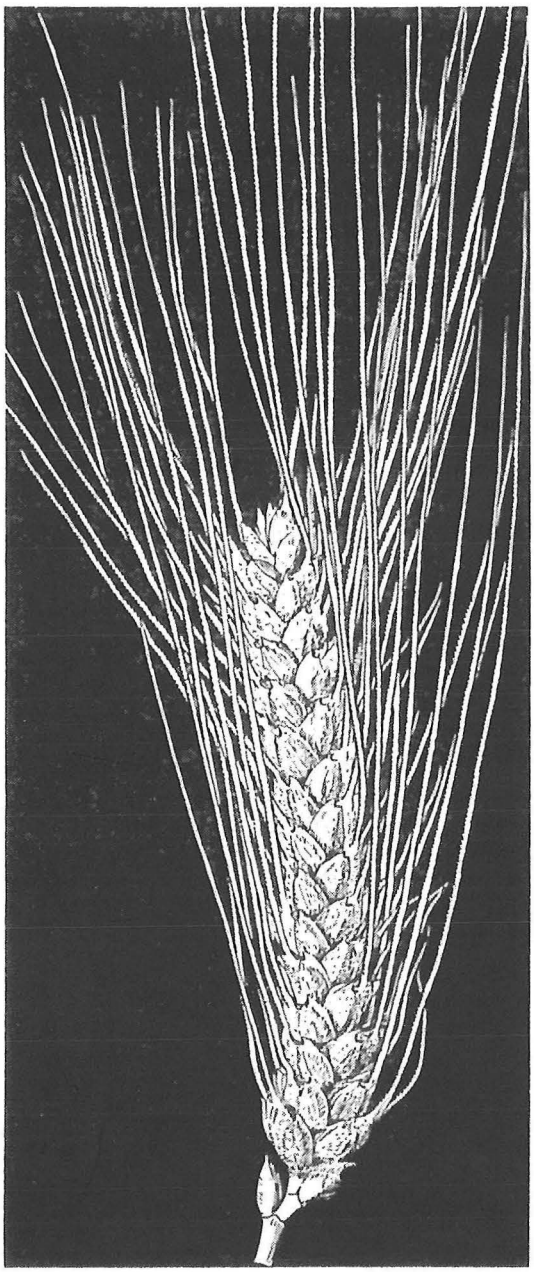
CELIAC SPRUE: A REAPPRAISAL



INTERNAL MEDICINE GRAND ROUNDS, JUNE 10, 1999
UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER
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This is to acknowledge that William Harford has no financial interests or other relationships with commercial concerns related directly or indirectly to this program.

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I wish to acknowledge the gracious help of Dr. Kenneth Fine and Dr. Esmail Elwazir.

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INTRODUCTION

Celiac sprue (CS) is a chronic disease of the small intestine characterized by inflammation and mucosal damage due to intolerance of protein components of certain cereals, including wheat, barley, and rye.

A Reappraisal

Population-based serological screening studies have suggested that CS is more common than previously recognized. It has become apparent that the clinical presentation of CS is varied, from classic overt generalized malabsorption to more subtle and under-recognized manifestations. CS often first presents in adult life. Internists should be aware of the various manifestations of CS, and test for it when appropriate.

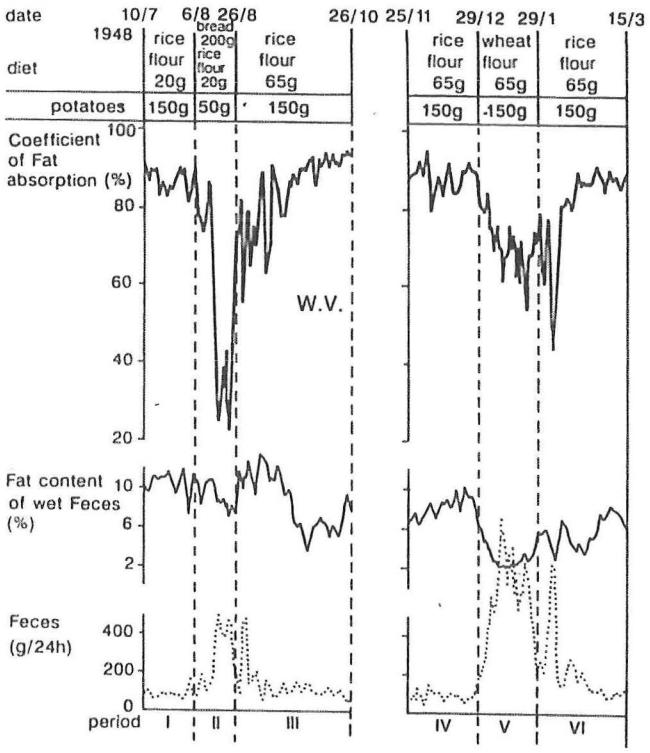
HISTORY

The first known reference to CS dates to about 100 CE, when the Greek physician Aretaeus described a chronic wasting illness with diarrhea in adults, which he termed the "coeliac affection." The first modern description of CS was published in 1888 by Samuel Gee, a physician at the Royal St. Bartholomew Hospital in London. He recognized the importance of diet for cure, and recommended that "the allowance of farinacious food be small." He speculated on the presence of "glandular atrophy...of the intestines" [1].

In the 1930's and 40's the Dutch pediatrician Willem Dicke developed the hypothesis that wheat, rye, and oatmeal products were responsible for CS. His suspicion was strengthened during the 1944 "Winter of Starvation" in Holland. When forced by wartime scarcity to eat tulip bulbs instead of bread, his CS patients improved. After World War II Dr. Dicke confirmed his hypothesis, assisted by H.A. Weijers, another pediatrician, and J.H. van de Kamer, a biochemist. Meticulous clinical studies of stool weight and lipid proved that cereal free diets reduced diarrhea and steatorrhea. The same effect was noted with addition of rice or potatoes. Diarrhea and steatorrhea recurred after challenge with wheat, rye, or oats. With similar studies they further demonstrated that the responsible component was not wheat starch, but rather a wheat protein component, gluten[2]. Figure 1 is from one of their original publications.

The histologic lesion of CS was not appreciated for many years. Villous atrophy noted at autopsy was attributed to post-mortem autolysis. In 1954 J.W. Paulley examined surgical biopsies from CS patients and gave the first accurate histologic description [3]. The development of practical small bowel biopsy capsules in the 1960s allowed McDonald and his colleagues from Seattle to describe healing of the histologic lesion with a gluten-free diet (GFD) [4]. They also described the presence of the same mucosal lesions in relatives of CS patients [5]. In 1972 Falchuk reported an association between a specific histocompatibility antigen (HL-A8) and CS[6]

Figure 1
From Gastrointestinal Disease, Sleisenger & Fordtran, Ed., 5th Edition, 1993
Stool weight and lipid chart from Dicke's CS studies



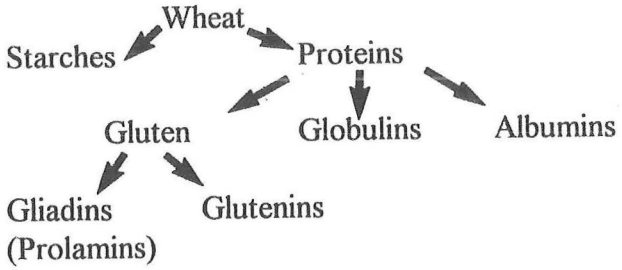
Dietary exclusion experiment with wheat products in Case 1. The coefficients of fat absorption during study periods II and V were significantly less than during periods I, III, IV, and VI (wheat-free periods).

PATHOPHYSIOLOGY

Prolamins

Dicke first proved that gluten, the protein component of wheat, rather than starch, leads to CS. Wheat is about 40% gluten by weight. A high gluten content improves the quality of bread, and has been selected for over several thousand years. Gluten includes glutenins and gliadins. It is the gliadin fraction of gluten that is toxic.

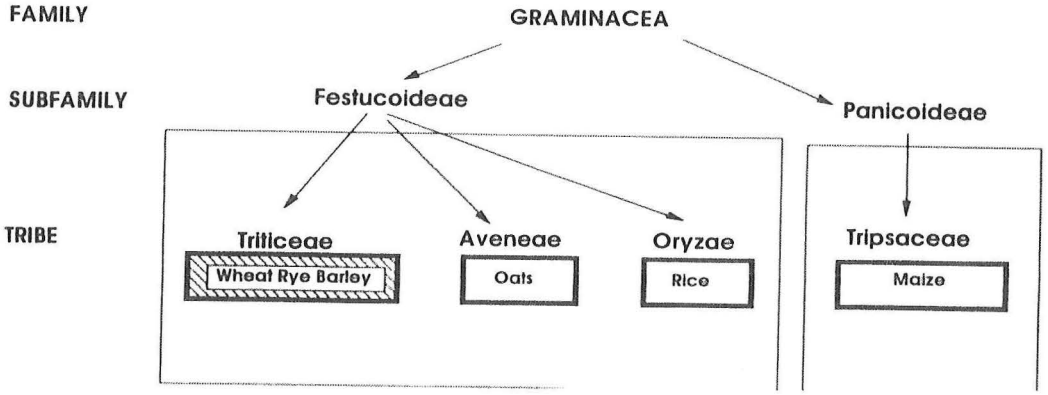
Figure 2
Constituents of Wheat



Gliadins are wheat prolamins. Prolamins are seed storage proteins restricted to grasses. Wheat, rye and barley are closely related. They are in the same subfamily and tribe and

contain similar prolamins. Oats are in the same subfamily but a separate tribe. Oats also contain prolamins (avenins), but in smaller quantities, and the toxicity of oats is still open to question. Grains which are not toxic in CS, such as rice, maize, sorghum, and millet are in a different subfamily and have prolamins of substantially different structure[7]. Prolamines contain repeated amino acid sequences rich in proline and glutamine. The sequences Pro-Ser-Gln-Gln and Gln-Gln-Gln-Pro are common in toxic prolamines and probably are recognized as immunogenic epitopes, but the common antigenic motifs have not been worked out [8].

