LETTERS TO THE EDITOR

Clinical and pathological spectrum of coeliac disease

EDITOR,—In their article, Ferguson *et al* propose new terminologies – that is, active, silent, latent, and potential to accommodate evolving concepts for gluten sensitivity ('coeliac disease') (*Gut* 1993; **34**: 150–1). There are, however, a number of problems in their thesis that requires examination.

The first difficulty lies in their method of defining terms. 'Silent' appears in the title but only once textually (line 6), while 'latent' and 'potential' become blurred by combined use, like 'potential latent', which then later equates with 'low grade coeliac'. A latent coeliac patient is identified as someone who (a) has a normal mucosa while eating a normal diet but who (b) either before or since, had a flat mucosa responsive to gluten withdrawal. In the final paragraph, it is suggested replacing 'latent' and 'low grade coeliac' by a more generally applicable expression – 'potential'.

A second difficulty arises from the 'two stage model' of coeliac disease[1] based on experiments in which either anaphylactic, or graft *v* host, reactions caused further, albeit modest, changes in mucosal architecture in gluten fed mice. This leads to the proposal that environmental (second) factors are vital in driving a mild intestinal lesion to the more severe, flat lesion typical of classic coeliac disease. As Weinstein showed first[2] and many others since, complete mucosal flattening simply requires (a) a sufficient intake of gluten on (b) an appropriate genetic background. The candidate 'second' factors proposed by the authors lack conviction: for example, what is the evidence that either impaired intraluminal digestion of gluten, or nutrient deficiency, or episodes of increased permeability cause mucosal flattening?

Equally it would seem unnecessary to propose an 'adjuvant effect of intestinal infection' as another factor in mucosal flattening. This is not so in the tropics where prolonged exposure to repeated microbial infections/toxin production fails to drive the mucosa to flatness in tropical sprue: indeed, in those subjects who mount host mediated mucosal responses to such a heavy intestinal microbial load, the lesion may be exceptionally mild, less than 5% (Indian or Caribbean) patients developing a really flat mucosa.[3,4]

As concepts ever change and widen, new terminologies will be required, but we must keep them simple. There seem to be reasonable grounds for getting away from earlier definitions of 'coeliac disease' as a malabsorption syndrome with a flat mucosa responsive to gluten withdrawal: such a definition is now redundant as it only encompasses about 30% of all sensitised subjects.[5] Thus 'coeliac disease' needs to be replaced by a more generally inclusive and flexible term such as 'gluten sensitivity', defined as a state of T cell sensitisation to gluten in a genetically predisposed subject (the occurrence of gluten sensitivity in patients with severe immunodeficiency excludes a primary role for antibody). Underlying that state of gluten sensitivity seem to be certain arbitrary mucosal gradings – namely, (a) infiltrative, (b) infiltrative-hyperplastic, (c) flat-destructive, and (d) irreversible hypoplastic/atrophic.[6]

Thus, a sensitised patient will either be (a) asymptomatic ('latent') irrespective of degree of mucosal damage, or (b) symptomatic (have gluten driven malabsorbtion (coeliac disease), skin blisters, or clinical features of malignancy) irrespective of degree of proximal mucosal damage. Note, however, that most gluten sensitised subjects are 'latent' or asymptomatic, even though many have a typical 'flat' proximal mucosal lesion. The difficulty lies in identifying subjects with minimal (infiltrative or infiltrative-hyperplastic) lesions that are a result of gluten sensitivity rather than to other known causes like giardiasis, cryptosporidiosis, tropical enteric disease, etc). Eventually, it is hoped that identification of all gluten sensitised subjects will be based on tests other than mucosal sampling and mucosal imagery. In the meanwhile, many physicians and pathologists need to acquaint themselves with these new concepts and vistas, which now typify the widening clinical and pathological spectrum of gluten sensitivity. Gluten sensitivity, in contrast with conventional beliefs, is extremely common, but because of its latency is often missed, or even never thought of.

