MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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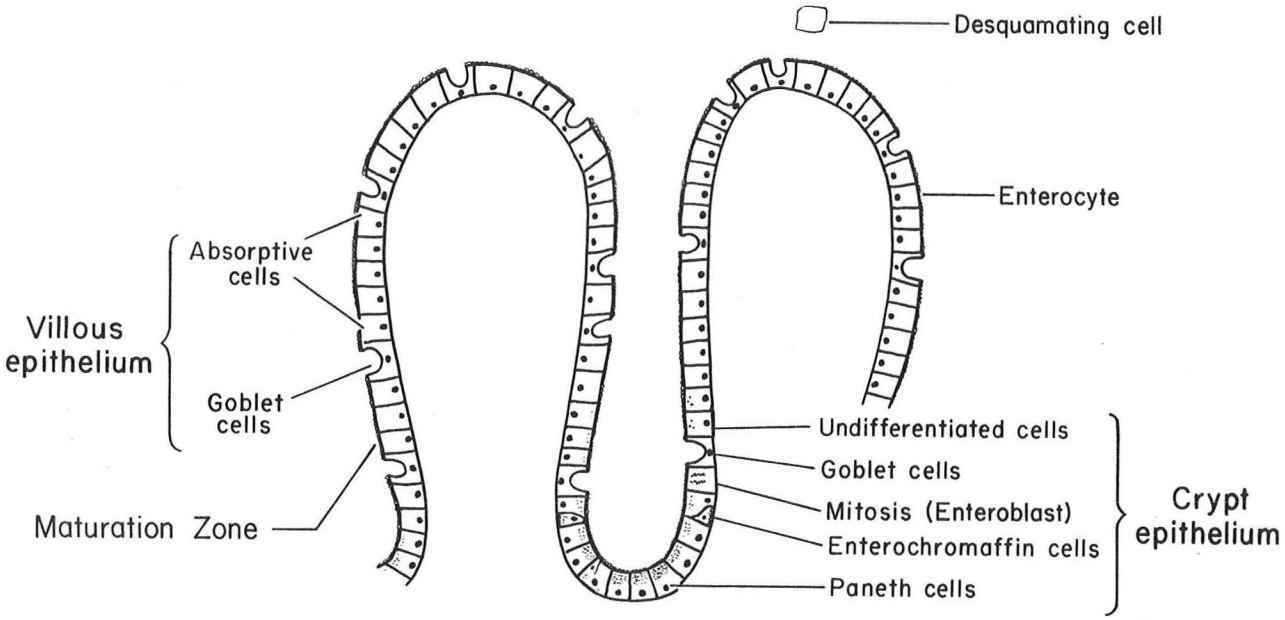
GLUTEN-SENSITIVE ENTEROPATHY AND NONRESPONSIVE CELIAC DISEASE

I. *The Normal Small Bowel Mucosa - A Brief Review:*



The epithelial cells lining the intestinal crypts and villi arise from proliferative epithelial cells (enteroblasts) at the base of the crypts. As a result of continued proliferation, epithelial cells (enterocytes) are pushed up the sides of the crypts and villi, and at the villous tips they are shed into the intestinal lumen.

As the epithelial cells pass the crypt-villous junction, they undergo morphologic and functional maturation. This consists in part of a great increase in cellular content of digestive enzymes located in the epithelial brush borders.

The normal lamina propria contains lymphocytes and plasma cells. These are not present at birth or in germ-free animals; they result instead from antigenic stimulation within the gut lumen (*47*).

II. Definition of Gluten-Sensitive Enteropathy and Celiac Disease:

Some authors, including most investigators in the U.S., restrict the term "celiac-sprue" to those patients who have a characteristic proximal small bowel lesion (loss of villi, elongated crypts, etc.) plus a definite clinical and histologic improvement after institution of a gluten-free diet. Patients who have the same proximal small bowel lesion histologically, but who do not respond favorably to a gluten-free diet, are diagnosed as having "unclassified sprue" (68A).

Others use the term "celiac syndrome (or disease)" to denote patients with a characteristic mucosal lesion (63). If they respond favorably to a gluten-free diet, these patients are said to have "gluten-sensitive enteropathy". If they do not respond favorably to a gluten-free diet, they are diagnosed as "unresponsive celiac syndrome (or disease)". Some patients in this latter category may be given additional diagnoses (e.g., ulcerative jejunitis, collagenous sprue, etc.), depending on the presence of some particular clinical or histological finding.

In the present author's opinion, the second of these definitions is more reasonable, since celiac disease and sprue are ancient terms used to describe patients with idiopathic steatorrhea long before it was recognized that some (or most) such patients respond favorably to a gluten-free diet. (Admittedly, there is some inconsistency in my reasoning, since I am using a histologic finding to define celiac disease, even though "celiac disease" was used long before it was recognized that some such patients had a lesion in the proximal small bowel.) Furthermore, some patients with a characteristic jejunal lesion respond initially to a gluten-free diet, but later they do not. In this instance, the terminology used in the first paragraph becomes more confusing than the terminology used in the second paragraph.

Therefore, for purposes of this Grand Rounds, the following arbitrary definitions are used:

Celiac Disease (or celiac sprue) - Characteristic jejunal lesion, usually but not necessarily associated with malabsorption. Other diseases of a generally accepted separate pathogenesis can rarely produce a similar histologic lesion, and these must be ruled out before a diagnosis of celiac disease is accepted. These include tropical sprue, kwashiorkor, Zollinger-Ellison syndrome, primary intestinal lymphoma, eosinophilic gastroenteritis, bacterial overgrowth syndromes, giardiasis, hookworm infestation, neomycin therapy, radiation damage, sensitivity to soy, and hypogammaglobulinemia.

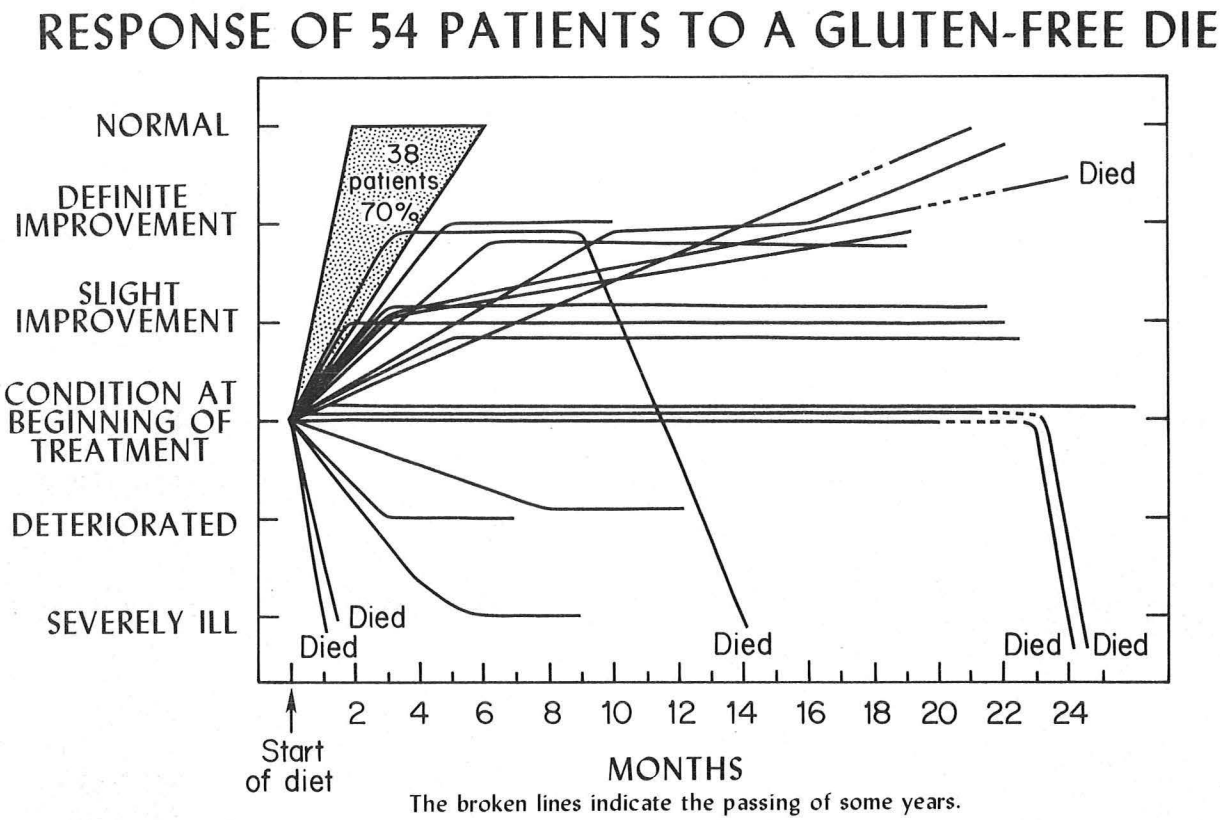
Gluten-Sensitive Enteropathy - Characteristic jejunal lesion with definite clinical and/or histologic improvement after a gluten-free diet. (Some workers insist that the disease be reproduced by gluten challenge before this diagnosis can be considered definite.)