Figure 3
Taxonomy of Grains



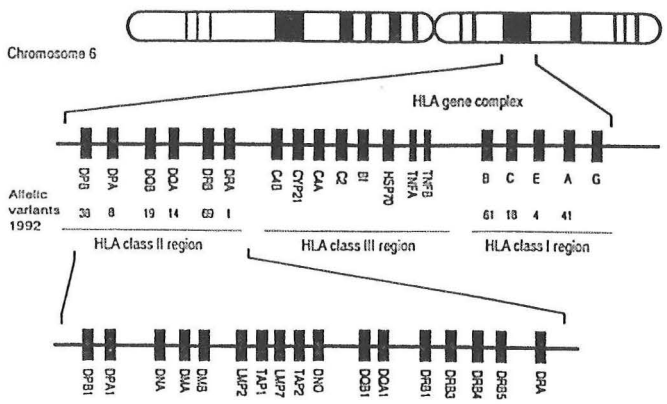
Genetic and Immunologic Basis of CS

CS has a strong genetic component. There is a 10% prevalence of CS in first degree relatives of patients with CS, and a 70% concordance among monozygotic twins.

HLA II and gliadin immunogenicity

CS is strongly associated with specific HLA class II D region genes. HLA class II genes code for cell surface molecules which present foreign antigens to T cells. The specific HLA II DQ alleles DQA1*0501 and DQB1*0201 are present in more than 95% of CS patients[9-11]. This haplotype is common in ethnic groups that have a high prevalence of CS, such as Europeans, and low among other groups, such as Africans and Asians, that have a low prevalence of CS. This haplotype codes for an antigen presenting surface molecule called DQ2. The 5% of CS patients who do not have DQ2 likely have similar molecules.

Figure 4
Diagram of the HLA Region on Chromosome 6



The HLA gene complex on the short arm of chromosome 6. Only loci with known protein products are shown.

Foreign antigens are taken up by antigen presenting cells (APCs) and partially digested in lysosomes. Peptide fragments of the antigen are then coupled to HLA II molecules and presented on the cell surface. It is the HLA II molecule-antigen complex which interacts with T lymphocytes. Not all HLA II-antigen complexes are recognized by or activate T lymphocytes. However, the DQ2 complex-gliadin complex is capable of activating T lymphocytes in patients with CS.

Figure 5
Antigen Processing and Presentation

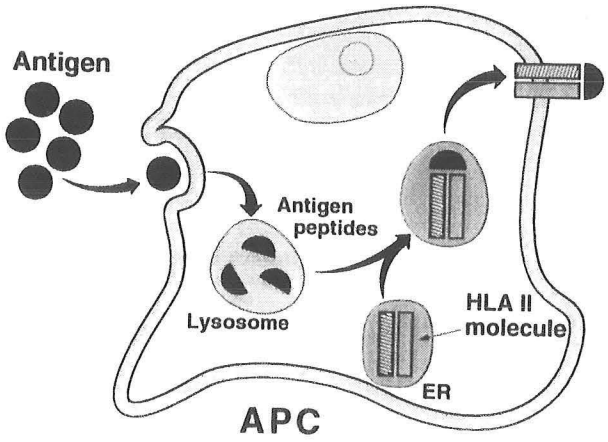
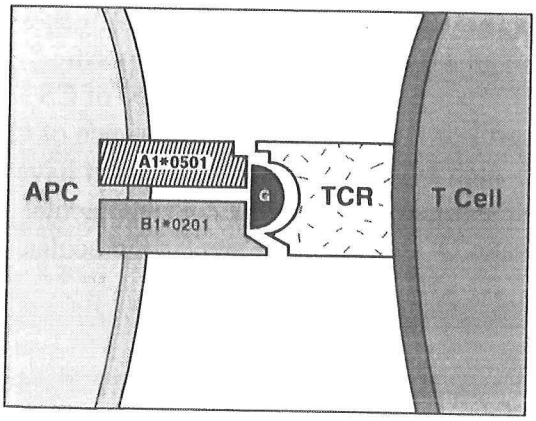


Figure 6
Gliadin Presentation by DQ2



Other Genes

The DQ2 allele (or one similar) is required but not sufficient for CS. In Europe up to 25% of the population carry the DQ2 allele, but only a small proportion develop CS. Furthermore, the concordance rate for CS among HLA identical siblings is about 30%, and among monozygotic twins 70%. Other genes are likely to contribute to the development of clinical CS. For example, there are multiple genes controlling various

aspects of T-cell responses including T-cell receptors, genes for other antigen processing pathways, and genes for cytokine regulation[9,12,13].

Environmental Factors

Environmental factors may also play a role in the development of CS. A high gluten intake may promote the development of CS. Viral infection might cause immune activation by molecular mimicry of gliadin. NSAID ingestion might increase mucosal permeability to gliadin.

Immune reactions in CS

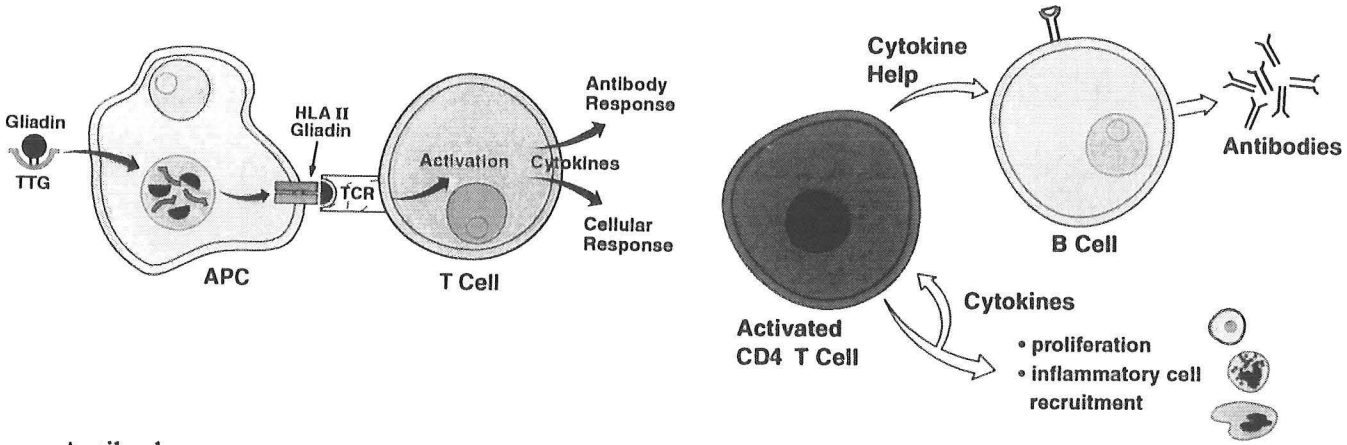
It is not clear how gliadin gains access to the lamina propria, where gut APCs are located. Abnormal mucosal permeability due to infections or NSAIDs has been mentioned. There is some evidence to suggest that gliadin may have early effects on epithelial cells which are not T-cell mediated[14,15]. However, we know most about the T-cell mediated response..

Tissue Transglutaminase (TTG)

TTG is an enzyme ordinarily involved in response to injury and located in the lamina propria. TTG deaminates proteins, including gliadin. TTG is thought to form a complex with gliadin. The TTG-gliadin is taken up and broken down by APCs. After processing, HLA II DQ2-gliadin complex is presented and activates gliadin-specific T lymphocytes. These stimulate both cellular immune and antibody responses. Interestingly, TTG has a role in the activation of TGF beta, which is important in epithelial cell differentiation[16,17].

Figure 7

Tissue Tranglutaminase and Immune Activation in CS



Antibody response

In response to T-cell stimulation, mucosal B cells produce both IgA and IgG antibodies to gliadin (AGA). Autoantibodies are also produced to TTG. The role of AGA and TTG Ab in mucosal injury has not been determined. It is possible that immune complexes may activate complement. However, a number of people have AGA, particularly IgG AGA, without evidence of gut pathology. AGA and TTG Ab are useful markers, regardless of their role in the pathophysiology of the mucosal injury. AGA and TTG Ab are almost

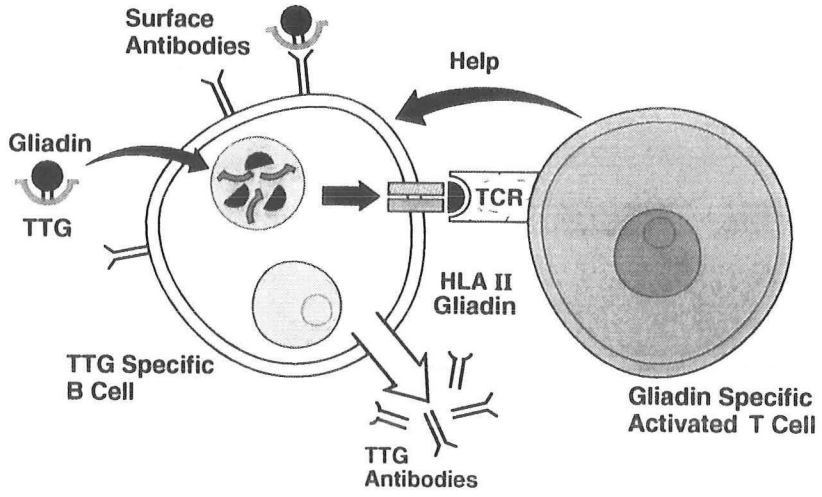
invariably present in untreated CS. TTG Ab have a high specificity for CS. Both AGA and TTG Ab decline with a GFD, and are thus helpful for monitoring compliance with diet.

