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# What's in a name? A critical review of our understanding of gluten sensitivity

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ONE might be excused (or even forgiven) to ask, in 1997, what is actually meant by the term "coeliac disease".

Over 100 years ago, the problem seemed relatively straightforward for Gee (1). His description was a keenly-observed account of advanced disease but restricted entirely to the domain of the paediatrician: coeliac disease was a disease of children.

During the early decades of this century, it became increasingly apparent that adults with gross steatorrhoea and wasting (or "intestinal insufficiency" as it was then called) could also be suffering from the same condition (2). This supposition was based on the realisation that many patients with steatorrhoea had coeliac-like complaints since early childhood.

The proof of this clinical relationship came with the development of peroral jejunal biopsy techniques which demonstrated that there was a pathogenetic link at mucosal level between children with "coeliac" disease, and adults with "idiopathic" steatorrhoea. Therefore it followed that coeliac disease is a lifelong disorder usually initially manifesting in childhood. So between 1960-1980 a new, but more compact, diagnostic basis for clinically- apparent coeliac disease emerged. This depended on (i) a previously (long) history of fatty diarrhoea and malabsorption (ii) the presence of a severe proximal mucosal lesion an biopsy, and (iii) a response to a gluten-free diet, this latter principle having recently been advanced by the Dutch paediatrician, Willem Dicke (3).

## Coeliac Disease - Its Natural History and Aetiopathogenesis

The ability to relate diagnosis to a specific, and identifiable, form of tissue injury (the flat jejunal biopsy) provided a stable base for some effective correlative research. Thus it was established that prevalence rates were of the order of 1 per 1-2000 population across Northern Europe, and that one might expect to see familial transmission of around 10-20%. Use of some of the new immunoserologic techniques provide additional firm evidence for this familial clustering, indicating that inheritance, and therefore predisposition, is related to specific MHC class II markers in the D-sublocus, namely DQw2 (DQA1.0501: DQB1.0201): approximately 90-95% of all known coeliac patients carry this gene (Figure 1). The field of (molecular) immunogenetics is complicated and we still do not know precisely what mechanism actually sensitizes the individual to gluten. The precise role of DQ2 itself needs clarification, since many 'normal' people with identical DQ2 A and B gene products are not predisposed. This strongly points to other genes which must either modulate the gluten-DQ2 interaction in susceptible individuals, or alternatively, provide a more basic abnormality which becomes active, perhaps, on a 'permissive' DQ2 background, analogous to other related diseases of so -called "autoimmune" type (4).

One of the more recent, fascinating aspects of coeliac disease has been its apparent change in prevalence across Europe since 1980, when coeliac disease was first reported to be 'disappearing' (5). Clearly this cannot have arisen because of widespread or rapid gene mutations and therefore environmental factors must be involved. These, in general, have tended to push the age of diagnosis upwards, that is, away from the toddler period and into childhood, adolescence and young adulthood where diagnostic rates appear to be increasing.

Secondly, the presentational face of coeliac disease has changed quite dramatically. It is clear that the classical features, current c1960-1970, are no longer reliable because many patients may either present with atypical symptoms (Table 1), or with a monosymptomatic form of the disease.

