Ann. Rev. Nutr. 1985. 5:241–66

CELIAC DISEASE

S. G. Cole and M. F. Kagnoff

Laboratory of Mucosal Immunology, Department of Medicine, University of California, San Diego, La Jolla, California 92093

CONTENTS

INTRODUCTION

Celiac disease, also known as gluten-sensitive enteropathy, celiac sprue, or nontropical sprue, is a disease in humans that is characterized by damage to the small intestinal mucosa and malabsorption. Symptoms most commonly appear

0199-9885/85/0715-0241$02.00

during the first three years of life after the introduction of cereals into the diet, with a second peak incidence occurring during the third decade (46). Clinical manifestations predominantly reflect the consequences of malabsorption.

This illness was noted as early as the second century AD and, in the late 19th century, an association of symptoms with the ingestion of farinaceous (flour-containing) foods was described (59). However, it was not until Dicke et al (38, 185) noted a decline in celiac disease in Holland during the grain-deprived years of World War II that the clear association between celiac disease and the ingestion of wheat was established.

CHEMISTRY AND GENETICS OF GRAIN PROTEINS

Celiac disease is activated when a susceptible host ingests proteins derived from wheat, rye, barley, and possibly oats. It is the alcohol-soluble gliadin fraction of wheat gluten and similar alcohol-soluble proteins in the other grains (termed prolamins) that lead to the intestinal damage.

Cereal grains belong to the grass family (Gramineae). It is interesting that grains other than wheat that activate celiac disease (e.g. rye and barley) bear a close taxonomic relationship to wheat (Figure 1). Oats, which in large quantities appear to activate disease are further removed from wheat, rye, and barley. Grains such as rice and maize that do not appear to activate disease are still further separated in their evolution from primitive grasses (82, 84, 87).

Common bread wheats *(Triticum aestivum)* have developed relatively recently in evolution (i.e. the last 10,000 years). They have a hexaploid genome (i.e. genome content AABBDD). Durum wheat, commonly used in the production of pasta, is tetraploid (genome content AABB), whereas rye and barley are diploid (82). Gliadin gene clusters are present on chromosomes of homologous groups 1 and 6 (58). Because gliadin proteins are coded for on multiple chromosomes (83, 85, 86), the breeding of wheat varieties devoid of disease-activating properties (87) thus far has not been successful (29).

Gluten is a major component of the wheat endosperm and serves as an important source of nitrogen for the germinating wheat embryo (82, 84). In addition, its elastic properties are important in the production of bread. Although both gliadins and glutenins are major protein components of gluten, only the gliadins have been clearly demonstrated to activate disease. In rye, barley, and oats, the alcohol-soluble proteins that appear to activate disease are termed secalins, hordeins, and avenins respectively.

Gliadins are single polypeptide chains that range in molecular weight from 30,000 to 75,000. They have a low charge (84) and a remarkably high glutamine and proline content (32–56 glutamine and 15–30 proline residues per 100 amino acid residues). Gliadin from a single variety of wheat, when examined by two-dimensional gel electrophoresis, can be shown to contain 40

Figure 1 Taxonomic relationships of major cereal grains (from Kasarda, D. D., et al. 1978. See Ref. 117).

or more different, but closely related components (84). Using starch or polyacrylamide gel electrophoresis in aluminum lactate buffer at pH 3.2, gliadins have been divided into four major electrophoretic fractions: alpha (α)-gliadins, beta (β)-gliadins, gamma (γ)-gliadins, and omega (ω)-gliadins (84, 191). Each fraction, in turn, contains several subcomponents (e.g. β_1-, β_2-, β_3-gliadins; γ_1-, γ_2-, γ_3-gliadins; ω_1-, ω_2-, ω_3-, and ω_4-gliadins) (79). Gliadins of the α, β, and γ_1 fraction usually share a similar amino acid composition and NH_2-terminal sequence (i.e. α-type sequence) (9, 81, 82, 84). Most γ_2, γ_3, and ω-gliadins differ markedly from the α-type sequence in their NH_2-terminal sequence and amino acid composition (i.e. γ-type sequence) (15, 19, 158, 159).

A-gliadin (18, 81) is a major α-gliadin fraction in certain varieties of wheat that is encoded on chromosome 6A and is known to activate celiac disease (48, 69, 82). Recently, the complete primary amino acid sequence of A-gliadin was determined from amino acid sequencing (88) and other α- and γ-gliadin sequences have been deduced from sequencing of cDNA clones (15, 88, 140). Such new information may allow more rapid resolution of the key amino acid sequences in wheat gliadins that are responsible for disease activation.

Gliadin that has been subjected to complete hydrolysis does not activate celiac disease in susceptible individuals. Nonetheless, considerable uncertainty still surrounds the issue of which fractions of wheat gliadin are capable of activating disease. Early reports suggested that only α-gliadins could do this (92). Later studies suggested that β- and perhaps γ- but not ω-gliadins also might activate disease (76). Because ω-gliadins have the highest content of glutamine and proline, the high content of those amino acids alone was not considered to be the determining factor in disease activation. Recent studies suggesting that all gluten fractions might activate disease (28, 73, 75) render this issue once again controversial, particularly since those findings have not been confirmed by others (95).

Controversy over which fractions of gliadin activate celiac disease may stem in part from (*a*) the use in different studies of gliadin preparations contaminated by other impurities (*b*) extrapolation of data from in vitro systems to in vivo disease, (*c*) differences in the time span after gliadin challenge at which biopsies are obtained, (*d*) different clinical and laboratory endpoints used to interpret in vivo challenge studies, and (*e*) the study of patients with a heterogeneous spectrum of susceptibility to gliadin challenge. With the exception of α-gliadins, definition of which wheat gliadin fractions can activate celiac disease appears to remain an open question.

EPIDEMIOLOGY OF CELIAC DISEASE

The reported incidence and prevalence rates for celiac disease in specific geographic areas increased after 1960, paralleling the widespread use of small intestinal mucosal biopsy in general clinical practice (17, 167). Nonetheless,

even now precise epidemiologic data on celiac disease are difficult to obtain because asymptomatic disease makes ascertainment of true prevalence rates problematic and gluten rechallenge is not commonly used to exclude transient gluten intolerance.

Celiac disease appears to be most common in Ireland (122, 172) and Northern Europe (5, 66, 67, 143, 145, 160, 178, 186). It has been reported also in other geographic regions including parts of India and West Pakistan (124, 162), the Middle East (2), and Cuba (139). It has been speculated that the reliance of the Irish on the potato, rather than wheat, as a major food staple may have protected this genetically susceptible population from celiac disease until the widespread introduction of wheat into the diet (172).

GENETICS

Family and Twin Studies

The occurrence of asymptomatic celiac disease among first-degree relatives of celiac disease patients may not be as great as the 5–10% initially quoted (44, 47, 106). Thus, when all 100 first-degree relatives of 32 Swedish patients were studied (166), only two individuals had convincing celiac disease. Further, in Cuba, when 85% of relatives of patients with celiac disease underwent biopsy, only 4.3% (3 individuals) had disease (146) and Ellis reported celiac disease in no more than 4.8% of relatives from 101 families (45).

Twenty-four pairs of identical twins with celiac disease have been described (98, 104, 138, 155) of which 18 (75%) were concordant. However, not all of those twin pairs were proven to be monozygous and in some the diagnosis of celiac disease was not unequivocally documented (155). Nonetheless, it is clear there are well-documented cases of discordance for celiac disease among monozygotic twins. Assuming such twins ingest similar dietary grains, this discordance suggests the possible importance of other environmental factors in the expression of this disease.

Genetic Markers in Celiac Disease

HLA MARKERS HLA serologic specificities encoded by class I major histocompatibility (MHC) genes (HLA-A, HLA-B, and HLA-C locus) and class II MHC genes [DQ, (DC, DS) and DR locus] on chromosome 6 have been studied in celiac disease over the past decade. The class I specificity HLA-B8 and the class II specificity HLA-DR3 are found in as many as 60 to 90% of celiac disease patients, depending on the geographic origin of the patients studied (1, 23, 37, 43, 50, 118, 138, 173). HLA-DR7 in association with HLA-DR3 was increased in celiac disease in many geographic regions, but not in Ireland or Holland (113, 132), although further investigation has revealed an increased frequency of HLA-DR3/DR7 in celiac disease patients in Holland (S. Pena,

personal communication). In a recent study, all 60 celiac disease patients had the DC locus marker DC3 (now termed DQw2) compared to 33% of controls (180). However, whether or not HLA-DQw2 has a greater association with celiac disease than the HLA-DR3 and HLA-DR7 specificities will require further study in that only one of the 60 celiac disease patients in that initial report (180) lacked HLA-DR3 and HLA-DR7. The DP (SB) locus (class II MHC genes) has not yet been evaluated.

Recent studies of DR and DQ restriction fragment length polymorphisms and studies of class II cell surface molecules reveal greater heterogeneity among HLA specificities than appreciated by serologic testing (32, 125). Thus, future studies may reveal a class II MHC haplotype(s) more closely associated with celiac disease than has been reported thus far. Finally, the observation that only 28% of siblings who share both HLA haplotypes with a propositus have celiac disease (118, 138) supports the likelihood that additional genetic loci and/or environmental factors are important in the pathogenesis of celiac disease.

NON-HLA GENETIC MARKERS The observation that the majority of HLA identical siblings are discordant for celiac disease (118, 138) led to a search for other genetic regions and markers associated with disease. In this regard, alloantigens on B cells that did not appear to be linked to HLA genes were present in as many as 60% of celiac disease patients but absent in most controls (108, 133, 134). However, further study suggests those alloantigens may, in fact, be HLA-D locus gene products (S. Pena, personal communication). More recent studies suggest a role for genes coding for immunoglobulin heavy chain allotype markers or closely linked genes in the pathogenesis of this disease (77, 80, 188). Allotype markers on the human IgG heavy chain are termed Gm markers, and represent inherited differences between individuals in the amino acid composition of the chromosome 14–encoded, heavy chain constant region.