TTG antibodies

The proposed mechanism for TTG Ab production in CS is interesting. B cells should not produce antibody to TTG, a self antigen, without T cell help. TTG-specific T-cells are suppressed in the thymus, as are T-cells specific for other autoantigens. However, in addition to their role in producing antibody, B cells can act as APCs. B cells that are capable of producing antibody to TTG exist under normal circumstances. Acting as APCs, these B cells can bind the TTG-gliadin and take it up. They can then present DQ2-gliadin on their cell surface. Gliadin-specific activated T-cells then recognize the DQ2-gliadin complex on the B cell and provide help for this cell to produce antibody to TTG. This is called hapten-carrier antibody stimulation. When gliadin is withdrawn, specific T-cells decline, and T-cell help for TTG antibody production declines. This model may explain why antibodies to TTG are more disease specific than AGA. TTG antibody production may require a localized T-cell response in an environment in which TTG is complexed to gliadin, that is, in a gut lamina propria. AGA, particularly, on the other hand, may result from T cell and B cell interactions in regional lymph nodes independent of intestinal mucosal disease[16].

Figure 8

Hapten-Carrier Mediated TTG Antibody Production



Cellular Immune Response in CS

It is likely that the cellular immune response rather than the antibody response causes mucosal damage in CS. In response to gluten challenge there is a dense infiltration of the lamina propria with CD4 + T lymphocytes. There is also infiltration of the epithelium with CD8+ T lymphocytes, but direct CD8 mediated cytotoxicity does not seem to be as important as cytokine-mediated changes. There is recruitment of a B cells and a number of other inflammatory cells, including mast cells, basophils, and eosinophils. Several cytokines have complex effects on the epithelium. TGF, for example, stimulates

proliferation of crypt cells and interferes with epithelial cell differentiation, effects which might help to explain the crypt hyperplasia seen in CS. Many aspects of the immune response in CS are still unclear.

Histology of CS

The intestinal lesion in celiac sprue is characterized by epithelial cell damage, with flattening of the columnar cells and loss of microvilli. The density of intraepithelial lymphocytes (IELs) is increased from the normal 10-30 IELs per 100 epithelial cells. The crypts are lengthened and increased mitoses are seen. There is a variable degree of damage to the villi, ranging from slight blunting to complete loss, with a resulting flat mucosa. There is a dense mucosal infiltrate consisting of lymphocytes (predominantly CD4+), plasma cells, mast cells, eosinophils, and basophils. The epithelial cell damage and villous atrophy lead to loss of brush border enzymes and absorptive surface.

There is a marked variation in the degree of mucosal damage from case to case. Some patients have a completely flat mucosa; others have villous blunting and crypt hyperplasia, while others have nearly normal mucosa, with only an increase in IELs and lamina propria infiltrate. Mucosal damage is always greatest in the proximal small bowel, but there is marked variation in the extent of bowel involved from patient to patient. The damage may also be patchy within a segment. For this reason multiple biopsies should be taken for diagnosis. Upon gluten withdrawal the distal bowel heals before proximal bowel. Symptomatic improvement often occurs within a few weeks, but the mucosal lesion may take much longer (up to 2 years) to heal.

Figure 9

Normal Jejunal Mucosa

The villi are 3-5 times the length of the crypts. The surface epithelial cells are tall. There are a few chronic inflammatory cells scattered in the lamina propria.

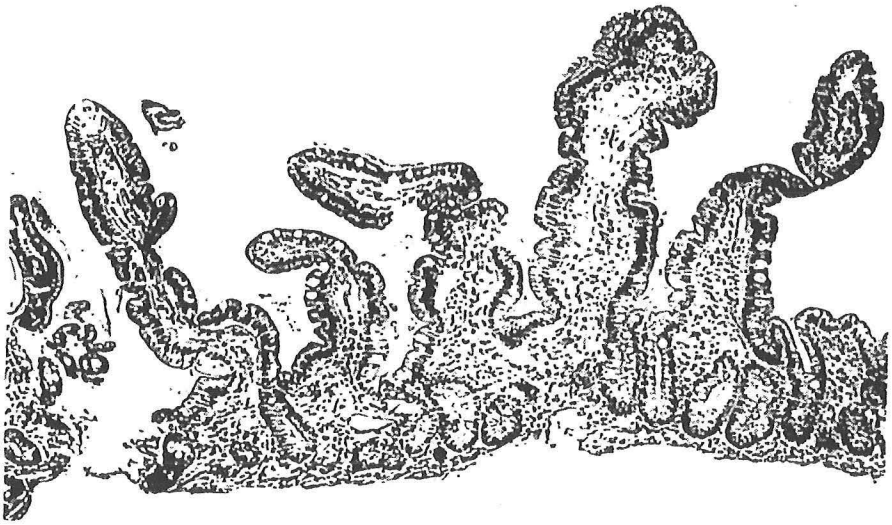


Figure 10
Moderate Celiac Sprue
Villi are still present, but are markedly blunted. The crypts are elongated. There is a moderate inflammatory infiltrate in the mucosa.

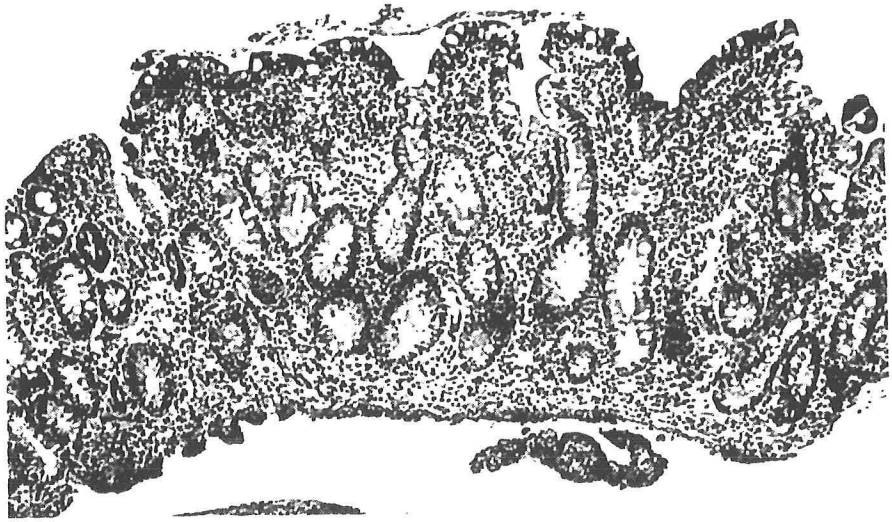
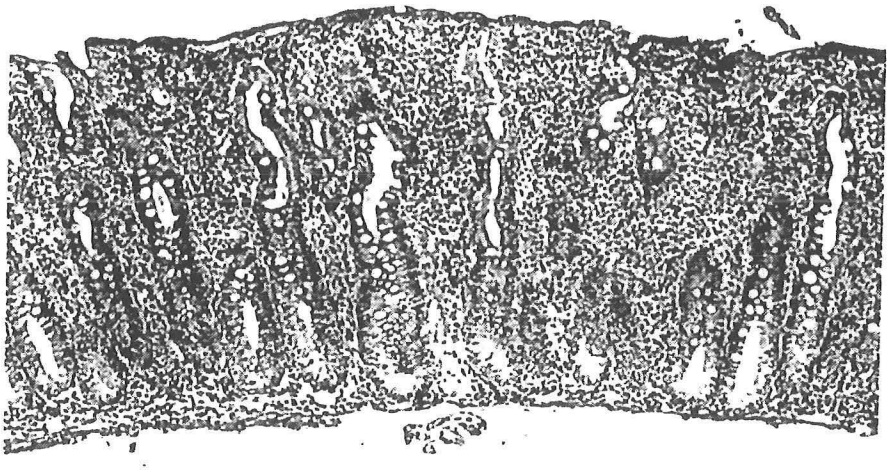


Figure 11
Severe Celiac Sprue
No villi can be appreciated in this flat mucosa. The crypts are markedly elongated, and there is a heavy inflammatory infiltrate in the mucosa.



Pathophysiology of malabsorption in celiac sprue

Malabsorption in CS is primarily due to loss of absorptive surface and digestive enzymes. Water and solute absorption by the jejunum is diminished. In fact, patients have been found to have net water and electrolyte secretion [18]. There is also significant disruption of hormonal control of secretion. In untreated CS patients the gallbladder contracts late, incompletely, or not at all. Normally, the gallbladder contracts in response to cholecystokinin (CCK) released from the duodenal mucosa. CCK release is diminished in untreated CS [19]. Patients may also have exocrine pancreatic insufficiency through a similar mechanism, and some require pancreatic enzyme replacement during the early phases of treatment with a GFD [20]. Bacterial overgrowth may complicate untreated CS and worsen malabsorption.