Nonresponsive Celiac Disease - A patient with celiac disease who fails to respond favorably to a gluten-free diet. To be included in this category,

it must be established within the realm of possibility that the patient is actually on a "gluten-free diet" and that the mucosal biopsy which established "celiac disease" was correctly sectioned and interpreted.

III. *Frequency of Response to a Gluten-Free Diet in Patients with Celiac Disease (Syndrome):*

This is variable, depending on whose series one reads. The following figure is taken from Pink and Creamer (*63*). Their results are in accord qualitatively with that of the present author.



Fifty-four patients with celiac syndrome were treated with a gluten-free diet. Only 70% returned quickly to full health. The remaining 30% (16 out of 54) who did not respond well could be separated into 3 groups.

Group I, 5 patients: Had severe and extensive small intestinal mucosal lesion and deteriorated after gluten withdrawal. These patients had a striking diminution in the number of Paneth cells in the crypts.

The downward course was somtimes arrested with steroids. The pancreas was normal at necropsy in 2 cases and no lymphoma was found. In the other 3 cases, a secretin test of pancreatic function was normal. One of these 5 patients had celiac disease as a child.

Group II, 3 patients: This group was chronically ill and had pancreatic insufficiency as well as a celiac lesion in the jejunum. They did not improve, even with a gluten-free diet and pancreatic enzymes. The pancreatic lesion was possibly due to chronic malnutrition.

Group III, 8 patients: These responded partially and questionably. Minor dietary indiscretions were probably present in 3. These three made a slow improvement, but only became "normal" after 2 years. In 4 cases, despite obsessive adherence to the diet, the patients have not had a clearcut response.

The mortality rate in these 54 patients was 17%. In the group who responded well to a gluten-free diet, the mortality was only 2.5%.

IV. *Brief Presentation of Two Typical Patients with Gluten-Sensitive Enteropathy - One Child and One Adult*

V. *Presentation of Two Patients with Nonresponsive Celiac Disease*

Case 1:

R.W.B. was a 57-year-old man when he was first seen in 1963. As an infant he had episodes of chronic diarrhea, which recurred when he was 15 years old. Since age 20 he had episodes of diarrhea and weight loss, lasting from a few weeks to 3 years, separated by episodes of relatively normal bowel habit. At age 56 he developed peripheral neuritis.

At age 55 he was diagnosed as having celiac disease. He was put on a gluten-free diet, without evidence of benefit. His maximum weight was 170 pounds; on admission to PMH in 1963, he weighed 125 pounds. He was wasted and had evidences of peripheral neuropathy. He was anemic, hypoproteinemic, had severe steatorrhea and xylose malabsorption. A small bowel biopsy showed typical severe celiac disease.

His gluten-free diet was continued, but he failed to improve. The patient's wife was a dietician, and the patient religiously adhered to his diet. It seems very unlikely that his failure to respond could be attributed to poor adherence to diet. A trial of antibiotics for one week was without effect. In October of 1963 (age 57), he was started on prednisone 15 mg per day. This produced symptomatic improvement and some weight gain, and he was able to return to work. However, steatorrhea persisted.

In 1971, when he was 65 years old, he presented to his physician with a sore throat, anemia, hypoalbuminemia and hypocalcemia and was admitted to

Baylor University Medical Center. Plaque-like skin lesions were noted. A diagnosis of histiocytic medullary reticulosis was made from skin and bone marrow biopsy. The patient died about 1 week later, and autopsy confirmed the presence of this rare malignancy. Proliferation of histiocytes involved almost every organ except the GI tract, pancreas, adrenals and prostate.

Case 2 - N.S. - 57 W/F

1970 - Episodes of vomiting. X-rays revealed mid-duodenal ulcer and stricture. Resected surgically, benign.

1971 - Admitted to PMH. Acid secretion normal. Mild steatorrhea (19 gm/day), xylose malabsorption, severe osteoporosis by x-ray (history of fractures). Per oral biopsy revealed classical celiac lesion in jejunum. Started on gluten-free diet, excellent adherence.

1973 - Recurrent ulceration with stricture in proximal jejunum (Dr. Kilman) in spite of strict gluten-free diet. Stricture resected (benign, mucosa typical of celiac disease) by Dr. McClelland.

1976 - Recurrent stricture in distal duodenum, resected surgically (fibrous, chronic inflammation). Adjacent mucosa typical of celiac disease. Remained on gluten-free diet. Mild steatorrhea still present.

1977 - Recurrent duodenal strictures (at least 3), in spite of strict adherence to gluten-free diet

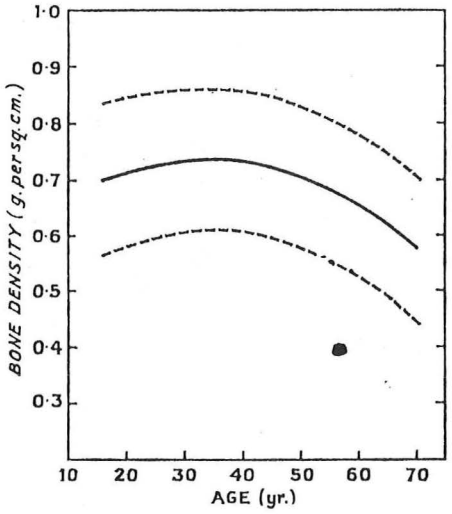
Urine calcium on 400 mg calcium diet - 10, 12, 11 mg/24 hr (very low, indicating severe calcium malabsorption). Bone density very low.

Bone biopsy done 1976 (result not available since patient is on protocol) and started on 20 µg/day 25-OH CC.

HLA Type (Stastny)
A 1, AW 24
BW, 40
B 7

Mann B-lymphocyte surface antigen (Ref. 33). Negative in 1976. (Sera sent to Dr. Mann by Dr. Richard Gilmore.)

See p. 12 for a further discussion of the significance of these typing results.



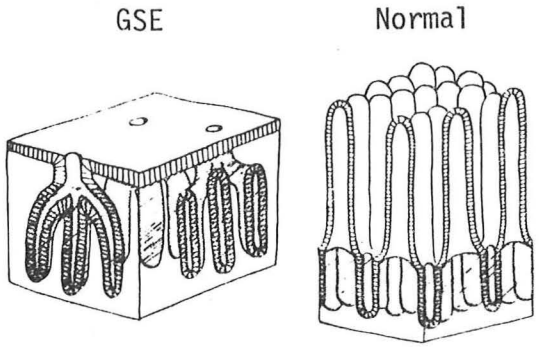
—Bone density in women

Pak, et al. Lancet July 5, 1975, p.7

VI. *Pathogenesis of Gluten-Sensitive Enteropathy:*

A. Histologic Findings:

1) Villous atrophy



Creamer, B.: Dynamics of the mucosa of the small intestine in idiopathic steatorrhea. Gut 3:295, 1962.

2) Remaining absorptive cells are abnormal (cuboidal instead of columnar), and microvilli are shortened and often fused. They may have characteristics of cells usually present in the crypts. Many mucosal enzyme concentrations, such as disaccharidases, are decreased; intraepithelial lymphocytes increased (*47*).

3) Crypts are hypertrophied, number of mitoses in crypts is markedly increased, hyperplasia of undifferentiated and endocrine* cells. This is presumably a compensation process in response to increased rates of epithelial cell loss from the villi.

4) Lamina propria - cellularity increased, mainly by immunoglobulin producing plasma cells and lymphocytes. Polys also increased.

