AGA Technical Review on Celiac Sprue

The literature review and the recommendations therein were prepared for the American Gastroenterological Association (AGA) Clinical Practice and Practice Economics Committee. The paper was approved by the Committee on September 23, 2000, and by the AGA governing board on November 12, 2000.

This report is a comprehensive review of the current state of knowledge of celiac sprue, its pathogenesis, clinical presentation, diagnosis, treatment, and outcome.

Definition
Celiac sprue may be defined as a condition in which there is an abnormal proximal small intestinal mucosa that improves morphologically on treatment with a gluten-free diet and relapses when gluten is reintroduced. The condition termed celiac sprue may also be called celiac disease or gluten-sensitive enteropathy. It was previously termed nontropical sprue, celiac syndrome, idiopathic steatorrhea, or primary malabsorption. The condition has a genetic predisposition.

Dermatitis herpetiformis (DH) is a related disorder in which there is an itchy blistering skin eruption that frequently affects the knees, elbows, buttocks, and back, with deposition of granular immunoglobulin (Ig) A at the dermoepidermal junction of the skin including areas not involved with the rash. Patients with DH have a degree of small intestinal enteropathy, which improves on gluten withdrawal.

Historical Aspects
Aretaeus the Cappadocian described the condition in the second century A.D., noting that “if diarrhea does not proceed from a slight cause of only one or two days duration and if, in addition, the patient’s general system be debilitated by atrophy of the body, the celiac sprue of a chronic nature is formed.”

Samuel Gee described the condition as we know it in 1887. He noted the disease affected all ages. It is of interest that he thought that “to regulate the food was the main part of treatment.” He recognized that “if the patient can be cured at all it must be by means of the diet.” He described “a child who was fed upon a quart of the best Dutch mussels daily, throve wonderfully but relapsed when the season for mussels was over. Next season he could not be prevailed upon to take them. This is an experiment I have not yet been able to repeat, but if the patient can be cured at all, it must be by means of the diet.”

In 1924, Haas described his treatment of celiac sprue. He thought it logical to try a banana diet in children with celiac sprue following his successful treatment of anorexia with this regime. He excluded bread, crackers, potatoes, and cereals. Bananas were gradually added to the diet usually from the fourth or eighth day. The treatment was continued indefinitely.

This dietary treatment of the condition continued well into the 1950s. In the Netherlands during World War II there had been a scarcity of cereals, and bread in particular. Dicke, a Dutch pediatrician, observed that celiac sprue diminished remarkably during this shortage. He observed that children with celiac disease quickly relapsed after Swedish planes dropped bread into the Netherlands. This helped Dicke to realize that wheat was toxic to individuals with celiac sprue. Dicke and coworkers proceeded to show that wheat flour was the offending substance and that the toxicity resided in the gluten fraction.

Early diagnosis was made on clinical grounds. The late description of the histology was due to the presumption that the abnormal changes seen at autopsy were postmortem artifacts. In 1954, Paulley et al. reported the histology of jejunal mucosa obtained operatively. Shiner and Royer independently developed methods for performing a biopsy on the duodenum, followed by Crosby, who developed the Crosby capsule.

Epidemiology
Celiac sprue is mostly a disease of Europe and those countries to which Europeans have emigrated, including North America and Australia. Celiac sprue was thought to affect 1:1500 throughout Europe with pockets of greater frequency. Hin et al. recently used serologic screening followed by diagnostic small intestinal biopsy to show that in the United Kingdom the true prevalence may be 1:300. In Southern and Northern
Ireland, the prevalence has recently been revised to 1:150 of the population. In the United States, where the prevalence of celiac sprue has always been lower than in Europe, a recent screening of blood from 2000 blood donors found a prevalence of raised endomysial antibodies of 1:250.

Celiac sprue occurs in non-Caucasoids, although the prevalence is apparently much lower. It has been reported in Indians, Arabs, Hispanics, Israeli Jews, Sudanese, and people of Cantonese extraction. It occurs rarely in those of Afro-Caribbean origin.

**Gender Incidence**

The female to male ratio is generally accepted to be 2:1, although some have suggested it may be more equal.

**Twin Studies**

Concordance in identical twins is well described. Although discordance has been reported in several cases, after prolonged follow-up in the majority of cases, the discordant twin has gone on to develop the condition.

**Mortality**

Before the introduction of the gluten-free diet, the outlook for individuals with celiac sprue was poor, with published mortality rates varying between 10% and 30%. After the introduction of the gluten-free diet, mortality rates fell markedly with a published rate of 0.4% in one series. Previous evidence suggested that the mortality rate was twice that of a matched control population, although there are no recent studies to support this.

**Pathology**

Celiac sprue affects the mucosa of the proximal small intestine with damage gradually decreasing in severity towards the distal small intestine, although in severe cases, the lesion extends to the ileum. The degree of proximal damage varies greatly depending on the severity of the disease. The proximal damage may be very mild in “silent” cases with little or no abnormality detectable histologically in the mid jejunum. Abnormalities of the gastric and rectal mucosa may be observed in some cases.

The best biopsy specimens of the proximal small intestinal mucosa are obtained using a suction guillotine biopsy capsule. If available, it may be useful to examine the biopsy specimens using a dissecting microscope. This allows observers to distinguish between normal villous mucosa and flat biopsy specimens that are present in celiac sprue with degrees of abnormality falling between these 2 categories. Normal mucosa exhibits digitate villi, leaf forms, and ridges. The villi vary in size, shape, and height but are usually 3 times taller than they are wide (Figure 1A). Convolutions, which are normal, are long ridges that can be regarded as villi that have fused and buckled. There are different appearances of the small intestinal mucosa, depending on whether subjects reside in temperate or tropical climates. Fully convoluted appearances occur in more than 5% of normal subjects in tropical areas. Infants exhibit broad leaves and villi, with finger-shaped villi rarely present.

The small intestinal mucosa in celiac sprue may be flat and featureless and may present a flat mucosal pattern caused by interaction of deep depressions leaving elevated mounds. Each mound has 8–40 crypt openings. If a dissecting microscope is available, examination of biopsy specimens by dissecting microscopy is of value in assessing specimens for patchiness of mucosal abnormality, particularly in DH, where a patchy lesion is more common.

The characteristic histologic appearance of small intestinal mucosa from a patient with untreated celiac
sprue classically exhibits a flat mucosa with reduction in the normal villous height to crypt depth ratio from between 5:1 and 3:1 (Figure 1B). The total thickness of the mucosa may be increased because of crypt hyperplasia and infiltration of the lamina propria by plasma cells and lymphocytes. Surface enterocyte height is reduced. Crypt mitotic activity is normally confined to the lower third of the crypt, but in celiac sprue this activity may be increased, although the histologic appearance of the crypt seems normal. The histologic differential diagnosis will be between celiac sprue, tropical sprue, eosinophilic enteritis, and Crohn’s disease. Confirmation of the diagnosis will include improvement in the histologic abnormalities on the small intestinal biopsy specimen as well as symptomatic improvement with a gluten-free diet. There is generalized lymphocytic infiltration of the epithelium that may extend into the crypts.