When mucosal damage is extensive and severe, there is generalized malabsorption and malnutrition. Since the proximal small bowel is most severely affected folate, iron, and calcium malabsorption are common. Fat malabsorption may worsen calcium loss through the formation of calcium soaps. When mucosal damage is less severe, isolated malabsorption, usually of iron or calcium, may present. Since the ileum is usually spared, Vitamin B12 absorption is usually normal.

DIAGNOSIS

ESPGAN Criteria 1990

The first formal criteria for the diagnosis of CS were developed in 1970 by the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) for diagnosis in children and required three biopsies to show:

1) abnormal small intestinal mucosa while on a gluten-containing diet;
2) unequivocal improvement in the mucosal lesion on a GFD, and
3) recurrence of the mucosal lesion on gluten challenge.

The reason for requiring repeat biopsy on a GFD and after gluten challenge was that other causes of enteropathy (such as cow's milk or soy intolerance) can produce identical mucosal changes, particularly in children under the age of 2.

The widespread use of specific antibody tests has influenced the approach to making the diagnosis. The ESPGAN criteria were revised in 1990 [21].

<u>Revised ESPGAN Criteria for Diagnosis of CS</u>

1) Structurally abnormal jejunal mucosa when taking a diet containing gluten;
2) Clear cut clinical remission on a strict GFD with relief of all symptoms of the disease; The response should be occur within a matter of weeks rather than many months.
3) The finding of positive serologies (AGA, EMA) at the time of diagnosis and their disappearance when the patient is taking a GFD adds weight to the diagnosis.

This approach is not applicable in patients who are asymptomatic at the time of diagnosis, and the ESPGAN Working Group recommended that follow-up biopsies continued be performed in such patients.

Biopsies

Diagnosis based on biopsy is usually simple, but can occasionally be difficult. Patients must be ingesting gluten when the biopsies are taken. The mucosal lesion may be patchy, and may be missed, particularly if biopsies are inadequate in quality and number. Biopsies should be taken from the distal duodenum or proximal jejunum if possible. Furthermore, it is now known that there can be considerable variation in the severity of the mucosal lesion. The histological definition should include patients with minimal changes, such as an increase in IEL and increased lamina propria infiltrate, sometimes with unappreciable villous blunting.

The histologic changes of sprue are not specific. Similar or identical changes in various conditions (Table 2)[22]. Thus improvement on a GFD is important for the diagnosis.

Table 2

Differential Diagnosis of Small Bowel Villous Atrophy

Celiac sprue
Tropical sprue
Giardiasis
Viral enteropathy
Cow's milk protein intolerance
Soy protein intolerance
Eosinophilic gastroenteritis
Collagen diseases (eg systemic sclerosis)
Radiation/drug enteritis
Chronic intestinal ischemia
Protein-calorie malnutrition
Immunoproliferative small intestinal disease
Acquired immunodeficiency syndrome
Bacterial overgrowth
Graft versus host disease

Endoscopic appearance of celiac sprue

Esophagogastroduodenoscopy (EGD) is commonly done for investigation of chronic dyspepsia and for iron deficiency anemia. EGD is the usual method for obtaining small bowel biopsies. In the 1970s it was noted that the endoscopic appearance of the duodenum may be abnormal in CS. Among the abnormalities which have been noted include: absence of duodenal folds in the second portion of the duodenum on full insufflation, scalloped folds, a mosaic pattern (particularly notable with vital dye staining) and visible blood vessels [23,24]. Endoscopists should be aware of these abnormalities. However, they should also remember that the mucosal disease may be subtle. The endoscopic appearance may be normal in mild villous atrophy, and the decision to take biopsies should not be based on the gross appearance of the mucosa.

Serology

Antigliadin antibodies

AGA were first demonstrated in CS in 1958 [25]. Both IgG and IgA AGA are found. IgG antibodies have a low specificity for CS, and may be found in a substantial number of normal persons and in patients with other bowel diseases [26]. They are useful in the 5% of patients with CS who have IgA deficiency. IgA AGA antibodies are less sensitive but more specific than IgG AGA.

Antiendomysial and TTG antibodies

In 1984 an antibody to endomysium (EMA), an extracellular component of smooth muscle, was demonstrated in untreated CS patients [27]. It has a high sensitivity and specificity [28]. EMA testing is widely used for CS, but has the disadvantage of being an indirect immunoflourescent test, and difficult to standardize. Interpretation of the test is subjective. In 1997 it was found that tissue transglutaminase (TTG) is the autoantigen detected by the EMA test [29]. The TTG IgA antibody test has the advantage of being an ELISA assay. It is quantitative and relatively easy to standardize. There is not nearly as much clinical experience with TTG Ab testing as with AGA and EMA, but there is little reason to suspect that it will not be equivalent to the EMA. TTG Ab may eventually replace EMA [29]. TTG antibody testing is commercially available in few laboratories.

Table 3 shows published data on the sensitivity and specificity of AGA IgG and IgA, EMA IgA, and TTG IgA for CS in untreated adults [30-32]

Table 3.
Serological Tests for CS

Test	Sensitivity	Specificity	Positive Pred Value	Negative Pred Value
IgG AGA	76-88 %	88-92	46-88	92-97
IgA AGA	52-91	85-94	45-87	74-99
IgA EMA	97-100	98-99	91-97	98-100
IgA TTG	~95	~94	~90	~95

IgA antibody tests will be negative in the 5% of CS patients who are IgA deficient, so it is probably prudent to order a panel including IgG AGA as well as the IgA AGA and EMA.

Approximate cost of serologies for CS

EMA IgA $50
AGA IgG and IgA AG $60-80
TTG Ab IgA $110

Although the published performance of antibody tests for CS, particularly EMA, is very good, some experts have questioned whether they are as sensitive in clinical practice as has been suggested. In a study including patients with a spectrum of mucosal lesions, the investigators found a sensitivity of 100% for EMA among patients with total villous

atrophy, but only 70% in those with subtotal villous atrophy, and 30% in those with the mildest lesion [33].

The main role of serologies in CS should be in screening patients when the level of suspicion is low or moderate, in order to avoid an unnecessary biopsy. However, experts in the field advise strongly against relying solely on serology for diagnosis. They point out that a diagnosis of CS carries the implication of a commitment to a lifelong GFD, and false positive serologies do occur. Patients strongly suspected of having the disease should probably have a biopsy as the first investigation. Serologies are also useful in follow-up, as they can be repeated six months after diagnosis in order to monitor compliance with a GFD.

PREVALENCE AND CLINICAL PRESENTATION

The use of population-based serological screening has altered our concepts of the prevalence and presentation of CS in Europe and in the US. It is currently recognized that at least 50% of patients with CS do not have overt symptoms of generalized malabsorption, and many present with subtle gastrointestinal symptoms or with other medical problems, such as anemia or osteopenia. There may also be a substantial number of individuals who, despite markers of predisposition to CS such as EMA and subtle microscopic changes of the small bowel mucosa, do not have any apparent clinical problems.

Prevalence

CS with overt generalized malabsorption is uncommon. The prevalence of this form of CS varies from 1 in 300 in Western Ireland to 1 in 1200 in the U.K. In a retrospective study conducted by the Mayo Clinic the overall incidence was found to be 1 in 100,000! [34]

On the other hand the prevalence of CS diagnosed in serological screening studies (using EMA, usually confirmed by biopsy in positives) is much higher and much more uniform in populations of European ancestry.

Table 4
Prevalence of CS by serological surveys [35-38]

Country	Prevalence	Population	Tests
Ireland	1:152	adults	EMA + Bx
Italy	1:184	school-age children	EMA + Bx
Sweden	1:256	blood donors	EMA + Bx
USA	1:250	blood donors	EMA, no Bx

Unrecognized CS

It is likely that many cases of CS go unrecognized. In the Italian study referenced above, 17000 school aged children were screened by AGA testing. Children with positive AGA

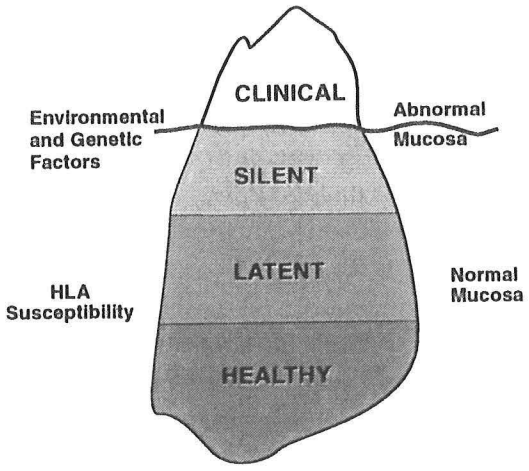
were called back for EMA, and those with positive EMA had small bowel biopsies. Combining the cases found on screening with the known cases in the same population, they found a prevalence of CS of 1 in 184. The ratio of known to previously undiagnosed cases was 1 to 7 [36].

In another Italian study, the authors reviewed the records of 226 consecutive adults diagnosed with CS between 1972 and 1989. The study period was divided into three consecutive intervals. They found that during the last 3 years of the study 70% of the cases were found by screening relatives and investigating minor gastrointestinal symptoms, isolated iron deficiency, osteopenia, and similar problems [39].