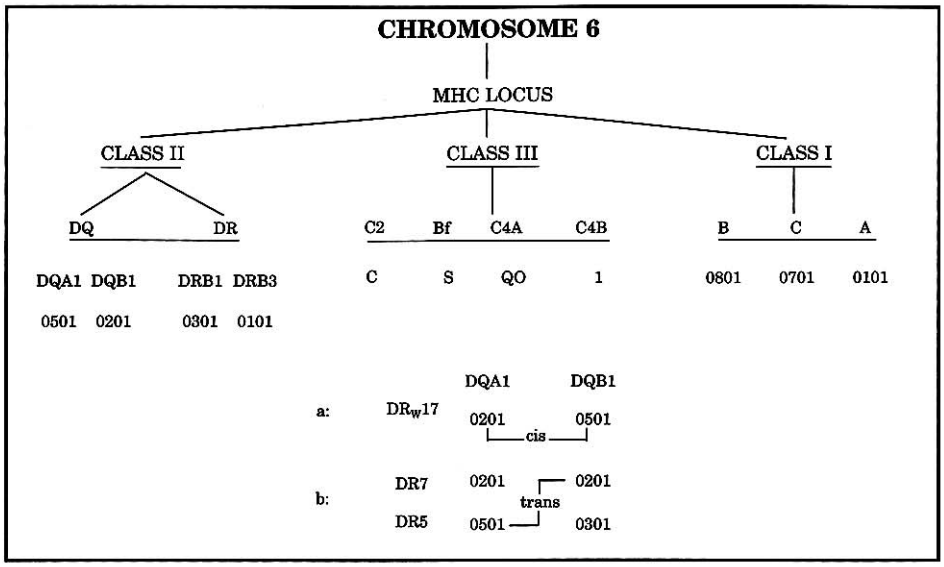


**Figure 1.** *The predisposition to develop gluten sensitivity depends on inheritance of the specific DQ2 haplotype, DQA1.0501; DQB1.0201. The latter can be effectively established either in cis (on the same chromosome) in DR3 (DRw17 individuals) or in trans in DR7/5 heterozygotes.*

More importantly, approximately 50% are virtually asymptomatic (6) or have a compensated-latent form of disease. In other words, the prevalence of compensated-latent disease also appears to be increasing.

In recent years two other factors have influenced diagnosis (i) the endomysial antibody test and (ii) perhaps a wider use of (routine) endoscopic biopsies for either diagnostic or surveillance purposes.

It has been clear, from the outset that endoscopic duodenal biopsies, despite difficulties with size and orientation, provide a highly sensitive screening technique for diagnosis (7). The more frequently biopsies ara taken from any patient coming for 'routine' endoscopy, the greater the diagnostic yield (8). Use of computerised image-analysis to quantitate cellular differences between various forms of 'duodenitis' will improve diagnostic precision (9) and hence avoid diagnostic false-positives which obviously may frustrate the original purpose.

Since its introduction the endomysial antibody has (like peroral jejunal biopsies c 1960) revolutionised our approach to coeliac disease, and contributed to a greater understanding of its natural history (10). This has been most dramatically shown in surveys which point to increased rates of diagnosis both in adult (11) and paediatric (12) populations. Thus, we are beginning to see prevalence rates of 3-4 per 1000 population. This is truly a remarkably increase, but an increase brought about by identifying the large pool of gluten-sensitized individuals in a compensated-latent phase of the disease.

But there are difficulties implicit in serological testing. Many studies have involved selected and hence, biased, populations (e.g. blood donors). Secondly, the failure to substantiate gluten sensitivity by some other independent parameter, means that the findings from these population-based serological screens are uninterpretable. In other words, we must have some other marker of certain diagnosis, other than the method being tested: if not, we are unable to advance our knowledge on

**Table 1.** *Presenting features in gluten sensitivity*

| *Classical Features* | *Atypical Presentations* |
|---|---|
| weakness, fatigue, lethargy | pigmentation, hypotension (?Addison's) |
| weight loss | |
| diarrhoea | rapid weight loss ± diarrhoea |
| abdominal distension | ?diabetes mellitus or hyperthyroidism |
| nausea, vomiting, anorexia | hair loss, and alopecia |
| cramps, tetany | unusual skin rashes |
| skin bleeding | arthropathy, 'rheumatism' (vit D deficiency) |
| oedema | |
| glossitis | arthropathy (mono/poly) (small/large joint inflammation); sacroileitis |
| aphthous ulceration | |
| | peripheral neuropathy |
| | abdominal pain |
| | dental hypoplasia |
| | infertility |
| | growth defect |
| | abnormal 'liver function tests' |
| | obesity |
| | fits and occipital calcification |