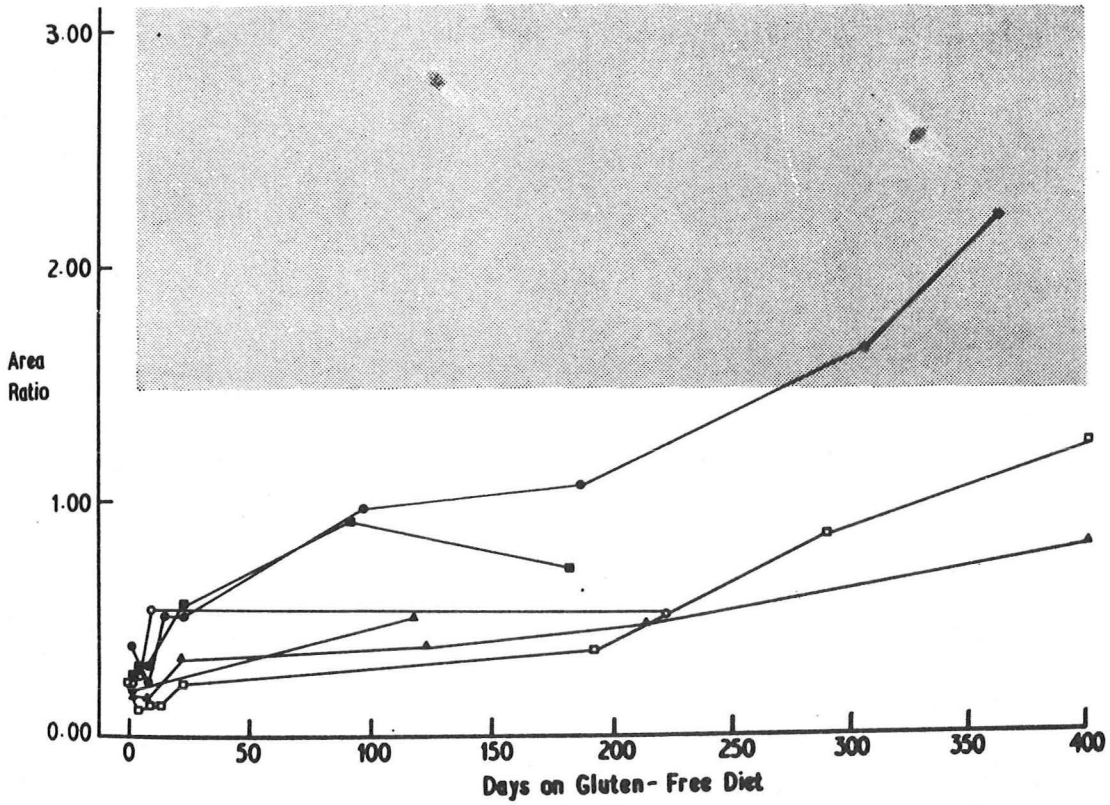
5) Proximal small bowel more involved than distal. Proximal sparing does not occur. Length of small bowel involvement determines clinical severity.

6) Most workers claim that the proximal small bowel is uniformly abnormal in patients with gluten-sensitive enteropathy. Recently it has been claimed that the lesion may be patchy (*4*), at least in some patients.

7) Histological response to gluten-free diet. Mucosa of the distal small bowel improves first. Complete recovery to normal is unusual. It may require months to years of a gluten-

*High 5-HIAA excretion may result from hyperplasia of the enterochromaffin cells (*16*).

free diet before histological improvement is evident (especially in the proximal jejunum in adults).



From ref. 9. Area ratios and time on a gluten-free diet: individual patients. The shaded area represents twice the standard deviation above and below the mean area ratio for control mucosae (Chapman, et al.: Gut 15:870-874, 1974). Area ratio = villous area divided by crypt area.

8) In contrast to the rather slow histological improvement on gluten withdrawal, re-introduction of gluten in a successfully treated patient causes histologic damage within a few hours. When wheat is instilled into the ileum, a near normal biopsy may convert to a typical lesion in a period of a few days after wheat instillation.

B. Toxic Fraction of Cereal Grains:

1) Wheat, rye and barley and sometimes oats are toxic. Rice and corn are not.

2) Toxic fraction is in the protein fraction of the cereals (gluten, gliadin). Amino acid constituents of gluten (after complete hydrolysis) are non-toxic.

C. Possible Mechanisms of Gluten Toxicity:

1) Immunological reaction.

2) Inborn metabolic disease - peptidase deficiency results in incomplete digestion of gluten, which allows a toxic polypeptide to directly damage the mucosa.

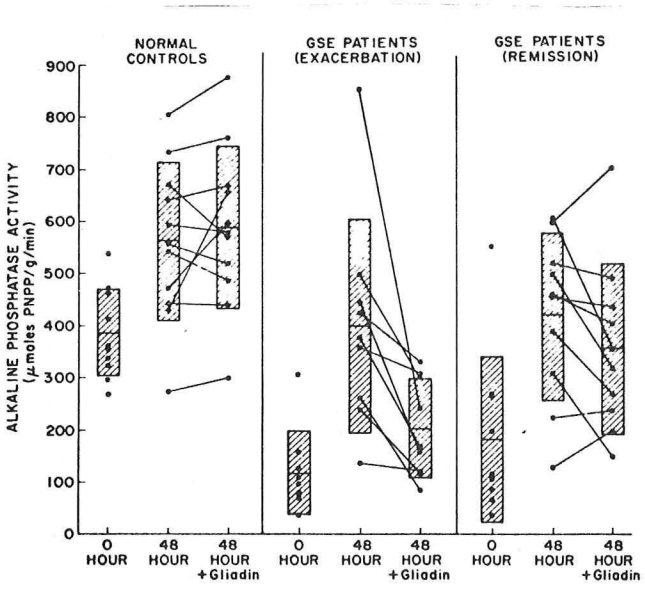
3) Toxic lectin (*20*)

D. In Vitro Organ Culture of Experiments (*23-25*)

1) Jejunal mucosa from patients with GSE (gluten-sensitive enteropathy) synthesizes 2-4 times more IgA and IgM (than biopsy specimens from normal subjects) when exposed to gluten. Much of these immunoglobulins have antigluten specificity.

2) Alkaline phosphatase concentration of mucosa is used by these authors as an index of maturation or differentiation. They believe that this is an in vitro model of gluten-sensitive enteropathy.

a) Results are shown in the next figure.



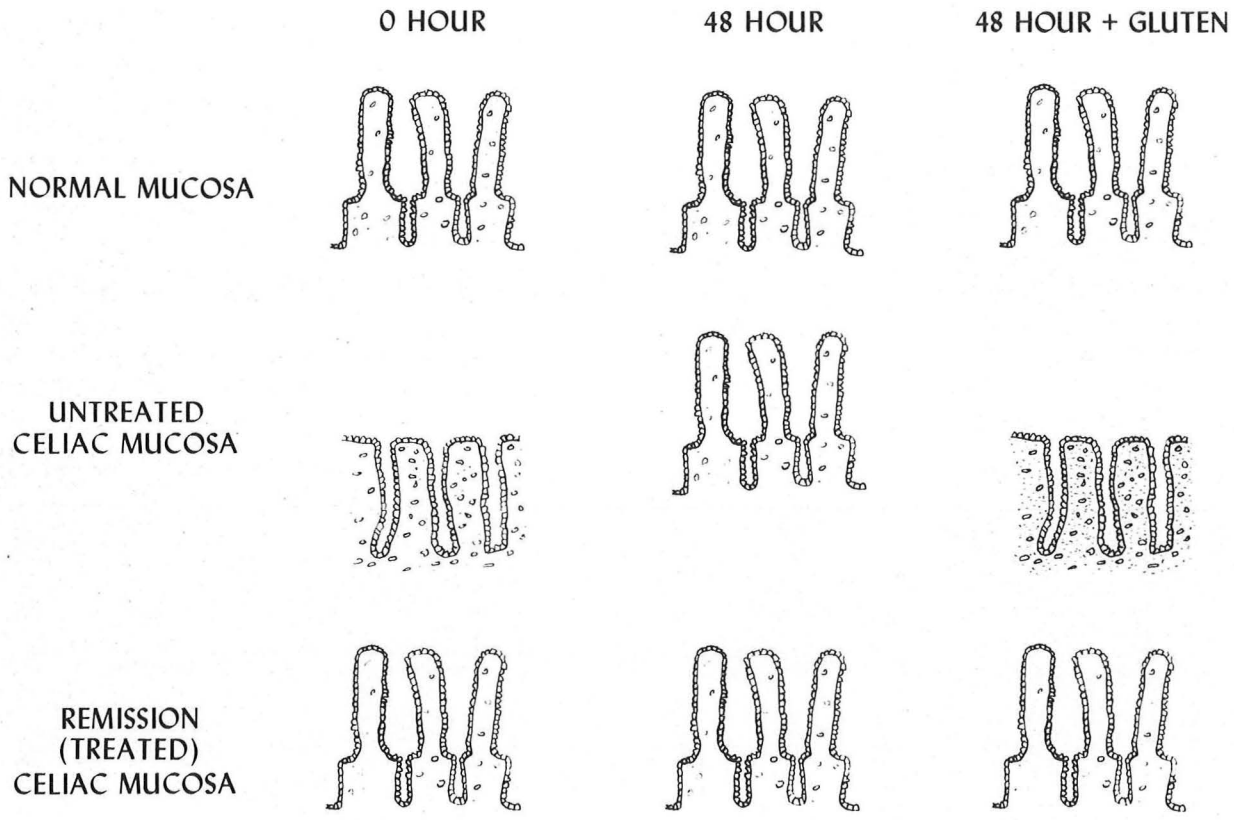
Alkaline phosaphatase activity during jejunal tissue culture of biopsies from normal controls (left panel), patients with gluten-sensitive enteropathy (GSE) in exacerbation (center panel), and patients with GSE remission (right panel). Each datum point represents a single study or the mean value of several studies done in the same patient. The shaded areas represent the mean ± 1 SD. Alkaline phosphatase activity is expressed as micromoles of p-nitrophenyl phosphate (PNPP) formed per gram of tissue per minute. (Strober, W.: Ann. Int. Med. 83:242-256, 1975).