The Celiac Iceberg

It is possible that we are seeing only the tip of what has been termed the "celiac iceberg [36,40]." Based on population-based serological screening, it seems that many patients have at least a genetic susceptibility to CS: about 1 in 200-300 in populations of European ancestry. Some of these may have normal mucosa, or minimal mucosal changes. They may remain healthy or may have "latent" CS, and develop overt CS with time. Others have silent or subclinical CS. These patients have abnormal small bowel mucosa. They may have no symptoms or problems, or they and their physicians may not recognize their vague symptoms or isolated malabsorption (anemia, osteopenia) as CS[41-43]. The tip of the iceberg consists of those patients recognized to have CS. The proportion of the iceberg that we see depends at least in part, on physician awareness of the various manifestations of CS.

Figure 12
The Celiac Iceberg



THE CELIAC ICEBERG

Clinical Presentations of CS

Table 5
Clinical Presentations of CS

- Generalized malabsorption & malnutrition
- Vague gastrointestinal symptoms
- General "ill health"
- Anemia
- Osteopenia
- Dermatitis Herpetiformis
- Hyposplenism
- Sexual dysfunction
- Neurological disease

Generalized malabsorption and malnutrition, vague GI symptoms

Overt generalized malabsorption is the classical presentation of CS. Patients have diarrhea, steatorrhea, weight loss, and malnutrition. CS may occur in children upon the introduction of dietary gluten, or in adults of any age. Less severe malabsorption may result in vague GI symptoms such as bloating, vague abdominal pain, and mild diarrhea, not recognized as CS. In areas where awareness of the disease is high among practitioners, and where serologic testing has been widely employed in recent years only about 50% of newly diagnosed CS patients present with gastrointestinal symptoms [44].

Anemia

In an Italian study of 1000 cases of CS diagnosed between 1990 and 1994, iron deficiency anemia was the presenting clinical problem in 46% of adults [44]. Most of these patients were otherwise asymptomatic. It is very important to recognize that iron deficiency may occur as an isolated clinical problem in CS, without overt clinical symptoms or generalized malabsorption.

Anemia is common among untreated CS patients. Anemia may be due to iron and/or folate deficiency. Iron deficiency is most likely the primarily result of malabsorption, although there may be increased gastrointestinal blood loss. In a study done by Dr. Ken Fine at BUMC, positive fecal occult blood (FOB) tests were found to be common in untreated CS. Using 2-3 day stool collections, 47% of patients with partial or total villous atrophy had positive Hemoccult tests compared to 6% of controls [45]. Upper gastrointestinal endoscopy (EGD) is often done in patients with iron deficiency anemia in whom no other source of blood loss has been found. In an Israeli study of such patients, 11 of 93 were found to have duodenal biopsy findings compatible with CS [46]. Whether small bowel biopsies should be taken whenever EGD is done for iron deficiency is open to question. At the very least a strong case could be made for this in any patient with diarrhea or any other evidence suggesting the possibility of CS.

Osteopenia

Osteopenia may also occur as an isolated clinical problem in CS, without other characteristic symptoms. Osteopenia is common in untreated CS. In one study, 16 of 17 untreated adult CS patients had bone mineral density at least 1 SD below control. A similar prevalence of osteopenia has been found in other studies [47,48]. Conversely, in a study of 92 patients with osteoporosis, 3 were found to have AGA and a small biopsy compatible with CS. None of the patients had gastrointestinal symptoms [49]. The most common mechanism is malabsorption of calcium and vitamin D with secondary hyperparathyroidism [47]. Osteopenia improves rapidly with gluten-free diet [48,50,51]. Clinicians should be aware that CS is a cause of osteopenia.

Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is a chronic condition characterized by crops of recurrent intensely pruritic erythematous papules or vesicles located over the extensor surfaces. The lesions may also be urticarial plaques and multiple erosions. Pruritus, which is severe, may precede the appearance of new lesions. Most of the lesions are found over the knees, elbow, buttocks, sacrum, back, and shoulders. The eruptions may wax and wane, but long-lasting spontaneous remissions are rare. The onset of DH may occur at any age, but the peak incidence is in the second through fourth decades. DH is most prevalent in persons of European ancestry, and rare in Africans and Asians. On skin biopsy, there are granular deposits of IgA at the dermal-epidermal junction, best seen in skin adjacent to the lesions.

DH is a common reason for investigating the possibility of CS [44]. Although only about 10% of patients with DH will have gastrointestinal symptoms, almost all have gluten-sensitive enteropathy and 20-30% have steatorrhea if studied. The small intestinal lesion is often less severe than in patients with typical CS. DH patients have a very high prevalence of the HLA-DQ2 haplotype. The rash of DH responds within a few weeks to treatment with Dapsone, but this has no effect on the intestinal lesion. Conversely, a GFD will control both the rash and heal the small intestinal lesion, although it may take up to six months [52].

Hyposplenism

There is a marked increase in the prevalence of hyposplenism among patients with CS. In an Italian study approximately 1/3 of patients were found to have hyposplenism as determined by counting pitted RBCs [53]. Other studies have reported a higher prevalence [54]. A few cases of septicemia have been reported. This suggests that patients with CS and hyposplenism should receive vaccination against streptococcus pneumonia.

Sexual dysfunction

CS is a cause or recurrent abortion and of infertility in both men and women. These problems are reversible with a GFD, but the opportunity for treatment may be missed if gastrointestinal symptoms are mild or absent and CS is not suspected [55,56].

Neurological disease

Rarely, CS may present as a neurological problem, most commonly ataxia. Peripheral neuropathy, posterior column disease, and cerebellar atrophy have been reported. Gastrointestinal symptoms may be absent. Vitamin B12 and E levels are normal and the syndrome rarely responds to treatment with vitamin B12 or folic acid. The response to GFD is inconsistent, and some patients have developed symptoms on a GFD [57,58].

Ill health

A number of CS patients have vague and chronic symptoms such as fatigue or indigestion which they and their physicians disregard. Only after diagnosis and treatment with a GFD do they appreciate the disability to which they had become accustomed [55].

Latent or potential CS

Patients who are found during screening to have AGA or EmA may have no clinical problems and virtually normal biopsies while on a gluten-containing diet. This condition has been termed latent or potential CS [41,42]. Subtle abnormalities of the mucosa may be found, such as increased IEL, increased crypt cells mitoses, increased epithelial MHC II expression, and increased IL-2 receptor-positive epithelial cells. Increased intestinal permeability may also be present. Patients with latent CS may have mucosal immunological systems primed to react to gluten with stimulation by an environmental factor. Non-specific environmental precipitants such as enteric infection or NSAIDs may trigger overt CS by this mechanism. In one study 7 of 25 patients with positive anti-reticulin Ab and initial normal histology developed villous atrophy over a 7 year follow-up [43]. Patients with positive AGA or EMA and normal biopsy should be followed. Repeat biopsy should be done if suspicious clinical problems are noted.

Diseases associated with an increased prevalence of CS

A number of conditions associated with CS are listed in Table 6

Table 6

Disorders Associated with CS

Insulin-dependent diabetes mellitus
Autoimmune thyroid disease
Sjogren's syndrome
Microscopic colitis
Isolated IgA deficiency
Epilepsy
Down's syndrome

Insulin dependent diabetes mellitus

Among the most important diseases associated with CS is insulin-dependent diabetes mellitus (IDDM). Several studies have shown that CS may be found in from 2.4-7% of patients with IDDM. In a large, multicenter European study of 1100 patients with IDDM, 63 (5.6%) were found to have positive serologies and villous atrophy. Of these, 22% were completely symptom-free [59]. Of 775 Finnish children newly diagnosed with IDDM, 19

(2.4%) were found to have CS [60]. In a US study of 47 adult patients with IDDM, 3 were found to have CS [61]. Conversely, in a recent study of 335 CS patients, IDDM was found in 5.4% compared to 1.5% in the matched control population [62].

Isolated IgA deficiency

Among 65 pediatric patients with isolated IgA deficiency, intestinal biopsies compatible with CS were found in 5 (8%) [63]. The prevalence of IgA deficiency is estimated to be about 1/700 in the general population. This is a reason for including IgG AGA in a serological screening panel.

Epilepsy

Several studies have suggested an increased prevalence of CS in patients with epilepsy. One large Irish study a 2% prevalence of CS among patients attending a seizure clinic [64]. An association with epilepsy and occipital cerebral calcifications has been reported in some studies but not others.

Autoimmune diseases

An association has been reported between CS and various autoimmune diseases, such as Graves disease and Sjogren's syndrome [62,65]. In one study of 34 Finnish patients with primary Sjogrens syndrome, 5 were found to have small bowel mucosal changes compatible with CS. All had the DQ2 HLA II allele and positive serology for AGA or EMA. On a GFD all patients had improvement in small bowel histology, but no change in sicca symptoms [65].

TREATMENT AND FOLLOW-UP

Diet

Education

It is important for physicians to give a careful explanation of the pathophysiology of the disease and of the toxicity and ubiquity of gluten, particularly for patients with minimal symptoms. Patients should understand the importance of a GFD for reversal or prevention of anemia, osteopenia, infertility, and for reducing the risk of malignancy. Patients should also understand that small amounts of gluten may cause mucosal damage, and mucosal damage may occur without symptoms.

Resources

A gluten-free diet (GFD) is straightforward in theory but difficult in practice. Physicians usually do not have the training, experience, or resources to properly advise patients regarding a GFD. Patients should be referred to an experienced dietitian. It is also helpful for patients to join and participate in a celiac support group, often the best source of advice about gluten-free products and recipes. A list of resources for CS patients is included at the end of this paper.

Hidden sources of gluten

Many foods are gluten-free, including fresh unprocessed meats, milk, unprocessed cheeses, beans, vegetables, and fruits. There are many gluten-free carbohydrate sources such as rice, maize, potatoes, and yams.

