The widening spectrum of celiac disease¹,²

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ABSTRACT  Celiac disease is a permanent intolerance to ingested gluten that results in immunologically mediated inflammatory damage to the small-intestinal mucosa. Celiac disease is associated with both human leukocyte antigen (HLA) and non-HLA genes and with other immune disorders, notably juvenile diabetes and thyroid disease. The classic sprue syndrome of steatorrhea and malnutrition coupled with multiple deficiency states may be less common than more subtle and often nonsymptomatic presentations of the disease. Diverse problems such as dental anomalies, short stature, osteopenic bone disease, lactose intolerance, infertility, and nonspecific abdominal pain among many others may be the only manifestations of celiac disease. The rate at which celiac disease is diagnosed depends on the level of suspicion for the disease. Although diagnosis relies on intestinal biopsy findings, serologic tests are useful as screening tools and as an adjunct to diagnosis. The treatment of celiac disease is lifelong avoidance of dietary gluten. Gluten-free diets are now readily achievable with appropriate professional instruction and community support. Both benign and malignant complications of celiac disease occur but these can often be avoided by early diagnosis and compliance with a gluten-free diet.


INTRODUCTION

Celiac disease, also known as gluten-sensitive enteropathy, is characterized by inflammation of the small-intestinal mucosa that results from a genetically based immunologic intolerance to ingested gluten. Celiac disease differs from traditional immunoglobulin E (IgE)-mediated food allergies in that a chronic inflammatory response is induced in the primary site of damage, the small-intestinal mucosa. The inflammation occurring in celiac disease classically produces a malabsorption syndrome, with diarrhea, steatorrhea, and loss of weight or failure to thrive (1). Deficiencies of the fat-soluble vitamins D, E, A, and K; iron; folic acid; and calcium are also common. Celiac disease results in a wide spectrum of both pathophysiologic changes in the intestines and clinical syndromes, many of which remain undiagnosed (2). Celiac disease as an inflammatory bowel disorder is unique in that a specific food component, gluten, has been identified as the culprit (3).

PATHOPHYSIOLOGY

Celiac disease is the end result of 3 processes that culminate in intestinal mucosal damage (4): genetic predisposition, environmental factors, and immunologically based inflammation. Celiac disease may be the result of an evolutionary collision between the cultivation of wheat and the human immune system, in particular between the human leukocyte antigen (HLA) system of self identification and the specific deleterious peptide sequences in wheat (5, 6).

Genetics

Celiac disease is a heritable condition. It seems to be more common in whites and family co-occurrence is common (Table 1) (7–13). Celiac disease is strongly associated with the extended HLA phenotypes B8, DR3, and DQw2, but most specifically with DQw2. A small percentage of patients are DQw2 negative. These patients usually have the genotype DR5/DR7.

Siblings who share the specific HLA type of DQW2 or DR5/DR7 have a 40% likelihood of concordance for celiac disease although monozygotic twins have a 70% concordance. This suggests that one gene is tightly associated with the HLA region and that there is at least one other gene that contributes to the risk. Variable penetrance and an environmental influence can be inferred from the < 100% concordance in monozygotic twins. The genotype that encodes DQw2 includes the DQA1*0501 and DQB1*0201 alleles. Individuals who are homozygous for the DQA1*0501 and DQB1*0201 alleles may develop the disease at an earlier age and with greater severity than heterozygotes (14–17). A second gene has been mapped to region 23 of the short arm of chromosome 6 (18). The DNA sequence and biological function of the associated gene at this site await elucidation and confirmation. The identification of a genotype not associated with celiac disease may have some negative predictive value in patients who are already consuming gluten-free diets.

Environmental factors

The most important environmental factor in celiac disease is gluten (19). The deleterious proteins are gliadins (wheat), hordeins (barley), secalins (rye), and possibly avidins (oats). The toxicity of these proteins was established many years ago in clin-
Directed against the antigen (25). Mucosa, where they are terminally differentiated to produce IgA patches to the mesenteric lymph nodes and return to the jejunal intestinal immune system. Primed B cells travel from Peyer this allows a controlled sampling of the antigenic milieu by the specialized population of thin enterocytes) over the Peyer patch where antigen-presenting cells process the antigens. In normal small intestine, Peyer patches are the immunologic sampling site. Luminal antigens are taken up by the m-cells (a specialization of enterocytes) from the gut lumen. Antigens are transported to lamina propria dendritic cells, which migrate to lymph nodes to present antigens to naive CD4+ T cells. This allows a controlled sampling of the antigenic milieu by the intestinal immune system. Primed B cells travel from Peyer patches to the mesenteric lymph nodes and return to the jejunal mucosa, where they are terminally differentiated to produce IgA directed against the antigen (25).

Other factors may have a role in precipitating symptoms. These include gastrointestinal surgery, pregnancy, high-dose gluten challenge, and viral infection (23), which may heighten the immunologic response to gluten, thus extending the disease distally and causing clinically apparent decompensation. Adenovirus 12 has been suggested as a possible trigger because of partial molecular sequence homology to a dodecapeptide fragment of wheat gliadin (14). Breast-feeding seems to reduce the likelihood of the infant developing celiac disease at an early age. It is still not clear, however, whether breast-feeding merely delays the age of onset or actually reduces the lifetime risk of developing celiac disease (24).