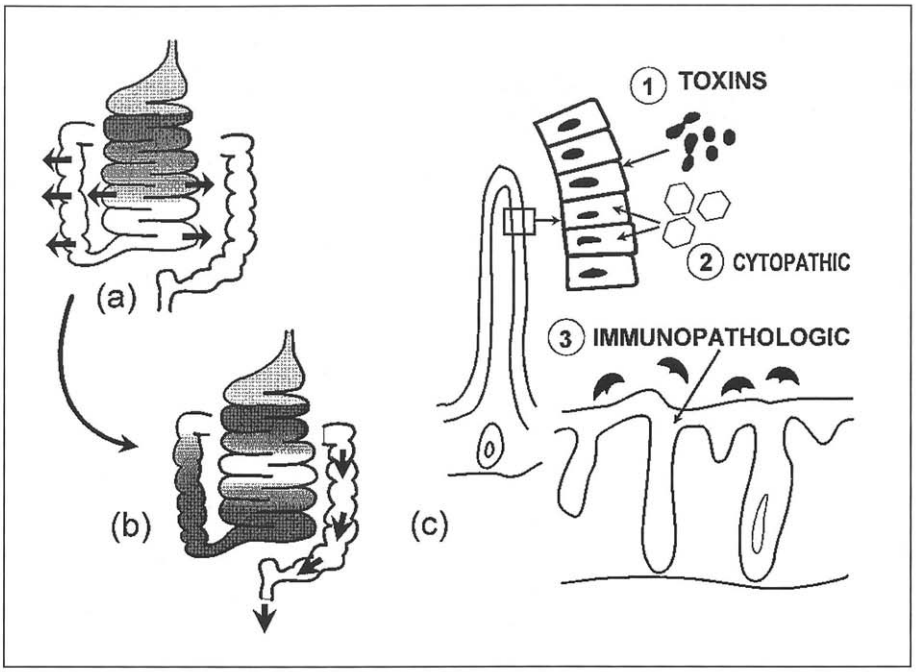


**Figure 2.** *In the compensated-latent phase of gluten-sensitivity (a), the adaptive hypertrophic response of distal ileum and proximal colon performs a 'salvage' duty (arrows) which prevents diarrhoea. This equilibrium is upset when the enterocytes belonging to this compensatory segment are damaged by some additional insult, thereby unmasking the latent gluten sensitivity (b). The most likely insults to these enterocytes (c) will be caused by bacterial toxins or invasion, viral cytopathic effects, or a further immunopathologic effect on intestinal function, such as with a super-added infestation by Giardia trophozoites. It is likely that similar mechanisms unmask compensated-latent "tropical enteropathy" into full-blown symptomatic "tropical sprue" and, possibly, cow's milks protein intolerance in some toddlers.*

a rational basis. That, I feel, is the situation in which we find ourselves at present. More stringent approches in future studies are critically required to assess the real meaning and value of endomysial antibodies-and that also requires use of a substantial body of disease-control patients with equally advanced mucosal lesions ("tropical sprue", milk protein sensitivity, giardiasis, AIDS, drug-induced lesions, and so on). Only by this type of critical approach will reliable, and definitive data, ensue.

## Gluten Sensitivity or Coeliac Disease?

At this point it is necessary to draw together some threads arising from points made above, pertaining to (i) the compensated-latent phase (ii) mucosal pathology and hence (iii) reactivity of sensitised mucosal cells to immunogenic motifs within the prolamins of wheat, rye and barley which results in a mucosal lesion.

**(i) The Compensated Latent state:** The paradox of disappearing classical "coeliac disease", as defined above, and the discovery of large numbers of cases with subclinical, monosymptomatic or atypical disease, warrants further brief discussion.

The problem here is that our techniques facilitate retrieval of proximal mucosal specimens only. We tend to become conditioned to assume that the entire small bowel mucosa is damaged throughout to a similar degree.

That clearly is not so: indeed, perhaps only one-third to one-half of the small bowel reveals major pathology (13,14). This implies that the distal bowel proximal colon do undergo an adaptive hypertrophic response which compensates any defects caused by the proximal segment of diseased bowel. Indeed, there are studies which demonsrate this adaptive, and hence salvage, capacity of distal intestine and proximal colon (15). Thus the degree of damage evident in the proximal small bowel biopsy has no relationship to whether symptoms will be present or not: a severely flattened jejunal biopsy is entirely consistent with a compensated-latent state (16). Neither is symptomatology contingent on the proximal lesion extending further distally, as suggested selsewhere (17): there is no evidence for that view. The appearance of symptoms, at whatever age in life, requires decompensation of the distally adapted bowel, and the most common and likely cause of this is infection. The mechanisms will either be direct cytotoxicity (or invasion); toxin release, or a superimposed enteroptahic lesion (e.g. giardiasis) (18) (Figure 2). Other factors may cause symptoms to appear (Table 2) and thus unmask the compensated-latent phase.