The time taken for the cells to migrate from the crypt to the surface is reduced from between 3 and 5 to between 1 and 2 days. The number of intraepithelial lymphocytes (IELs) in relation to the number of surface cell enterocytes is increased in patients with active disease. Chronic inflammatory cells infiltrate the small intestinal mucosa in untreated celiac sprue. There are increased numbers of plasma cells in the lamina propria and lymphocytes in the surface epithelium. Most IELs express the common leukocyte antigen CD3, 70% express the suppressor/cytotoxic phenotype CD8, 5%–10% express the helper/inducer CD4 phenotype, and 20% of the cells are CD3+, CD4−, and CD8−. There is also an increase in the number of IELs expressing the more primitive γ/δ T-cell receptor in the untreated condition.
Types of Mucosal Lesions

The mucosal lesion has been classed into 5 types.9

Type 0 preinfiltration lesion. Five percent of patients with DH have small intestinal biopsy specimens that appear normal but secrete antigliadin antibody.

Type 1 infiltrative lesion. There is a normal mucosal architecture but with an increased number of IELs. This lesion occurs in 40% of patients with DH and 10% of first degree relatives of patients with celiac sprue.9 This lesion is not associated with any symptoms or signs of malabsorption and intestinal permeability studies are normal.

Type 2 hyperplastic lesion. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villous height. Gluten challenge can induce these changes, which are seen in 20% of untreated DH patients and in celiac patients.

Type 3 destructive lesion. This is the classical celiac lesion. It is found in 40% of DH patients and 10%–20% of first degree relatives of celiac patients, and, despite marked mucosal changes, many individuals are asymptomatic and therefore classified as subclinical. This lesion is characteristic of, but not diagnostic for, celiac sprue and can also be seen with severe giardiasis, infantile food sensitivities, graft versus host disease, chronic ischemia of the small intestine, tropical sprue, Ig deficiencies, and other immune deficiencies and allograft rejection.

Type 4 hypoplastic lesion. This can be considered the end-stage lesion in a very small group of patients who are unresponsive to gluten withdrawal and may develop malignant complications. There is deposition of collagen in the mucosa and submucosa (collagenous sprue), which is usually unresponsive to treatment with steroids, immunosuppressive agents, or chemotherapy.

Categories of Celiac Sprue

The increased awareness of the genetic basis for celiac sprue, disease associations, and changes in patterns of presentation is consistent with the development of new techniques for screening, which have produced a large number of individuals who cannot be classified simply by the presence or absence of celiac sprue. Large scale population screening studies suggest that the diagnosed celiac population may represent the tip of an iceberg of undiagnosed cases. Those not diagnosed with the condition will fall into one of the following categories.

Undiagnosed celiac sprue. These individuals have classical mucosal lesions and are symptomatic but have not been diagnosed.

Silent celiac sprue. Individuals in this group have characteristic morphologic changes in the small intestinal biopsy in the absence of clinical signs and symptoms. If only the proximal small intestine is affected, there may be physiologic compensation by normal small bowel, although it is likely that symptoms might be manifest if the gluten load is increased.

Latent celiac sprue. Those individuals who have genetic susceptibility to the disease but do not manifest clinical or histologic evidence of the disorder. It is likely that the timing and quality of gluten load, possibly combined with other environmental triggers or intercurrent illness, may be a factor in the age of presentation in these individuals.

True normals. These individuals lack genetic susceptibility to the condition and do not manifest either histologic or clinical symptoms at any stage. However, there is a separate condition in which there is an IgE-based allergy to gluten or other wheat proteins.

Characterization of Toxic Cereal Peptides

Classification of Cereal Protein

The precise structure of the part of gluten, which causes the damage in celiac sprue, remains unclear. Wheat grains have 3 major constituents that are separated by milling: the outer husk or bran, the germ, and the endosperm or white flour, which constitutes 70%–72% of the whole grain by weight and contains the toxic components. The storage proteins of cereals fall into 2 major groups: the ethanol-soluble fraction termed prolamins and the glutenins. Prolamins from the different cereals are termed gliadins from wheat, secalins from rye, hordeins from barley, avenins from oats, and zeins from celiac nontoxic maize.

Wheat proteins are divided into classes according to their solubility characteristics: gliadins are soluble in 40%–90% ethanol, and glutenins are insoluble in neutral aqueous solution, saline, or ethanol. The gliadins may be further subdivided into alpha, beta, gamma, and omega subfractions either according to their relative electrophoretic mobility, or alpha, beta, and omega according to their N-terminal amino acid sequences. The molecular masses of gliadins range from 32 to 58 kilodaltons.

After Dicke’s discovery that the toxic fraction of wheat resided in the endosperm or flour fraction of wheat, Frazer10 purified and separated wheat protein peptides after physiologic digestion of the proteins. He showed that the majority of these peptides were toxic to celiac patients in remission. Hekkens et al.11 went on to show
that α-gliadin exacerbated celiac sprue in vivo and more recently all 4 gliadin subfractions were shown to exacerbate celiac sprue both in vitro and in vivo.

Kagnoff et al.\textsuperscript{12,13} reported that A-gliadin shares an 8 amino acid sequence homology, in a span of 12 amino acids, with an identical pentapeptide with the 54-kilodalton Elb protein of human adenovirus 12, an adenovirus usually isolated from the gastrointestinal tract. Others were unable to find a correlation between the presence of celiac sprue and serum antibody titers to the adenovirus 12 protein. However, while the adenovirus hypothesis is attractive and has analogies to theories regarding the pathogenesis of autoimmune disease, it is no longer generally accepted.

Glutamine comprises 35% of the amino acids in gliadin and may play a central role in its toxicity. Evidence for this lies in the fact that complete deamidation of glutamine removes the toxic properties; however, partial deamidation has been found to increase the sensitivity of cloned gluten-sensitive T cells to these proteins. Sequences of A-gliadin, a major component of α-gliadin, were published by Kasarda et al.\textsuperscript{14} Subsequent to this, the toxicity of various synthetic peptide sequences from A-gliadin has been assessed using celiac small bowel biopsy organ culture techniques. Toxicity has been shown using peptide sequences corresponding to residues 3-24, 25-55, 31-55, and 1-30 of A-gliadin.\textsuperscript{15} Gjertson et al.\textsuperscript{16} reported that a peptide corresponding to amino acid residues 31-49 was recognized by CD4\textsuperscript{+} T cells obtained from the peripheral blood of a patient with celiac sprue when presented by the HLA-DQ2 heterodimer. Sturgess et al.\textsuperscript{17} subsequently reported that this same peptide exacerbated celiac sprue in vivo after intraduodenal infusion and using a multiple small intestinal biopsy technique.