Gm markers are inherited in groups known as haplotypes. The haplotypes inherited from both parents comprise an individual's Gm phenotype. Recently, the IgG2 allotype marker known as G2m(n), was associated with the persistence of anti-gliadin antibody in celiac disease patients maintained on a gluten-free diet (188). Although there was no association between Gm phenotypes and celiac disease, studies have suggested that the Gm phenotype termed Gm(f;n;b) may be a predisposing factor to celiac disease among HLA-B8 and -DR3 negative individuals (80) or among males (26). It is clear, however, that greater numbers of patients need to be studied before definite conclusions are drawn.

ROLE OF THE IMMUNE SYSTEM IN CELIAC DISEASE

Humoral Immunity

Recent studies in mice provided important new insights into the regulation of B-cell and T-cell responses to wheat gliadins (77, 79, 181). T-cell-dependent

antibody responses to A-gliadin in mice are governed both by genes that map to the I-A locus of the murine H-2 major histocompatibility complex on chromosome 17 (i.e. a class II gene locus) (181) and by genes that map to the immunoglobulin heavy chain locus on chromosome 12 (77). In addition, studies of T-cell proliferative responses to peptide fragments of the A-gliadin molecule indicate that selected regions of the molecule are key in the activation of T helper cell responses to intact A-gliadin (79).

Serum antibodies to whole gluten and the various electrophoretic fractions of gliadin can be detected by radioimmunoassay in a majority of celiac disease patients with active (27, 47) or inactive (101) disease. Note, however, that caution must be applied to the interpretation of many earlier studies of anti-gliadin antibody in celiac disease inasmuch as nonpurified gliadin preparations frequently were used in antibody detection systems. This makes it difficult to be certain whether the reported antibodies were directed against epitopes on gliadin or against contaminants (e.g. wheat albumins or globulins) in the gliadin preparations.

Recent studies with highly purified gliadin preparations indicate that IgG and to a lesser extent IgA anti-gliadin antibody can persist for long periods (up to 20 years) in more than 70% of clinically asymptomatic patients maintained on a "gluten-free diet" (188). The IgG anti-gliadin antibody may be directed against any one or as many as all four (α, β, γ, ω) of the major electrophoretic fractions of gliadin (101). Such antibody does not appear to be directed to self-determinants (i.e. autoimmune) because flare-ups of celiac disease in patients having anti-gliadin antibody requires, in addition, the dietary ingestion of gliadin or other appropriate grain proteins.

If IgG anti-gliadin antibody is involved in the pathogenesis of celiac disease, it likely plays a role after the ingestion of gliadin. This may occur via immune complex formation. Alternatively, it may occur via an antibody-dependent cell-mediated cytotoxic reaction. In such a reaction, anti-gliadin antibody would recognize and bind to a peptide of gliadin on the surface of an intestinal mucosal structure. The mucosal structure on which the gliadin peptide and anti-gliadin antibody are present could then serve as a target for immune injury by killer (K) lymphocytes that recognize the Fc portion of the anti-gliadin antibody. In support of this notion, lymphocytes and plasma cells producing IgG antibody that can participate in such reactions are markedly increased in the lamina propria of celiac disease during disease activity (13, 150) and organ culture studies demonstrate increased local production of anti-gliadin antibody in celiac small intestinal mucosa after gliadin challenge (51, 150).

The importance of antibody to gliadin in patients with celiac disease has been a subject of debate since serum from such patients also may contain antibodies against proteins in other food substances such as milk, eggs, and soya (62). Thus, antibodies to those dietary proteins and to gliadin may be a consequence of increased permeability of the damaged intestinal mucosa in celiac disease. In

this regard, antibodies to food proteins including gliadin are found also in approximately 15% of Crohn's disease patients in whom the small intestinal mucosa is disrupted (189). Determination of the significance of serum anti-gliadin antibodies and of anti-reticulin antibodies in celiac disease patients (169) will require further study.

Cell-Mediated Immunity

Cell-mediated immune mechanisms may play a role in the pathogenesis of celiac disease, but their importance requires further definition. Mitogenic stimulation of peripheral blood lymphocytes with phytohemagglutinin (PHA) as a test of T-cell function variably has been reported as normal or altered in celiac disease (6). Leukocyte migration assays using α-gliadin or a gluten fraction obtained by peptic-tryptic digestion of whole gluten indicated lymphocytes from the peripheral circulation of celiac disease patients are sensitized to components in those fractions as well as to other food proteins (127, 163). Other studies reported the production by intestinal biopsies of factors that inhibit leukocyte migration when biopsies from celiacs with active but not treated disease were cultured with α-gliadin or Fraser's gluten fraction III (53, 72). The above studies have not always included rigorous specificity or dose-response controls and have not defined the specific role of cell-mediated immune mechanisms in disease pathogenesis.

The majority of intraepithelial lymphocytes (IEL) from celiac disease patients, as well as from normal individuals, bear a cell surface phenotypic marker termed OKT8 (54, 154). The OKT8 marker when present on peripheral blood lymphocytes is generally associated with T cells that mediate suppressor/cytotoxic functions. However, among the IEL population the function and lineage of most of the lymphocytes having the OKT8 marker remain an enigma. It has been found that culturing small intestinal biopsies from patients with celiac disease with gluten results in an increase in the numbers of lymphocytes with the OKT8 marker within the intraepithelial region (54). Those lymphocytes could be responsible for epithelial damage, but such a sequence of events has not been demonstrated.

The intestinal mucosal villous atrophy and crypt hyperplasia reported in mice undergoing a graft-versus-host reaction (123) or during infection with the parasite *Trichinella spiralis* (109) suggest that cell-mediated immune mechanisms can lead to a pattern of intestinal tissue injury similar to that observed in patients with celiac disease. However, those experimental lesions in mice lack the characteristic epithelial cell abnormalities seen in human celiac disease.

THEORIES OF PATHOGENESIS

Epidemiologic, genetic, and immunologic data have spawned several hypotheses regarding the etiopathogenesis of celiac disease. In a geographic hypoth-

esis, Simoons (162) noted a low prevalence of HLA-B8 within long-standing agrarian populations. In addi n, the observations of (*a*) a high HLA-B8 gene frequency in Northern and Central Europe and the Northwest Indian subcontinent, (*b*) the relatively recent (1000 BC) development of wheat cultivation in those areas, and (*c*) the greater prevalence of celiac disease in those areas compared to other parts of the world (124, 162), led to the suggestion that celiac disease and the HLA genes resulting in disease susceptibility may have been selected against (by means of a reproductive disadvantage) in areas with the longest history of farming (162). This hypothesis does not provide the mechanism by which HLA-encoded gene products play a role in the pathogenesis of celiac disease.

Genetic hypotheses in celiac disease are based on data arising from family and twin studies, and from studies showing a strong association between celiac disease and the MHC class II genes that code for the serologic specificities HLA-DR3, HLA-DR7, and HLA-DQw2. Class II MHC genes are thought to play a role in disease pathogenesis through their influence on specific T-cell-regulated immune responses. Early studies demonstrated that leukocytes from individuals having the class I specificity HLA-B8 responded to a greater extent than those from individuals lacking HLA-B8 in mixed leukocyte reactions (129). In addition, lymphocyte transformation in response to wheat antigens was increased in normal individuals having HLA-B8- compared to HLA-B8-negative blood donors (36), although those studies appear controversial (55, 149). Finally, organ culture of small intestinal biopsies from celiac disease patients with HLA-B8 were more susceptible to gluten-induced damage than biopsies from HLA-B8-negative patients (49). The above studies focused on the HLA-B8 class I specificity and class II MHC specificities were not assessed. Thus, it is possible that the reported associations with HLA-B8 may simply reflect the presence of class II MHC genes that are known to exist in strong linkage disequilibrium with HLA-B8.

Several studies have examined non-HLA genetic loci in celiac disease. Genes linked to immunoglobulin heavy chain constant region allotype loci are known to be important in determining antibody specificity (i.e. variable region genes) and in regulating antibody responses. Such genes have been studied extensively in mice (24, 102).

Genes coding for or closely linked to those coding for immunoglobulin heavy chain allotype markers were found to be important in determining the magnitude of the murine T-cell-dependent antibody response to A-gliadin, an α-gliadin component (77) known to activate human celiac disease (48, 69, 82). In humans, the presence of anti-gliadin antibody in celiac disease patients on a gluten-free diet was associated with the presence of the G2m(n) IgG2 heavy chain immunoglobulin allotype marker (188). Whether this association reflects the presence of variable region (V-region) genes that determine antibody specificity or of a regulatory gene that determines the magnitude of the

antibody response to gliadin is not known. Nonetheless, it appears that genes regulating or determining the specificity of the anti-gliadin antibody response may play a primary or contributory role in the pathogenesis of celiac disease.

Based on the discordance of celiac disease among monozygotic twins (98, 104, 138, 155), genetic factors and dietary grains alone do not appear sufficient to explain the pathogenesis of this disease. Thus, additional environmental factors have been considered of possible importance. A-gliadin and a protein coded for by a human enteric adenovirus were recently shown to have a region of amino acid sequence homology (78). That finding raises the possibility that immunologic cross-reactivity between a viral determinant and determinants on gliadin may be important in the pathogenesis of celiac disease (78). Hypotheses based on an interaction between genetic, immunologic, environmental, and dietary factors can accommodate a specific role for HLA class II genes, immunoglobulin heavy chain complex genes, grain proteins, viral products, and immune mechanisms in the pathogenesis of celiac disease. Such hypotheses also can explain the discordance of disease in monozygotic twins.

Other hypotheses have also been put forth to explain the pathogenesis of celiac disease. Carbohydrate side chains on gliadins were postulated to be important in activating celiac disease based on the observation that gliadin treated with a carbohydrase enzyme was nontoxic in a small number of celiac disease patients (136). However, there is little evidence to support this in that A-gliadin, an α-gliadin component known to activate celiac disease, lacks such carbohydrate side chains (82). Similarly, little direct evidence supports the notion that gluten has lectin-like properties or that lectin-like properties of gluten are important in disease pathogenesis (42, 179, 187, 189). Finally, others have considered that there may be an abnormality of intestinal peptidase activity in the small bowel of celiac disease patients (168), but no definite proof exists and the small intestinal mucosa is known to contain multiple peptide hydrolases with overlapping substrate specificity.