Celiac patients must be very careful, however. For example, wheat products include durum, semolina, and spelt. Commercial french fries, some potato chips, and other potato products may be treated with gluten. Corn flakes might be assumed to be safe, but there have been reports of contamination due to the use of multipurpose grain processing equipment.

Unfortunately, many processed foods contain gluten in one form or another. Examples of processed foods which may contain gluten products as thickeners and fillers include: processed meats, such as luncheon meat or hot dogs; ice cream, commercial chocolate milk; processed cheese, cheese sauces; canned soup and dried soup mixes; salad dressings; instant coffee, teas and cocoa; some soy sauces, catsup, mustards, and vinegar; a number of candies, and beer, whiskey, and bourbon. Even communion wafers have been reported to cause symptoms! [22].

Labeling is often not reliable. Many products contain no indication of the gluten content, or contain misleading information. Products which contain hydrolyzed vegetable or plant protein, modified food starch, malt, binders, or excipients must be suspect. Products labeled as gluten-free in the U.S. are very likely to be safe, but products from Europe labeled as gluten-free are allowed to contain 3-5% gluten.

A number of medications are manufactured with gluten fillers and other excipients, and may be responsible for inadvertent gluten ingestion.

The safety of oats in CS

There is disagreement about the safety of oats for CS patients. Several studies have been done [66-68]. In one recent randomized trial 92 adults were given either a GFD with or without oats. Symptoms, nutritional status, and laboratory measures were observed for 6-12 months, and small bowel biopsies were done at the beginning and the end of the observation period. The mean oat intake was 40-50 gm per day. No adverse consequences were note in the group randomized to oats [66]. However, in each of the studies great care was taken to provide oats uncontaminated by gluten during milling. Since this cannot be guaranteed for commercial oats, many experts still recommend that celiac patients avoid oats[69].

Follow-up

Patients will usually experience improvement in symptoms within a few weeks of starting a GFD. Recovery of the mucosa, however, takes much longer. If a repeat biopsy is done, most will have recovery within 6 months, but healing may take as long as 2 years. AGA and EMA titers will fall and become negative as early as 6 months if the patient has followed a GFD successfully. It is reasonable to recommend a yearly visit to question the

patient regarding symptoms, and to monitor laboratory studies such as CBC, folate, calcium, and bone density.

Lack of response to GFD

A substantial minority of patients diagnosed with CS, from 7-30% , do not respond to a GFD. Lack of response may be primary, following the initial diagnosis, or secondary, when a patient previously responsive to GFD develops recurrent symptoms. It should be considered that although a symptomatic response is usually apparent within a few weeks, mucosal healing may take much longer, up to several years. It would seem reasonable to wait a year before making a diagnosis of non-responsiveness [22].

Diet

The most common cause of lack of response is continued gluten exposure, either intentional or inadvertent. Thus, the first step is a careful review of the patient's diet. Persistent or recurrent elevation of the EMA suggests gluten ingestion. As discussed, patients may have an imperfect understanding of the requirements of diet, and there are many potential sources of gluten. They may lack motivation to follow a strict GFD for a variety of reasons.

Complicating gastrointestinal disorders

In a study done at BUMC, 12 of 80 treated CS patients had persistent diarrhea. The causes of diarrhea in these patients included microscopic colitis in 4, carbohydrate malabsorption in 2, pancreatic insufficiency in 2, irritable bowel syndrome in 2, and fecal incontinence in 2 [70].

Microscopic colitis

Patients with persistent diarrhea while on a GFD may have microscopic colitis. Microscopic or collagenous colitis is a condition in which the mucosa is grossly normal, but there is a dense chronic inflammatory infiltrate in the lamina propria, and, in some cases, an abnormal band of collagen under the basement membrane.

Lactose and other dietary intolerances

Early in the course of treatment, secondary lactose intolerance may complicate CS. This may lead to persistent bloating, cramping, and diarrhea. Other carbohydrates, such as fructose and sorbitol may also cause diarrhea. In children cow's milk and soy intolerance may complicate CS, and there have been reports of intolerance to eggs, chicken, and fish

Pancreatic insufficiency

Exocrine pancreatic insufficiency may complicate CS. Diminished cholecystokinin-pancreozymin release from the abnormal duodenal mucosa leads to diminished pancreatic enzyme output, and may also lead to pancreatic atrophy [20]. In children pancreatic enzyme supplements may be required in the first 30 days after diagnosis [71].

Lymphoma

As discussed in the following section, CS patients are at increased risk of small intestinal T-cell lymphoma. This possibility should be considered in patients who fail to respond to GFD initially or who develop recurrent symptoms after an initial response.

Refractory sprue

A small number of patients with CS may be truly refractory to a GFD. Lack to response to GFD is a paradox in CS, as an essential part of the diagnosis (by ESPGAN criteria) is response to GFD. However, the diagnosis may be supported by such information as family history, typical HLA serotype, and the presence of AGA and EMA.

In some refractory patients there seems to be an end-stage irreversible mucosal lesion. There is extreme mucosal atrophy and reduced numbers of crypts with few mitoses. In other refractory patients a dense layer of sub-epithelial collagen is seen. This is termed collagenous sprue. It is not clear whether this is a distinct clinical entity, or simply reflects long-standing disease. Some patients with refractory celiac sprue suffer relentless decline, with persistent severe malabsorption, diarrhea and malabsorption. Steroid therapy and immunosuppressives such as azathioprine and cyclosporine have been tried in a few cases [11,22,72]

MORTALITY & MALIGNANCY IN CS

There is a slight increase in mortality for CS patients. One study of about 650 patients found a relative risk of 1.9 for overall mortality. Mortality was highest in the first year after diagnosis and decreased to control levels by 15 years later. Most of the excess mortality was due to an excess of certain malignancies[73].

Malignancy in CS

CS is associated with an increased risk of intestinal lymphoma, adenocarcinoma of the small bowel, and squamous carcinoma of the oropharynx and esophagus. Even patients with mild enteropathy share the risk of cancer [73-76]. One study found that the risk of malignancy was reduced in patients who followed a GFD. In 210 patients followed for 11 years or more, the relative risk of malignancy was about 7 fold greater than controls in CS patients following a GFD, but 40 fold greater in those not adhering to a strict GFD [75].

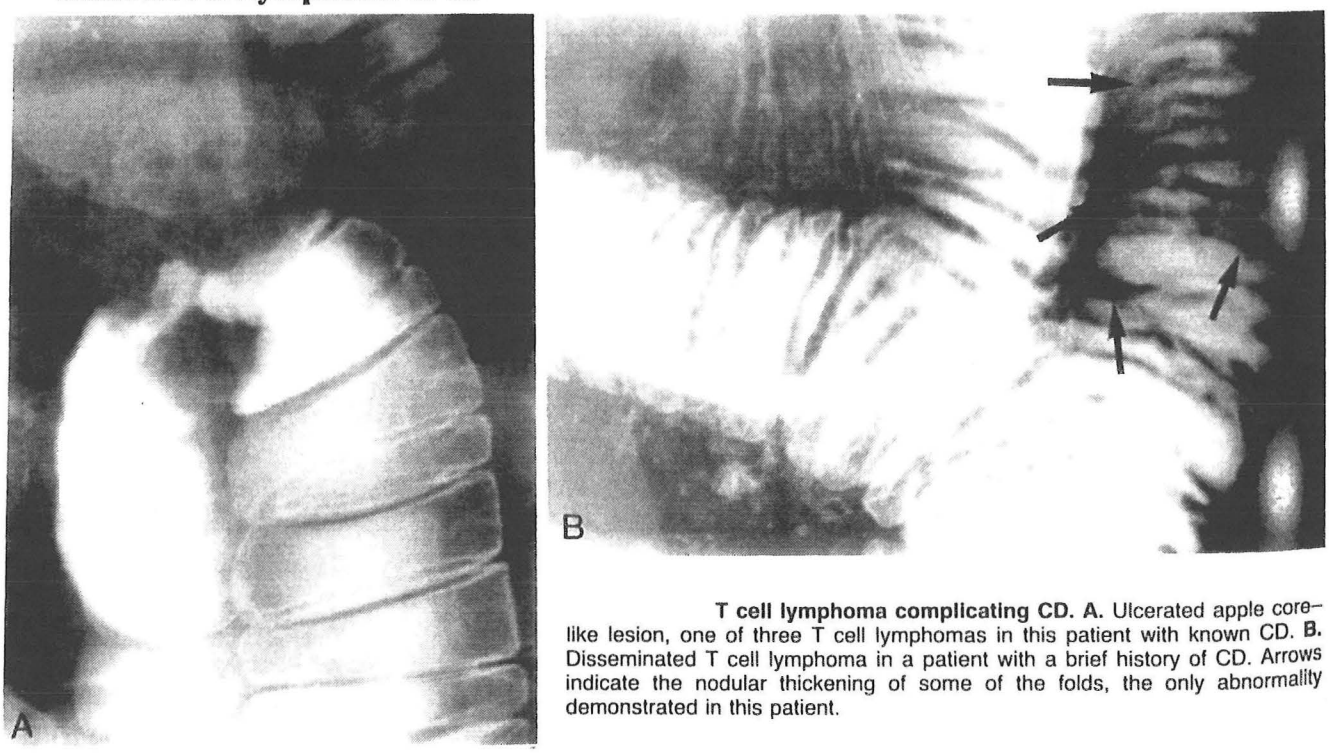
Lymphoma of the small bowel

About ½ of the excess malignancies associated with CS are T-cell lymphomas of the small bowel [74]. The relative risk in untreated patients has been estimated to be 30-40 times that of controls [73,75]. Since small bowel lymphoma is rare, even a marked increase risk of lymphoma does not translate into a high absolute risk.