**(ii) Mucosal Pathology-Spectrum of Change:** Recent advances in the realm of mucosal pathology have revealed a spectrum of mucosal changes (19,20) which, on the basis of other experimental approaches (18,21,22,23), are presumed to reflect host-driven T lymphocyte responses at mucosal le-

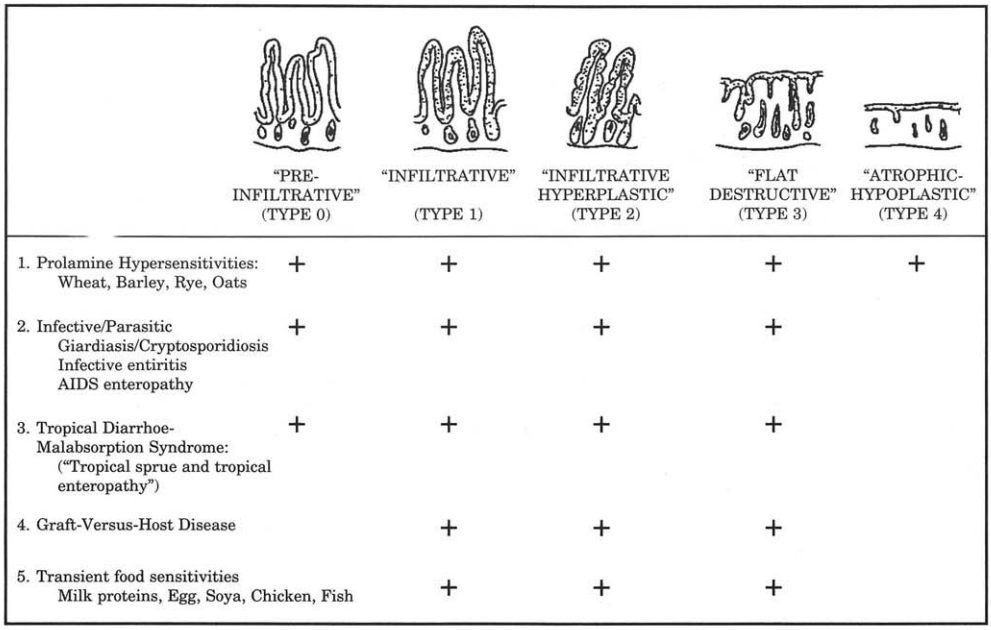


**Figure 3.** *The host driven-mucosal response to presumptive T lymphocyte sensitisation is progressive and stereotyped, irrespective of the inciting environmental antigen (food derived; microbial; parasitic; tissue histocompatibility etc.). The development of a 'flat' mucosa proceeds through earlier phases occasioned by lymphoid infiltration of villous epithelium, followed by crypt enlargement (a specific T-dependent architectural event) and crypt infiltration. Lymphoma development, however, is exclusive to gluten sensitivity; secondary tumour development has never been reported for any of these other allied forms of enteropathy.*

vel to luminal antigen (gluten) in sensitised individuals (19,24) (Figure 3). These are inducible in a dose-responsive, time-dependent manner leading to progressively severer mucosal lesions (25). Thus, irrespective of presentation, i.e. with classic disease, with DH, with monosymptomatic or atypical forms (Figure 4), or those in a compensated-latent phase, we must realise that all patients immunologically are gluten-sensitised i.e. have sensitized mucosal T lymphocytes.

Thus in distinction to classical, symptomatic coeliac disease, gluten sensitivity needs to be defined as a state of heightened cell-mediated (T lmphocyte) and humoral (B lymphocyte) reactivity to gluten proteins on an inherited DQw2 background. This is the only way in which we can encompass (Figure 4) the high proportion of individuals who lack the classical (and restrictive) features which define symptomatic coeliac disease (26).

**(iii) Reactivity to Gluten Peptide:** That gluten sensitivity rests, fundamentally, on a T cell basis, arises from the observation that coeliac disease, according to classical criteria, occurs with severe immunodeficiency (humoral immunity). Therefore, although in most patients antibody levels are high (and provide a useful diagnostic tool) they play no significant role in pathogenesis.