Interpretation: GSE mucosa initially has a low contration of alkaline phosphatase activity, which is evidence of cellular injury. During organ culture in the absence of gluten peptides, the tissue assumes a more normal functional state. Gluten peptides are toxic, in that maturation towards normal does not occur when they are present in the organ culture media.

In contrast, tissue obtained from patients with inactive (treated) GSE mucosa was not sensitive to gluten in vitro, i.e., maturation was normal even when gluten was present in the organ culture media. These findings imply that gluten-peptides do not adversely affect susceptible mucosa directly, but that they must first activate in the host an endogenous effector mechanism of toxicity.

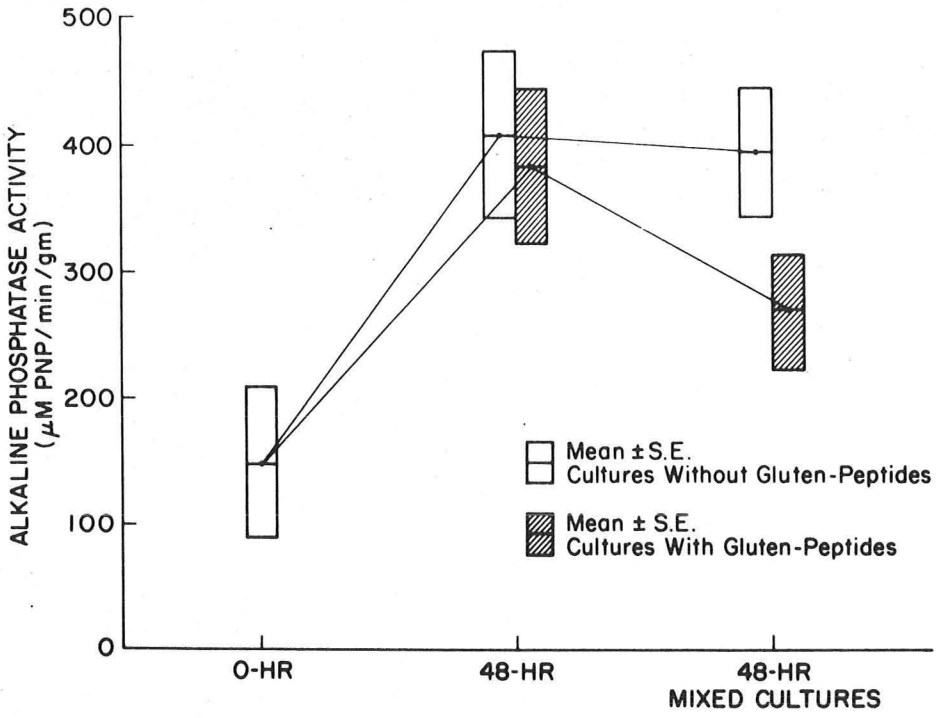
The authors indicate that morphologic changes parallel the changes in alkaline phosphatase, i.e., as phosphatase increases, the mucosal cells become more normal, and vice versa. The authors do not state that the mucosa of a GSE patient returns completely to normal when cultured in a gluten-free environment. Nevertheless, for purposes of understanding the significance of their results and interpretations, the next figure depicts their results in morphologic terms. It is emphasized that this is only my interpretation of the qualitative changes in morphology observed by these authors.

IN VITRO ORGAN CULTURE STUDIES



To be consistent with the definitions given at the beginning of this protocol, this figure should refer to GSE mucosa, rather than celiac mucosa.

b) One further study by this group is shown in the next figure.

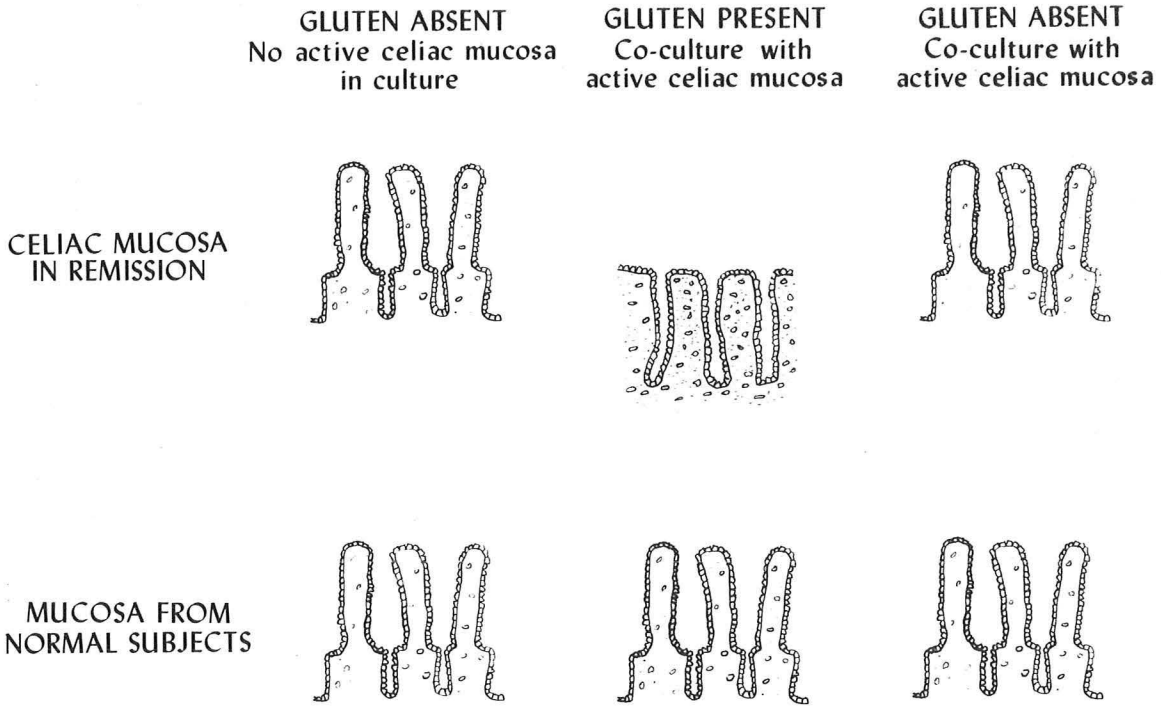


Alkaline phosphatase activity during jejunal tissue culture of biopsies from patients with gluten-sensitive enteropathy in remission cultured alone (with and without gluten peptides) and co-cultured with specimens from patients with gluten-sensitive enteropathy in exacerbation (with and without gluten peptides). Alkaline phosphatase activity is expressed as micromoles of p-nitrophenyl phosphate (PNP) per min formed per gm of tissue (*Ref. 24*).

Gluten-peptides significantly inhibited the increase in alkaline phosphatase activity in tissue obtained from patients with inactive GSE when that tissue was cultured together with tissue obtained from patients with active GSE. This effect of active on inactive disease was seen in the presence but not in the absence of gluten. On the other hand, gluten had no effect on mucosa from patients with inactive disease when that tissue was cultured together with tissue obtained from other patients with inactive disease. Similarly, gluten did not inhibit maturation in tissue obtained from control persons when the latter was cultured in the presence of tissue obtained from patients with active disease.

A morphologic interpretation of these results is shown in the next figure to help clarify their meaning. Again, it is emphasized that this is an interpretative maneuver of mine, and that the authors did not claim such dramatic histological changes.

ORGAN CULTURE OF JEJUNAL MUCOSA AT 48 HOURS



Interpretation. First, gluten-peptides are detrimental in culture to tissues from patients with inactive GSE when that tissue is co-cultured with tissue from patients with active GSE, but not to tissues from patients with the inactive disease when the tissue is cultured alone. This supports the concept that gluten is not directly toxic to GSE mucosa. Second, active disease tissue exerts an effect on inactive mucosa in the presence of gluten, even though the two tissues are physically separated in the culture. This suggests than an endogenous mechanism is necessary for injury and that this is mediated by a humoral substance. The latter, in conjunction with gluten, then leads to mucosal injury.

The authors of these interesting studies suggest that the endogenous mechanism is the local mucosal immune system.

E. Immunohistochemical studies (*47*)

In normals, the majority of plasma cells in the jejunal mucosa contain IgA (IgA:IgM:IgG = 10:2:1). This same relation holds for the concentration of jejunal secretion in normal subjects.