In summary, the pathogenesis of celiac disease remains an enigma despite numerous attempts to clarify it. In that celiac disease represents one of the most approachable models of a disease governed by genetic, immunologic, and environmental factors, significant efforts to define precisely its etiopathogenesis should be a high priority. Such definition will likely have significant implications for other diseases that manifest similar genetic, environmental, and immunologic associations.

PATHOLOGY

The small intestinal lesion of celiac disease has a highly characteristic morphology, but it may vary from individual to individual depending on the severity and extent of disease. Moreover, similar histologic changes can be seen in

patients with tropical sprue, soy and milk protein allergy, diffuse intestinal lymphoma, and viral gastroenteritis, to mention a few. In mild disease the lesion may be difficult to identify.

The parameters most helpful in diagnosis are abnormalities, compared to normal, in the villous : crypt ratio and surface epithelial cells, increased infiltration of the surface epithelium with intraepithelial lymphocytes (61, 110), and an increase in plasma cell and lymphocytic infiltration of the lamina propia (144). After gluten challenge, an increase in the number of intraepithelial lymphocytes appears within hours (99), often in the absence of other overt histologic changes. Caution is required in interpreting biopsies from children, as up to 30% of normal children are reported to have shorter villi and longer crypts than normal adults (135).

Recent studies noted increased numbers of mucosal mast cells and intestinal enterochromaffin cells in the mucosa of celiac disease patients (164, 174). The role, if any, those cell types play in disease is unknown.

Electron microscopy demonstrated fewer microvillous intramembrane particles and abnormal tight junctions between epithelial cells in patients with celiac disease (107). These findings may explain, in part, the disaccharidase deficiency and alterations in intestinal permeability in celiac disease. After initiation of a gluten-free diet, morphologic improvement noted by scanning electron microscopy may precede that evident by light microscopy (68).

CLINICAL ASPECTS

The clinical presentation of celiac disease varies markedly among patients depending on age, the duration and extent of disease, and the presence of extraintestinal pathology.

Breast feeding has been reported to delay the onset of symptoms, and also to decrease the risk of ultimately developing celiac disease independent of the time of introduction of gliadin into the diet (7, 8). Such studies may have important implications and thus require further corroboration.

Although celiac disease is thought to remit during the teenage years, the extent of true remission is not certain. The persistent hematologic and morphologic abnormalities (112, 121, 157) documented in some patients suggest that perhaps symptoms, rather than the disease, remit. In other individuals, the original diagnosis may have been erroneous, especially if controlled gluten rechallenge was not done to exclude transient gluten intolerance.

Associated Diseases

Diseases such as insulin-dependent diabetes mellitus (156) (the majority are HLA-DR3) and abnormalities in thyroid function (52) have been well described in association with celiac disease. Immune mechanisms may represent the common link between these conditions and celiac disease.

Psychiatric disorders, including schizophrenia, have been associated with both gluten ingestion and celiac disease. Patients were released faster from locked hospital psychiatric wards if they were placed on a gluten-free diet (40), and peptides with opioid activity were found in pepsin hydrolysates of wheat gluten (194). Although case-control studies showed an increased prevalence of psychiatric disorders in celiac patients (64, 65), matching was not done for nonceliac intestinal disease or other causes of malabsorption.

Case reports of associated disease in other organ systems have been published. Some may be secondary to nutritional deficiency. In many instances, however, further proof is required to show that the associations with celiac disease are more than simply coincidental.

Diagnosis

Mucosal biopsy is the cornerstone for the diagnosis of celiac disease. Its importance is underscored by the reported high false-positive rate of diagnosis when it was not performed (165). However, three issues remain incompletely resolved: (*a*) the correct approach to diagnose transient gluten intolerance, (*b*) the number of mucosal biopsies that should be performed to diagnose celiac disease, and (*c*) the utility of noninvasive screening tests in diagnosis.

TRANSIENT GLUTEN INTOLERANCE This disorder is poorly characterized and lacks strict definition (115). It is best illustrated by citing the sizeable proportion of individuals (7.5–22%) with apparent celiac disease in symptomatic and mucosal remission who fail to relapse when returned to a normal diet (116, 130), with follow-up as long as six years in some cases (116). Although such individuals may have "transient gluten intolerance," celiac disease is considered to be a lifelong condition. An alternative possibility must be considered—either the duration or the intensity of the dietary challenge was not sufficient to provoke recurrence. One view would suggest that "transient gluten intolerance" cannot be diagnosed unless patients are followed for many decades with repeated biopsies. It is known, for example, that patients may be symptom-free despite enteropathy. Others may have had symptoms after gluten ingestion that are unrelated to celiac disease, perhaps secondary to the malabsorption of carbohydrate in wheat flour (4, 35). In some individuals, changes in jejunal mucosal architecture may have been related to a direct toxic effect of gluten (41), perhaps associated with the early introduction of cereals into the diet or the result of a self-limited viral or bacterial gastroenteritis.

ROLE OF SMALL INTESTINAL BIOPSY IN DIAGNOSIS A small intestinal mucosal biopsy at the onset of illness that demonstrates mucosal morphology characteristic of celiac disease, a biopsy while on a gluten-free diet demonstrating improvement, and another biopsy after deliberate gluten challenge clearly

avoids misdiagnosis (47). The question of whether three biopsies and supervised gluten rechallenge are necessary or advisable is a matter of debate. In children, support for such a detailed evaluation seems valid (94, 115) as the corollary of diagnosis is commitment to a lifelong gluten-free diet. In adults, biopsy at the time of initial diagnosis and following a gluten-free diet is warranted. However, the potential benefit of gluten rechallenge and rebiopsy does not seem sufficiently great enough to warrant the additional risk. In practice, patients often conduct their own rechallenge experiment by dietary indiscretion with a return of symptoms. Nonetheless, controlled gluten challenge seems justifiable in adults who are thought to have celiac disease and who have been placed on a gluten-free diet, if they have not had a prior biopsy (94). Finally, endoscopic duodenal biopsy may yield tissue adequate for diagnosis (119), but further data are needed before recommending this technique.

NONINVASIVE SCREENING TESTS Noninvasive screening tests for celiac disease would be of considerable aid in diagnosis, but tests currently available lack sufficient validation to warrant widespread clinical application. The assessment of serum antibodies to defined wheat gliadin fractions could be of potential use in the follow-up of celiac disease and, in conjunction with a clinical response to gluten-free diet, might obviate the need for additional biopsies. However, reports of serum antibodies in celiac disease yield disparate results. This may be due in part to the use of varying screening antigens, often including impure gliadin preparations, and a variety of different assay methods having different specificities and sensitivities (21, 74, 128, 148, 161, 170, 171). In general, such studies showed a greater proportion of false-positive than false-negative results.

Studies of small intestinal mucosal biopsies in organ culture using gluten-containing medium (48, 89) at the time of initial biopsy might obviate the need for additional biopsies in some patients. However, the specialized methodology required makes it unlikely that this technique will be broadly available for clinical diagnosis, and the validity of extrapolating from organ culture to in vivo disease is not clear.

The intestinal mucosa in celiac disease is impermeable to small polar molecules (e.g. monosaccharides) but not to intermediate-sized polar molecules (e.g. disaccharides). In this regard, determination of cellobiose (disaccharide) compared to mannitol (monosaccharide) absorption (31) or lactulose (disaccharide) compared to L-rhamnose (monosaccharide) absorption (120) may be more specific for celiac disease than *d*-xylose absorption (70), but thus far too few cases of nonceliac intestinal mucosal disease have been studied. A ^{51}chromium EDTA absorption test has been used to show that abnormal permeability of the small intestinal mucosa may persist in patients with celiac disease despite clinical and histologic remission (20). As with all

oral tests of absorptive function, variability of gastric emptying, particularly when test substances having different volumes, osmolarity, and temperature are administered, can pose a problem. Furthermore, the specificity for celiac disease of the alterations in mucosal permeability is unknown. It appears that techniques in molecular biology may offer the best hope for an effective screening test in celiac disease.

Complications

ULCERATIVE ILEOJEJUNITIS Patients with ulcerative ileojejunitis frequently have a past history of celiac disease. Fortunately, this serious and poorly understood complication is uncommon. Organ culture studies with gliadin in one patient with ulcerative ileojejunitis documented gliadin sensitivity paralleling that noted in other celiac disease patients (175). One hypothesis envisions that an autoimmune reaction directed to intestinal epithelial cells supersedes celiac disease in patients who develop ulcerative ileojejunitis (175).

MALIGNANCY The prevalence of neoplastic disease is reported to be as high as 10% and involves predominantly older celiac disease patients (33, 153). In a recent study of 235 patients with malignant neoplasms and histologically confirmed celiac disease (176), approximately one half of the malignancies were lymphoma (mainly histiocytic). Of the remaining nonlymphomatous tumors, one half arose from the gastrointestinal tract; small bowel adenocarcinoma and squamous cell carcinoma of the esophagus were the most frequent solid neoplasms. In view of these findings, an argument could be made that the celiac mucosa is a premalignant condition. However, the potential value of screening examinations for the early detection of malignancy, which tests are appropriate, and what parameters define the celiac population at highest risk are not known. Furthermore, villous atrophy sometimes accompanies small bowel malignancy. It is not clear whether this reflects silent celiac disease complicated by cancer or a "carcinomatous enteropathy," although HLA-typing studies have provided some support for the former possibility (126). Although short-term adherence to a gliadin-free diet may not protect patients from the malignant complications of celiac disease, the issue of whether lifetime adherence to a strict gluten-free diet offers protection from malignancy still remains an open question (34, 71).