### Immunologic factors

The intestinal lesion in celiac disease is an immunologically mediated inflammation of the intestine that is characterized by architectural and inflammatory changes of the mucosa of the proximal small intestine. Much of what is known about this response is based on the study of established intestinal lesions and thus may not reflect early pathogenic processes. The inflammatory response consists of increased numbers of lymphocytes, plasma cells, and macrophages in the lamina propria and increased numbers of lymphocytes in the surface layer of the epithelium. The surface enterocytes are shorter, wider, and have more poorly ordered nuclei than is normal. The normally tall, thin villi are shortened and flattened (Figure 1). The cryptal layer in increased in depth. The changes may be patchy and affect a variable length of the small intestine; significant variation is possible between biopsy samples taken from adjacent areas in the small intestine.

### Trigger factors

Little is known about the process that leads to celiac disease. In normal small intestine, Peyer patches are the immunologic sampling site. Luminal antigens are taken up by the m-cells (a specialized population of thin enterocytes) over the Peyer patch by pinocytosis and delivered to the subepithelial layer of the Peyer patch where antigen-presenting cells process the antigens. This allows a controlled sampling of the antigenic milieu by the intestinal immune system. Primed B cells travel from Peyer patches to the mesenteric lymph nodes and return to the jejunal mucosa, where they are terminally differentiated to produce IgA directed against the antigen (25).

In celiac disease, there is a generalized increase in permeability to macromolecules, making it likely that Peyer patches are not the only site where gliadins are in contact with the immune system. Gluten peptides may encounter the gut immune system in a fashion that bypasses the normal controlled sampling, leading to sensitization or loss of tolerance to the antigen.

### Cellular immunity

Cellular immunity seems to play the major role in the intestinal damage in celiac disease. The pathogenic sequence of events has been elucidated primarily through in vivo challenge studies in treated patients with celiac disease and in vitro challenge studies in biopsy samples from treated and untreated patients (26–28). These studies show an early increase in the expression of HLA antigen markers on cells in the surface layers of the intestinal mucosa after 2–4 h of exposure to gluten. T cell clones reacting specifically to gluten in an HLA-restricted fashion have been isolated from the lamina propria of affected intestinal tissue and the peripheral blood (29, 30). These cells release interferon γ and tumor necrosis factor along with other proinflammatory cytokines (31). There follows a migration of lymphocytes into the surface epithelium; subsequent recruitment of activated lymphocytes, macrophages, and plasma cells into the lamina propria; and deposition of complement in the subepithelial layer (32).

The surface epithelial layer is infiltrated with increased numbers of T lymphocytes (Figure 2). These cells predominantly express the αβ receptor, but an increased proportion of cells express the γδ receptor. What these γδ cells are doing in the epithelium is unknown, but they may alter the transfer and presentation of antigens by the enterocytes. The inflammatory sequence depends on a competent cellular immune response in the small intestine and shares many features with experimental graft versus host disease (33). The inflammatory response likely also affects the structural support and microcirculation of the villus, leading to collapse of the villus (34). The thickening of the crypt is not so much a response to loss of surface enterocytes but represents inflammation of the mucosa (35). This damage is the most intense in proximal small intestine and decreases caudally. The extent of the damage to the intestine determines the malab-

### Table 1

<table>
<thead>
<tr>
<th>Population</th>
<th>Risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family member of affected patient</td>
<td>5–20</td>
<td>(7, 8)</td>
</tr>
<tr>
<td>Persons with type 1 diabetes</td>
<td>5–7</td>
<td>(9, 10)</td>
</tr>
<tr>
<td>Persons with Sjögren disease</td>
<td>3</td>
<td>(11)</td>
</tr>
<tr>
<td>Persons with thyroid disease</td>
<td>4</td>
<td>(12)</td>
</tr>
<tr>
<td>Persons with selective immunoglobulin A deficiency</td>
<td>7</td>
<td>(13)</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Endoscopically obtained duodenal biopsy specimen showing the typical architectural changes of the mucosal lesion of celiac disease. Loss of the villous structures and hyperplasia of the crypts results in established (stage 3) celiac disease. Lymphocytes and plasma cells predominate in the inflamed lamina propria and there is an increased density of intraepithelial lymphocytes. 100× magnification, hematoxylin and eosin staining.
CLINICAL PRESENTATION

The classic constellation of symptoms and signs characterizing malabsorptive syndrome is a readily recognized manifestation of celiac disease. Frank malabsorptive symptoms include steatorrhea, weight loss or failure to thrive, bloating, and flatulence, with multiple deficiency states. More common but more difficult to recognize, however, are the other diverse ways in which celiac disease presents. Celiac disease may mimic many common clinical entities. These atypical modes of presentation include deficiencies of single micronutrients; nonspecific gastrointestinal complaints such as bloating, abdominal pain, diarrhea, constipation, flatulence, secondary lactose intolerance, and dyspepsia; and nongastrointestinal complaints such as fatigue, depression, arthralgia, milk intolerance, osteomalacia or osteoporosis, and iron deficiency anemia (11, 48–50). Iron deficiency anemia can occur with or without heme-positive stool (51). In children, celiac disease can result in stunting of growth and intellectual development, epilepsy, and dental abnormalities as single symptoms without the more classic malabsorptive symptoms of malnourished, potbellied infants with steatorrhea (52–54).