No local abnormalities in the production of IgG, D or E have been detected in GSE, but changes have been observed for IgA and IgM.

Plasma cells in GSE are mainly of the IgA class, and IgA is the predominant immunoglobulin in jejunal secretion. In GSE the IgA plasma cell density is either normal or decreased. However, there is a great increase in the population density of IgM plasma cells.

These findings are in keeping with the fact that patients with GSE respond to gluten with an increase in mucosal IgA and IgM synthesis, and that this increase is largely due to synthesis of antigluten antibodies.

Further studies have shown an increase in extracellular IgA and complement in the basement membrane and lamina propria. IgG has also been demonstrated with complement in untreated patients (*24, 41*).

F. Peripheral serum complement levels fall when treated GSE patients are challenged with dietary gluten *(36)*.

G. Genetic Factors (*26-30*):

1) Latent GSE is present in about 10% of first order relatives. However, although several relatives may be affected in some families, only a single case might be found (on biopsy) in other large families. Moreover, both concordance and discordance have been documented in identical twins (*2*). Thus, although genetic factors are of great importance, the mode of inheritance is not clear.

2) Genetic surface glycoproteins (*31-38*):

a) HLA-B8: This histocompatibility antigen is present in 80% of GSE patients, compared to 20% of control populations.

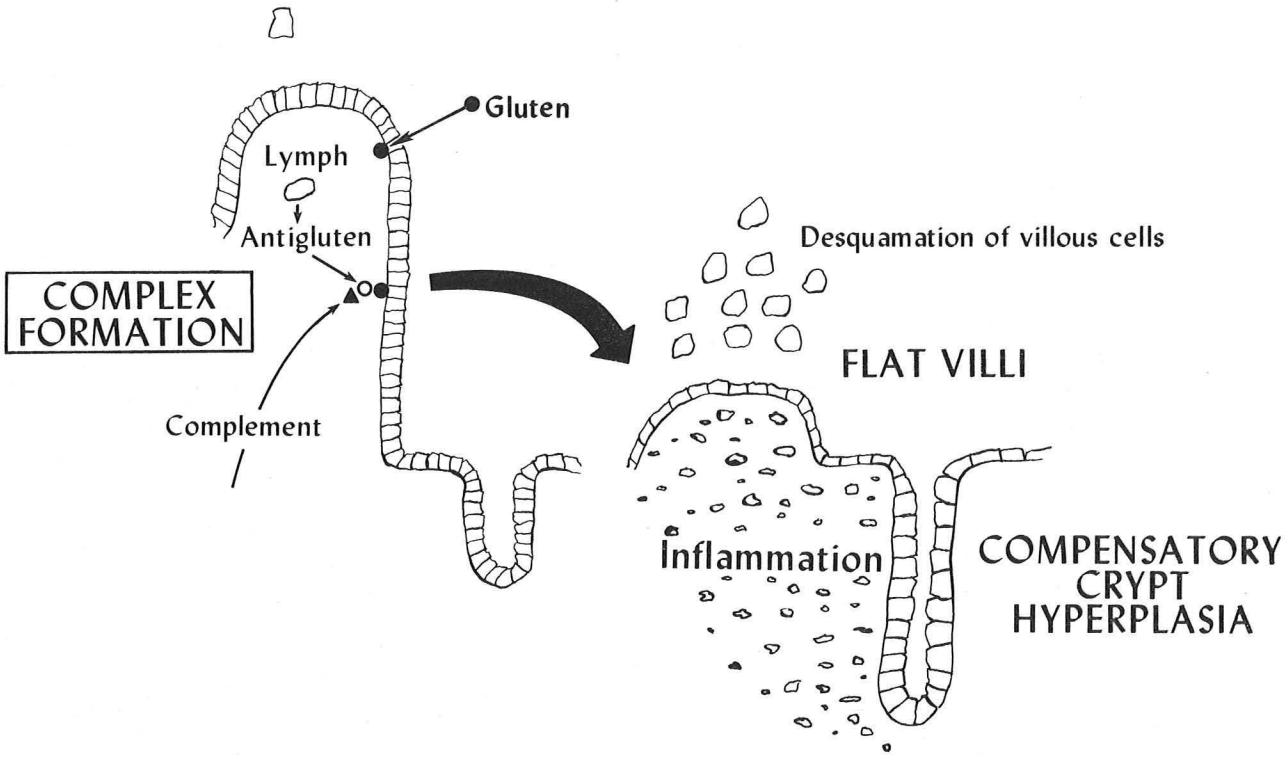
b) HLA-DW3: This antigen has been found in 27 of 28 GSE patients, compared to only 27 of 73 controls (*34*).

c) "Specific B-cell antigens" (*33*):
B-lymphocyte surface antigen recognized by maternal antisera. Two antisera (B-1 and W-1) reacted with B-lymphocytes from GSE patients. Antiserum B-1 reacted with cells from 13 of 16 GSE patients, while antiserum W-1 reacted with cells from 15 of 16 GSE patients. None of the sera reacted with B-lymphocytes from 37 normal subjects.

Postulated that this antigen may represent the gene product of an abnormal Ir gene, which in turn results in an abnormal immune response to gluten. A second possibility is that B-lymphocyte antigen is a receptor or binding site for gluten, perhaps on the surface of gut epithelial cells.

The authors suggest this antigen might be a diagnostic test for GSE, and even might make jejunal biopsy unnecessary (*3*).

H. Current immunologic-genetic hypothesis for GSE, based mainly on concepts described in Refs. 24, 25, 41 and 47, is presented in the next figure. This model is purposely vague with regard to what class of antibodies (IgA, IgM or IgG) take part in the putative complex, since the articles reviewed under Immunological Reactions (*36-49*) seem to disagree.



Several fundamental defects could underlie this sequence of events:

1) Abnormal binding site for gluten on the surface of gut epithelial cells. This would presumably be composed of some particular gene product. Because of this abnormal binding,

an immunologic response is facilitated. The bound gluten not only induces the immune response, but also provides a target.

2) Abnormal gluten binding site on lymphocytes facilitates immune response.

3) Abnormal immune response gene.

It should be emphasized that this or any other immunologic-genetic model for GSE has not been conclusively established. Some authors seem rather dubious (*37*), although most are enthusiastic about this concept.

A combination of genetic makeup which somehow determines an immunologic response to dietary gluten cannot entirely explain GSE, since identical twins are not always concordant for the disease. Some additional environmental factor, such as nutrition or infection, is probably also required.

VII. *Association Between Celiac Disease (CD) and Other Diseases (50-62):*

A. There is a higher than expected association between CD and several other diseases. The CD may be either latent or overt. Three main mechanisms are probably involved:

1) Common genetic predisposition
2) Circulating immune complexes (perhaps containing gluten peptides)
3) Lymphoreticular dysfunction with decreased immune surveillance

B. The following is a list of these supposed associations. Some are discussed in more detail below.

1) Dermatitis herpetiformis
2) Lymphoma and cancer
3) Recurrent apthous ulcers
4) IgA deficiency
5) Hypogammaglobulinemia
6) Diabetes, Addison's disease, Grave's disease
7) Chronic liver disease
8) Cutaneous vasculitis
9) Fibrosing alveolitis
10) Sjogren's syndrome

11) Polyarteritis, SLE, rheumatoid arthritis

12) Idiopathic pulmonary hemosiderosis

13) Glomerulonephritis

In this list, numbers 1-5 seem fairly well established, while the data on 6-13 are less convincing to weak. It should be recalled, however, that CD may be asymptomatic, and that the absence of malabsorption does not rule out its presence. The lesion was only found in dermatitis herpetiformis after a systematic search for the disease in patients with various skin lesions. If one were to embark on a search for CD in patients with these or other diseases, the sometimes patchy nature of CD and the masking effect of steroids would need to be kept in mind.

The mucosal lesion associated with some of these diseases was not always demonstrated, but was inferred from the fact that a patient had dermatitis herpetiformis.

Not all patients with one of these diseases and a jejunal lesion will respond to a gluten-free diet with improvement in the mucosal disease; however, in some or most patients with these diseases the mucosal lesion responds favorably to a gluten-free diet, hence justifying the designation of GSE.

C. Additional notes about some of the disorders associated with CD:

1) Dermatitis herpetiformis (*3*):

The vesicular skin lesions are characterized by deposition of IgA immunoglobulin, complement and fibrin just below the basement membrane. Also present in areas of skin that do not have a visible lesion. DH responds well to sulphones and sulfonamides (? antibiotic or ? anti-inflammatory effect). No infectious organism has been cultured.

Most if not all patients with DH have a mucosal lesion similar to that in GSE, and the gut lesion responds to gluten exclusion. The jejunal lesion is usually mild, and GI symptoms are usually minimal. Occasionally, the lesion is severe and malabsorption dominates the clinical picture. Dapsone does not improve the gut lesion.