Molberg et al.\textsuperscript{18} have recently shown that tissue transglutaminase (tTG) causes selective deamidation of gluten proteins, which increases their stimulating effect on gluten-sensitive T cells obtained from the small intestine of patients with celiac sprue. It has been postulated that this results in neoepitopes in wheat proteins, which are then involved in the disease pathogenesis.

**Genetics**

Celiac sprue is an HLA-associated condition, the primary association being with major histocompatibility complex class II alleles DQA1*0501 and DQB1*0201.\textsuperscript{19} This HLA-DQ2 allelic combination is found in 98% of celiac patients from Northern Europe. The association of celiac sprue with DR3 is thought to be through linkage disequilibrium with DQ2. In Southern Europe, DQ2 is also the major susceptibility genotype, being present in 92% of celiac patients, where it is inherited either in cis with DR3 or in trans in DR3, DR7 heterozygotes (i.e., the DQA and B alleles are encoded on different chromosomes). In Southern Europe and Israel, there is another smaller group of affected subjects who carry HLA-DQ8 in association with DR4.\textsuperscript{20}

Despite the strong HLA association, there is only about 30%–50% concordance for celiac sprue in HLA identical siblings, compared with concordance approaching 100% in monozygotic twins. The risk in first degree relatives is between 10% and 20%.\textsuperscript{21,22} It should also be recognized that 25% of the “normal” Northern European population carries DQ2. Thus other genetic influences, probably non-HLA linked, may be required for development of the disease. Two genome-wide searches for such genes have been undertaken,\textsuperscript{23,24} but as yet no conclusive results have emerged.

The susceptibility to celiac sprue therefore seems to be genetically determined by possession of certain HLA-DQ alleles together with 1 or more non-HLA genes. Linkage analysis was used to study T-cell receptor α/β and γ/δ genes using microsatellite markers, in 21 multiply affected pedigrees. No evidence of linkage was found.\textsuperscript{25}

**Pathogenesis**

The known antigen, that is wheat gluten, and the HLA predisposition are brought together in the currently accepted theory of pathogenesis. It has been proposed that gluten-sensitive T cells recognize gluten-derived peptide epitopes when presented in association with DQ2.\textsuperscript{26} Evidence suggests that upon activation, these CD4\textsuperscript{+} gluten-sensitive T cells develop a Th1/Th0 type inflammatory response,\textsuperscript{27} which produces the observed mucosal damage. The exact epitope(s) within gluten remain unknown, although there is mounting evidence for the role of a 19 mer peptide from the N-terminal region of A-gliadin, a constituent of gluten, corresponding to amino acid residues 31-49, comprising one of several possible toxic epitopes. This peptide has been shown to cause histologic features of celiac sprue by in vitro organ culture\textsuperscript{28} and in vivo challenge studies.\textsuperscript{17} It has also been shown to bind to DQ2 molecules\textsuperscript{29,30} and stimulate T cells derived from the peripheral blood of celiac patients, when presented in association with DQ2.\textsuperscript{16}

**Clinical Features**

**Infancy and Childhood**

The classical presentation of celiac sprue occurs after weaning and introduction of cereals into the diet. There is failure to thrive associated with apathy, pallor,
anorexia, and muscle wasting. There is generalized hypotonia and abdominal distention with the child passing soft, bulky, clay-colored, offensive stools. Very young children may present with vomiting, which is often effortless, of large volume, and usually associated with abdominal distention and little or no diarrhea. Abdominal pain may be so severe that a laparotomy is undertaken because of a mistaken diagnosis of intestinal obstruction. In some cases, this pain is caused by constipation. Retardation of motor activity has been observed. Presenting symptoms are extremely varied and include rectal prolapse, although this is more common in cystic fibrosis. Intussusception can occasionally occur.

Older children tend to have more varied symptomatology and may present with anemia or failure to grow normally. Rickets may occur, particularly in Asian children. Unexplained short stature is an indication for performing a small intestinal biopsy, even when gastrointestinal symptoms are mild or absent. After diagnosis and introduction of a gluten-free diet, there is often a significant increase in height and weight.

Gastrointestinal symptoms may date from birth in 25% of children, whereas more than half become symptomatic in the first 6 months of life. After the age of 6 months, the development of symptoms may be caused by the introduction of cereals to the diet during weaning. The notable exception to this is Sweden, where infant feeding practices have returned to the early introduction of gluten to infants within the first weeks of life. Later introduction of large amounts of gluten had previously been associated with an upsurge of cases presented during infancy. It has been suggested that celiac sprue occurs predominantly in infants who had not been breast fed, although this has not been substantiated.

**Adult Life**

Adult and adolescent patients with celiac sprue may present with symptoms in almost any hospital department (Table 1). Diarrhea is the main presenting feature, whereas those with constitutional disturbances such as lassitude, loss of weight, glossitis, and symptoms of anemia form another group. A small group present because of abnormal psychological or psychiatric symptoms, including schizophrenia. There may be presentation with problems related to osteomalacia, including spontaneous fractures, and myopathy, skin complaints, bleeding diathesis, or infertility.

Many individuals have long-standing ill health for many years and, never having had severe symptoms, accept this as normal. Abdominal pain occurs in 5% of cases. Aphthous stomatitis may be the sole presenting symptom, and therefore celiac sprue should be excluded in cases of severe unexplained recurrent mouth ulceration.

The stress of an operation or infection can occasionally induce severe diarrhea. Pregnancy may precipitate macrocytic or iron-deficiency anemia and the onset of unexplained diarrhea. After pregnancy, the symptoms may abate and the diagnosis may be missed.

Presenting symptoms in many patients with celiac sprue are nonspecific and therefore a high diagnostic suspicion should be aroused with minor abnormalities such as hematological or biochemical profiles, including persistent transaminitis. The finding of a mild unexplained macrocytic anemia with persistently low serum or red cell folate should suggest further investigation and may lead to a diagnosis of celiac sprue. A previous diagnosis of celiac sprue in childhood can be overlooked by both the patient and doctor only to become a source of symptoms in adult life. Clinicians should therefore explore possible childhood disturbances such as short stature, anemia, or rickets.