Occasionally, celiac disease is diagnosed incidentally during endoscopy (55). Several studies have shown that there is often a significant delay of many years between the initial appearance of symptoms and the diagnosis of celiac disease (56). The symptoms are often ascribed to a functional cause such as irritable bowel syndrome and patients are prescribed high-fiber diets or other nonspecific dietary measures to little avail. A worsening of symptoms with a high-fiber diet is probably a result of the high gluten content of the whole grains, wheat bran, and other grain-derived foods used in the diet. Psychiatric referral is also common before diagnosis; often, patients require a great degree of determination to persist in seeking an organic cause for their symptoms (57). Most patients do not recognize a temporal association between the ingestion of gluten and the appearance of symptoms, but it is often patients who suggest the diagnosis of celiac disease to physicians, who should not ignore it. Both the general public and practitioners of alternative medicine commonly ascribe a vast collection of ill effects to dietary gluten and prescribe wheat-free or gluten-free diets for many complaints without any attempt to confirm the existence of celiac disease or even without an awareness of the disease. This can lead to diagnostic difficulties.

Celiac disease should be considered in many clinical scenarios, including chronic diarrhea with or without steatorrhea, lactose intolerance, fat-soluble vitamin deficiency, persistent iron deficiency anemia, folate or vitamin B-12 deficiency, osteopenic bone disease, abnormal results on liver blood tests, and unexplained short stature and in patients with a close relative with celiac disease (Table 2). The presence of obesity, normal or tall stature, absence of diarrhea, or advanced age or even the absence of a deficiency state does not discount the possibility of celiac disease. Celiac disease should be considered in all patients presenting with chronic diarrhea; in some populations, celiac disease may be more common than Crohn disease.

Epidemiology

The impression that celiac disease is uncommon in the United States and rarely deserves consideration is a self-fulfilling prophesy (2). Epidemiologic studies done in several countries and in different patient groups suggest that the prevalence of...
celiac disease has been significantly underestimated. A heightened suspicion or awareness of celiac disease results in a substantially increased rate of diagnosis (58, 59). Retrospective reviews have shown that the rate of diagnosis in defined geographic areas varies widely (60, 61). The disease is diagnosed more often in females (62). The age at diagnosis varies dramatically and may be skewed by whether the reporting center is focusing on an adult or pediatric population. A gradual rise in the age at diagnosis is evident in most populations (63). A change in the nature of presentation away from the classic malabsorptive findings and a dramatic increase in the rate of diagnosis are evident in several locations where data have been available over a long period of time. Celiac disease is common in many different ethnic groups, including Scandinavians, Italians, Irish, British, Spaniards, Jews, and Palestinians. It has been estimated that 1 in 300 people in many European countries will eventually develop celiac disease (64). The disease has also been described in populations from South America, Eastern Europe, the Near East, Pakistan, Cuba, and North Africa (65–67).

Population-based serologic surveys revealed a prevalence of celiac disease of 1 in 250–500 in most countries studied, including the United States (68–70). Surveys of blood donors have shown that equal numbers of males and females have celiac disease, and few have nutritional abnormalities (70).

Several other diseases are associated with a high incidence of celiac disease. Celiac disease is particularly common in patients with type 1 diabetes, thyroid disease, Addison disease, osteopenic bone, Down syndrome, and rheumatologic complaints (9, 10, 71). It has been suggested that untreated celiac disease may predispose children to diabetes (72). These associations seem to be similar wherever the disease is studied. It is likely that the true prevalence of celiac disease in the United States is much greater than the actual rate of diagnosis.

**DIAGNOSIS OF CELIAC DISEASE**

The syndrome of celiac sprue was well described long before either the etiologic role of gluten or the intestinal lesion was identified (1). The diagnosis rested on the classic description of steatorrhea, weight loss, and malnutrition. When gluten was identified as the culprit, the response to the removal of gluten from the diet was added as a requirement for making the diagnosis. When the intestinal lesion was identified initially in surgical specimens and subsequently by less invasive methods, the requirement for histologic confirmation was added (73). A working party of the European Society for Pediatric Gastroenterology and Nutrition established the criteria for the diagnosis in children in 1969 and revised these in 1989 (Table 3). The original criteria, which required 3 biopsies, were adopted widely for adults as well. The diagnosis of celiac disease currently rests on the histologic demonstration of the characteristic lesion in the small intestine (Figure 1) and the subsequent clinical response to the introduction of a gluten-free diet. The prior requirement for 3 biopsies was both cumbersome and in most cases unnecessary. Three biopsies may be necessary, however, in infants aged <2 y, in whom alternate diagnoses are common, or when the results of the original biopsy are indefinite.