DH and GSE patients have common HLA types - HLA - B8, and surface antigen (*52*). This argues for a common underlying disease mechanism.

It is speculated that IgA skin deposits in DH are composed of gluten-antigluten complexes, which were formed in the gut mucosa. (No proof for this yet.) These complexes fix in the skin because of the presence of skin specific binding sites for gluten

and this initiates the skin lesion.

A gluten-free diet improves the skin lesion in at least some patients with DH.

2) Malignancy (*93-100, 47*):

Deaths Due to Malignancy Among 210 Patients with Celiac Disease (*94*)

	Expected	Observed	P
All malignancies	5	21	< .001
Reticulum cell sarcoma	0.1	13	< .001
Ca esophagus	0.1	2	< .01
Ca pharynx	0.003	2	< .001

In this series of 210 patients (*94*), malignancy was the cause of 21 of 43 deaths.

In addition, there have been 19 cases of an association between either celiac disease or GSE and small bowel adenocarcinoma (*96*). In all but one, the tumor was in the jejunum. This seems a much higher incidence than would be expected in the general population.

The lymphomas that may develop almost always involve the GI tract. They may, in addition, become disseminated.

Several reasons for this striking association have been proposed. Some believe that the association is not as impressive as it seems, because they think that malignancies of the GI tract may produce a celiac-like lesion, and thus that some of these patients did not really have a pre-existing celiac disease or GSE. Most workers do not agree with this concept, and it seems much more likely that celiac disease and GSE are indeed complicated by the development of malignant disease. Some of the evidence for this latter opinion is that: 1) symptoms of celiac disease preceded the diagnosis of lymphoma by a mean of 21 years; symptoms of celiac disease preceded the diagnosis of carcinoma by a mean of 38 years; and 3) some patients who ultimately died of malignancy had earlier had a dramatic response to a gluten-free diet.

There is no convincing evidence that the incidence of lymphoma is reduced in patients who adhere to a gluten-free diet or in those who have a good symptomatic response to this diet (*94*). This

question is not settled, however. Theoretically, a gluten-free diet might help prevent malignancy only if it were adhered to for life.

There are several reasons why patients with GSE or celiac disease might have a tendency to develop malignancy.

a) Decreased immune surveillance. It seems clearly established that these patients often have splenic and lymphoreticular atrophy or hypoplasia (*102-104, 4, 46, 47*). In addition, patients with IgA deficiency may have an increased likelihood of developing GSE or celiac disease.

b) The HLA types that predispose to gluten sensitivity may also predispose to lymphoma (*47*).

c) Lymphoid hyperactivity in the lamina propria, characteristic of celiac disease, may enhance the chance of malignant change.

d) Damaged small bowel mucosa may allow absorption of carcinogens.

Case I (p. 4) presumably had life-long celiac disease, which at age 55 (when celiac disease was diagnosed) was unresponsive to a gluten-free diet, and his disease was complicated by the development of a rare leukemia-lymphoma. His case is unusual in that the malignancy did not involve the gastrointestinal tract. Which of the four predisposing causes of malignancy were involved in this patient are not known. He died before HLA typing was generally available. He did not have ↓ IgA. ? Predisposition by steroids.

3. Recurrent Apthous Ulceration (*57*):

35 consecutive patients with recurrent apthous ulceration were studied. Seven had a flat jejunal biopsy, 28 had a normal biopsy. Thus, 20% incidence of celiac disease. No overt evidence of malabsorption. Response to gluten-free diet was not described.

4. IgA Deficiency:

Appears to predispose to celiac disease (*24, 46*). The clinical and morphological response to a gluten-free diet is generally good *(46)*, indicating that these patients have GSE. However, in one recently reported case (*59*) severe celiac disease was associated with IgA deficiency and was unresponsive to a gluten-free diet (even elemental diet and IVH).

5. Hypogammaglobulinemia (*105-107*):

Such patients may have a celiac lesion indistinguishable from

typical GSE except for absence of plasma cells. The lesion usually does not respond to a gluten-free diet, although some have reported clinical improvement in response to the diet (without repeat biopsy to look for histologic improvement) (*105*).

In one patient (*105*) a celiac lesion with mild malabsorption was unimproved by a gluten-free diet. This patient had a severe deficiency of serum IgG, IgA and IgM. She had scant peripheral lymphoid tissue with only rare plasma cells. Functionally, she rejected a homograph in normal time.

Three cases were studied in Ref. 106. None responded to a gluten-free diet. There was complete absence of fluorescent IgG, IgA and IgM cells in the mucosa of one patient; in the other two, there were no IgA-containing cells, but a few containing IgM and IgG. All three patients had defective immune responses.

Defective local immunoglobulins, which normally may play a protective role, may predispose to mucosal injury in this disorder. Gluten toxicity is apparently not involved.

VIII. *Unresponsive Celiac Disease:*

A. As noted on Page 3, not all patients with malabsorption and a typical mucosal lesion improve significantly on a gluten-free diet. Furthermore, some respond at one point in time, but later do not, in spite of what appears to be strict adherence to the diet. In some such patients, even autopsy has failed to reveal any cause for development of the nonresponsive state (*68B*). The mortality rate is much higher in nonresponders than in responders, at least according to one report (*63*).

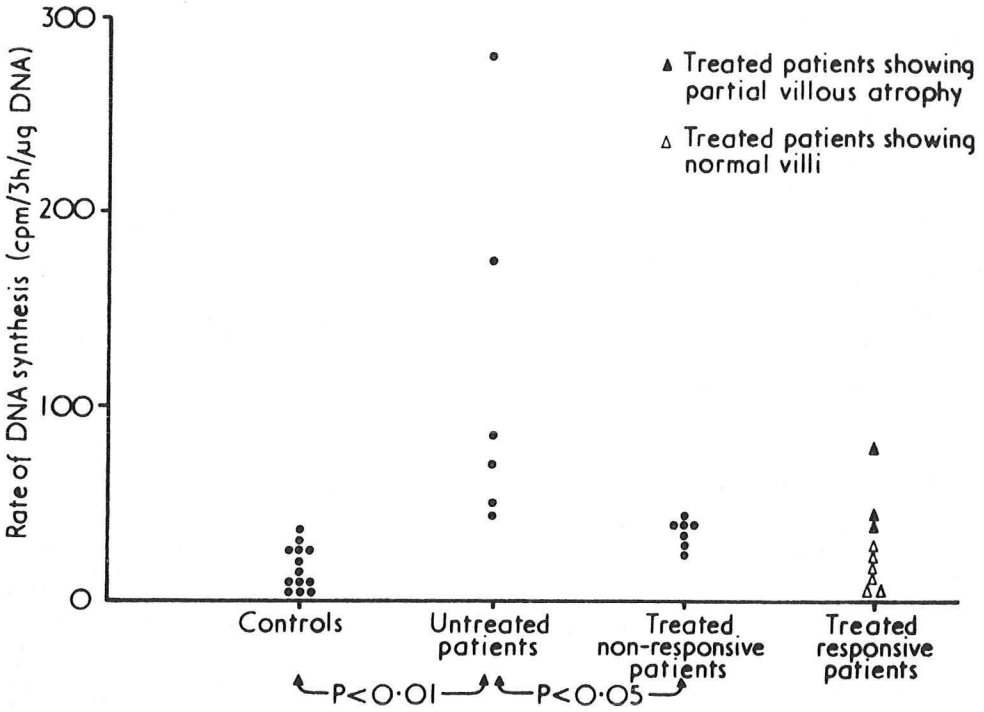
Although almost all workers agree that nonresponsive cases exist, there is a difference of opinion as to its frequency. Some think it is quite rare, whereas others think it occurs in up to 30 per cent of cases (see Ref. 108 for references).

Whether one designates the unresponsive patient "unresponsive celiac disease" (as in this protocol), "refractory sprue", or "unclassified sprue" is a semantic question that has generated some heat, but is of little real importance, provided one defines his terms. In my opinion, however, to insist on improvement by a gluten-free diet before making a diagnosis of "celiac disease" or "celiac sprue" is similar to insisting on a good response to reduction of gastric acidity before diagnosing duodenal ulcer in a patient with a duodenal ulcer.

Although failure to adhere to a gluten-free diet may be the explanation in some or most cases (see below), it is probably not the explanation in all, since some patients fail to respond even on elemental diets or on intravenous hyperalimentation without any food intake (*67, 72*). Some

think that the longer the duration of the disease, the less the chance of a good response (*3*). Those who embrace the immunologic-genetic theory of GSE believe that once the antigen-antibody reaction has been set in motion that it may (in nonresponsive patients) become self-perpetrating (*47*). Others do not think age or apparently duration of disease is the important factor; they believe that almost all failures are due to continued gluten ingestion (*108*). When response to a gluten-free diet takes a very long time (years), one has to raise the question of spontaneous remission.