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1 Troncone R, Ferguson A. An animal model of gluten-induced enteropathy in mice. *Gut* 1991; **32**: 871–5.
2 Weinstein WM. Latent celiac sprue. *Gastroenterology* 1974; **66**: 489–93.
3 Chacko C, Job C, Johnson S, Baker SJ. Histopathological changes in the upper jejunum in tropical malabsorption syndrome studied by transoral biopsy. *Indian J Pathol Bacteriol* 1961; **4**: 203–13.
4 Schenk E, Samloff I, Klipstein F. Morphologic characteristics of jejunal biopsy in celiac disease and tropical sprue. *Am J Pathol* 1965; **47**: 765–81.
5 Marsh MN. Gluten, major histocompatibility complex, and the small intestine: a molecular and immunobiologic approach to the spectrum of gluten-sensitivity ('celiac sprue'). *Gastroenterology* 1992; **102**: 330–54.
6 Marsh MN. Mucosal pathology in gluten sensitivity. In: Marsh MN, ed. *Coeliac disease.* Oxford: Blackwell Scientific, 1992: 136–91.

EDITOR,—Ferguson *et al* have reviewed some of the new concepts concerning the clinical and pathological spectrum of coeliac disease.

Unfortunately, the view expressed in their leading article may bring confusion rather than clarity.

We agree with Ferguson *et al* that the pathological description of coeliac disease as generally accepted in the past, needed to be revised. We think, however, that this has already been done by Marsh in his excellent review.[1] Based on his own experiments, Marsh has shown that the small intestinal pathology of coeliac disease occurs in a continuum: from a mucosa with (nearly) a normal architecture (preinfiltrative lesion), to increased lymphocytic infiltrate (infiltrative lesion), and finally to the classic 'flat' mucosa (hypertrophic lesion). Marsh has shown too that coeliac patients may develop any of these types of mucosal lesions and yet be asymptomatic. Whether it is the degree and the extent of the lesion, or alternatively the influence of environmental factors (infection, pregnancy, extra gluten intake) determine the clinical presentation of the disease, deserves further investigation.

We agree with Ferguson *et al* that a gluten free diet should be advised to more patients with minor or atypical forms of the enteropathy. We disagree, however, with their suggested two stage model of coeliac disease. This classification is a simplification of a proteiform condition. Recognising all (sub) clinical forms of coeliac disease is a diagnostic utopia for clinicians and is, to some extent, a reflection of the uncommon diagnosis of this disease in the USA and in some European countries, for example in the Netherlands.[2,3] The use of different terms such as active, silent, latent, potential, high density intraepithelial lymphocyte enteropathy, the coeliac like intestinal antibody pattern, is potential coeliac disease, all refer to an asymptomatic state with different degree of mucosal change. The term latent coeliac disease should only be used in those states in which a (sub) normal histological examination of small intestinal biopsy specimen is found in patients consuming gluten before developing typical small intestinal lesions characteristic of coeliac disease.

The importance, however, of the recognition of these atypical forms of presentation and asymptomatic cases, is that these patients may be at risk of developing malignancies and that the adherence to a gluten free diet may be protective.[4]

Immunogenetic studies in families of coeliac patients will help to define the subjects at risk. Until otherwise proved, a gluten free diet should be advised to all patients with the corresponding immunogenetic markers and histological abnormalities. When the diagnosis is uncertain, a gluten challenge under appropriate surveillance followed by the study of the intestinal morphology is often helpful to clarify the situation. Revised criteria for the diagnosis of the spectrum of coeliac disease should be formulated by working parties, as was done before.[5,6]

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1 Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity (celiac sprue). *Gastroenterology* 1992; **102**: 54: 330–54.
2 Jansen TLThA, Mulder CJJ, Karssen PHZ, Wagenaar CGJ. Epidemiological survey of the Dutch Coeliac Disease Society: an update 1992. *Eur J Gastroenterol Hepatol* 1993; **5**: 73–8.
3 Loft DE. The epidemiology and diagnosis of coeliac disease. *Eur J Gastroenterol Hepatol* 1993; **5**: 69–72.
4 Holmes GKT, Prior P, Lane MR, Pope P, Allan RN. Malignancy in coeliac disease – effect of gluten-free diet. *Gut* 1989; **30**: 333–8.
5 Meeuwisse GW. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970; **59**: 461–3.