The major challenge is not in confirming the diagnosis but in identifying those individuals who may have celiac disease and selecting the appropriate tests to screen for it. Many practitioners are not familiar with the many ways in which celiac disease presents or with the noninvasive methods available for identifying the disease. The cost and invasiveness of endoscopy and biopsy have been significant factors in pushing celiac disease lower on the differential list; additionally, the disease may not even be considered by specialists unfamiliar with it. With the advent of sensitive serologic tests, screening for celiac disease is now within reach of all practitioners. Celiac disease should be considered in anyone with conditions associated with a high risk of the disease, such as type 1 diabetes, autoimmune thyroid disease, T cell lymphoma, osteoporosis, and infertility, and in those with a family history of celiac disease or dermatitis herpetiformis. Gastroenterologists should consider performing a biopsy of the duodenum in patients who undergo gastroscopy but do not have an obvious endoscopic cause for their symptoms. Occasionally, celiac disease will be suspected by an astute endoscopist as a result of the suggestive appearance of the duodenal mucosa (Figure 3).

**DERMATITIS HERPETIFORMIS**

Dermatitis herpetiformis is an extremely itchy, bullous skin rash that affects the extensor surfaces of the limbs, trunk, and scalp. It is a skin manifestation of the intestinal immune response to ingested gluten, characterized by the deposition of IgA granules at the dermal-epidermal junction (74). The exact source of these IgA deposits in the skin is unknown, but the IgA may be produced in the intestinal mucosa. There is sequence homology between dermal elastin and high-molecular-weight glutenin, suggesting molecular mimicry as a pathogenic mechanism.

The enteropathic damage in the intestine may be asymptomatic when the skin rash appears, but is indistinguishable from that seen in celiac disease. Some patients with essentially normal results on intestinal biopsies have gone on to develop frank enteropathic damage with regular consumption of a gluten-containing diet. The presence of endomyosal or reticulin antibodies correlates with the degree of enteropathy in individuals with dermatitis herpetiformis (75, 76). A positive serologic test strengthens the certainty of the skin diagnosis. A positive test also mandates investigation for consequences of malabsorption, although it is not necessary to perform these antibody tests or even an...
industrial biopsy to establish the etiologic role of intestinal gluten exposure in dermatitis herpetiformis. That can be reliably inferred by the appearance of granular IgA deposits in the skin (Figure 4). Serologic tests for celiac disease may be useful in cases in which some doubt remains, such as when dermatitis herpetiformis must be distinguished from a linear IgA disease of childhood that is not a gluten-sensitive disorder. Gliadin antibodies may be seen in other bullous skin disorders and are not particularly helpful in this setting (77, 78).

Many patients in the United States with dermatitis herpetiformis are not treated with gluten-free diets, but rather are prescribed dapsone, which suppresses the skin rash. Dapsone has no effect on the intestinal damage, however, other than delaying the institution of the appropriate diet. Many of these patients present years later with gastrointestinal symptoms or anemia. Celiac disease should be high on the list of possible diagnoses in patients with bullous skin rashes. Often patients do not volunteer the history of the skin rash. Intestinal biopsies at this point may help to confirm enteropathic damage as a cause for the gastrointestinal symptoms and convince the patient to begin a gluten-free diet.

### TABLE 3

<table>
<thead>
<tr>
<th>Diagnostic criteria for celiac disease</th>
<th>1969</th>
<th>1989</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Biopsies</td>
<td>1 Biopsy at time of initial presentation</td>
<td>Clinical response to a gluten-free diet</td>
</tr>
<tr>
<td>First at time of initial presentation</td>
<td>Positive test of gliadin antibodies supports diagnosis</td>
<td></td>
</tr>
<tr>
<td>Second after initiation of a gluten-free diet</td>
<td>Age &gt; 2 y</td>
<td></td>
</tr>
<tr>
<td>Third after a gluten challenge</td>
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<td></td>
</tr>
</tbody>
</table>

### SCREENING TESTS FOR CELIAC DISEASE

Several noninvasive tests of malabsorption are used to decide whether a biopsy should be performed. These include tests of deficiency states, such as measurements of hemoglobin and red cell indexes, carotene, vitamin D, prothrombin time, and iron and folate concentrations; tests of absorption, including the D-xylose test; qualitative or quantitative fecal fat tests; and contrast radiography. These tests may be important for identifying malabsorption but have variable sensitivity for celiac disease. For example, fecal fat measurements may be normal in 30% of persons with celiac disease. Many patients with celiac disease also have normal concentrations of hemoglobin and vitamins, which may be due to the widespread use of supplements.

The identification of celiac disease by contrast radiography depends on the demonstration of edema of the mucosa folds or jejunalization of the ileum. Patterns of flocculation described in the past rarely occur with current methods because modern barium emulsions resist flocculation, making this an insensitive test for celiac disease. The primary use of the contrast study is to identify a complication of celiac disease such as ulcerative jejunitis or strictures or neoplasms of the small intestine.

Measurement of intestinal permeability has become fashionable and may be a sensitive test of intestinal damage. The simplest method is the measurement of the ratio of lactulose to mannitol in the urine after an oral challenge. Although this test may be sensitive, however, it is not specific for celiac disease (79, 80).