REFRACTORY OR UNCLASSIFIED SPRUE Patients may respond initially to a gluten-free diet, and subsequently relapse despite maintaining their diet. Such patients may then be refractory to further dietary therapy. Others are refractory to dietary treatment from its inception and, assuming the validity of their gluten-free diet, may not have celiac disease (i.e. unclassified sprue). Collage-

nous sprue (182) has been regarded as a separate entity from celiac disease. However, subepithelial collagen also has been noted in up to 36% of patients with classic celiac disease and in tropical sprue (22). Furthermore, the presence of large amounts of subepithelial collagen does not always preclude a successful response to a gluten-free diet (22).

GLUTEN-FREE DIET AND NUTRITION

Celiac disease, as noted previously, is activated by alcohol-soluble proteins termed prolamins in wheat, rye, barley, and possibly oats. Of note, major grains that do not activate celiac disease also have a significant prolamin content (25). It is still not clear whether all wheat gliadin fractions (α, β, γ, ω) activate disease (28, 75, 76, 92, 95) and which specific peptide sequences in the gliadins are responsible for disease activation. Although significant amino acid sequence homology in the NH_2-terminal amino acid residues exists between the hordeins (prolamins of barley) and ω-type gliadins (158), it is controversial as to whether pure ω-gliadins activate disease (28, 95); to date structural information on the hordeins is incomplete. Recent advances in protein chemistry and molecular biology have elucidated the primary amino acid sequences of several α-gliadins and a γ-gliadin (15, 88, 140). Thus, it should be possible in the near future to determine the specific peptide sequences in wheat gliadins that activate celiac disease.

Maintenance of a strict gluten-free diet is not a simple matter, particularly in the United States where prepared gluten-free foods are less available than in England and Europe. Patients must exercise considerable caution in their food purchases, as gliadins and other disease-activating prolamins are ubiquitous in many processed foods. Wheat starch flour, which lacks gliadins, forms the basis for the preparation of gliadin-free breads. However, it is considered unpalatable by many. Durham wheat (a tetraploid variety) used in the preparation of pasta may be less injurious than the common hexaploid bread wheats (7) and has been suggested as an alternative for some patients. However, Durham wheat can cause mucosal atrophy in celiac disease patients (7), and probably is best avoided.

Significant differences exist with respect to the permissibility of other grains in the diet. Direct studies using *d*-xylose excretion (12) and intestinal biopsy (3) indicate that barley is harmful in the majority of patients. Nevertheless, some medical centers permit its use (12) unless the patient is refractory to wheat and rye withdrawal (25). Oats have $\sim$ 25% of the prolamin content of other cereal grains known to activate celiac disease (12). Their toxicity may be dose dependent (11, 12) and opinions differ regarding whether or not they should be restricted in a gluten-free diet (11, 12, 14, 39).

Corn and rice do not appear to activate celiac disease but the data regarding several other grains is less certain. Buckwheat does not derive from the grass family and usually is permitted in the diet (25). Millet and sorghum appear more closely related to corn and rice and are allowed in most diets (25). However, one variety of millet was noted to induce symptoms in several patients with celiac disease, and was observed to share immunologically cross-reacting determinants with A-gliadin when probed with a highly specific anti-A-gliadin antibody (M. F. Kagnoff, unpublished observations). Whether the sample was contaminated with wheat during milling or is inherently toxic is unknown. Finally, triticale, a hybrid of wheat and rye, is sold in many health food stores. Although it may activate disease in celiacs, it is often not included on lists of prohibited foods (25).

Gluten is not present in distilled spirits. Thus, rye whiskey, scotch whiskey, and other cereal-derived spirits can be consumed. Similarly, brandy and wine which are made from fruit should cause no problem. Beer and ale are produced from barley. Their approval in the diet differs among medical centers (16, 25, 190), although there is a lack of clinical evidence that they activate disease.

Malt made from barley should be avoided. However, the disease-activating proteins are removed in the production of malt extract and malt flavoring. Hydrolyzed vegetable proteins (hvp) are flavor enhancers in processed foods and may be made from soy, wheat, or other cereal proteins. Their source is generally not provided on food labels and therefore foods containing hvp seem best avoided.

A lifelong gluten-free diet is recommended for both symptomatic and asymptomatic celiac disease patients (47, 114). How strict should the diet be? Should it be tailored according to the level of gluten sensitivity of the patient (94, 116), or should it involve total elimination of gluten? Because clinical improvement correlates with the strictness of the diet and because gliadin and related prolamins result in damage to the mucosa, in theory their restriction should be complete for all patients. However, our current ignorance regarding which specific peptides in the prolamins activate celiac disease and our gaps in knowledge regarding the etiopathogenesis of disease allow us to individualize diets somewhat according to symptoms and histology; whether or not this is ideal is not known.

Multivitamin supplements are advised for all celiac disease patients and specific vitamin, mineral, and trace element deficiencies should be corrected. Treatment with iron supplements should be considered in children having evidence of iron deficiency, even in the absence of frank anemia (93).

Drug bioavailability may be altered in celiac disease. Although this was not an important factor in the case of propranolol (147), very few common medications have been studied.

FAILURE TO RESPOND

Following institution of a gluten-free diet clinical improvement begins promptly within days to weeks. If this does not occur, three possibilities should be considered: (*a*) poor dietary compliance, (*b*) presence of an associated disease or complication, and (*c*) erroneous diagnosis.

Dietary treatment may be improperly prescribed or not followed (14, 151). Non-gluten-containing foods also have been suggested to be responsible for persisting symptoms (10, 137). In the enigmatic patient, hospitalization and institution of a supervised dietary plan may be warranted. Should this fail, total parenteral nutrition and reintroduction of one nutrient at a time into the diet can be considered. Refractory disease in four patients was reported to improve when zinc deficiency was corrected (105).

DERMATITIS HERPETIFORMIS

It is now well recognized that the majority of patients with dermatitis herpetiformis (DH) have a celiac disease-like enteropathy (60, 90, 97) although the small intestinal lesion may be patchy and vary in severity from area to area. In some DH patients gluten ingestion may be required to provoke histologic abnormalities. In general, the small bowel mucosal abnormality is morphologically and functionally not as severe as in celiac disease (90). Many patients have no intestinal symptoms and the majority of patients with DH do not manifest severe nutrient malabsorption. As in celiac disease, an increased incidence of lymphoma has been reported in DH (142, 183).

Immunology

IgA deposits with two different patterns have been reported at the dermal-epidermal junction of uninvolved skin in DH. Most common is a granular or speckled pattern; a linear pattern is seen less often (90, 97). When patients were categorized on this basis, partial or total small intestinal villous atrophy was found exclusively in the group of patients with granular deposits (90, 97). In addition, complement components (C3, C5) have been found in association with the IgA deposits in the skin (90).

It is not yet clear whether IgA in the skin of DH patients is directed against specific skin and connective tissue proteins or against dietary proteins that have been deposited in the skin or cross-react with skin proteins (131, 152, 193). Studies of immune complex deposition (63, 195) and clearance (96) in DH thus far have not defined the pathogenesis of this disease.

HLA-B8 and -DR3 are present in 85% or more of DH patients (91, 177). Further, when patients are classified according to the type of IgA deposit in the

skin (linear versus granular) the above HLA markers are associated with DH only in patients with the granular type of IgA deposits (97). As in celiac disease, increased numbers of T cells of the OKT8 phenotype were reported in duodenal epithelium in DH (103), and anti-gliadin antibodies were noted in the circulation (184). Nevertheless, the precise pathogenetic relationship between celiac disease and DH is not known and it is not clear why only a small fraction of celiac patients have clinically evident DH.

Treatment

Therapy with dapsone usually leads to prompt clinical improvement in patients with DH. In addition, the skin lesions slowly respond to treatment with a strict gluten-free diet, which permits a reduction or discontinuation of dapsone over a period of months (56, 57, 141). This phenomenon appears to be unrelated to an increased absorption of dapsone accompanying the improvement in mucosal histology with diet (192). Of interest, improvement in the DH skin lesion on a gluten-free diet was reported even in patients whose small intestinal mucosa appears normal (57). However, jejunal lesions in those individuals may not have been detected by random biopsy because of the aforementioned patchy nature of the intestinal mucosal lesion. Subepidermal IgA in the skin decreases, but often does not disappear in DH patients on a prolonged gluten-free diet (56, 57). Finally, DH patients whose rash has been controlled on a strict gluten-free diet usually experience recurrence of the rash when rechallenged with gluten (100).

CONCLUSIONS

Immunogenetics, protein chemistry, and molecular biology are leading to new understandings of the pathogenesis of celiac disease and likely will lead to new diagnostic modalities and approaches to treatment. Nonetheless, much work remains to be done. Epidemiologic studies are required to determine the specific role viral infection might play in disease pathogenesis. It can be predicted over the next several years that the disease-activating peptides in wheat, rye, and barley will be defined. Further, studies of noninvasive diagnostic tests hold promise for new approaches to diagnosis and for monitoring the effectiveness of therapy. More information is needed on the importance of adherence to a strict gluten-free diet in both symptomatic and asymptomatic patients as regards the long-term morbidity and mortality of this disease. Finally, celiac disease holds forth the challenge of a well-defined disease in which environmental, genetic, immunologic, and nutritional factors interplay to result in human illness. Lessons learned in this disease will likely have broad applications to the understanding of other intestinal diseases and certain HLA-linked autoimmune diseases.

ACKNOWLEDGMENTS

The authors thank Ms. Debby Sagall for preparation of the manuscript. Supported by the National Institutes of Health Grants AM17276 and AM35108.