This view, in recent years, has been considerably enhanced by studies of cloned mucosal T cells, their behaviour to gluten and gluten oligopeptides (Figure 5), and the restrictive effects of DQw2

**Table 2.** *Common factors involved in unmasking latent gluten-sensitivity (irrespective of proximal mucosal pathology)*

**1. Gastrointestinal infections:**
enteric bacteria/toxins:
(Escherichia coli, Salmonella, Yersinia, Campylobacter, Aeromonas)
viral:
(rotavirus/astrovirus/adenovirus)
parasitic:
(Giardia/cryptosporidium)

**2. Co-existing nutritional deficiencies:**
iron deficiency:
poor dietary intake (low iron-content food)
excessive losses (pregnancy/menstruation)
folate deficiency:
poor dietary intake (vegetables)
increased utilisation (pregnancy/skin disease/increased enterocyte turnover)
vitamin D:
diet low in fish/fish oil/dairy products
low exposure to sunlight

**3. Metabolic stress:**
surgery of stomach/gall bladder/appendix:
acute pancreatitis/trauma:
pregnancy/post-partum period:
acute febrile illness (influenza/pneumonia)

**4. Malignancies:**
diffuse lymphoma: (unresponsive end-stage disease ± inflammatory jejuno-ileitis)
mass lesions: (intestinal obstruction/pain/haemorrhage/perforation)
oesophagus: (dysphagia)
stomach: (anorexia)
other: (breast, uterus, bladder, brain)

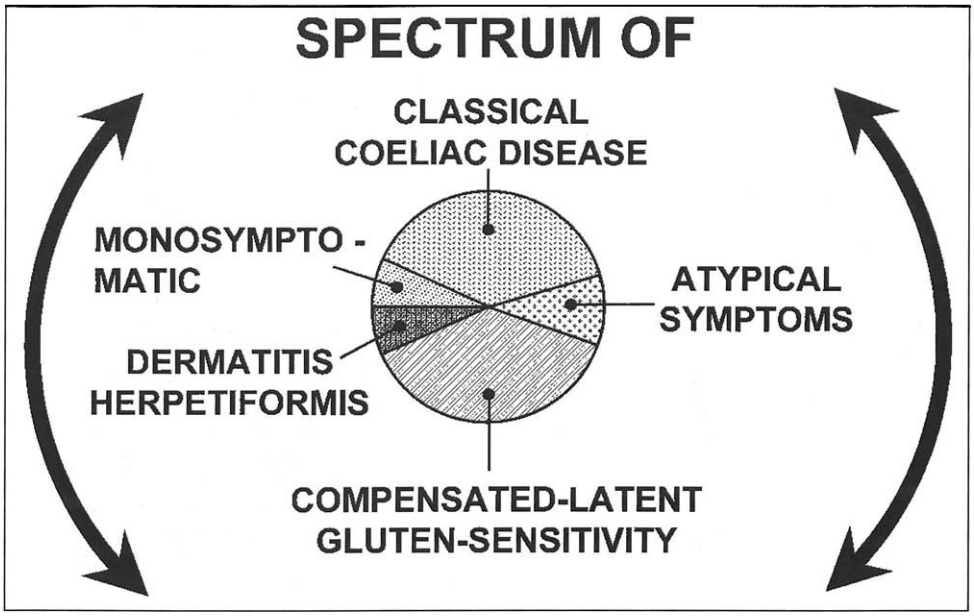


**Figure 4.** *The spectrum of gluten- sensitivity. This includes those with calssical presentations and symptoms (i.e. "coeliac disease"). There are other groups of individuals who are not included in that restrictive definition, and these include patients with atypical or monosymptomatic disease, and those with dermatitis herpetiformis. The remainder comprises a sizeable population of those in a compensated-latent phase of gluten hypersensitivity.*

expression (27): these are exciting developments. Moreover they will facilitate the testing of multiple oligopeptides of gliadin, which hopefully will overcome some of the immense problems in deploying expensive quantities of peptide by in vivo challenge (28,29,30).