An important factor to consider with all tests is whether the patient has been consuming a gluten-free diet before testing. Results on all of the tests, including intestinal biopsies, may return to normal with consumption of gluten-free diets, making confirmation difficult without a gluten challenge.

Physicians should consider screening at-risk family members, including siblings, children, and possibly parents; ≥50% of patients with celiac disease have a family member with undiagnosed disease (7). Serologic screening tests could be used for asymptomatic relatives, but those with symptoms suggestive of celiac disease should undergo interstitial biopsy. Children may have to be screened more than once. Family members should be ingesting gluten to maximize the accuracy of the screening tests.

### Intestinal biopsies

Biopsies may be performed either by endoscopy or by various devices designed to obtain specimens blindly. The former method is generally preferred because multiple biopsies can be taken from the distal duodenum and proximal jejunum while the patient is conscious but sedated. Assuming the specimens are well oriented and that adequate sampling is performed, a definite diagnosis should be obtainable in most cases. Biopsy specimens obtained too close to the stomach may be distorted by underlying Brunner glands or coincidental peptic inflammation.

Pathologists need to be aware of the spectrum of change that occurs in celiac disease. The histologic changes in celiac disease vary from severe villous atrophy to more subtle changes well characterized by Marsh and others (27, 34) in acute challenge studies carried out in treated patients with celiac disease. The earliest stages include increased density of intraepithelial lymphocytes (Figure 2), crypt hyperplasia, and finally, the development of villous atrophy.

Pathologists should consider the villus-to-crypt ratio, the intraepithelial lymphocyte-to-enterocyte ratio, and chronic inflammation of the lamina propria. The term chronic, nonspecific duodenitis.
should be used and interpreted with caution because this is often
understood by pathologists or gastroenterologists to imply a pepti
c process, thereby obscuring the significance of the finding in
patients with celiac disease. Review of previous histologic spec
imens may reveal changes suggestive of celiac disease. Occa
sionally, celiac disease is incorrectly diagnosed as a result of
improperly oriented or fragmented biopsies.

Although villous atrophy is not specific to celiac disease, only a
few other diseases associated with villous atrophy occur in
developed countries, especially in adults. Graft-versus-host dis
ease, radiation treatment, and ischemia are readily differentiated
by patient history or other tests. Tropical sprue is a considera
tion in persons who have traveled to or lived in tropical areas. These
patients should be treated for tropical sprue and discouraged
from avoiding gluten. A failure to respond to the appropriate
therapy for tropical sprue should suggest the possibility of celiac
disease. Serologic tests may help to distinguish the 2, but few
cases of tropical sprue have been included in the validation stud
ties of serologic testing. Intestinal lymphangiectasia, Whipple
disease, and amyloidosis are readily differentiated by the histo
logic appearance of the intestine. Immune deficiency states that
may coexist with celiac disease can usually be identified by elec
trophoresis or HIV testing. Giardiasis rarely produces such
severe damage as that seen in celiac disease except in immunod
efficiency states. In very young children, cow milk, soy, and rare
other foods may induce villous atrophy similar to that in celiac
disease, although the damage is usually not as severe. Crohn dis
ease of the duodenum is rare but may mimic celiac disease and
occasionally the 2 diseases coexist (81).

**Gluten challenge**

Demonstrating a response to a formal gluten challenge is no
longer a requirement for diagnosing celiac disease. In patients in
whom initial biopsy results were inconclusive and in whom a
follow-up biopsy result was normal with consumption of a
 gluten-free diet, a challenge may be helpful primarily to con
vince a doubting patient of the correct diagnosis. A gluten chal
lenge may also be necessary in persons who have been consum
ing gluten-free diets for many months or years and desire con
firmation of the diagnosis. This is not usually necessary if the
patient has had a prior intestinal biopsy during consumption of a
 gluten-containing diet. Review of the original histology slides
may suffice for confirming the diagnosis. The length of time it
takes to relapse with a gluten challenge is variable. Adequate
gluten, 3–4 slices of whole-wheat bread/d, should produce dam
age in 2–4 wk. This dose may need to be reduced in some
extremely sensitive patients to prevent severe symptoms. Patients
who do not develop symptoms should be followed up and biopsy delayed until the occurrence of symptoms or positive
endomysial antibodies, whichever is first (82). Most patients will
relapse within 6 mo although in rare cases it may take years.

**Serologic tests for celiac disease**

Tests to detect antibodies to connective tissue (endomysium
and reticulin) and to gliadin are readily available through refer
ence laboratories. The available tests all show some variability in
sensitivity and specificity (Table 4) (43, 82–98). Low titers of
antibodies to gliadin are often detectable in the general popula
tion, so cutoffs are needed to separate normal results from abnor
mal ones (98). The endomysial tissue antibody test is an indirect
immunofluorescent assay that depends on the identification of a
specific pattern of staining (Figure 5). Results of this test are
usually negative in a healthy population. The dilution of serum
used as the initial stain may affect the reliability of the test.
Antigliadin IgA may be raised in extensive Crohn disease in the
small bowel or in individuals genetically susceptible to celiac
disease without intestinal histologic abnormality. There is signi
ficant variability in the accuracy of the antibodies to gliadin,
whether IgA or IgG, and these tests are less specific in young
children. Antibodies to connective tissue have a greater specifi
city and hence a higher positive predictive value, although anti
bodies to gliadin have been shown to have a greater sensitivity in
some studies. Combinations of both probably maximize negative
predictive value (>95%). The positive predictive value of the
gliadin test may be low and depends on the prevalence of the dis
ease in the population being studied (98).