Lymphoma may be present at the time of initial diagnosis in a patient not previously known to have CS. These patients will have persistent symptoms on a GFD. In the majority of cases the lymphoma is widespread at presentation. Fever, weight loss and diarrhea are common. Many have abdominal pain, which is uncommon in otherwise uncomplicated CS. Some present with obstruction, perforation, or bleeding [77].

Lymphoma may also present months to years after the initial diagnosis of CS, often as recurrent symptoms in a patient previously in remission on a GFD. The diagnosis is can be very difficult to make. The lymphoma may be patchy, and biopsies may be negative. Small bowel barium x-rays and CT scans may be negative. Laparotomy and multiple small bowel biopsies may be necessary.

Figure 14
From Textbook of Gastrointestinal Radiology, Gore, Levine, Laufer, 1994
Small Bowel Lymphoma in CS



T cell lymphoma complicating CD. A. Ulcerated apple core–like lesion, one of three T cell lymphomas in this patient with known CD. **B.** Disseminated T cell lymphoma in a patient with a brief history of CD. Arrows indicate the nodular thickening of some of the folds, the only abnormality demonstrated in this patient.

Adenocarcinoma of the small bowel

The relative risk of adenocarcinoma of the small bowel is also markedly increased, although it is uncommon because of the rarity of this cancer in the normal population [73,74]

Squamous cell cancer of the oropharynx and esophagus

There is also an increased incidence of both squamous cell cancer of the oropharynx and esophagus in patients with CS [73,74]

Ulcerative jejunitis

Ulcerative jejunitis is a rare syndrome characterized by severe malabsorption, bleeding, obstruction, and perforation associated with the presence of multiple small intestinal ulcers. A number of series have been reported [78]. It is commonly believed to be a complication of CS, but the etiology is not straightforward. Patients with ulcerative jejunitis may have either 1) proven CS, 2) normal mucosa between ulcers, 3) lymphoma , or 4) villous atrophy unresponsive to a GFD . The largest group consists of those with villous atrophy unresponsive to a GFD. There is indirect evidence to support the diagnosis

of CS in these patients. Patients with ulcerative jejunitis usually do poorly. Steroids and other immunosuppressives may help, but mall bowel resection is frequently necessary [78]

Summing Up

1) Celiac sprue seems to be relatively common in people of European ancestry.
2) Physicians should consider the diagnosis of CS in cases of iron deficiency, osteopenia, and other conditions in which the prevalence of CS is known to be increased
3) Screening is relatively easy with serological studies
4) The potential benefits of making a diagnosis of CS are substantial.

Resources for CS Patients

Celiac Sprue Association/United States of America, Inc. (CSA/USA)
P.O. Box 31700
Omaha, NE 68131-0700
Tel. 402-5580600
Fax. 402-5581347
e-mail: celiacs@csaceliacs.org
Website: http://www.csaceliacs.org

Dallas Chapter of CSA/USA
Lone Star Celiac Support Group
Contact: Julie Tennant
Tel. 214-5039117
e-mail: jtdesign@airmail.net

National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK)
National Diseases Information Clearinghouse
Website: http://www.niddk.nih.gov

Baylor University Medical Center, Dallas
Dr. Kenneth Fine
Baylor University Medical Center
GI Research, 2nd Floor Hoblitzelle
3500 Gaston Avenue
Dallas, TX 75246
Tel: 214-8201911
Website: http://www.bhcs.com/BaylorHome

Mayo Clinic
http://www.mayohealth.org

Celiac Disease Foundation
13251 Ventura Blvd., Suite 1
Studio City, California 91604-1838
Tel. 818-9902354
Fax. 818-9902379
e-mail: cdf@celiac.org
Website: http://www.celiac.org

Celiac WWW Page
Website: http://www.enabling.org/ia/celiac

Celiac Support Page
hppt://www.celiac.com

Bibliography

1. Dowd B, Walder-Smith J. Samuel Gee, Aretaeus, and the coeliac affection. BMJ 1974; 2:(April 6)45-47.

2. Van Berge-Henegouwen GP, Mulder CJJ. History of Dicke's discovery of the gluten-free diet for celiac sprue. In: Sleisenger MH, Fordtran JS, editors. Gastrointestinal Disease. Pathophysiology/Diagnosis/Management. Fifth ed. Philadelphia: W. B. Saunders Company, 1993:1072-1077.

3. Paulley JW. Observations on the aetiology of idiopathic steatorrhea. Jejunal and lymph-node biopsies. BMJ 1954; (Dec 4)1318-1321.

4. MacDonald WC, Brandborg LL, Flick AL, Trier JS, Rubin CE. Studies of celiac sprue. IV. The response of the whole length of the small bowel to a gluten-free diet. Gastroenterology 1964; 47:573-589.

5. MacDonald WC, Dobbins III WO, Rubin CE. Studies of the familial nature of celiac sprue using biopsy of the small intestine. N Engl J Med 1965; 272:448-456.

6. Falchuk ZM, Rogentine GN, Strober W. Predominance of histocompatibility antigen HL-A8 in patients with gluten-sensitive enteropathy. J Clin Invest 1972; 51:1602-1605.

7. Shewry PR, Napier JA, Tatham AS. Seed storage proteins: structures and biosynthesis. The Plant Cell 1995; 7:945-956.

8. Wieser H. Relation between gliadin structure and coeliac toxicity. Acta Paediatr 1996; Suppl 412:3-9.

9. Sollid LM, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology 1993; 105:910-922.

10. Gjertsen HA, Lundin KEA, Sollid LM, Eriksen JA, Thorsby E. T cells recognize a peptide derived from alpha-gliadin presented by the celiac disease-associated HLA-DQ (alpha1*0501, beta1*0201) heterodimer. Hum Immunol 1994; 39:243-252.

11. Trier JS. Celiac sprue and refractory sprue. In: Feldman M, Scharschmidt BF, Sleisenger MH, Klein S, editors. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. Pathophysiology/Diagnosis/Management. Sixth ed. Philadelphia: W. B. Saunders Company, 1998:1557-1571.

12. Houlston RS, Ford D. Genetics of coeliac disease. Q J Med 1996; 89:737-743.

13. Greco L, Corazza GR, Babron MC, et al. Genome search in celiac disease. Am J Human Genet 1998; 62:669-675.

14. Maiuri L, Picarelli A, Boirivant M, Coletta S, Mazzilli MC, De Vincenzi M, et al. Definition of the initial immunologic modifications upon in vitro gliadin challenge in the small intestine of celiac patients. Gastroenterology 1996; 110:1368-1378.

15. Godkin A, Jewell D. The pathogenesis of celiac disease. Gastroenterology 1998; 115:206-210.

16. Sollid LM, Molberg O, Mcadam SN, Lundin KEA. Autoantibodies in coeliac disease: tissue transglutaminase-guilt by association? Gut 1997; 41:851-852.

17. Molberg O, Mcadam SN, Korner R, Quartsen H, Kristiansen C, Madsen L, et al. Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. Nat Med 1998; 4:713-717.

18. Fordtran JS, Rector FC, Locklear TW, Ewton MF. Water and solute movement in the small intestine of patients with sprue. J Clin Invest 1967; 46:287-298.

19. Maton PN, Selden AC, Fitzpatrick ML, Chadwick VS. Defective gallbladder emptying and cholecystokinin release in celiac disease. Reversal by gluten-free diet. Gastroenterology 1985; 88:391-396.

20. DiMagno EP, Go VLW, Summerskill WHJ. Impaired cholecystokinin-pancreozymin secretion, intraluminal dilution, and maldigestion of fat in sprue. Gastroenterology 1972; 63:25-32.

21. Working Group of the European Society of Paediatric Gastroenterology and Nutrition. Revised criteria for diagnosis of coeliac disease. Arch Dis Child 1990; 65:909-911.

22. O'Mahony S, Howdle PD, Losowsky MS. Review article: management of patients with non-responsive coeliac disease. Aliment Pharmacol Ther 1996; 10:671-668.

23. Niveloni S, Fiorini A, Dezi R, Pedreira S, Smecuol E, Vazquez H, et al. Usefulness of videoduodenoscopy and vital dye staining as indicators of mucosal atrophy of celiac disease: assessment of interobserver agreement. Gastrointest Endosc 1998; 47:223-229.

24. Jabbari M, Wild G, Goresky CA, Daly DS, Lough JO, Cleland DP, et al. Scalloped valvulae conniventes: an endoscopic marker of celiac sprue. Gastroenterology 1988; 95:1518-1522.

25. Murray JA. Serodiagnosis of celiac disease. Clin Lab Med 1997; 3:445-464.

26. Burgin-Wolff A, Gaze H, Hadziselimovic F, Huber H, Lentze MJ, Nussle D, et al. Antigliadin and antiendomysium antibody determination for coeliac disease. Arch Dis Child 1991; 66:941-947.

27. Chorzelski TP, Beutner EH, Sulej J, Tchorzewska H, Jablonska S, Kumar V, et al. IgA anti-endomysial antibody: a new serological marker of dermatitis herpetiformis and coeliac disease. Br J Dermatol 1984; 111:395-404.