Literature Cited

1. Albert, E. D., Harms, K., Wank, R., Steinbauer-Rosenthal, I., Scholz, S. 1973. Segregation analysis of HL-A antigens and haplotypes in 50 families of patients with coeliac disease. *Transplant. Proc.* 5:1785–89
2. Al-Hassany, M. 1975. Coeliac disease in Iraqi children. *J. Trop. Pediatr. Environ. Child Health* 21:178–79
3. Anand, B. S., Piris, J., Truelove, S. C. 1978. The role of various cereals in coeliac disease. *Q. J. Med.* 47:101–10
4. Anderson, I. H., Levine, A. S., Levitt, M. D. 1981. Incomplete absorption of the carbohydrate in all-purpose wheat flour. *N. Engl. J. Med.* 304:891–92
5. Arthur, L. J. H., Langman, J. J. S. 1981. Prevalence of coeliac disease in Derby. See Ref. 111, pp. 15–16
6. Ashkenazi, A., Levin, S., Idar, D., Handzel, Z. T., Altman, Y., et al. 1982. Cellular immunity in children with coeliac disease. *Eur. J. Pediatr.* 138:250–53
7. Auricchio, S. 1983. Gluten-sensitive enteropathy and infant nutrition. *J. Pediatr. Gastroenterol. Nutr.* 2(Suppl. 1):S305–S309
8. Auricchio, S., Follo, D., de Ritis, G., Giunta, A., Marzorati, D., et al. 1983. Working hypothesis. Does breast feeding protect against the development of clinical symptoms of celiac disease in children? *J. Pediatr. Gastroenterol. Nutr.* 2:428–33
9. Autran, J. C., Lew, E. J. L., Nimmo, C. C., Kasarda, D. D. 1979. *N* terminal amino acid sequencing of prolamins from wheat and related species. *Nature* 282:527–29
10. Baker, A. L., Rosenberg, I. H. 1978. Refractory sprue: recovery after removal of nongluten dietary proteins. *Ann. Intern. Med.* 89:505–8
11. Baker, P. G. 1974. Oats and coeliac disease. *Br. Med. J.* 4:588–89
12. Baker, P. G., Read, A. E. 1976. Oats and barley toxicity in coeliac patients. *Postgrad. Med. J.* 52:264–68
13. Baklien, K., Brandtzaeg, P., Fausa, O. 1977. Immunoglobulins in jejunal mucosa and serum from patients with adult celiac disease. *Scand. J. Gastroenterol.* 12:149–59
14. Barry, R. E., Henry, C., Read, A. E. 1978. The patients view of a gluten-free diet. See Ref. 117, pp. 487–93
15. Bartels, D., Thompson, R. D. 1983. The characterization of cDNA clones coding for wheat storage proteins. *Nucleic Acids Res.* 11:2961–77
16. Bell, L., Hoffer, M., Hamilton, J. R. 1981. Recommendations for foods of questionable acceptance for patients with celiac disease. *J. Can. Diet. Assoc.* 42:143–58
17. Berg, N. O., Lindberg, T. 1979. Incidence of coeliac disease and transient gluten intolerance in children in a Swedish urban community. *Acta Paediatr. Scand.* 68:397–400
18. Bernardin, J. E., Kasarda, D. D., Mecham, D. K. 1967. Preparation and characterization of α-gliadin. *J. Biol. Chem.* 242:445–50
19. Bietz, J. A., Huebna, F. R., Sanderson, J. E., Wall, J. S. 1977. Wheat gliadin homology revealed through *N*-terminal amino acid sequence analysis. *Cereal Chem.* 54:1070–83
20. Bjarnason, I., Peters, T. J., Veall, N. 1983. A persistent defect in intestinal permeability in coeliac disease demonstrated by a ^{51}Cr-labelled EDTA absorption test. *Lancet* 1:323–25
21. Blazer, S., Naveh, Y., Berant, M., Merzbach, D., Sperber, S. 1984. Serum IgG antibodies to gliadin in children with celiac disease as measured by an immunofluorescence method. *J. Pediatr. Gastroenterol. Nutr.* 3:205–9
22. Bossart, R., Henry, K., Booth, C. C., Doe, W. F. 1975. Subepithelial collagen in intestinal malabsorption. *Gut.* 16:18–22
23. Braun, W. E., ed. 1979. *HLA and Disease: A Comprehensive Review.* Boca Raton: Fla: CRC
24. Brodeur, P. H., Riblet, R. 1984. The immunoglobulin heavy chain variable region (Igh-V) locus in the mouse. I. One hundred Igh-V genes comprise seven families of homologous genes. *Eur. J. Immunol.* 14:922–30
25. Campbell, J. A. 1982. Foods for patients with celiac disease. *CMA J.* 127:963–65
26. Carbonara, A. O., DeMarchi, M., van Loghem, E., Ansaldi, N. 1983. Gm

markers in celiac disease. *Hum. Immunol.* 6:91–95
27. Ciclitira, P. J., Ellis, H. J., Evans, D. J. 1983. A solid phase radioimmunoassay for measurement of circulating antibody titres to wheat gliadin and its subfractions in patients and adult celiac disease. *J. Immunol. Methods* 62:231–39
28. Ciclitira, P. J., Evans, D. J., Fagg, N. L. K., Lennox, E. S., Dowling, R. H. 1984. Clinical testing of gliadin fractions in celiac patients. *Clin. Sci.* 66:357–64
29. Ciclitira, P. J., Hunter, J. O., Lennox, E. S. 1980. Clinical testing of bread made from nullisomic 6A wheats in celiac patients. *Lancet* 2:234–36
30. Deleted in proof
31. Cobden, I., Rothwell, J., Axon, A. T. R. 1980. Intestinal permeability and screening tests for coeliac disease. *Gut* 21:512–18
32. Cohen, D., Cohen, O., Marcadet, A., Massart, C., Lathrop, M., et al. 1984. Class II HLA-DC β-chain DNA restriction fragments differentiate among HLA-DR2 individuals in insulin-dependent diabetes and multiple sclerosis. *Proc. Natl. Acad. Sci. USA* 81:1774–78
33. Cooper, B. T., Holmes, G. K. T., Cooke, W. T. 1982. Lymphoma risk in coeliac disease of later life. *Digestion* 23:89–92
34. Cooper, B. T., Holmes, G. K. T., Ferguson, R., Cooke, W. T. 1980. Celiac disease and malignancy. *Medicine* 59:249–61
35. Cooper, B. T., Holmes, G. K. T., Ferguson, R., Thompson, R. A., Allan, R. N. 1980. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology* 79:801–6
36. Cunningham-Rundles, S., Cunningham-Rundles, C., Pollack, M. S., Good, R. A., Dupont, B. 1978. Response to wheat antigen in in vitro lymphocyte transformation among HLA-B8-positive normal donors. *Transplant. Proc.* 10:977–79
37. DeMarchi, M., Carbonara, A., Ansaldi, N., Santini, B., Barbera, C., et al. 1983. HLA-DR3 and DR7 in coeliac disease: immunogenetic and clinical aspects. *Gut* 24:706–12
38. Dicke, W. K., Weijers, H. A., van de Kamer, J. H. 1953. Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. *Acta Paediatr.* 42:34–42
39. Dissanayake, A. S., Truelove, S. C., Whitehead, R. 1974. Lack of harmful effect of oats on small-intestinal mucosa in coeliac disease. *Br. Med. J.* 4:189–91
40. Dohan, F. C. 1980. Hypothesis: genes and neuroactive peptides from food as cause of schizophrenia. In *Neural Peptides and Neuronal Communication*, ed. E. Costa, M. Trabucchi, pp. 535–48. New York: Raven
41. Doherty, M., Barry, R. E. 1981. Gluten-induced mucosal changes in subjects without overt small-bowel disease. *Lancet* 1:517–20
42. Douglas, A. P. 1976. The binding of a glycopeptide component of wheat gluten to intestinal mucosa of normal and coeliac human subjects. *Clin. Chim. Acta* 73:357–61
43. Ek, J., Albrechtsen, D., Solheim, B. G., Thorsby, E. 1978. Strong association between the HLA-Dw3-related B cell alloantigen-DRw3 and coeliac disease. *Scand. J. Gastroenterol.* 13:229–33
44. Ellis, A. 1981. Coeliac disease: previous family studies. See Ref. 111, pp. 197–200
45. Ellis, A., Evans, A. P., McConnell, R. B., Woodrow, J. C. 1981. Liverpool coeliac family study. See Ref. 111, pp. 265–86
46. Falchuk, Z. M. 1979. Update on gluten-sensitive enteropathy. *Am. J. Med.* 67:1085–96
47. Falchuk, Z. M. 1983. Gluten-sensitive enteropathy. *Clin. Gastroenterol.* 12: 475–94
48. Falchuk, Z. M., Gebhard, R. L., Sessoms, C., Strober, W. 1974. An *in vitro* model of gluten-sensitive enteropathy. Effect of gliadin on intestinal epithelial cells of patients with gluten-sensitive enteropathy in organ culture. *J. Clin. Invest.* 53:487–500
49. Falchuk, Z. M., Nelson, D. L., Katz, A. J., Bernardin, J. E., Kasarda, D. D. 1980. Gluten-sensitive enteropathy. Influence of histocompatibility type on gluten sensitivity in vitro. *J. Clin. Invest.* 66:227–33
50. Falchuk, Z. M., Rogentine, G. N., Strober, W. 1972. Predominance of histocompatibility antigen HL-A8 in patients with gluten-sensitive enteropathy. *J. Clin. Invest.* 51:1602–5
51. Falchuk, Z. M., Strober, W. 1974. Gluten-sensitive enteropathy: synthesis of antigliadin antibody *in vitro*. *Gut* 15:947–52
52. Farthing, M. J. G., Rees, L. H., Edwards, C. R. W., Byfield, P. G. H., Himsworth, R. L. 1982. Thyroid hormones and the regulation of thyroid function in men with celiac disease. *Clin. Endocrinol.* 16:525–35
53. Ferguson, A., MacDonald, T. T., McClure, J. P., Holden, R. J. 1975. Cell-mediated immunity to gliadin within the