There is a 10% prevalence among first degree relatives. Certain symptoms, in particular lassitude, may be attributed to psychiatric illness. Glossitis, angular stomatitis, and cheilosis may be present. Nausea and vomiting are common, particularly during episodes of diarrhea in children. There may be anorexia, although appetite may be increased in some patients and polyphagia has been reported. Abdominal distention is common and often associated with flatulence.
Symptoms of cramp and tetany may occur, usually associated with low serum calcium or magnesium levels. Bowel disturbance is the most frequent problem, usually in the form of loose stools. The motion may be paler than normal, sometimes offensive, occasionally frothy, and difficult to flush away. Bowel frequency varies, but is commonly 3–4 times a day and rarely more than 8 times a day. Normally formed and colored stools do not preclude the diagnosis. Steatorrhea may be present even though the patient has stools with a normal appearance. Physicians should remember to enquire specifically about a subject’s stool because patients with long-standing bowel disturbance frequently make no complaint. In addition, clinicians should examine patients’ stools to avoid any problem pertaining to the patients’ powers of observation. It has been reported that 10% of patients suffer incontinence complicating nocturnal diarrhea. A recent study has shown that 10% of patients suffering from irritable bowel syndrome were subsequently found to be suffering from celiac sprue. Constipation has been reported to occur in 10% of cases, although this may be an underestimate.

Abdominal pain is uncommon and may indicate the need for investigation to exclude intra-abdominal pathology complicating celiac sprue, in particular such conditions as volvulus, intussusception, mesenteric adenitis, cholelithiasis, peptic ulceration, and pancreatitis.

Scurvy and epistaxis have been reported, and occasionally there may be bleeding into the skin and subcutaneous tissue. This may reflect vitamin K deficiency.

Osteomalacia, rickets, or bone pain lead to the diagnosis of celiac sprue in an appreciable number of subjects reflecting low calcium and vitamin D absorption. Symptoms of rickets and osteomalacia are frequently insidious in onset and may become severe before they are recognized.

**Dermatitis Herpetiformis**

This skin disorder is associated with celiac sprue because some degree of gluten-sensitive enteropathy is common to both conditions. It is characterized by an itchy papular, vesicular eruption. This rash is usually symmetrical and located on the elbows, knees, buttocks, sacrum, face, neck, trunk, and occasionally within the mouth. The predominant symptoms are itching and burning, which may be so severe as to cause pain. Rupture of the blisters results in a rapid relief of symptoms.

The earliest abnormality consists of a small erythematous macule 2–3 mm in diameter, which quickly develops into a papule. Small vesicles then seem to coalesce. Scratching causes them to rupture, dry up, and possibly leave an area of pigmentation and scarring. The vesicles appear tense and shiny (Figure 2), containing a clear fluid that clouds as the lesion progresses and may be tinged with blood in rapidly growing blisters. Solitary vesicles may occur. The lesions tend to occur in crops, although all stages may be evidenced at one time. The blisters take 7–10 days to evolve. The rash was found to respond to sulphapyridine and subsequently to dapsone.

Associated symptoms are the same as for celiac sprue. These include lassitude, diarrhea, abdominal pain, and distention. The degree of malabsorption found in patients with DH is less than that found in celiac sprue. Only 10% of patients have symptoms attributable to malabsorption, although almost 100% have a histologically abnormal jejunal mucosa. There is a slight predominance in males.

The diagnosis depends on the demonstration of granular IgA in the skin in areas not affected by blistering. This granular deposition occurs at the dermoepidermal junction, distinguishing DH from linear IgA deposition, a separate condition not associated with celiac sprue.

The majority of patients with DH have an abnormal small intestinal mucosa, reaching nearly 100% when several biopsy specimens are taken, suggesting that the lesion is patchy. Some patients have apparently normal small intestinal biopsy specimens but increased lymphocyte counts in the epithelium (Marsh type 1), the numbers of which fall towards normal after treatment with a gluten-free diet. The degree of mucosal change may depend on the amount of gluten ingested, as well as individual sensitivity. The exact relationship of the gluten-sensitive enteropathy found in patients with DH to that found in celiac sprue remains unclear.

The treatment of DH is dapsone at a dose of 50–100 mg/day, although a smaller dosage may be used, which does not affect the small intestinal enteropathy. Patients should be advised to take a gluten-free diet as, in many cases, this results in a significant improvement after 6–12 months, permitting reduction in the dose of dapsone required to control the rash. The diet may even completely eliminate the need for dapsone. However, the full benefits are not seen for months or years, resulting in many patients discontinuing their gluten-free diets.

**Physical Signs**

Children with celiac sprue are usually irritable and miserable. Adults may suffer depression, paranoia, Korsakov’s syndrome, and neurasthenia. Most individuals experience an improved outlook on life when they exclude gluten from their diet.
Celiac patients are generally shorter than their peers. However, a height of over 1.8 m does not preclude the diagnosis. Both adults and children frequently experience weight loss, with an average of 12 kg in one series.31 Children may exhibit delayed eruption of teeth, and hypoplasia of the dental enamel has been described. A low-grade fever associated with anemia may be encountered and may be a manifestation of a complication such as lymphoma. Clubbing and koilonychia have both been reported. Edema and ascites may rarely be present reflecting hypoproteinemia. Frequently there is abdominal distention making the abdomen feel like dough.

The menarche is, on average, delayed 1 year in individuals subsequently shown to have celiac disease. Amenorrhea lasting more than 3 months unrelated to pregnancy occurs in one third of women of childbearing age. The average age of the menopause in untreated celiac sprue is 45 compared with 53 years on a gluten-free diet. Many celiac patients are relatively infertile and spontaneous abortion occurs in 18% of pregnancies compared with 9% of patients on a gluten-free diet. Recurrent miscarriage may be a presenting symptom.

Men may experience a reduction in potency. Both fertility and normal sperm counts are restored by a gluten-free diet. A delay in puberty and development of secondary sexual characteristics may occur in untreated celiac patients. These abnormalities revert to normal after prolonged treatment.

**Hematologic and Biochemical Abnormalities**

The characteristic blood picture is of a mild normocytic anemia, with severe anemia occurring uncommonly. The blood film may exhibit target cells, Howell–Jolly bodies, siderocytes, irregular and crenated cells, Heinz bodies, microspherocytes, acanthocytes, occasional erythroblasts, with possible evidence of hyposplenism. The serum levels of iron and folic acid are usually low. A macrocytic megaloblastic anemia may occasionally occur. Examination of the bone marrow usually reveals megaloblastic erythropoiesis when iron and folic acid are invariably reduced and 14% of patients have a B12 level that is lower than controls. Iron and folic acid should be therapeutically replaced, and possibly B12, although levels normally rise without replacement.