The mucosal immune system (or gut-associated lymphoid tissue, GALT) is a complex 'organ' which exclusively subserves protection of the gastrointestinal mucosa (31). One of its features concerns the recirculatory capacity of both its T and B lymphocytes to home back to the intestine. Because of this recirculatory potential of mucosal lymphocytes, secondary recall responses may be evoked at sites remote from the original site of antigen priming. This physiological background clearly underpins the reactivity of the entire gastrointestinal tract to gluten, although priming occurs only in proximal intestine (Figure 6).

Studies from our laboratory have provided in

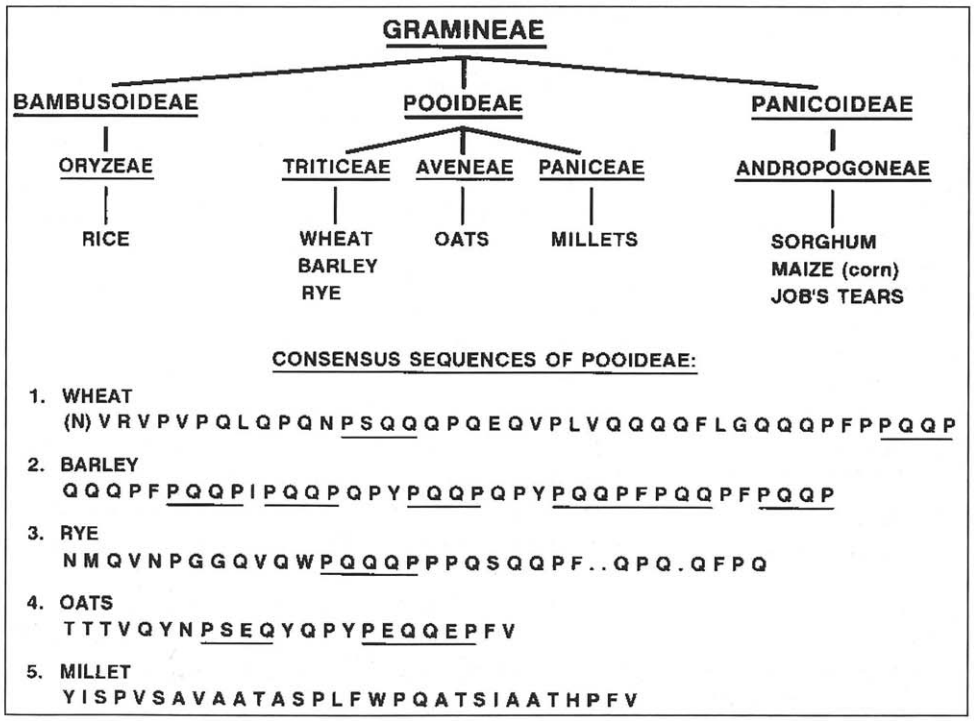


**Figure 5.** *Classification of the edible grasses. Coeliac-associated prolamins (peptides rich in proline and glutamine residues) from the Triticeae contain multiple repetitive sequences which may therefore play a role in pathogenesis. This view has still to be finalised by appropriate experimental approaches.*