small-intestinal mucosa in coeliac disease. *Lancet* 1:895–97
54. Flores, A. F., Winter, H. S., Bhan, A. K. 1982. In vitro model to assess immunoregulatory T lymphocyte subpopulations in gluten sensitive enteropathy (GSE). *Gastroenterology* 82:1058 (Abstr.)
55. Frew, A. J., Bright, S., Shewry, P. R., Munro, A. 1980. Proliferative response of lymphocytes of normal individuals to wheat proteins (gliadins). *Int. Arch. Allergy Appl. Immunol.* 62:162–67
56. Frodin, T., Gotthard, R., Hed, J., Molin, L., Norrby, K., Walan, A. 1981. Gluten-free diet for dermatitis herpetiformis: the long-term effect on cutaneous, immunological and jejunal manifestations. *Acta Derm. Venereol.* 61:405–11
57. Fry, L., Leonard, J. N., Swain, F., Tucker, W. F. G., Haffenden, G., et al. 1982. Long-term follow-up of dermatitis herpetiformis with and without dietary gluten withdrawal. *Br. J. Dermatol.* 107:631–40
58. Garcia-Olmeda, F., Carbonero, P., Jones, B. L. 1982. Chromosomal locations of genes that control wheat endosperm proteins. In *Advances in Cereal Science and Technology,* ed. Y. Pomeranz, pp. 1–47. St. Paul, Minn: American Association of Cereal Chemists
59. Gee, S. 1888. On the coeliac affliction. *St. Bartholomew's Hosp. Rep.* 24:17
60. Gillberg, R., Kastrup, W., Mobacken, H., Stockbrugger, R., Ahren, C. 1982. Endoscopic duodenal biopsy compared with biopsy with the watson capsule from the upper jejunum in patients with dermatitis herpetiformis. *Scand. J. Immunol.* 17:305–8
61. Guix, M., Skinner, J. M., Whitehead, R. 1979. Measuring intraepithelial lymphocytes, surface area, and volume of lamina propria in the jejunal mucosa of coeliac patients. *Gut* 20:275–78
62. Haeney, M. R., Goodwin, B. J. F., Barratt, M. E. J., Mike, N., Asquith, P. 1982. Soya protein antibodies in man: their occurrence and possible relevance in coeliac disease. *J. Clin. Pathol.* 35:319–22
63. Hall, R. P., Lawley, T. J., Heck, J. A., Katz, S. I. 1980. IgA-containing circulating immune complexes in dermatitis herpetiformis, Henoch-Schonlein purpura, systemic lupus erythematosus and other diseases. *Clin. Exp. Immunol.* 40:431–37
64. Hallert, C., Astrom, J. 1982. Psychic disturbances in adult coeliac disease. II. Psychological findings. *Scand. J. Gastroenterol.* 17:21–24
65. Hallert, C., Derefeldt, T. 1982. Psychic disturbances in adult coeliac disease. I. Clinical observations. *Scand. J. Gastroenterol.* 17:17–19
66. Hallert, C., Gotthard, R., Jansson, G., Norrby, K., Walan, A. 1983. Similar prevalence of coeliac disease in children and middle-aged adults in district of Sweden. *Gut* 24:389–91
67. Hallert, C., Gotthard, R., Norrby, K., Walan, A. 1981. On the prevalence of adult coeliac disease in Sweden. *Scand. J. Gastroenterol.* 16:257–61
68. Halter, S. A., Greene, H. L., Helinek, G. 1982. Gluten-sensitive enteropathy: sequence of villous regrowth as viewed by scanning electron microscopy. *Hum. Pathol.* 13:811–18
69. Hekkens, W. T. J. M., Haex, A. J. C., Willighagen, R. G. J. 1970. Some aspects of gliadin fractionation and testing by a histochemical method. In *Coeliac Disease,* ed. C. C. Booth, R. H. Dowling, pp. 11–19. Edinburgh: Churchill Livingston
70. Hill, R., Cutz, E., Cherian, G., Gall, D. G., Hamilton, J. R. 1981. An evaluation of D-xylose absorption measurements in children suspected of having small intestinal disease. *J. Pediatr.* 99:245–47
71. Holmes, G. K. T., Stokes, P. L., Sorahan, T. M., Prior, P., Waterhouse, J. A. H., Cooke, W. T. 1976. Coeliac disease, gluten-free diet, and malignancy. *Gut* 17:612–19
72. Howdle, P. D., Bullen, A. W., Losowsky, M. S. 1982. Cell-mediated immunity to gluten within the small intestinal mucosa in coeliac disease. *Gut* 23:115–22
73. Howdle, P. D., Ciclitira, P. J., Simpson, F. G., Losowsky, M. S. 1984. Are all gliadins toxic in celiac disease? An in vitro study of α, β, γ, and ω gliadins. *Scand. J. Gastroenterol.* 19:41–47
74. Jonsson, J., Schilling, W. 1981. Some characteristics of immunofluorescence tests for antibodies against gluten, using wheat grain sections or gliadin coated sepharose beads. *Acta Pathol. Microbiol. Scand. Sect. C.* 89:253–62
75. Jos, J., Charbonnier, L., Mosse, J., Olives, J. P., de Tand, M.-F., et al. 1982. The toxic fraction of gliadin digests in coeliac disease. Isolation by chromatography on Biogel P-10. *Clin. Chim. Acta* 119:263–74
76. Jos, J., Charbonnier, L., Mougenot, J. F., Mosse, J., Rey, J. 1978. Isolation and characterization of the toxic fraction of wheat gliadin in celiac disease. See Ref. 117, pp. 75–90
77. Kagnoff, M. F. 1982. Two genetic loci control the murine immune response to

A-gliadin, a wheat protein that activates coeliac sprue. *Nature* 296:158–60
78. Kagnoff, M. F., Austin, R. K., Hubert, J. J., Kasarda, D. D. 1984. Possible role for a human adenovirus in the pathogenesis of celiac disease. *J. Exp. Med.* 160:1544–57
79. Kagnoff, M. F., Austin, R. K., Johnson, H. C. L., Bernardin, J. E., Dietler, M. D., Kasarda, D. D. 1982. Celiac sprue: correlation with murine T-cell responses to wheat gliadin components. *J. Immunol.* 129:2693–97
80. Kagnoff, M. F., Weiss, J. B., Brown, R. J., Lee, T., Schanfield, M. S. 1983. Immunoglobulin allotype markers in gluten-sensitive enteropathy. *Lancet* 1:952–53
81. Kasarda, D. D. 1980. Structure and properties of α-gliadins. *Ann. Tech. Agric.* 29:151–73
82. Kasarda, D. D. 1981. Toxic proteins and peptides in celiac disease: relations to cereal genetics. In *Food, Nutrition and Evolution*, ed. D. Walcher, M. Kretchmer, pp. 201–16. New York: Masson
83. Kasarda, D. D., Autran, J. C., Lew, E. J. L., Nimmo, C. C., Shewry, P. R. 1983. *N*-terminal amino acid sequences of ω-gliadins and ω-secalins: implications for the evolution of prolamin genes. *Biochim. Biophys. Acta* 747:138–50
84. Kasarda, D. D., Bernardin, J. E., Nimmo, C. C. 1976. Wheat proteins. In *Advances in Cereal Science and Technology*, ed. Y. Pomeranz, 1:158–236. St. Paul Minn: American Association of Cereal Chemists
85. Kasarda, D. D., Bernardin, J. E., Qualset, C. O. 1976. Relationship of gliadin protein components to chromosomes in hexaploid wheats. *Proc. Natl. Acad. Sci. USA* 73:3646–50
86. Kasarda, D. D., Lafiandra, D., Morris, R., Shewry, P. R. 1984. Genetic relationships of wheat gliadin proteins. *Kulturpflanze* 32:41–60
87. Kasarda, D. D., Nimmo, C. C., Bernardin, J. E. 1974. Structural aspects and genetic relationships of gliadins. In *Proc. 2nd Int. Celiac Symp.*, ed. W. T. J. M. Hekkems, A. S. Pena, pp. 25–36. Leiden: Stenfert Kroese
88. Kasarda, D. D., Okita, T. W., Bernardin, J. E., Baecker, P. A., Nimmo, C. C., et al. 1984. Nucleic acid (cDNA) and amino acid sequences of α-type gliadins from wheat (*Triticum aestivum* L.). *Proc. Natl. Acad. Sci. USA* 81:4712–16
89. Katz, A. J., Falchuk, Z. M. 1978. Definitive diagnosis of gluten-sensitive enteropathy. Use of an in vitro organ culture model. *Gastroenterology* 75:695–700
90. Katz, S. I., Hall, R. P., Lawley, T. J., Strober, W. 1980. Dermatitis herpetiformis: the skin and the gut. *Ann. Intern. Med.* 93:857–74
91. Katz, S. I., Hertz, K. C., Rogentine, N., Strober, W. 1977. HLA-B8 and dermatitis herpetiformis in patients with IgA deposits in skin. *Arch. Dermatol.* 113:155–56
92. Kendall, M. J., Cox, P. S., Schneider, R., Hawkins, C. F. 1972. Gluten subfractions in coeliac disease. *Lancet* 2:1065–67
93. Kosnai, I., Kuitunen, P., Silmes, M. A. 1979. Iron deficiency in children with coeliac disease on treatment with gluten-free diet. *Arch. Dis. Child.* 54:375–78
94. Kumar, P. J., O'Donoghue, D. P., Stenson, K., Dawson, A. M. 1979. Reintroduction of gluten in adults and children with treated coeliac disease. *Gut* 20:743–49
95. Kumar, P. J., Sinclair, T. S., Farthing, M. J. G., Ohannesian, A. D., Jones, D., et al. 1984. Clinical toxicity testing of pure gliadins in coeliac disease. *Gastroenterology* 86:1147 (Abstr.)
96. Lawley, T. J., Hall, R. P., Fauci, A. S., Katz, S. I., Hamburger, M. I., Frank, M. M. 1981. Defective Fc-receptor functions associated with the HLA-B8/DRw3 haplotype. Studies in patients with dermatitis herpetiformis and normal subjects. *N. Engl. J. Med.* 304:185–92
97. Lawley, T. J., Strober, W., Yaoita, H., Katz, S. I. 1980. Small intestinal biopsies and HLA types in dermatitis herpetiformis patients with granular and linear IgA skin deposits. *J. Invest. Dermatol.* 74:9–12
98. Lee, F. I., Prior, J., Murray, S. M. 1982. Celiac disease in monozygotic twin boys. Asynchronous presentation. *Dig. Dis. Sci.* 27:1137–40
99. Leigh, R. J., Marsh, M. N. 1984. Gluten-challenge causes time-related, dose-dependent lymphocyte responses in celiac sprue. *Gastroenterology* 86:1157 (Abstr.)
100. Leonard, J., Haffenden, G., Tucker, W., Unsworth, J., Swain, F., et al. 1983. Gluten challenge in dermatitis herpetiformis. *N. Engl. J. Med.* 308:816–19
101. Levenson, S. D., Austin, R. K., Dietler, M. D., Kasarda, D. D., Kagnoff, M. F. 1985. Specificity of anti-gliadin antibody in celiac disease. *Gastroenterology*. In press
102. Lieberman, R. 1978. Genetics of IgC_H (allotype) locus in the mouse. *Springer Semin. Immunopathol.* 1:7–30
103. Ljunghall, K., Loof, L., Forsum, U. 1982. T lymphocyte subsets in the duodenal epithelium in dermatitis her-