**Diagnosis**

**Small Intestinal Biopsy**

The diagnosis may be suspected on clinical grounds and as a result of various screening tests. However, for confirmation, it is mandatory to proceed to a small intestinal biopsy, which should be regarded as the gold standard for diagnosis. A biopsy procedure is indicated in any patient with a history suggestive of celiac sprue. This includes individuals with mild symptoms, particularly if they are relatives of probands. All patients with DH require biopsy, not only to confirm the presence of concomitant gluten-sensitive enteropathy, but also to determine the severity of the enteropathy. However, in the United States not all physicians perform small intestinal biopsies in patients with DH. The most common indications for performing a biopsy in childhood are diarrhea, failure to thrive, anemia, and short stature.

It is customary to take biopsies endoscopically. Hemoglobin concentration, platelet count, and prothrombin time should be checked before biopsy because of the significant number of untreated celiac patients who have an increased prothrombin time. Anemia is not a contraindication to small intestinal biopsy unless very marked because the risk of hemorrhage with a normal prothrombin time is small.

Endoscopic biopsy specimens should be obtained from the second part of the duodenum using the largest forceps available. It is advisable to take at least 3 biopsy specimens to avoid difficulties in interpretation because of the normal villous mucosa overlying Brunner’s glands.32 The macroscopic appearance of the duodenum at endoscopy should be noted because a duodenal ulcer or patchy duodenitis may produce a pattern of inflammation similar to that found in celiac sprue. Sometimes the endoscopist may note either a loss or scalloping of the normal duodenal folds (Figure 3).

Previously, small intestinal biopsy specimens were taken with a suction-guillotine biopsy capsule, most commonly that of Crosby–Kugler or Watson. Certain pediatricians continue to use this biopsy technique to avoid the risk of general anesthesia in young children, although endoscopy with sedation for children may be used. The alternative capsule described by Bradburg, frequently termed a Quinton capsule or Ruben tube, may be used to take multiple biopsy specimens of the small intestine but is usually reserved for research purposes.

**Serologic Markers**

In untreated celiac sprue, there are raised serologic antibodies to gliadin, reticulin, jejenum, endomy-sium, and tTG (Table 2).32–36 It is important to remember that these tests become negative when patients with celiac sprue take a gluten-free diet. Other food-related antibodies may also be raised in a nonspecific manner, which is thought to be a consequence of the increased
permeability of the small intestine in untreated celiac sprue.

Antireticulin antibodies. Antireticulin antibodies were described in 1971 using immunofluorescence. It has recently been noted that they are specific but not very sensitive for celiac sprue, a finding confirmed in a recent study of 50 celiac children and 25 controls. Antireticulin antibodies are not commonly used having been superseded by antiendomysial and tTG antibody testing.

Antigliadin antibodies. Antibodies to wheat gliadin, termed antigliadin antibodies (AGAs), have been extensively studied in celiac sprue. In one study, the sensitivity of IgG AGAs and IgA AGAs were 100% and 89%, respectively, in children with celiac sprue. The specificity was 86% for IgG and 95.5% for IgA AGAs. Subsequent investigators have confirmed that IgA AGAs are more specific for celiac sprue but less sensitive than IgG AGAs. In the 2%–3% of individuals with celiac disease, who are IgA deficient, all IgA antibody-based tests will be negative. Therefore, screening for celiac disease should include IgG AGAs, or IgG tTG antibodies or at least measurement of total serum IgA. Should IgA deficiency be found, it would be necessary to then proceed to the IgG antibody tests. Care should be taken in the interpretation of positive results because AGAs may also be raised in other conditions including cow’s milk intolerance and IgA nephropathy. Gliadin antibodies may be found in a variety of other conditions, namely Crohn’s disease, eosinophilic enteritis, tropical sprue, and some apparently normal individuals.

Antijejunum antibodies. Antibodies to the jejunum have been identified, although they have not been extensively studied in screening programs. It seems that they exhibit similar binding characteristics to antireticulin and antiendomysial antibodies.

Antiendoemysial antibodies. An antibody directed against endomysium, a connective tissue protein found between myofibrils in the gastrointestinal tract of primates, was found to be associated with gluten-sensitive enteropathy. Replacement of primate esophagus with human umbilical cord as the substrate for antiendoemysial antibodies (EMAs) facilitated wider application of this test. The sensitivity and specificity of EMAs using primate esophagus or human umbilical cord as substrate are reported as 97%–100% and 98%–99%, respectively. EMAs seem to be superior to AGAs for screening populations with a high prevalence of celiac sprue. The combination of AGAs and EMAs has positive and negative predictive values approaching 100%. Thus, if either test is positive, the patient should be referred for diagnostic small intestinal biopsy. However, if both tests are negative, it is highly unlikely that the individual has celiac disease.

Another potential substrate for EMAs is cell culture–derived human umbilical vein endothelial cells. Whelan et al. has demonstrated 100% sensitivity and specificity for untreated celiac sprue using such a method, although the figures obtained by other investigators are somewhat lower. It has been suggested that the sensitivity of the assay may fall to as low as 50% in certain commercial laboratories.

Anti-tTG antibodies. The demonstration that the antigen for EMA was tTG has allowed the development of an enzyme-linked immunosorbent assay for both IgA and IgG tTG to screen for celiac sprue. Sulkanen et al. found that the IgA assay had a sensitivity of 95% and specificity of 94% in untreated celiac patients. In addition, all 14 of the IgA-deficient celiac patients were detected using the IgG tTG enzyme-linked immunosorbent assay. It should not be forgotten that the sensitivity of the serologic screening tests may be lower in certain commercial laboratories.

Bone Metabolism

Osteomalacia is well recognized in celiac sprue, even in the absence of symptoms, and responds to calcium and vitamin D supplementation. Bone pain, pseudo fractures, or deformity occur, but osteomalacia is frequently asymptomatic and only found after noting a raised serum alkaline phosphatase level. Calcium and phosphate levels are frequently normal. Vitamin D (25(OH)D₃) and parathyroid hormone levels are also

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA AEA</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>IgA ARA</td>
<td>91</td>
<td>68</td>
</tr>
<tr>
<td>IgA AGA</td>
<td>91</td>
<td>52</td>
</tr>
<tr>
<td>IgG AGA</td>
<td>76</td>
<td>88</td>
</tr>
</tbody>
</table>

Data from (A) Ferreira et al. and (B) Lerner et al.

IgA AEA, antiendomysial antibodies; IgA ARA, antireticulin antibodies; IgA/IgG AGA, antigliadin antibodies.
useful. Bone biopsy gives absolute confirmation, although this is not frequently performed.