Recently, it has been suggested that DNA synthesis is not elevated in nonresponders (as it is in patients who will later respond to a gluten-free diet). See next figure (*65*). The reason for the nonresponsive patients' failure to show an enhanced rate of DNA synthesis (a corollary of crypt cell hyperplasia) is unknown. The authors suggest that the reduced DNA synthesis indicates reduced enterocyte production, and that this might explain the failure to regenerate villi.



B. What To Do with Celiac Disease Patient Who Does Not Respond to Gluten-Free Diet

1) Be sure other diseases are excluded (as noted on p. 2).
2) Review biopsy.
3) Assess adherence to gluten-free diet.
4) HLA typing (p. 12).
5) Look for complications of celiac disease - especially malignancy (p. 16) and ulcer-stricture formation (p. 24)
6) Consider steroid therapy (p. 25).

C. Is the biopsy adequate?

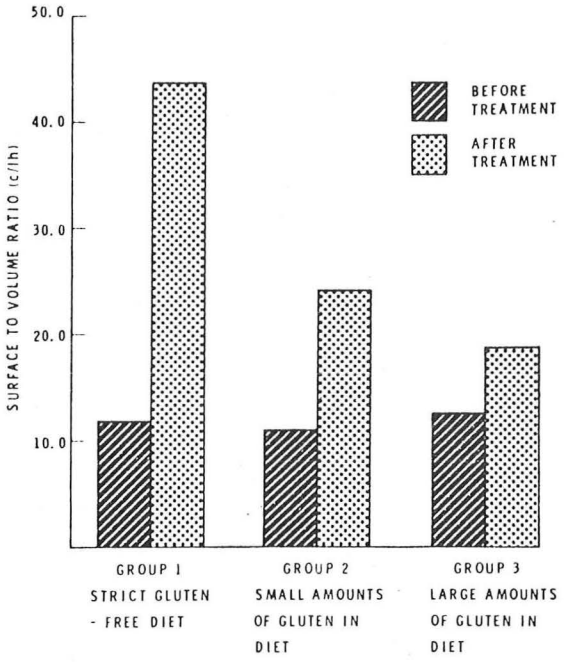
It is very difficult to properly orient specimens, and over-diagnosis of celiac disease is easily done if specimens are not handled properly (68A). It is obviously important to rule out those recognized diseases (p. 2) that can produce a lesion similar to the celiac lesion. Some of these may be recognized from the biopsy itself (i.e., absence of plasma cells in hypogammaglobulinemia), but others must be excluded by separate tests. The biopsy should also be evaluated for evidence of "collagenous sprue" (*66*) and for absence of Paneth cells (*63*), since these histologic features are believed by these authors to portend nonresponse to gluten withdrawal. However, neither "collagenous sprue" nor absence of Paneth cells are confirmed entities, insofar as I am aware.

D. Is the Patient Adhering to a Gluten-Free Diet?

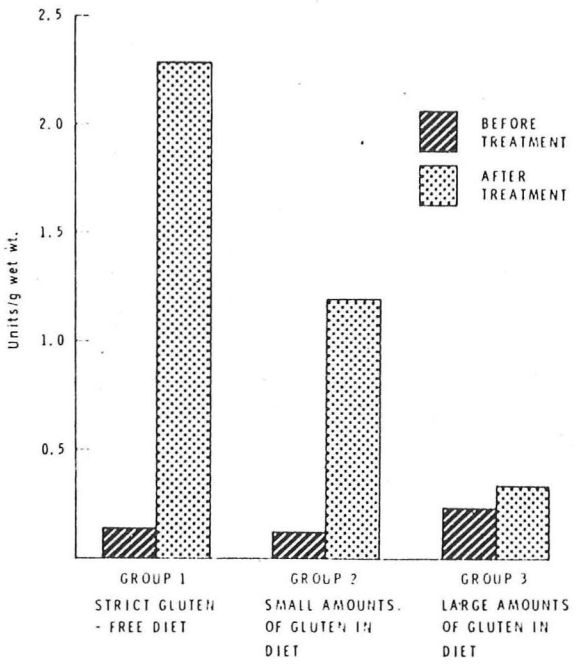
1) The gluten in an average diet is about 7 gm/day. One slice of ordinary white bread contains about 2 gm.

2) Dissanayke, Truelove and Whitehead *(108)* studied 38 patients with celiac disease (defined as in this protocol). In patients who adhered strictly to the diet, all were symptomatically greatly improved, and 90% had "normal or near-normal" jejunal histology (i.e., 10% did not return to near-normal status). In patients judged to be taking only small amounts of gluten in their diet, 80% showed persistent mucosal abnormalities. In patients ingesting more than 0.5 gm/day, there was little or no histologic improvement (in the proximal jejunum), but most were clinically improved, presumably because their dietary gluten was much lower than normal intake of 7 gm/day which resulted in mucosal improvement in lower segments of the small intestine. The next two figures are taken from this article. Obviously, the histologic and enzymatic response for groups of patients is dependent in a major way on dietary gluten intake. Although previous workers have

suggested that young patients with celiac disease show a better recovery with a gluten-free diet than older patients, this study suggests that the degree of recovery is independent of age and is dependent instead on the degree to which the patient adheres to a gluten-free diet.



Surface to Volume Ratio of Jejunal Mucosa



Jejunal Lactase Concentration

3) Baker, Barry and Read (*14*) studied 51 adult celiac disease patients. It is not clear whether or not they required a good clinical response to gluten withdrawal before making this diagnosis. The patients had been on a gluten-free diet for from 4 to 132 months, and they were carefully assessed by retrospective and prospective questionnaires, repeat jejunal biopsy and for serum antibodies to gluten.

Results of Prospective Questionnaire	No. of Patients	No. with Anti-Gluten Antibodies
No gluten in diet	18	3
< 2 gm/day	24	10
> 2 gm/day	9	9

Therefore, 33 of these 51 patients were continuing to ingest gluten, and 9 were ingesting what was considered large amounts (> 2 gm/day). Of the 9 patients ingesting large amounts of gluten, 4 said they were keeping to a completely gluten-free diet. The main source of gluten in these patients was breads, cakes and pies, so it is unlikely that continued gluten ingestion was accidental.

All 24 patients in the group taking some but less than 2 gm/day of gluten claimed that they were on a gluten-free diet. The most common gluten-containing foods in this group were confectioneries, sauces and gravies. Direct questioning at a later date showed that these patients were almost invariably unaware of the fact that these foods contained gluten.

38/51 (75%) of these patients still had an abnormal jejunal mucosa on biopsy, 13 having "subtotal villous atrophy" (a fairly severe lesion), and 25 having "partial villous atrophy" (a milder lesion).

Biopsy Results Correlated with Gluten Ingestion

Biopsy Result	No. Patients	Gluten Intake		
		Nil	< 2 gm	> 2 gm
Normal	13	5	8	0
Partial Villous Atrophy	25	9	16	0
Subtotal Villous Atrophy	13	4	0	9

Thus, 4 of the 13 patients with subtotal villous atrophy did not seem to be ingesting any gluten, whereas the other 9 were ingesting large amounts.

There was a highly significant correlation ($P < .001$) between large gluten intake and persistent subtotal villous atrophy and an even greater correlation when both subtotal villous atrophy and serum gluten antibodies were present. There was also a significant correlation between the presence of gluten antibodies and continuing gluten ingestion.

It is especially interesting to consider the 18 patients whose gluten intake was judged to be nil, since this probably represents the true response to gluten withdrawal.

Jejunal Biopsy	Years on Gluten-Free Diet	Anti-Gluten Antibody
Normal		
Case 8	6	0
" 17	4	0
" 32	7	0
" 33	6	0
" 45	3	0
Partial Villous Atrophy		
Case 13	1.5	0
" 14	10	0
" 18	1.5	0
" 19	7	0
" 26	1.5	32
" 28	1.0	0
" 29	0.5	0
" 40	1.0	0
" 43	3	16
Subtotal Villous Atrophy		
Case 4	2.5	4096
" 27	7	0
" 42	0.4	0
" 50	0.6	0

Thus, of the 4 patients who still had a fairly severe mucosal lesion (subtotal villous atrophy), even though they were apparently really on a gluten-free diet, 2 had been on the diet for less than a year and one had a high titer of anti-gluten antibody. If the latter is an index of continued gluten intake, then only one patient who was on a gluten-free diet for more than a year (case 27) continued to have a fairly severe mucosal lesion. (The results of this excellent study are somewhat

difficult to interpret any further because it is not certain whether or not the authors excluded patients who had not had a good symptomatic response to gluten-free diet, and because the severity of mucosal lesion prior to starting a gluten-free diet was not given.)