28. Vogelsang H, Genser D, Wyatt J, Lochs H, Ferenci P, Granditsch G, et al. Screening for celiac disease: a prospective study on the value of noninvasive tests. Am J Gastroenterol 1995; 90:394-398.

29. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 1997; 3:797-801.

30. Ferreira M, Lloyd Davies S, Butler M, Scott D, Kumar P. Endomysial antibody: Is it the best screening test for coeliac disease? Gut 1992; 33:1633-1637.

31. Lerner A, Kumar V, Iancu TC. Immunological diagnosis of childhood coeliac disease: comparison between antigliadin, antireticulin, and antiendomysial antibodies. Clin Exp Immunol 1994; 95:78-82.

32. Sulkanen S, Halttunen T, Laurila K, Kolho K, Korponay-Szabo IR, Sarnesto A, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology 1998; 115:1322-1328.

33. Rostami K, Kerckhaert J, Tiemessen R, von Blomberg ME, Meijer JWR, Mulder CJJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. Am J Gastroenterol 1999; 94:888-894.

34. Fasano A. Where have all the American celiacs gone? Acta Paediatr 1996; (Suppl 412)20-24.

35. Johnston SD, Watson RGP, McMillan SA. Preliminary results from follow-up of a large scale population survey of antibodies to gliadin, reticulin, and endomysium. Acta Paediatr 1996; 85:(Suppl 412)61-64.

36. Catassi C, Fabiani E, Ratsch IM, et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. Acta Paediatr 1996; 85:(Suppl. 412)29-35.

37. Grodzinsky E. Screening for coeliac disease in apparently healthy blood donors. Acta Paediatr 1996; (Suppl 412)36-38.

38. Not T, Horvath K, Hill ID, Fasano A, Hammed A, Magazzu G. Endomysium antibodies in blood donors predicts a high prevalence of celiac disease in the USA. Gastroenterology 1996; 110:A351 Abstract.

39. Corazza GR, Frisoni M, Tregiarri EA. Subclinical celiac sprue: increasing occurence and clues to its diagnosis. J Clin Gastroenterol 1993; 16:16-21.

40. Parnell NDJ, Ciclitira PJ. Review article: coeliac disease and its management. Aliment Pharmacol Ther 1999; 13:1-13.

41. Troncone R, Greco L, Mayer M, Paparo F, Caputo N, Micillo M, et al. Latent and potential coeliac disease. Acta Paediatr 1996; Suppl 412:10-14.

42. Ferguson A, Arranz E, O'Mahony S. Clinical and pathological spectrum of coeliac disease-active, silent, latent, potential. Gut 1993; 34:150-151.

43. Johnston SD, Watson RGP, McMillan SA, Sloan J, Love AHG. Coeliac disease detected by screening is not silent-simply unrecognized. Q J Med 1998; 91:853-860.

44. Bottaro G, Cataldo F, Rotolo N, Spina M, Corazza GR. The clinical pattern of subclinical/silent celiac disease: an analysis on 1026 consecutive cases. Am J Gastroenterol 1999; 94:691-696.

45. Fine KD. The prevalence of occult gastrointestinal bleeding in celiac sprue. N Engl J Med 1996; 334:1163-1167.

46. Ackerman Z, Eliakim R, Stalnikowicz R, Rachmilewitz D. Role of small bowel biopsy in the endoscopic evaluation of adults with iron deficiency anemia. Am J Gastroenterol 1996; 91:2099-2102.

47. Corazza GR, Di Sario A, Cecchetti L, Tarozzi C, Corrao G, Bernardi M, et al. Bone mass and metabolism in patients with celiac disease. Gastroenterology 1995; 109:122-129.

48. Mautalen C, Gonzalez D, Mazure R, Vazquez H, Lorenzetti MP, Maurino E, et al. Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients. Am J Gastroenterol 1997; 92:313-318.

49. Lindh E, Ljunghall S, Larsson K, Lavo B. Screening for antibodies against gliadin in patients with osteoporosis. J Int Med 1992; 231:403-406.

50. Mora S, Barera G, Beccio S, Proverbio MC, Weber G, Bianchi C, et al. Bone density and bone metabolism are normal after long-term gluten-free diet in young celiac patients. Am J Gastroenterol 1999; 94:398-403.

51. Valdimarsson R, Lofman O, Toss G, Strom M. Reversal of osteopenia with diet in adult coeliac disease. Gut 1996; 38:322-327.

52. Otley C, Hall III RP. Dermatitis herpetiformis. Dermatologic Clinics 1990; 8:759-769.

53. Corazza GR, Zoli G, Di Sabatino A, Ciccocioppo R, Gasbarrini G. A reassessment of splenic hypofunction in celiac disease. Am J Gastroenterol 1999; 94:391-397.

54. O'Grady JG, Stevens FM, Harding B, O'Gorman TA, McNicholl B, McCarthy CF. Hyposplenism and gluten-sensitive enteropathy. Natural history, incidence, and relationship to diet and small bowel morphology. Gastroenterology 1984; 87:1326-1331.

55. Holmes GKT. Non-malignant complications of coeliac disease. Acta Paediatr 1996; (Suppl 412)68-75.

56. Sher KS, Mayberry JF. Female fertility, obstetric and gynaecological history in coeliac disease: a case control study. Acta Paediatr 1996; (Suppl 412)76-77.

57. Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, Davies-Jones GAB, Gibson A, Jarratt JA, et al. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet 1998; 352:1582-1585.

58. Muller AF, Donnelly MT, Smith CML, Grundman MJ, Holmes GKT, Toghill PJ. Neurological complications of celiac disease: a rare but continuing problem. Am J Gastroenterol 1996; 91:1430-1435.

59. De Vitis I, Ghirlanda G, Gasbarrini G. Prevalence of coeliac disease in type I diabetes: a multicenter study. Acta Paediatr 1996; (Suppl 412)56-57.

60. Saukkonen T, Savilahti E, Reijonen H, Ilonen J, Tuomilehto-Wolf E, Akerblom HK, et al. Coeliac disease: frequent occurrence after clinical onset of insulin-dependent diabetes mellitus. Diabetic Medicine 1995; 13:464-470.

61. Rensch MJ, Merenich JA, Lieberman M, Long BD, Davis DR, McNally PR. Gluten-sensitive enteropathy in patients with insulin-dependent diabetes mellitus. Ann Int Med 1996; 124:564-567.

62. Collin P, Reunala T, Pukkala E, Laippala P, Keyrilainen O, Pasternack A. Coeliac disease-associated disorders and survival. Gut 1994; 35:1215-1218.

63. Meini A, Pillan NM, Villanacci V, Monafo V, Ugazio RG, Plebani A. Prevalence and diagnosis of celiac disease in IgA-deficient children. Ann Allergy Asthma Immunol 1996; 77:333-336.

64. Cronin CC, Jackson LM, Feighery C, Shanahan F, Abuzakouk M, Ryder DQ, et al. Coeliac disease and epilepsy. Q J Med 1998; 91:303-308.

65. Iltanen S, Collin P, Korpela M, Holm K, Partanen J, Polvi A, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjogren's syndrome. Am J Gastroenterol 1999; 94:1042-1046.

66. Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma V, Jarvinen RMK, Uusitupa MIJ, et al. A comparison of diets with and without oats in adults with celiac disease. N Engl J Med 1995; 333:1033-1037.

67. Srinivasan U, Leonard N, Jones E, Kasarda DD, Weir DG, O'Farrelly C, et al. Absence of oats toxicity in adult coeliac disease. BMJ 1996; 313:1300-1301.

68. Hardman CM, Garioch JJ, Leonard JN, Thomas HJW, Walker MM, Lortan JE, et al. Absence of toxicity of oats in patients with dermatitis herpetiformis. N Engl J Med 1997; 337:1884-1887.

69. Parnell NDJ, Ellis HJ, Ciclitira PJ. Absence of toxicity of oats in patient with dermatitis herpetiformis. N Engl J Med 1998; 338:1470

70. Fine KD, Meyer RL, Lee EL. The prevalence and causes of chronic diarrhea in treated celiac sprue. Gastroenterology 1997; 112:1830-1838.

71. Carroccio A, Iacono G, Montalto G, Cavataio F, Lorello D, Greco L, et al. Pancreatic enzyme therapy in childhood celiac disease. A double-blind prospective randomized study. Dig Dis Sci 1995; 12:2555-2560.

72. Rolny P, Sigurjonsdottir HA, Remotti H, Nilsson LA, Ascher H, Tlaskalova-Hogenova H, et al. Role of immunosuppressive therapy in refractory sprue-like disease. Am J Gastroenterol 1999; 94:219-225.

73. Logan RFA, Rifkind EA, Turner ID, Ferguson A. Mortality in celiac disease. Gastroenterology 1989; 97:265-271.

74. Swinson CM, Coles EC, Slavin G, Booth CC. Coeliac disease and malignancy. Lancet 1983; 1:(Jan 15)111-115.

75. Holmes GKT, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease-effect of a gluten free diet. Gut 1989; 30:333-338.

76. Ferguson A, Kingstone K. Coeliac disease and malignancies. Acta Paediatr 1996; (Suppl 412)78-81.

77. Mathus-Vliegen EMH, Van Halteren H, Tytgat GNJ. Malignant lymphoma in coeliac disease: various manifestations with distinct symptomatology and prognosis? J Int Med 1994; 236:43-49.

78. Baer AN, Bayless TM, Yardley JH. Intestinal ulceration and malabsorption syndromes. Gastroenterology 1980; 79:754-765.