Although antigliadin IgG is produced in celiac disease, it can
also be detected in other diseases and is absent in 10–40% of per
sons with celiac disease. The major diagnostic importance of these
antibodies is their presence in patients with selective IgA defi
ciency (12). Endomysial IgA and gliadin IgA antibody titers dimin
ish with the institution of a gluten-free diet, often within weeks,
and by 6 mo may be undetectable (94). Repeat testing is used to
monitor the effects of a gluten-free diet on the small-intestinal
mucosa. If the clinician plans to monitor the titers, the assays
should be performed in the same lab. Antigliadin IgG tends to be
more persistent than endomysial IgA antibodies and may be pres
ent 1 y after the start of gluten restriction (99). Small amounts of
gluten may produce both symptoms and damage to the intestine but
not elevate amounts of antibodies to gliadin (100, 101).

Endomysial antibodies may be more sensitive to gluten conta
mination (94, 102). The increased association of celiac disease with selective IgA
deficiency may be a potential source of false-negative results on
tests for endomysial IgA antibodies (103). IgA-deficient patients
with celiac disease seem to have high titers of IgG antibodies to
the endomysium and gliadin (86). When family members of
patients with celiac disease are screened, positive results on tests
for endomysial antibodies may be found in the presence of nor
mal intestinal biopsies. These subjects have a high likelihood of
subsequently developing celiac disease, whereas those patients
who test positive for gliadin antibodies but have normal biopsy
results have a relatively lower risk of subsequently developing
celiac disease (104).
TABLE 4
Serologic tests for celiac disease

<table>
<thead>
<tr>
<th>Antibody type</th>
<th>Substrate or antigen</th>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>Gliadin</td>
<td>ELISA</td>
<td>31–100</td>
<td>85–100</td>
</tr>
<tr>
<td>IgG</td>
<td>Gliadin</td>
<td>ELISA</td>
<td>46–100</td>
<td>67–100</td>
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<tr>
<td>IgA</td>
<td>Endomysium</td>
<td>IFA</td>
<td>57–100</td>
<td>95–100</td>
</tr>
<tr>
<td>IgA</td>
<td>Reticulin</td>
<td>IFA</td>
<td>29–100</td>
<td>95–100</td>
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<tr>
<td>IgA</td>
<td>Tissue</td>
<td>ELISA</td>
<td>?–100</td>
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</table>

1Ig, immunoglobulin; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay. From references 43 and 82–98.

Clinical utility of serologic tests

Serologic tests for celiac disease have several uses: as screening tests for use in family members of persons with celiac disease, in persons with type 1 diabetes, and in other high-risk groups and in population-based screening; for determining in which patients biopsies should be performed; for monitoring compliance and healing; for determining the best time to perform a biopsy of the intestine during a gluten challenge; and for confirming celiac disease when the results of biopsies are inconclusive or unobtainable. The predictive value of the tests depends on the prevalence of the disease in the population being studied. Although the gliadin antibody test alone does not have the specificity required to confirm a diagnosis, in patients in whom celiac disease is highly likely, endomysial antibody tests may be specific enough to render biopsy unnecessary (105, 106). The subsequent clinical response to a gluten-free diet would confirm the diagnosis. However, a negative test does not rule out the possibility of celiac disease nor does it detect any other malabsorptive diseases (107).

In patients in whom celiac disease is a diagnostic consideration but in whom frank features of malabsorption are absent, serologic tests are often used to determine which patients should undergo intestinal biopsy. In patients in whom there is one malabsorptive symptom or sign, intestinal biopsy should be performed regardless of the antibody test results because many other mucosal diseases can cause malabsorption. Antiepipithelial IgA may be especially predictive in populations who have a high prevalence of other causes of flat mucosa. In this instance, a biopsy indicating villous atrophy with a positive endomysial antibody test would differentiate celiac disease from conditions such as cow milk enteropathy and other enteropathies. Gliadin antibodies may give false-positive results in these cases.

Much evidence supports screening high-risk populations for the presence of celiac disease. Screening is justified on the basis of the prevention of malignant complications and the prevention or correction of subtle but important problems such as osteopenic bone disease (108).

Miscellaneous tests

Salivary antibodies to gliadin lack sensitivity and specificity for celiac disease. Blood tests that determine the presence of IgE to gliadin are also not useful in diagnosing celiac disease. Skin testing of intradermal gliadin is relatively insensitive and can be painful. Rectal challenge with gliadin does produce a measurable change in the numbers of intraepithelial T lymphocytes in untreated celiac disease and could serve a surrogate test for diagnosing gluten sensitivity, but as currently performed does not help to diagnose celiac disease in patients already consuming gluten-free diets.