Osteopenia and osteoporosis are common features of celiac sprue, although the exact mechanisms are unclear. Bone mineral density is invariably reduced in untreated celiac sprue but has also been found to be reduced in a high percentage of patients receiving a gluten-free diet. One study involving dual energy x-ray absorptiometry scanning, where osteoporosis was defined as a T score of less than −2SD, revealed that of 65 patients on a gluten-free diet, 50% of women and 47% of men exhibited osteoporosis. Osteoporosis carries a significant risk with increased morbidity, mortality, and socioeconomic implications. Thus, screening of celiac sprue patients for osteoporosis by dual energy x-ray absorptiometry is now recommended. Osteoporosis in children frequently responds to a gluten-free diet. In adults, besides strict adherence to a gluten-free diet and consideration of a repeat small intestinal biopsy, treatment may comprise hormone replacement therapy in postmenopausal women, biphosphonates, or calcitonin.

In patients with osteopenia who are not actually osteoporotic, repeat small intestinal biopsy procedures should be considered and the importance of strict adherence to a gluten–free diet emphasized. Dietary calcium supplementation up to 1500 mg/day has been recommended, particularly for women at the menopause who will suffer significant bone loss. Monitoring by repeat dual energy x-ray absorptiometry scan at 1 year should be considered because it permits an estimate of rate of change of bone mineral density.

Splenic Atrophy

This occurs commonly in celiac sprue, the mechanisms being unknown. The finding of blood film features of hyposplenism, with Howell–Jolly bodies, without an obvious cause should prompt a search for celiac sprue. It has been suggested that pneumococcal immunization for those with hyposplenism should be considered, although the value of this remains unproven.

Radiology

Dilatation of the colon was an early radiologic feature to be noted. Segmentation and dilatation of the bowel and “moulage” resembling “a tube into which wax had been poured and allowed to harden” were added later. After introduction of colloidal preparations of barium, flocculation and segmentation were noted to occur. The most common feature remains dilatation. The upper limit for the diameter of the normal proximal small bowel on barium follow through is 30 mm in adults, 24 mm in children aged 10 years, and 14 mm up to the age of 6 months. The ileum does not show much distention but measures up to 24 mm in the normal adult. Values for the technique of enteroclysis or small bowel enema in which barium is placed into the duodenum through a peroral or pernasal tube are higher. The upper limit for the diameter of the small intestine in normal adults using this technique is 50 mm.

Barium follow through examination of the small intestine reveals a loss of the fine, feathery mucosal pattern with thin mucosal folds in 85% of subjects (Figure 4). The normal appearance of the small bowel enema does not, however, include this feathery pattern. There is usually a degree of straightening of the valvulae conniventes, thickening of the mucosal folds, and an increase in their separation. Superimposed upon dilatation and thickening of the mucosal folds are varying degrees of flocculation, segmentation, and clumping, which are more relevant when they occur early in the examination. These features are not specific to celiac sprue.

Some patients have findings resembling Crohn’s disease, but this usually involves strictures and ulceration. Other features resemble scleroderma, but this should readily be differentiated on screening by the finding of decreased motility. A quarter of patients with untreated celiac sprue do not have any radiologic abnormality. Radiologic examination, however, remains important particularly in the presence of abdominal pain to exclude complicating lesions such as jejunal ulceration with stricture, lymphoma, or carcinoma.

Treatment

Gluten-free Diet

Once a diagnosis of celiac sprue has been established, the conventional treatment is a gluten-free diet, which involves avoiding products containing wheat, rye, and barley. There is disagreement concerning the toxicity of oats; some physicians permit oats to be taken in the diet. Care should be exercised because the majority of commercially available oat flour is contaminated with wheat gluten. Dietary therapy should be initiated in conjunction with a dietician experienced in this area. There needs to be a careful explanation of the disease as well as the provision of diet sheets. This is particularly important in patients with few or absent symptoms. The avoidance of future ill health and reversal of current problems, including anemia, osteoporosis, depression, and infertility, should be explained. Explaining increased risk of malignancy and in particular small intestinal lymphoma is debatable and should be decided with discretion on a patient-by-patient basis. However, failure to disclose information about the patient’s illness that
may influence their perceived necessity for treatment may be hard to defend should later complications arise. Symptomatic improvement after the institution of a gluten-free diet further confirms the diagnosis of celiac sprue.

It is helpful for patients to join a celiac support group that publishes lists of gluten-free products. There is now a wide range of gluten-free breads, biscuits, pasta, etc. In Europe, these can frequently be obtained by prescription. Beer should be avoided because it contains considerable quantities of barley gluten prolamin (hordeins). The physician should be aware of foods that contain hidden sources of gluten, such as prepackaged breakfast cereals. These often contain malted barley, therefore small amounts of gluten. The small amounts involved are not a problem for the majority, but may cause important combined symptoms in very sensitive celiacs. The most common cause of relapse is gluten consumption, inadvertent or otherwise. Physicians should not forget that gluten may also be present in the excipient in certain medications. It has recently been shown in a Finnish study that the majority of treated patients may ingest pure oats in the diet.39 Oats should not be included in the diet because commercial oat flour is frequently contaminated with wheat. However, if pure oat flour is available, this may be included in the diet. A gluten-free diet is low in roughage and therefore may induce troublesome constipation. This usually responds to the addition of regular dietary rice bran and ispaghula husks. Specific dietary deficiencies that occur should be corrected. These include iron, folic acid, calcium, and, very rarely, vitamin B12 deficiency.

After 3–4 months of therapy with a gluten-free diet, a repeat small intestinal biopsy specimen may be undertaken to show improvement in the appearance of the small intestinal mucosal biopsy morphology. If abnormalities persist, other possible causes of small intestinal villous atrophy such as giardiasis, or cow’s milk allergy, should be excluded. Even if symptomatic improvement has occurred, the diet should be continued and a small intestinal biopsy procedure may be repeated after a further 6–9 months.

An improvement in small intestinal biopsy morphology and symptoms normally occurs with a decrease in antibody titers to gliadin, reticulin, endomysium, and tTG. Should there be any doubt concerning the correct diagnosis, further confirmation of the diagnosis by demonstration of deterioration of the small intestinal morphology in a repeat small intestinal biopsy procedure after a gluten challenge is recommended. This is particularly important in children in whom conditions such as infectious diarrhea and cow’s milk intolerance may produce abnormalities in small intestinal morphology. The most convenient way to give a gluten challenge is to ask the patient to ingest at least 10 g of gluten in the form of 4 slices of normal gluten bread per day for 4–6 weeks. Should this induce severe symptoms, then the date of the biopsy procedure may be brought forward. The European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) has recently suggested that it is not mandatory to proceed to a repeat small intestinal biopsy procedure after a gluten challenge if a gluten-free diet has produced a good improvement in symptoms and in the morphology of a follow-up small intestinal biopsy specimen.40 Many clinicians do not practice gluten challenge. In general, patients will experience significant symptomatic improvement within days or weeks of commencing a gluten-free diet.

