

## Leading article

# Clinical and pathological spectrum of coeliac disease – active, silent, latent, potential

### Currently recognised forms of gluten sensitive enteropathy

Within the framework of the current definition (a permanent gluten sensitive enteropathy), clinical, pathological, epidemiological, and immunological approaches are revealing several forms of coeliac disease. In so called active coeliac disease, malabsorption, and nutritional deficiencies range from profound to minimal; clinically silent coeliac disease is being increasingly recognised – for example, in family studies. Pathologically there is also a degree of heterogeneity. Descriptive terms such as 'flat mucosa', or 'subtotal villus atrophy', are the pathologist's shorthand for a cluster of features (villus, crypt sizes, epithelial cell damage, intraepithelial and lamina propria lymphoid cell infiltrates) which together characterise the enteropathy of coeliac disease. Quantitative histology and computerised image analysis have shown that these features occur in a continuum, with the flat lesion at one end of the spectrum and a mucosa with normal villus and crypt architecture, but an abnormally high density or count of villus intraepithelial lymphocytes, at the other.<sup>1,2</sup> The latter would be reported as normal by most clinical pathologists. This fact is important when the evidence for the existence of latent coeliac disease is reviewed. This term should only be applied to patients who fulfil the following conditions: (i) have a normal jejunal biopsy while taking a normal diet; (ii) at some other time, before or since, have had a flat jejunal biopsy which recovers on a gluten free diet.

The suggestion that there might be a 'precoeliac' state was first made by Weinstein who described two patients with dermatitis herpetiformis and normal jejunal biopsies in whom typical coeliac like enteropathy developed some weeks after 20 g gluten was added to their already gluten containing diet.<sup>3</sup> Two studies from the United Kingdom have confirmed this observation<sup>4,5</sup> and the concept is supported by case reports of coeliac patients in whom, by chance, a jejunal biopsy has previously been taken and reported as normal.<sup>6-8</sup>

### Subtle pathological and immunological abnormalities in some latent coeliacs

If full morphometric analysis were to show changes at the mild end of the spectrum of coeliac like enteropathy in the original biopsies (as has been reported in two such patients)<sup>9</sup> this would require that the descriptive term in these cases be revised from latent to low grade or mild gluten sensitive enteropathy. Furthermore, it would greatly facilitate research and clinical management of such patients if there was a means of identifying them, more widely available and less technically demanding than computerised image analysis.

Coeliacs whose intestinal lesions have resolved on a gluten free diet and whose jejunal biopsies are classified as 'normal' for diagnostic purposes may still express subtle pathological or immunological abnormalities similar to those of untreated coeliacs. These abnormalities include a high count of villus IEL<sup>9</sup>; increased gamma/delta T cell receptor expression by intraepithelial lymphocytes<sup>10</sup>; abnormal jejunal permeability<sup>11</sup>; and high concentrations of IgM antigliadin antibody, other IgM class antibodies, and IgA antigliadin antibody (the

'coeliac like intestinal antibody' pattern) in specimens of jejunal fluid and whole gut lavage fluid.<sup>12</sup>

One approach to the recognition of potential latent or low grade coeliacs is by studies of intraepithelial lymphocyte T cells expressing gamma/delta receptors. This presents logistic problems, as the relevant immunohistochemical studies must be done on frozen sections, but positive results have been reported in a single case of latent coeliac disease detected during family studies in Finland.<sup>7</sup>

We recently reported that the characteristic coeliac like intestinal antibody pattern of intestinal fluid antibodies also occurs in dermatitis herpetiformis patients without enteropathy, a group of patients in whom it is likely that all or most are in fact latent coeliacs.<sup>13</sup> Similar studies of intestinal antibodies might facilitate the detection of latent coeliac disease in other situations.

### Two stage model of coeliac disease

We have proposed a two stage model of gluten sensitive enteropathy, latent and fully expressed.<sup>13</sup> This derived from the confluence of several lines of clinical and experimental work and can be stated as follows: induction of a state of inappropriate immunity (hypersensitivity) to gliadin is a relatively frequent occurrence, genetically restricted. The effects of abnormal interaction between the immune system and gluten may be expressed not only in gut (coeliac disease) and skin (dermatitis herpetiformis), but also in the mouth (recurrent aphthae), kidneys (IgA nephropathy) and joints (some arthritides). Within the intestinal mucosa, expression of T cell mediated immunity to gliadin in the gut occurs across a spectrum of histological and functional abnormalities. The minimal lesion may appear histologically normal, or as a virtually normal biopsy with a high count of villus intraepithelial lymphocytes; the fully expressed lesion is a flat mucosa with crypt hyperplasia, typical of coeliac disease.