TREATMENT OF CELIAC DISEASE

Once celiac disease has been diagnosed, physicians should explain to patients the lifelong nature of the condition and the necessity of adhering to a gluten-free diet. Patients often react with grief and may have a hard time understanding or accepting that something so fundamental to their diet could be injuring them. Patients may have blamed other food substances, such as lactose, for their symptoms and may find it hard to accept the identity of the culprit. Teenagers especially have a hard time accepting the dietary restrictions and may have partial suppression of symptoms even when they consume gluten in their diets, increasing the chances that they will be noncompliant (109). Patients can be motivated by the expectation of dramatic improvements in their general well-being and gastrointestinal symptoms. Advanced age, obesity, cognitive impairment, and institutionalization should not detract from the decision to treat with gluten-free diets, even though special efforts may be required in these situations for success. A positive, optimistic attitude on the part of the physician is crucial to the future success of the patient. Patients need to know that they cannot depend on their reactions to questionable foods as a measure of safety. Cheating on the diet should be actively discouraged. An active interest on the part of the clinician can improve compliance as can patient knowledge that follow-up blood tests can detect gross gluten ingestion. There had been a trend in treating patients with low-gluten diets, but such treatment may result in significant damage to the intestine and increased risk of complications (100, 101, 108).

The institution of gluten-free diets should result in prompt and often dramatic improvements in symptoms. Recovery is more rapid and complete in children than in adults (110). Resolution of symptoms may take 3–6 mo; complete healing of the intestine may take longer, however, especially in the elderly.

Dietary management: the gluten-free diet

Professional dietary advice from a dietitian experienced in gluten-free diets is a necessity but may not be available locally. It is important that any information given on how to achieve a gluten-free lifestyle be up-to-date. Patients should be encouraged to join both local and national support groups as an essen-

FIGURE 5. Immunofluorescence micrograph illustrating the selective staining of the connective tissue surrounding the smooth muscle fibers of monkey esophagus. Magnification: 40×.
tial adjunct to the management of their disease. Patients who are active members in a support group are often much more compliant with and knowledgeable about the diet. Self-taught patients may not fully grasp the nuances of the diet or may overly restrict their diets, making them insufficient in energy, macronutrients, and occasionally micronutrients.

The goal of the gluten-free diet is to achieve healing and maintain health through the adoption of a well-balanced, varied diet that avoids gluten. Gluten is defined in the setting of celiac disease as any protein-containing derivative of the following grains or their derivatives: wheat, barley, rye, oats, spelt, kamut, and triticale. The toxic role of oats is much more controversial. A case-control study suggested that inclusion of a purified oat product in a gluten-free diet does not prevent healing of the intestine or alter outcome compared with a diet that does not contain oats (111). However, a specially grown and tested oat product was used in these studies and the results may not be applicable to commercially obtained oats, which may be subject to contamination in the field or during milling or processing.

The grain proteins that are toxic in celiac disease can be identified by their ability to induce damage when given to patients with celiac disease. Toxicity may also be inferred by similarities between the protein structure of the grain and that of wheat. The term gluten has several meanings, which can lead to misinformation, especially when making inquiries of a food manufacturer about food ingredients. Bakers think of gluten as the sticky part of any grain, including corn and rice, grains that are safe for celiac patients to consume. Chemists use the terms gliadin and glutenin to refer to the storage proteins of wheat and use other terms for the proteins of barley (prolamin), rye (hordein), and oats (avidin). It is more useful to inquire whether a food has any ingredient that is in any way derived from or processed with wheat, barley, rye, or oats than to ask, “is this food gluten free?”

Hidden sources of gluten are frequently present in what seem to be safe foods. Suspicious ingredients include hydrolyzed vegetable protein, modified food starch (and starch in foreign foods), malt or malt flavoring, vegetable gum (oat), mono- and diacylglycerols, and natural flavorings. Listings of gluten-free foods must be reviewed regularly for changes in the manufacturer’s ingredient list. It may be difficult to ascertain the exact grain source of ingredients as a result of outsourcing of ingredients. Even nonfood items may be sources of trace gluten and can cause symptoms in more sensitive patients. Such sources include medications (both prescription and over-the-counter); glues, pastes, and dry wall filler; airborne flour; communion wafers; fat replacers; cross contamination; and grain-derived alcoholic drinks (112, 113). Contamination of supposedly gluten-free products can also occur during harvesting, processing, and packaging; in the store (for example, in flour bins); and in the kitchen. Obtaining flour substitutes from reliable sources that cater to patients with celiac disease is encouraged.

Secondary lactose intolerance is common but usually resolves once the damage to the gut has healed. Temporary restriction of lactose ingestion or use of a lactase preparation may suffice for treatment. Many patients with celiac disease report intolerances to other non-gluten-containing foods (114). The mechanism of these intolerances is not known.