petiformis. *Acta Derm. Venereol.* 62:485–89
104. Lord, C., MacGregor, G. A. 1981. Coeliac disease in identical infants. *Postgrad. Med. J.* 57:658–59
105. Love, A. H. G., Elmes, M., Golden, M. K., McMaster, D. 1978. Zinc deficiency and celiac disease. See Ref. 117, pp. 335–42
106. MacDonald, W. C., Dobbins, W. O., Rubin, C. E. 1968. Studies on the familial nature of celiac sprue using biopsy of the small intestine. *N. Engl. J. Med.* 272:448–56
107. Madara, J. L., Trier, J. S. 1980. Structural abnormalities of jejunal epithelial cell membranes in celiac sprue. *Lab. Invest.* 43:254–61
108. Mann, D. L., Katz, S. I., Nelson, D. L., Abelson, L. D. 1976. Specific B-cell antigens associated with gluten-sensitive enteropathy and dermatitis herpetiformis. *Lancet* 1:110–11
109. Manson-Smith, D. F., Bruce, R. G., Parrott, D. M. V. 1979. Villous atrophy and expulsion of intestinal *Trichinella spiralis* are mediated by T cells. *Cell Immunol.* 47:285–92
110. Marsh, M. N. 1980. Studies of intestinal lymphoid tissue. III. Quantitative analyses of epithelial lymphocytes in the small intestine of human control subjects and of patients with celiac sprue. *Gastroenterology* 79:481–92
111. McConnell, R. B., ed. 1981. *The Genetics of Coeliac Disease*. Lancaster, England: MTP Press
112. McCrae, W. M., Eastwood, M. A., Martin, M. R., Sircus, W. 1975. Neglected coeliac disease. *Lancet* 1:187–90
113. Deleted in proof.
114. McNeish, A. S. 1980. Coeliac disease: duration of gluten-free diet. *Arch. Dis. Child.* 55:110–11
115. McNeish, A. S., Harms, H. K., Rey, J., Shmerling, D. H., Visakorpi, J. K., et al. 1979. The diagnosis of coeliac disease. A commentary on the current practices of members of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN). *Arch. Dis. Child.* 54:783–86
116. McNicholl, B., Egan-Mitchell, B., Fottrell, P. F. 1979. Variability of gluten intolerance in treated childhood coeliac disease. *Gut* 20:126–32
117. McNicholl, B., McCarthy, C. F., Fottrell, P. F., eds. 1978. *Perspectives in Celiac Disease*. Baltimore: University Park Press
118. Mearin, M. L., Biemond, I., Pena, A. S., Polanco, I., Vazquez, C., et al. 1983. HLA-DR phenotypes in Spanish coeliac children: their contribution to the understanding of the genetics of the disease. *Gut* 24:532–37
119. Mee, A. S., Burke, M., Newman, J., Cotton, P. B. 1980. Comparison of capsule and duodenoscopic biopsy specimens in the diagnosis of small intestinal disease. *Gut* 21:A913 (Abstr.)
120. Menzies, I. S., Laker, M. F., Pounder, R., Bull, J., Heyer, S., et al. 1979. Abnormal intestinal permeability to sugars in villous atrophy. *Lancet* 2:1107–9
121. Mortimer, P. E., Stewart, J. S., Norman, A. P., Booth, C. C. 1968. Follow-up study of coeliac disease. *Br. Med. J.* 3:7–9
122. Mylotte, M., Egan-Mitchell, B., McCarthy, C. F., McNicholl, B. 1973. Incidence of coeliac disease in the west of Ireland. *Br. Med. J.* 1:703–5
123. Nield, G. H. 1981. Coeliac disease: a graft-versus-host-like reaction localized to the small bowel wall? *Lancet* 1:811–12
124. Nelson, R., McNeish, A. S., Anderson, C. M. 1973. Coeliac disease in children of Asian immigrants. *Lancet* 1:348–50
125. Nepom, G. T., Nepom, B. S., Antonelli, P., Mickelson, E., Silver, J., et al. 1984. The HLA-DR4 family of haplotypes consists of a series of distinct DR and DS molecules. *J. Exp. Med.* 159:394–404
126. O'Driscoll, B. R. C., Stevens, F. M., O'Gorman, T. A., Finnegan, P., McWeeney, J. J., et al. 1982. HLA type of patients with coeliac disease and malignancy in the west of Ireland. *Gut* 23:662–65
127. O'Farrelly, C., Feighery, C., Greally, J. F., Weir, D. G. 1982. Cellular response to alpha-gliadin in untreated coeliac disease. *Gut* 23:83–87
128. O'Farrelly, C., Kelly, J., Hekkens, W., Bradley, B., Thompson, A., et al. 1983. Gliadin antibody levels: a serological test for coeliac disease. *Br. Med. J.* 286:2007–10
129. Osoba, D., Falk, J. 1978. HLA-B8 phenotype associated with an increased mixed leukocyte reaction. *Immunogenetics* 6:425–32
130. Packer, S. M., Charlton, V., Keeling, J. W., Risdon, R. A., Ogilvie, D., et al. 1978. Gluten challenge in treated coeliac disease. *Arch. Dis. Child.* 53:449–55
131. Pehamberger, H., Gschnait, F., Menzel, J., Holubar, K. 1979. Failure to detect gliadin or gliadin binding sites in the skin of patients with dermatitis herpetiformis: Immunofluorescence, organ culture and autoradiographic studies. *J. Invest. Dermatol.* 73:174–75
132. Pena, A. S., Biemond, I., Rosekrans, P.

C. M., van Leeuwen, A., Schreuder, I., et al. 1981. DR locus-controlled B-cell alloantigens in coeliac disease in the Netherlands. See Ref. 111, pp. 161–68
133. Pena, A. S., Mann, D. L., Hague, N. E., Heck, J. A., van Leeuwen, A., et al. 1978. B-cell alloantigens and the inheritance of coeliac disease. See Ref. 117, pp. 131–33
134. Pena, A. S., Mann, D. L., Hague, N. E., Heck, J. A., van Leeuwen, A., et al. 1978. Genetic basis of gluten-sensitive enteropathy. *Gastroenterology* 75:230–35
135. Penna, F. J., Hill, I. D., Kingston, D., Robertson, K., Slavin, G., Shiner, M. 1981. Jejunal mucosal morphometry in children with and without gut symptoms and in normal adults. *J. Clin. Pathol.* 34:386–92
136. Phelan, J. J., Stevens, F. M., McNicholl, B., Fottrell, P. F., McCarthy, C. F. 1977. Coeliac disease: the abolition of gliadin toxicity by enzymes from *Aspergillus niger*. *Clin. Sci. Mol. Med.* 53:35–43
137. Pock-Steen, O. C. 1973. The role of gluten, milk, and other dietary proteins in chronic or intermittent dyspepsia. *Clin. Allergy* 3:373–83
138. Polanco, I., Biemond, I., van Leeuwen, A., Schreuder, I., Meera Kahn, P., et al. 1981. Gluten-sensitive enteropathy in Spain: Genetic and environmental factors. See Ref. 111, pp. 211–31
139. Rabassa, E. B., Sagaro, E., Fragoso, T., Castaneda, C., Gra, B. 1981. Coeliac disease in Cuban children. *Arch. Dis. Child.* 56:128–31
140. Rafalski, J. A., Scheets, K., Metzler, M., Peterson, D. M., Hedgcoth, C., et al. 1984. Developmentally regulated plant genes: the nucleotide sequence of a wheat gliadin genomic clone. *EMBO J.* 3:1409–15
141. Reunala, T., Blomqvist, K., Tarpila, S., Halme, H., Kangas, K. 1977. Gluten-free diet in dermatitis herpetiformis. I. Clinical response of skin lesions in 81 patients. *Br. J. Dermatol.* 97:473–80
142. Reunala, T., Helin, H., Kuokkanen, K., Hakala, T. 1982. Lymphoma in dermatitis herpetiformis: report on four cases. *Acta Derm. Venereol.* 62:343–46
143. Rifkind, E. A., Logan, R. F. A., Busuttil, A., Gilmour, H., Ferguson, A. 1982. Coeliac disease in Edinburgh and the Lothians 1900–1980. *Scott. Med. J.* 27:256
144. Rosekrans, P. C. M., Meijer, C. J. L. M., Polanco, I., Mearin, M. L., Van der Wal, A. M., et al. 1981. Long-term morphological and immunohistochemical observations on biopsy specimens of small intestine from children with gluten-sensitive enteropathy. *J. Clin. Pathol.* 34:138–44
145. Rossipal, E. 1981. On the incidence of coeliac disease in Austria: A study comprising a nine-year period. See Ref. 111, pp. 23–27
146. Sagaro, E., Jimenez, N. 1981. Family studies of coeliac disease in Cuba. *Arch. Dis. Child.* 56:132–33
147. Sandle, G. I., Ward, A., Rawlins, M. D., Record, C. O. 1982. Propranolol absorption in untreated coeliac disease. *Clin. Sci.* 63:81–85
148. Savilahti, E., Viander, M., Perkkio, M., Vainio, E., Kalimo, K., Reunala, T. 1983. IgA antigliadin antibodies: a marker of mucosal damage in childhood coeliac disease. *Lancet* 1:320–22
149. Scott, H., Brandtzaeg, P., Thorsby, E., Baklien, K., Fausa, O., Ek, J. 1983. Mucosal and systemic immune response patterns in celiac disease. *Ann. Allergy* 51:233–39
150. Scott, H., Ek, J., Baklien, K., Brandtzaeg, P. 1980. Immunoglobulin-producing cells in jejunal mucosa of children with coeliac disease on a gluten-free diet and after gluten challenge. *Scand. J. Gastroenterol.* 15:81–88
151. Scotta, M. S., de Giacomo, C., Maggiore, G., Siena, S., Ugazio, A. G. 1982. Eucharistic problems for celiac patients. *N. Engl. J. Med.* 307:898 (Letter to the Editor)
152. Seah, P. P., Fry, L., Hoffbrand, A. V., Holborow, E. J. 1971. Tissue antibodies in dermatitis herpetiformis and adult coeliac disease. *Lancet* 1:834–36
153. Selby, W. S., Gallagher, N. D. 1979. Malignancy in a 19-year experience of adult celiac disease. *Dig. Dis. Sci.* 24:684–88
154. Selby, W. S., Janossy, G., Bofill, M., Jewell, D. P. 1983. Lymphocyte subpopulations in the human small intestine. The findings in normal mucosa and in the mucosa of patients with adult coeliac disease. *Clin. Exp. Immunol.* 52:219–28
155. Shale, D. J., Johnston, D. G., Hall, R., Robert, D. F. 1982. Coeliac disease in monozygotic twins. *Postgrad. Med. J.* 58:797–98
156. Shanahan, F., McKenna, R., McCarthy, C. F., Drury, M. I. 1982. Coeliac disease and diabetes mellitus: a study of 24 patients with HLA typing. *Q. J. Med.* 51:329–35
157. Sheldon, W. 1969. Prognosis in early adult life of coeliac children treated with a gluten-free diet. *Br. Med. J.* 2:401–4
158. Shewry, P. R., Autran, J.-C., Nimmo,