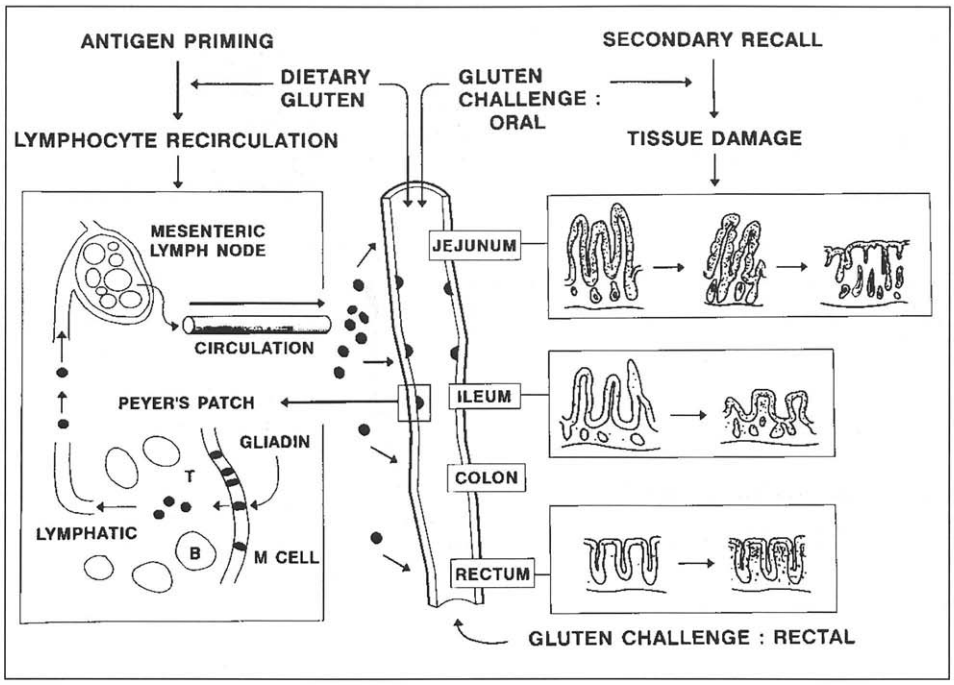


**Figure 6.** *Initial priming in the mesenteric immune system to ingested antigen (left-hand panel) is presumed to occur through Peyer's patches, from whence primed T and B cells emigrate via lymphatics to the mesenteric nodes. After recirculating in the blood they randomly home to the epithelial and mucosal regions of the intestinal tract. Secondary (recall) challenge (right-hand panel) leads to their re-activation and the generation of an immune/inflammatory response with non-specific recruitment of many other cell types to the place where antigen is located. The response, in terms of recognisable tissue damage, has been shown to occur in proximal jejunum, distal ileum, and the rectal mucosa.*

depth observations on the response of rectal mucosa to gluten. These observations indicate a unique increase of CD3+ and TCR lymphocytes both within lamina propria and epithelial tissues, that is responsive to gluten withdrawal (32,33). This specific sensitivity of rectal mucosa to gluten (Figure 6) is remarkable and presumed due to recruitment and activation of mesenteric T lymphocytes via upregulated expression of adhesion molecules on the local microvasculature (34).

## Post Script

From all this emerges a clearer, yet far more complex, overview of gluten-sensitivity which involves classical disease, monosymptomatic and atypical presentations, and a group with asymptomatic compensated-latent disease (Figure 4). The interplay between (i) symptoms, if present, (ii) the spectrum of presumptive host-driven, T lymphocyte-mediated mucosal responses and (iii) the role of environmental factors that render the patient symptomatic are given in Figure 7. Gluten sensitivity is no longer a simple disease: neither is it rare: furthermore, the concept of the compensated-latent phase of the disease needs to be carefully understood (16).

**Table 3.** *Diagnostic options in gluten-sensitivity*

| | |
|---|---|
| 1. Antibody screen: | a) anti-gliadin<br>b) anti-endomysial |
| 2. Jejunal biopsy: | a) spectrum of mucosal pathology<br>b) high gdCD3 IEL ratio |
| 3. Gluten challenge: | a) oral → deterioration in mucosal architecture<br>b) rectal → influx gdCD3 cells: calculate discriminant score |

To label the compensated-latent phase of the disease as either "silent" or "potential" is absurd. as indicated above, asymptomatic patients may still have a severe proximal mucosal lesion and thus be equally exposed to the risk of developing a malignant complication as those who are symptomatic. What must be understood is that the disease process, at mucosal level, is still active in the face of continued gluten ingestion, and it is this fact that puts the latent (dictionary definition: 'present, but not manifest') individual at far greater risk than the symptomatic patient, who is sooner likely to receive a gluten free diet. Furthermore, latent female-compensated patients are at greater risk (compared with age-matched non-coeliac females) for severe osteopenia as well as other deficiencies, in particular, chronic iron deficiency (26,35). Thus the importance, as stressed above, of improving the stringency of population screening methods, and relating 'positive' scores to other independent evidence of gluten sensitivity, in order to exclude non-specific false-positives (36). This still remains a vital problem: but much more needs to be learned and applied, especially with regard to diagnosis (Table 3). Nevertheless we have come a long way, and Dr Gee would certainly be very impressed with our progress to date.

