are *not* diagnostic because a similar appearance can develop in tropical sprue, eosinophilic enteritis, and milk-protein intolerance in children and occasionally in lymphoma, bacterial overgrowth, Crohn's disease, and gastrinoma with acid hypersecretion. However, a characteristic histologic appearance that reverts toward normal after the initiation of a gluten-free diet establishes the diagnosis of celiac disease (Fig. 349-4*C*). Readministration of gluten, with or without an additional small-intestinal biopsy, is not necessary.

A number of patients exhibit *gluten sensitivity*; i.e., they have gastrointestinal symptoms that respond to gluten restriction but do not have celiac disease. The basis for such gluten sensitivity is not known.

Failure to Respond to Gluten Restriction The most common cause of persistent symptoms in a patient who fulfills all the criteria for the diagnosis of celiac disease is *continued intake of gluten*. Gluten is ubiquitous, and a significant effort must be made to exclude all gluten from the diet. Use of rice flour in place of wheat flour is very helpful, and several support groups provide important aid to patients with celiac disease and to their families. More than 90% of patients who have the characteristic findings of celiac disease respond to complete dietary gluten restriction. The remainder constitute a heterogeneous group (whose condition is often called *refractory celiac disease* or *refractory sprue*) that includes some patients who (1) respond to restriction of other dietary protein (e.g., soy); (2) respond to glucocorticoid treatment; (3) are "temporary" (i.e., whose clinical and morphologic findings disappear after several months or years); or (4) fail to respond to all measures and have a fatal outcome, with or without documented complications of celiac disease, such as the development of intestinal T cell lymphoma or autoimmune enteropathy.

Therapeutic approaches that do not include a gluten-free diet are being developed and include the use of peptidases to inactivate toxic gliadin peptides and of small molecules to block toxic peptide uptake across intestinal tight junctions.

Mechanism of Diarrhea The diarrhea in celiac disease has several pathogenetic mechanisms. Diarrhea may be secondary to (1) steatorrhea, which is primarily a result of changes in jejunal mucosal function; (2) secondary lactase deficiency, a consequence of changes in jejunal brush border enzymatic function; (3) bile acid malabsorption resulting in bile acid–induced fluid secretion in the colon (in cases with more extensive disease involving the ileum); and (4) endogenous fluid secretion resulting from crypt hyperplasia. Celiac disease patients with more severe involvement may improve temporarily with *dietary lactose and fat restriction* while awaiting the full effects of total gluten restriction, which constitutes primary therapy.

Associated Diseases Celiac disease is associated with dermatitis herpetiformis (DH), but this association has not been explained. Patients with DH have characteristic papulovesicular lesions that respond to dapsone. Almost all patients with DH have histologic changes in the small intestine consistent with celiac disease, although usually much milder and less diffuse in distribution. Most patients with DH have mild or no gastrointestinal symptoms. In contrast, relatively few patients with celiac disease have DH.

Celiac disease is also associated with diabetes mellitus type 1, IgA deficiency, Down syndrome, and Turner's syndrome. The clinical importance of the association with diabetes is that, although severe watery diarrhea without evidence of malabsorption is most often diagnosed as "diabetic diarrhea" (Chap. 417), assay of antiendomysial antibodies and/or a small-intestinal biopsy must be considered to exclude celiac disease.

Complications The most important complication of celiac disease is the development of cancer. The incidences of both gastrointestinal and nongastrointestinal neoplasms as well as intestinal lymphoma are elevated among patients with celiac disease. For unexplained reasons, the frequency of lymphoma in patients with celiac disease is higher in Ireland and the United Kingdom than in the United States. The possibility of lymphoma must be considered whenever a patient with celiac disease who has previously done well on a gluten-free diet is no longer responsive to gluten restriction or a patient who presents with clinical and histologic features consistent with celiac disease does not respond to a gluten-free diet. Other complications of celiac disease include the development of intestinal ulceration independent of lymphoma and so-called refractory sprue (see above) and collagenous sprue. In *collagenous sprue*, a layer of collagen-like material is present beneath the basement membrane; patients with collagenous sprue generally do not respond to a gluten-free diet and often have a poor prognosis.

TROPICAL SPRUE

Tropical sprue is a poorly understood syndrome that affects both expatriates and natives in certain but not all tropical areas and is manifested by chronic diarrhea, steatorrhea, weight loss, and nutritional deficiencies, including those of both folate and cobalamin. This disease affects 5–10% of the population in some tropical areas.

Chronic diarrhea in a tropical environment is most often caused by infectious agents, including *G. lamblia, Yersinia enterocolitica, C. difficile, Cryptosporidium parvum*, and *Cyclospora cayetanensis*. Tropical sprue should not be entertained as a possible diagnosis until the presence of cysts and trophozoites has been excluded in three stool samples. **Chronic infections of the gastrointestinal tract and diarrhea in patients with or without AIDS are discussed in Chaps. 160, 161, and 226.**

The small-intestinal mucosa of individuals living in tropical areas is not identical to that of individuals who reside in temperate climates. In residents of tropical areas, biopsies reveal a mild alteration of villous architecture with a modest increase in mononuclear cells in the lamina propria, which on occasion can be as severe as that seen in celiac disease. These changes are observed both in native residents and in expatriates living in tropical regions and are usually associated with mild decreases in absorptive function, but they revert to "normal" when an individual moves or returns to a temperate area. Some have suggested that the changes seen in tropical enteropathy and in tropical