C. C., Lew, E. J.-L., Kasarda, D. D. 1980. *N*-terminal amino acid sequence homology of storage protein components from barley and a diploid wheat. *Nature* 286:520–22

159. Shewry, P. R., Lew, E. J.-L., Kasarda, D. D. 1981. Structural homology of storage proteins coded by the *Hor-1* locus of barley (*Hordeum vulgare* L.) *Planta* 153:246–53
160. Shmerling, D. H. 1981. Incidence of age distribution of coeliac disease in North-Eastern Switzerland. See Ref. 111, pp. 19–22
161. Signer, E., Burgin-Wolff, A., Berger, R., Birbaumer, A., Just, M. 1979. Antibodies to gliadin as a screening test for coeliac disease. A prospective study. *Helv. Paediatr. Acta* 34:41–52
162. Simoons, F. J. 1981. Celiac disease as a geographic problem. See Ref. 82, pp. 179–99
163. Simpson, F. G., Robertson, A. F., Howdle, P. D., Losowsky, M. S. 1982. Cell-mediated immunity to dietary antigens in coeliac disease. *Scand. J. Gastroenterol.* 17:671–76
164. Sjolund. K., Alumets, J., Berg, N.-O., Hakanson, R., Sundler, F. 1982. Enteropathy of coeliac disease in adults: increased number of enterochromaffin cells in the duodenal mucosa. *Gut* 23:42–48
165. Stenhammar, L. 1981. Transient gastrointestinal disorders during infancy and early childhood. *Acta Paediatr. Scand.* 70:383–87
166. Stenhammar, L., Brandt, A., Wagermark, J. 1982. A family study of coeliac disease. *Acta Paediatr. Scand.* 71:625–28
167. Stenhammar, L., Johansson, C.-G. 1981. The incidence of coeliac disease in children of South-East Sweden. *Acta Paediatr.* 70:379–81
168. Sterchi, E. E., Woodley, J. F. 1978. Peptidases of the human intestinal brush border membrane. See Ref. 117, pp. 437–49
169. Stern, M., Bender, S. W., Gruttner, R., Posselt, H. G., Strobel, S. 1980. Serum antibodies against gliadin and reticulin in a family study of coeliac disease. *Eur. J. Pediatr.* 135:31–36
170. Stern, M., Fischer, K., Gruttner, R. 1979. Immunofluorescent serum gliadin antibodies in children with coeliac disease and various malabsorptive disorders. I. Technique, clinical evaluation and diagnostic use of a gliadin antibody assay using pyruvic aldehyde-treated human red cells. *Eur. J. Pediatr.* 130:155–64
171. Stern, M., Fischer, K., Gruttner, R. 1979. Immunofluorescent serum gliadin antibodies in children with coeliac disease and various malabsorptive disorders. II. Specificity of gliadin antibodies: immunoglobulin classes, immunogenic properties of wheat protein fractions, and pathogenic significance of food antibodies in coeliac disease. *Eur. J. Pediatr.* 130:165–72
172. Stevens, F. M., Egan-Mitchell, B., McCarthy, C. F., McNicholl, B. 1981. Factors in the epidemiology of coeliac disease in West Ireland. See Ref. 111, pp. 7–14
173. Stokes, P. L., Holmes, G. K. T., Asquith, P., Mackintosh, P., Cooke, W. T. 1972. Histocompatibility antigens associated with adult coeliac disease. *Lancet* 2:162–64
174. Strobel, S., Busuttil, A., Ferguson, A. 1983. Human intestinal mucosal mast cells: expanded population in untreated coeliac disease. *Gut* 24:222–27
175. Strober, W., Falchuk, Z. M., Rogentine, G. N., Nelson, D. L., Klaeveman, H. L. 1975. The pathogenesis of gluten-sensitive enteropathy. *Ann. Intern. Med.* 83:242–56
176. Swinson, C. M., Slavin, G., Coles, E. C., Booth, C. C. 1983. Coeliac disease and malignancy. *Lancet* 1:111–15
177. Thune, P., Husby, G., Fausa, O., Gedde-Dahl, D., Baklien, K., et al. 1979. Immunologic and gastrointestinal abnormalities in dermatitis herpetiformis. *Int. J. Dermatol.* 18:136–41
178. Tobiasen, K. 1981. Recent Scandinavian data on the epidemiology of coeliac disease. See Ref. 111, pp. 47–50
179. Torres-Pinedo, R. 1983. State of the art lectins and the intestine. *J. Pediatr. Gastroenterol. Nutr.* 2:588–94
180. Tosi, R., Vismara, D., Tanigaki, N., Ferrara, G. B., Cicimarra, F., et al. 1983. Evidence that celiac disease is primarily associated with a DC locus allelic specificity. *Clin. Immun. Immunopathol.* 28:395–404
181. Trefts, P. E., Kagnoff, M. F. 1981. Gluten-sensitive enteropathy. I. The T-dependent anti-A-gliadin antibody response maps to the murine histocompatibility locus. *J. Immunol.* 126:2249–52
182. Trier, J. S., Falchuk, M., Carey, M. C., Schreiber, D. S. 1978. Celiac sprue and refractory sprue. *Gastroenterology* 75:307–16
183. Tucker, W. F. G., Leonard, J. N., Fry, L. 1983. Increased risk of lymphoma in dermatitis herpetiformis. *J. R. Soc. Med.* 76:95–97
184. Unsworth, D. J., Leonard, J. N., McMinn, R. M. H., Swain, A. F., Holborow, E. J. 1981. Anti-gliadin anti-

bodies and small intestinal mucosal damage in dermatitis herpetiformis. *Br. J. Dermatol.* 105:653–58

185. van de Kamer, J. H., Weijers, H. A., Dicke, W. K. 1953. Coeliac disease. IV. An investigation into the injurious constituents of wheat in connection with the action on patients with coeliac disease. *Acta Paediatr.* 42:223–31
186. van Stirum, J., Baerlocher, K., Fanconi, A., Gugler, E., Tonz, O., Shmerling, D. H. 1982. The incidence of coeliac disease in children in Switzerland. *Helv. Paediatr. Acta* 37:421–30
187. Vasmant, D., Feldmann, G., Fontaine, J.-L. 1982. Ultrastructural localization of concanavalin A surface receptors on brush-border enterocytes in normal children and during coeliac disease. *Pediatr. Res.* 16:441–45
188. Weiser, M. M., Douglas, A. P. 1978. Cell surface glycosyltransferases of the enterocyte in coeliac disease. See Ref. 117, pp. 451–58
189. Weiss, J. B., Austin, R. K., Schanfield, M. S., Kagnoff, M. F. 1983. Gluten-sensitive enteropathy. Immunoglobulin G heavy-chain (Gm) allotypes and the immune response to wheat gliadins. *J. Clin. Invest.* 72:96–101
190. Wood, M. N. 1972. *Gourmet Food on a Wheat-Free Diet.* Springfield, Ill: Thomas
191. Woychik, J. H., Boundy, J. A., Dimler, R. J. 1961. Starch gel electrophoresis of wheat gluten proteins with concentrated urea. *Arch. Biochem. Biophys.* 94:477–82
192. Wright, J. T., Das, A. K. 1980. The absorption of dapsone by patients with dermatitis herpetiformis and coeliac disease. *Clin. Exp. Dermatol.* 5:27–30
193. Yaoita, H., Katz, S. I. 1977. Circulating IgA antibasement membrane zone antibodies in dermatitis herpetiformis. *J. Invest. Dermatol.* 69:558–60
194. Zioudrou, C., Streaty, R. A., Klee, W. A. 1979. Opioid peptides derived from food proteins. The exorphins. *J. Biol. Chem.* 254:2446–49
195. Zone, J. J., Provost, T. T. 1979. IgA immune complexes in dermatitis herpetiformis. *Clin. Res.* 27:539A (Abstr.)