Specific nutritional supplementation may be used to correct deficiency states. The most common are supplementation with iron, folate, calcium, and fat-soluble vitamins. Bone density should be measured in adults at or shortly after the time of diagnosis because osteopenic bone disease is common and may be profound in patients with newly diagnosed celiac disease. Patients with decreased axial bone density should be advised to obtain $\geq 1200$ mg Ca and 100% of the recommended dietary allowance of vitamin D daily. Higher doses may be needed if vitamin D deficiency is detected. Secondary hyperparathyroidism may occur but tetany is rare. Intensive nutritional support and fluid replacement may be needed in extremely ill patients. Pancreatic enzyme supplementation may be useful in extremely malnourished patients and may accelerate weight gain (115). All patients should be followed up to ensure compliance with and response to the gluten-free diet. Cholesterol concentrations may rise and patients may gain excess weight with reversal of the malabsorption.

### Persistent diarrhea

Patients with previously diagnosed celiac disease with persistent diarrhea should undergo careful dietary review and endomyosal and gliadin antibody tests. If there is no evidence that patients are consuming gluten, if tests of endomyosal and gliadin antibodies are negative, and if it has been $< 6$ mo since the diagnosis of celiac disease, a lactose-restricted diet, pancreatic supplements (especially if there are features of malabsorption), antibiotics for bacterial overgrowth, and a colonic biopsy should be used to rule out coexistent microscopic colitis (51). If it has been $> 6$ mo since the diagnosis, it may be prudent to perform another biopsy of the small intestine to assess improvement. If there was any doubt about the original diagnosis, other conditions should be considered, particularly Crohn disease and small-bowel ischemia if postprandial pain is a feature. Immunoelectrophoresis can be used to detect immunodeficiency states.

### Refractory celiac disease

Particular challenges in the management of celiac disease are presented by patients with refractory disease. This state could be defined as continued diarrhea and malabsorption associated with progressive malnutrition despite consumption of a gluten-free diet for $\geq 6$ mo and continued villous atrophy. Biopsies may reveal the deposition of a thickened layer of collagen in the epithelium. So-called collagenous sprue is rare and may respond to immunosuppressive agents. For a diagnosis of this syndrome, antibody tests should be negative and a detailed dietary review, including examination of a diet record, should not reveal any possibility of gluten in the diet. Patients may have this syndrome as their first presentation of celiac disease. It can also result from noncompliance with the gluten-free diet. Patients with collagenous sprue are often elderly and have poor nutritional status, with multiple complications of malabsorption. They may have extensive ulcerative jejunoileitis with a high risk of perforation, obstruction, and development of lymphoma. Protein-losing enteropathy may be marked. In the past, the prognosis for these patients was poor (116). Parenteral nutritional support now allows correction of the nutritional problems and antibiotics and pancreatic enzyme supplements have been used with occasional success. The widening armamentarium of immunomodulating drugs may provide potent tools to reverse what in these patients becomes a self-perpetuating process. Coexisting malignancy should be considered because it has been suggested that these patients harbor a malignant expansion of T cells.
Malignancy and celiac disease

Another complication of celiac disease is T cell lymphoma of the small intestine. This usually affects the proximal small intestine and may appear as either a return of malabsorptive symptoms or as a surgical emergency associated with obstruction, perforation, or sometimes bleeding. Occasionally, patients will have painless lymph node enlargements or systemic symptoms of fever, sweating, and weight loss. The outlook of patients who first present with abdominal symptoms requiring surgery is better than that of patients with previously diagnosed celiac disease who present with recurrent sprue symptoms (117). The risk for developing lymphoma diminishes with duration of compliance with a gluten-free diet. Lymphoma rarely occurs before 40 y of age in persons with celiac disease. Patients diagnosed as children and who are compliant with the gluten-free diet have a low risk of malignancy. The development of hypoalbuminemia, anemia, recurrent steatorrhea, weight loss, fever, or malaise in a previously stable patient should prompt a search for neoplasm. Small-intestinal enterolysis and computerized tomographic scanning of the abdomen may identify the malignancy; however, it may be difficult to diagnose. In some patients, laparoscopically obtained segments of the bowel will reveal clonal expansion of T cells.

Patients with celiac disease are also at risk of developing adenocarcinoma of the small intestine, although the mechanism for this is unknown (118). Nasopharyngeal and esophageal cancer, benign intestinal strictures, and recurrent pancreatitis may also complicate celiac disease and may require surgical or endoscopic intervention (119, 120).

THE FUTURE OF CELIAC DISEASE

The future should bring a better understanding of why celiac disease covers such a broad spectrum, both pathologically and clinically. I believe that as the tests become more reliable and standardized, serologic testing will replace the need for biopsies for diagnostic purposes in many patients in the next 5 y. This single change will place celiac disease within the realm of what can easily be diagnosed by generalists. Increased rates of detection and hence greater experience on the part of the diagnosing physician and treating dietitian will lead to a greater awareness of the disease and improve dietary management.

More stringent regulations and more precise identification of ingredients in processed foods would make it easier for those affected to obtain a safe and varied diet in our culture of heavily processed food. An area of practical concern to celiac patients is whether alternative treatments to a lifelong gluten-free diet may become available. It is unlikely that the antigenicity of wheat for celiacs will be successfully altered through genetic manipulation of the wheat. The focus for nondietary treatment will be on modulating immune responses to gliadin in the intestine. Potential avenues of treatment may include altering the presentation of the antigen to the T cell, the induction of anergy in the activated T cell, or the modification of cytokine release or activity.

REFERENCES