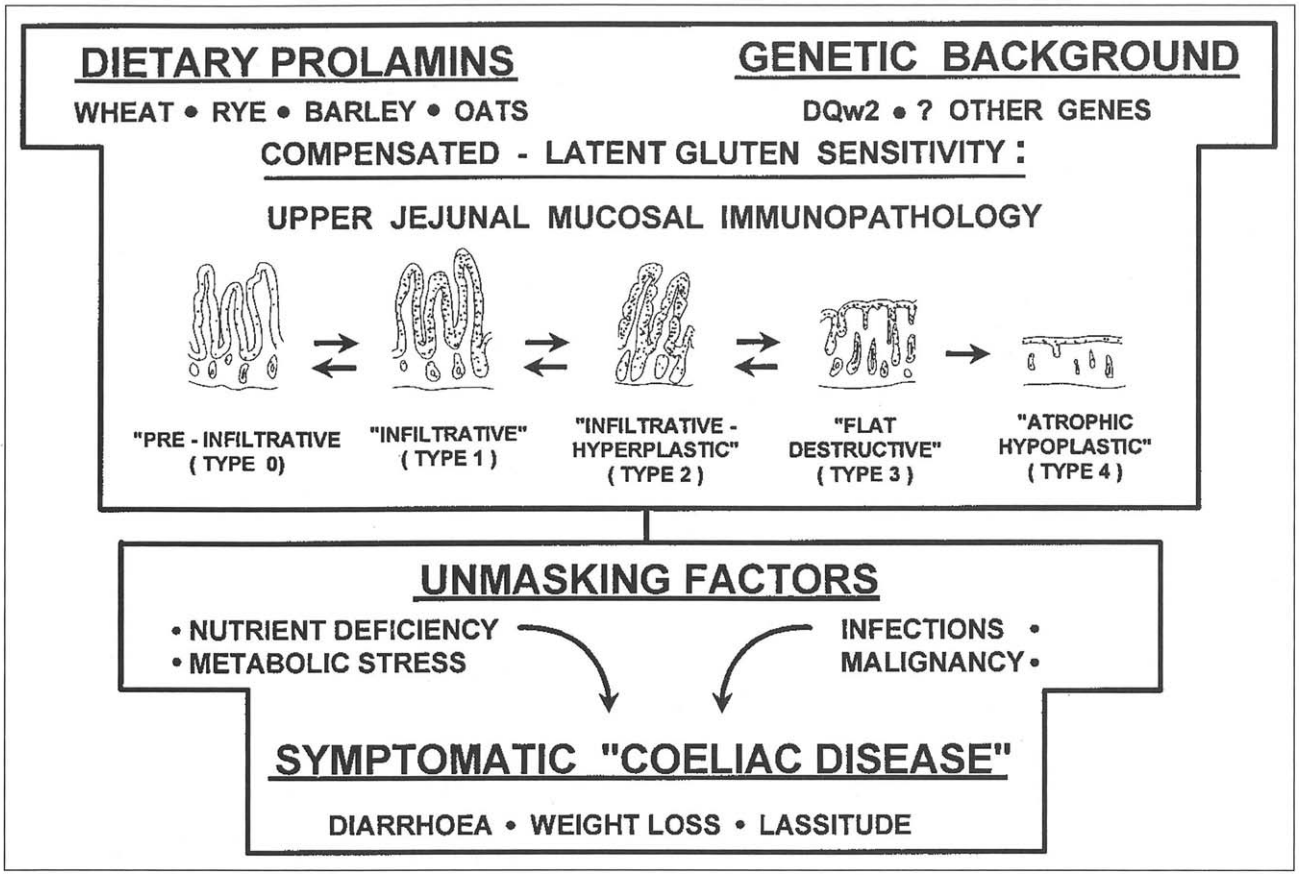


**Figure 7.** *Pathogenetic events in gluten-sensitivity. The view proposed is that the proximal gluten-induced lesion usually results in a compensated-latent phase of the disease. If that was not the case, everyone would develop symptoms and be diagnosed within 6-12 months of age, which clearly does not happen. We can classify those environmental factors which unmask the condition at any age throughout life (see Table 2). This occurs irrespective of the severity of the proximal lesion, which has no relationship whatsoever to the presence, or absence, of intestinal symptoms. The unmasking will reveal a variable cluster of symptoms; these will be dependent on the factor active in decompensating the latent state.*

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