**Failure to Respond to a Gluten-free Diet**

Patients who fail to adhere strictly to a gluten-free diet frequently continue with ill health and recurring symptoms that can usually be traced to dietary lapses, either deliberate or accidental. Earlier literature reported that 70% of celiac patients on a gluten-free diet quickly return to normal health with improvement in 2 weeks. The remaining 30% can be divided into 3 groups. The first group experienced progressive deterioration, which was halted in some cases by corticosteroids, but in other cases progressed to death. Patients in the second group were found to have an associated pancreatic lesion, and those in the third group were found not to adhere strictly to the diet, but even when this was corrected, their minor abdominal symptoms and diarrhea persisted.41

**Steroids and Celiac Sprue**

Celiac sprue can be controlled with systemic steroids with rapid cessation of diarrhea, weight gain, and improvement of fat absorption. However, within a few days of stopping treatment, there is usually deterioration. Steroids are indicated in the treatment of celiac crisis including severe diarrhea, dehydration, weight loss, acidosis, hypocalcemia, and hypoproteinemia. They are also used to treat gliadin shock, an anaphylactic reaction to gluten challenge, which can rarely occur in treated patients.

Long-term steroids are rarely required in celiac sprue but are given to complement a gluten-free diet in cases in which the serum albumin is markedly depressed. Here, steroids may also bring the associated protein-losing enteropathy under control. The use of 6-mercaptopurine or azathioprine as a steroid-sparing agent has been reported.42 Although there is a theoretical potential
for the use of more specific immunotherapy in the form of cyclosporin A, experience has shown that this agent does not help (Ciclitira PJ, personal observation).

The dose of steroids varies. Should a patient require intravenous fluid replacement because of vomiting, diarrhea, or surgery, hydrocortisone should be given intravenously, 100 mg 6 hourly. A patient who is eating normally but exhibits a crisis should be given 40–60 mg prednisolone daily. The usual dose used for celiac sprue that has not responded adequately to a gluten-free diet is 7.5–20 mg per day. It should be possible within a number of weeks to reduce the higher dose. Failure to be able to do so should alert to the possibility of either failure to adhere to the diet or a complication such as lymphoma or ulcerative jejunitis.

**Follow-up**

Following the initial assessment, diagnosis, and initiation of a gluten-free diet, the question arises of how closely and frequently the follow-up should occur. It has been suggested that the vast majority of patients remain well with strict adherence to a gluten-free diet. It is advised that yearly assessment be undertaken with weight, full blood count, folate, calcium, and alkaline phosphatase. Serologic assessment with antibodies to gliadin, reticulin, endomysium, or tTG may be useful because elevated titers imply continued gluten ingestion. Follow-up should be lifelong. This allows reinforcement of the continuing need for strict adherence to the gluten-free diet and the early detection of any problem.

A significant proportion of patients do experience problems, and conditions known to be associated with celiac sprue should be watched for. These particularly include diabetes mellitus, hypothyroidism, pernicious anemia, and hypoadrenalism.

**Treatment of Complications**

Many patients with celiac sprue exhibit lactose and sucrose intolerance at diagnosis. A small percentage of treated celiac patients continue to be troubled with disaccharidase deficiency. These conditions may be diagnosed by either a hydrogen breath test or enzyme assays of a small intestinal biopsy or by the appropriate sugar permeability study. Should concomitant disaccharidase deficiency be diagnosed, then the appropriate disaccharide should also be excluded from the gluten-free diet.

There are a small number of celiac patients who have concomitant small intestinal bacterial overgrowth. This may be diagnosed by hydrogen breath test, bile acid breath test, or by an abnormally high bacteriologic count in a small intestinal aspirate. Should small intestinal bacterial overgrowth be a persistent problem, patients may be treated with antibiotics such as 250 mg oxytetracycline 4 times a day, which may be rotated fortnightly with another, such as cotrimoxazole, 1 tablet twice a day. A short 10-day course of 200 mg metronidazole 3 times a day is frequently helpful if small bowel bacterial overgrowth is a problem, although the agent should not be continued long-term because of neurologic side effects.

**Complicating Ulcerative Enteritis**

This is a rare complication of celiac sprue. It is characterized by multiple chronic small bowel ulcers, which are frequently caused by complicating lymphoma.40

There is usually unexplained deterioration in a patient with celiac sprue, although in many cases the latter may not have been diagnosed. There is chronic diarrhea, abdominal pain, and weight loss. Small bowel radiographs are frequently abnormal, and the most suggestive appearance is a narrowing of the intestine with effacement of the mucosal pattern, termed the moulage sign. Duodenal or jejunal strictures may be seen. Enteroscopy is useful because it allows multiple biopsy specimens of the small intestine to be taken. Laparotomy with a full thickness biopsy of the small intestine may be required. Biopsy specimens should be investigated for T-cell receptor clonality using polymerase chain reaction amplification since T-cell receptor clonality should be considered to suggest evidence of a T-cell lymphoma.

Many patients will require surgery either for diagnosis or for management of complications such as stricture or perforation. When feasible, surgical excision of the worst affected segment of small bowel is the most appropriate therapy. Corticosteroids are useful in a limited number of patients. Should a lymphoma be diagnosed, then appropriate chemotherapy should be instituted with the aid of an oncologist.

**Malignancy**

The prevalence of carcinoma of the gastrointestinal tract in celiac sprue is more common than in controls, particularly small intestinal adenocarcinoma and esophageal and pharyngeal squamous carcinoma (Table 3).5

The prevalence of lymphoma in celiac sprue is 6%–8%, the incidence falling on prolonged treatment with a gluten-free diet. Most cases present during the sixth decade. Presentation often involves a return of symptoms of diarrhea, associated with both weight loss and pain. Manifestations such as fever, lymphadenopathy, hepatosplenomegaly, or abdominal masses or ascites may help the diagnostic conundrum but imply more advanced disease. Alternative presentations include acute perforation, obstruction, or hemorrhage.
Enteroscopy is useful, but an exploratory laparotomy may be required. Histology of peripheral lymph nodes, the liver, or bone marrow may provide a diagnosis. Abdominal ultrasonography, computer-generated tomography, or nuclear magnetic resonance screening may be useful. Blood tests are unhelpful, although hypoalbuminemia and a high erythrocyte sedimentation rate are diagnostic pointers but are nonspecific. Thus, laparotomy with resection of suspicious areas of intestine together with lymph node and liver biopsy procedures are frequently indicated.