4) The general conclusion that one can reach from the two studies just reviewed is that most patients don't adhere to a strict gluten-free diet, and that "nonresponsive celiac disease" is, in many instances, caused by continued gluten ingestion. The use of prospective dietary questionnaires is strongly advised in such patients. Further studies are needed before the anti-gluten antibody test can be used to assess adherence to the diet. As already noted, when the diet must be continued for years before improvement, the question of spontaneous remission needs to be considered.

IX. *Celiac Disease Complicated by Ulceration and Stricture or Ulcerative Ileojejunitis (69-77):*

This disease is usually fulminant, and most patients die within 2-4 years of recognition. Perforation and stricture are more common than hemorrhage. Some patients, like Case II (p. 5), run a more benign and recurrent course (*72, 74, 77*). Malabsorption is present, and the jejunal mucosa reveals a typical celiac lesion. There is no response to a gluten-free diet; indeed, fatal perforation and recurrent stricture may develop during therapy with a gluten-free diet. In some patients, adrenal steroid therapy may apparently result in clinical improvement.

By definition, these patients don't have GSE, and there is disagreement about whether this is a complication of celiac disease or a separate entity; and there is no way to be certain when dealing with most such individual patients. The following argue in favor of this being a complication of GSE.

1) Two-thirds of such patients had proven or probably GSE prior to development of ulceration-stricture (*3*). Some of these had responded favorably to a gluten-free diet (but there is typically no response after the development of ulceration-stricture).

2) At least one such patient had dermatitis herpetiformis (*76*) which strongly suggests that the jejunal lesion is closely related to GSE (see p. 15).

3) In vitro studies in one such patient revealed many characteristics similar to what is observed with GSE mucosa (*72*), even though in vivo there was no response to a gluten-free diet.

4) The HLA type in one case (72) was HLA-B8, which somewhat favors a relation to GSE (see p. 12).

Strober suggests that this is a complication of GSE wherein a supravening immunological process, presumably autoimmune in nature, occurs which is not gluten-dependent (*3*). This concept is supported by the fact that some of these patients develop other manifestations suggesting autoimmunity (vasculitis, for example).

However, our Case II (p. 5) did not have the HLA types that are characteristic of GSE. It seems especially significant that she did not have the surface antigen reported by Mann to be uniformly present in patients with GSE (*33*). However, this finding is unconfirmed, as far as I am aware.

Sometimes adrenal steroids will result in clinical improvement. So far, we have not used them in Case II, mainly for fear of worsening her bone disease. One might argue that steroids should be tried in hope that they will correct her malabsorption and thus arrest the bone disease. We are, instead, trying to prevent further bone disease with oral calcium and vitamin D (25-OHD). If her bone density falls while she is on this treatment, or if her strictures recur so frequently that surgical therapy becomes impractical, adrenal steroids will be started. We have continued the gluten-free diet because she tolerates it well and because of fear (perhaps unfounded) that she might get worse if she eats gluten.

Before accepting a diagnosis of ulcer-stricture as a complication of celiac disease, other causes of small bowel ulceration and stricture must be ruled out (*81-92*). These include:

Regional enteritis

Lymphoma (as the only disease or as a complication of celiac disease)

Adenocarcinoma, and other tumors

Z-E Syndrome

Drugs (including slow K, ? steroids, ? aspirin, ?? Indomethacin)

Infections

X. *Adrenal Steroids in Celiac Disease (78-80):*

Patients with unresponsive celiac disease (such as Case I) and with ulcer-stricture complication of celiac disease (such as Case II) may favorably respond to adrenal steroid therapy. It has been suggested that the beneficial effect of steroids is related to stabilization of lysosomal membranes (*78*). They may also act as anti-inflammatory agents or reduce local hypersensitivity reactions.

It has been demonstrated that rapid histological and enzymatic recovery

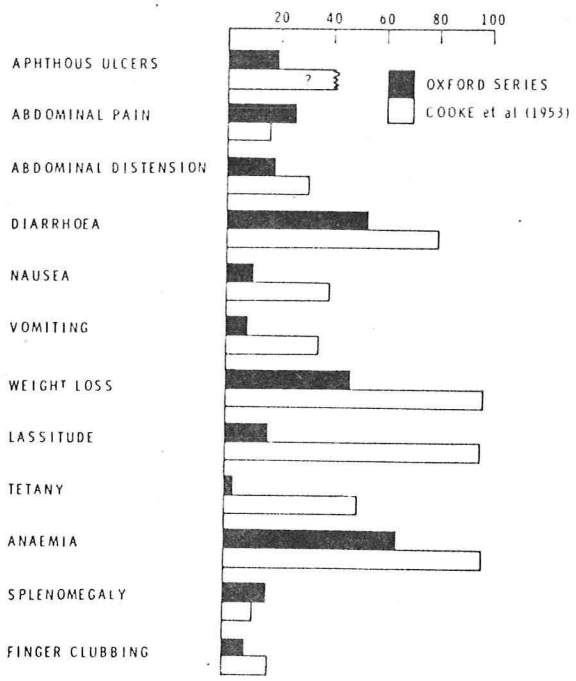
in serial jejunal biopsies occurs during therapy by prednisolone while patients continued to ingest gluten (*78*). The improvement was apparently just as great as with a gluten-free diet. Relapse was rapid when the drug was withdrawn.

Cartisol prevents the harmful effects of gluten on biopsies from patients with GSE in vitro (*79*).

XI. Is Celiac Disease Underdiagnosed in Dallas?

We don't see much of it, whereas in some parts of the U.S. and in the U.K. celiac disease is very common. For example, in Galway County (Ireland) the incidence of the disease is one in 450 to one in 300 births (*109*).

Most likely, the variable incidence of celiac disease is related to genetic factors. However, it should also be pointed out that at the present time celiac disease presents more often with non-GI symptoms (especially anemia) than with symptoms usually suggestive of malabsorption. This is shown in the next figure, taken from Reference 108. Although not shown in this figure, celiac disease may also present as osteomalacia and osteoporosis.



XII. A History of Celiac Disease - The Major Events:

1888 - First description. Gee, S.: On the coeliac Affection. St. Barts. Hosp. Reports 24:17, 1880. ". . . if the patient can be cured at all, it will be by means of diet."

1908 - Suggestion of starch intolerance. Herter, C.A., on Infantilism from Chronic Intestinal Infection, New York, The MacMillan Company.

1940 - 1950 Restriction of cereal grains recommended, but this diet was not proven helpful. Haas, S. U. and Haas, M. P.: Diagnosis and treatment of celiac disease. Postgraduate Medicine 7:239, 1950. "No food may be ingested that contains an appreciable amount of carbohydrates other than that found in fruits and to a lesser degree in vegetables and in milk. The basis of the diet is ripe bananas. Any cereal grain is strictly and absolutely forbidden."

These ideas (Herter, and Haas and Haas) probably set the stage for the next and most important clinical observation.

1950 - 1953 Proof that wheat was harmful and that the harmful effect was wheat protein (gluten), not starch. Dicke, W. K.: Coelakie. Doctoral Thesis, University of Utrecht, 1950; and van de Kamer, J. H., Weijers, H. A. and Dicke, W. K.: An investigation into the injurious constituents of wheat in connection with their action on patients with coeliac disease. Acta Paediat. 42:223, 1953.

1952 - First use of gluten-free diet in adults. McIver, C.: Gluten-free diet in idiopathic steatorrhea. Report of a Case. Lancet 2: 1112, 1952.

1954 - Mucosal lesion demonstrated (tissue obtained at laparotomy). Paulley, S. W.: Observations on the aetiology of idiopathic steatorrhea. Brit. Med. J. 2:1318, 1954. Paulley did these studies in order to look for inflammation which he suspected because of psychosomatic similarities between patients with celiac disease and those with regional enteritis and ulcerative colitis. In retrospect, this seems like doing the right thing for the wrong reasons.

1956 - 1957 Development of a per oral small bowel biopsy technique. Shiner, M.: Duodenal biopsy. Lancet 1:17, 1956; and Crosby, W. H.: Intraluminal biopsy of the small intestine. Am. J. Dig. Dis. 2: 236, 1957.

1966 - Association with dermatitis herpetiformis. This led to a broader concept of the disease. Apparently resulted from a systematic search of a variety of skin diseases for enteric pathology. Marks, J., Shuster, S. and Watson, A. J.: Small bowel changes in dermatitis herpetiformis. Lancet 2:1280, 1966.

1972 - HLA Associations
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Stokes, P. L., Asquith, P., Holmes, G.K.T., McKenzie, P. and Cooke, W. T. Histocompatibility (HLA) antigens associated with adult

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1974 - (If confirmed.) In vitro model, which appears to be revealing important insight into the pathogenesis of celiac disease. Falchuck, Z. M., Gebhard, R. G., et al. Ref. 25.

Oct. 10,- The completion of this protocol.
1977

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