Studies in mice<sup>14</sup> showed that immunological sensitisation to gliadin does not trigger the development of a T cell mediated lesion of the intestine when the diet contains gluten. Additional factors, such as those occurring during intestinal anaphylaxis or a graft-versus-host reaction, were necessary. Enhanced antigen presentation, recruitment of specific T cells in the mucosa, up-regulation of the expression of class II antigens and failure of suppression, are all candidate mechanisms for the effects observed.

By analogy, although mucosal immunological sensitisation is an invariable feature of coeliac disease, it is not the precipitating factor for the expression of the full intestinal lesion; a second factor drives the enteropathy from minimal (latent) to overt, either by immunological mechanisms or by direct ancillary effects on enterocytes. Candidate factors include an episode of hyperpermeability, nutrient deficiency, increased dietary gluten, impaired intraluminal digestion of ingested gluten, adjuvant effects of intestinal infection and a non-HLA associated gene.

**Significance of a high count of intraepithelial lymphocytes**  
In animal work on delayed type hypersensitivity in rodent

intestine, a rise in the count of villus intraepithelial lymphocytes was a sensitive and early feature of the expression of mucosal delayed type hypersensitivity<sup>15</sup> and is induced by signals from activated lamina propria CD4 T cells.<sup>16</sup> By analogy, in clinical practice a high count of intraepithelial lymphocytes in an architecturally normal small bowel biopsy will also imply a state of T cell activation, either antigen driven – for example, by gluten, giardia, histocompatibility antigens – or as a result of aberrant mucosal immunoregulation (as in some theories of the pathogenesis of inflammatory bowel disease).

There is now a substantial body of evidence that the expression of gluten hypersensitivity as enteropathy may be minimal, measurable only if a count of intraepithelial lymphocytes is performed. An accepted name for this type of pathology is needed, such as ‘high density intraepithelial lymphocyte enteropathy’. This must be clearly differentiated from various other forms of non-coeliac enteropathy, such as that of HIV infection.<sup>17</sup> Further work will show how a high count of intraepithelial lymphocytes relates to gamma delta intraepithelial lymphocyte counts, and whether these are merely sensitive indices of mucosal delayed type hypersensitivity expression, and all associated with production of IL2 and gamma interferon, or whether high density of intraepithelial lymphocytes, the unusual up regulation of IgM and/or gamma delta T cell numbers are independent factors, perhaps genetically determined, relevant to the induction of a state of aberrant immunity to gluten, and thus directly to the pathogenesis of coeliac disease.

#### Clinical importance of an extension of the pathological criteria for coeliac disease

We have recently assessed the frequency of the coeliac like intestinal antibody pattern, a candidate marker of latent coeliac disease, in patients referred for diagnostic small bowel biopsy. Studies of jejunal fluid revealed the coeliac like intestinal antibody pattern in 16 of 98 non-coeliac cases, of whom six also had a high count of intraepithelial lymphocytes (Arranz and Ferguson, submitted). If further research shows that some of these patients are clinically gluten sensitive (and we already have some evidence to support this), then by implication, the previous definition of coeliac disease (a flat mucosa) may have excluded up to half of symptomatic patients, referred for jejunal biopsy, who would benefit clinically from a gluten free diet. The present pathological description of coeliac disease may need to be revised and treatment with a gluten free diet (carefully monitored)

offered to symptomatic patients with minor forms of enteropathy.

Only rarely, and usually by chance – for example, previous biopsy in a research investigation – does a patient fulfil criteria for latent coeliac disease. A more generally applicable expression is needed to describe people who should have the diagnosis of latent or low grade coeliac disease considered – such as those with high intraepithelial lymphocyte count, positive coeliac like intestinal antibody pattern, high gamma delta expression of intraepithelial lymphocytes, relatives of coeliacs, IgA deficient individuals. The term ‘potential coeliac disease’ is proposed.<sup>18</sup>

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