Psychological and Neurologic Complications of Celiac Disease

Some patients with untreated celiac sprue have psychological disturbances and may exhibit frank psychotic disease in the form of schizophrenia. These symptoms usually respond to a gluten-free diet. Patients with celiac sprue may rarely exhibit severe neurologic disease. This may take the form of encephalopathy, cerebellar dysfunction, myelopathy, peripheral neuropathy, or a combination of these. Calcification of the cerebral cortex has been described.

An overview of neurologic complications reveals a mainly male predominance compared with a background of a higher incidence of celiac sprue in women. Unsteadiness of gait is a universal feature of the cerebellar degeneration. Cranial nerves palsies and myoclonus may also be seen. Two contrasting patterns of neuropathological abnormalities predominate. These are dorsal spinal column degeneration of a type not dissimilar to that encountered in subacute combined degeneration and a diffuse cerebellar degeneration mainly affecting the cortical Purkinje cell population but also involving the dentate nuclei. The role of circulating antineuronal antibodies, although postulated as a mechanism, remains unclear.

In the majority of affected subjects, the neurologic disease progresses inexorably despite treatment with essential dietary trace constituents. However, the spinal disease may improve in subjects receiving vitamins A, B, and E. Multivitamins and trace element supplements should always be tried. It has been suggested that response to vitamin E implies that the development of neurologic changes in celiac sprue may be related to deficiency of this substance.

Disease Associations

Numerous diseases are associated with celiac sprue (Table 4). There is an association with a variety of autoimmune disorders that are linked to a raised prevalence of HLA-DR3 and DQ2.

The coexistence of diabetes and celiac sprue is well recognized. The prevalence of insulin-dependent diabetes mellitus is reported to be between 6% and 8%. There is a higher than expected incidence of chronic hepatitis, biliary cirrhosis, and sclerosing cholangitis in celiac sprue. Chronic fibrosing alveolitis and other interstitial lung diseases including idiopathic pulmonary hemosiderosis have been reported in association with celiac sprue. Ten percent to 15% of patients with celiac sprue exhibit concomitant distal ulcerative colitis. Patients with proctocolitis complicating celiac sprue report improvement with a gluten-free diet. They may require therapy with oral salazopyrine or mesalazine or corticosteroid enemas. There is also an increased prevalence of microscopic and lymphocytic colitis in celiac sprue, the significance of which is not fully understood. The demonstration of an inflammatory infiltration of the rectal mucosa in response to local gluten challenge in celiac sprue implies that the origin of the proctocolitis is similar to that of the small intestinal enteropathy.45,46

Future Directions

Work continues on full characterization of all epitopes within gluten from wheat and related cereals. Such research may allow the development of novel cereals with the baking and nutritional qualities of wheat, rye, and barley, but which do not exacerbate celiac sprue.

| Table 3. Malignancy Occurring With Increased Incidence in Celiac Sprue |
|----------------|------------------|
| Malignancy                      | Overall relative risk |
| All cancers                     | 2–3               |
| Enteropathy-associated T-cell lymphomas | 30–40 (7%) (if no gluten-free diet, no increase if gluten-free diet >5 years) |
| Small intestinal adenocarcinoma | 83                |
| Mouth, pharynx, esophagus       | 23 (no/partial gluten-free diet) |

<table>
<thead>
<tr>
<th>Table 4. Diseases Associated With Celiac Sprue</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis</td>
<td>U</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>2%–3%</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>U</td>
</tr>
<tr>
<td>Epilepsy—with or without cerebral calcification</td>
<td>U</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>2%–5%</td>
</tr>
<tr>
<td>IgA mesangial nephropathy</td>
<td>U</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>8%</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>U</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>U</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>U</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>6%–8%</td>
</tr>
</tbody>
</table>

U, unknown.
Such approaches also include the possible development of immunomodulation for the future management of the condition.

Current work on the genetics of the condition should clarify our understanding of the inheritance and pathogenesis of the condition, including the role of tTG in partial deamidation of gluten proteins.

PAUL J. CICLITIRA
Professor of Gastroenterology
Gastroenterology Unit (GKT)
The Rayne Institute
St. Thomas’ Hospital
London, England

References

19. Ferreira M, Lloyd Davies S, Butler M, Scott S, Clark M, Kumar P.
Endomysial antibody: is it the best screening test for coeliac

33. Lerner A, Kumar V, Iancu TC. Immunological diagnosis of child-
hood coeliac disease: comparison between antigliadin, antireti-
95:78–82.

34. Yiannakou JY, Dell’Olio D, Saaka M, Ellis HJ, Rosen-Bronson S,
Dumonde DC, Ciclitira PJ. Detection and characterisation of anti-
endomysial antibody in coeliac disease using human umbilical
cord. Int Arch Allergy Immunol 1997;112:140–144.

35. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO,
Schuppan D. Identification of tissue transglutaminase as the

IR, Sarmesto A, Savilahto E, Collin P, Maki M. Tissue transglu-
taminase autoantibody enzyme-linked immunosorbent assay in
1328.

and metabolism in patients with celiac disease. Gastroentero-

38. McFarlane XA, Bhalla AK, Reeves DE, Morgan LM, Robertson DA.
Osteoporosis in treated adult coeliac disease. Gut 1995;36:
710–714.

39. Janatuinen EK, Pikkarainen PH, Kemppanen TD, Kosma VM,
Jarvinen RM, Usitupa MI, Julkunen RJ. A comparison of diets with

40. Walker-Smith JA, Guandalini S, Schmitz J, Schmerling DM, Visa-
korpi JK. Revised criteria for diagnosis of coeliac disease. Arch

41. Pink IJ, Creamer B. Response to a gluten-free diet of patients with

42. Hamilton JR, Chambers RA, Wynn-Williams A. Role of gluten,
prednisone and azathioprine in non-responsive coeliac disease.

43. Menzies IS. Transmucosal passage of inert molecules in health
and disease. In: Intestinal absorption and secretion. Heintze K,

44. Bagdi E, Doss TT, Munson P, Isaacson PJ. Mucosal intra-epithelial
lymphocytes in enteropathy-associated T-cell lymphoma, ulcer-
ative jejunitis and refractory celiac disease constitute a neoplasmic

45. Loft DE, Marsh MN, Jandle GI, Crowe PT, Garner V, Gordon D,
Baker R. Studies of intestinal lymphoid tissue XII. Epithelial
lymphocyte and mucosal responses to rectal gluten challenge in

46. Loft DE, Marsh MN, Crowe PT. Rectal gluten challenge and

Address requests for reprints to: Chair, Clinical Practice and Practice Economics Committee, AGA National Office, c/o Membership Depart-
ment, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814. Fax: (301) 654-5920.
This work was supported by the American Gastroenterological As-