

## 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<sup>1</sup> 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<sup>2</sup> 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.<sup>3,4</sup>

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.<sup>5</sup> 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.<sup>6</sup>

Thus, a sensitised patient will either be (a) asymptomatic ('latent') irrespective of degree of mucosal damage, or (b) symptomatic (have gluten driven malabsorption (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.

M N MARSH  
Hope Hospital,  
Eccles Old Road,  
Salford M6 8HD

- 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.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4</sup>

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.<sup>5,6</sup>

C J J MULDER  
Department of Hepatogastroenterology,  
Rijnstate Hospital,  
Arnhem

M L MEARIN  
Department of Pediatrics,  
Academic University Hospital,  
Leiden

A S PEÑA  
Department of Gastroenterology,  
Free University,  
Amsterdam,  
The Netherlands

- 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.

- 6 Walker-Smith JA, Guandalini S, Schmitz J, Schmerling DH, Visakorpi JK. Revised criteria for the diagnosis of coeliac disease. Report of the working group of the European Society for Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990; 65: 909-11.

### Reply

EDITOR,—It was during the 1970s that Wright and Watson highlighted the significance of crypt hyperplasia in the mucosal pathology of coeliac disease, not only in a severely damaged flat mucosa but also in less severe lesions. Large crypts, with abnormally high cell count per crypt, increased crypt cell mitotic rate, and crypt cell production rate have been found in coeliac disease by many workers using a variety of techniques. Mulder *et al* misquote Marsh's suggested terminology for the severe end of the spectrum of the pathology of coeliac disease — his 'hyperplastic' grade equates to Wright and Watson's crypt hyperplasia with short or virtually normal sized villi. Marsh recommends the term 'flat' for the avillus lesion, which (except in the unusual circumstances of a true mucosal atrophy) also has crypt hyperplasia.

There is also wide, general agreement, for at least a decade and using a variety of methods of quantitative histological tests, that when the surface epithelium itself is used as the reference (length, cell number or tissue volume) the density of lymphocyte infiltrate is high, not only in coeliac disease with crypt hyperplasia but in some treated coeliac patients with entirely normal villus and crypt architecture. Marsh has shown this by using computerised image analysis of tissue volumes in his *in vivo* gluten challenge work, and in dermatitis herpetiformis patients. We are not persuaded that 'infiltrative' is the best way to describe this specific pathological entity. In various diseases there may be abnormal infiltration of the mucosa by lymphocytes, plasma cells, eosinophils, mast cells, macrophages, tumour cells or parasites, and the microenvironment that is infiltrated maybe intraepithelial, the villus lamina propria, or pericryptal regions.

Much more important than semantics is the plea to pathologists that they should formally quantify the intraepithelial lymphocyte density in some way, when on subjective assessment it seems probable that this feature of intestinal pathology is abnormal. A high count or density of intraepithelial lymphocytes, and increased mitotic activity of intraepithelial lymphocytes, can, of course, occur in conditions other than coeliac disease, for example, in travellers' diarrhoea and giardiasis.

Patients with classic, unarguable, gluten sensitive biopsy pathology of coeliac disease are often comparatively asymptomatic. Paediatricians in Europe use the terms 'active' and 'silent' in relation to the presence or absence of symptoms and signs of malabsorption and we find this a clinically useful way of subdividing patients who, of course, all fulfil current diagnostic criteria for coeliac disease.

On the other hand, 'latent' coeliac disease as defined 20 years ago referred to patients with normal jejunal biopsy histology while receiving a normal diet, but who have a gluten sensitive enteropathy at some other time. Despite much research effort, no one has yet found a way to measure antigen specific T cell sensitisation in the gut mucosa, though cytokine production by antigen challenged biopsy specimens in organ cultures holds potential. When *in vivo* challenge tests are done, the evolution of enteropathy, or of changes in the rectal mucosa, are good evidence that gluten intolerance exists, but do not show the precise mechanism. There is still much work to be done before we can confidently assign the diagnosis of latent gluten sensitivity to any patient with a histologically normal jejunal biopsy specimen, whether on the basis of genetic makeup, intestinal IgM anti-gliadin antibodies or gamma/delta intraepithelial lymphocyte counts.

In our early enthusiasm for the use of such immunological tests to identify patients at the mild end of the pathological spectrum of coeliac disease, we carelessly used the term 'latent coeliacs' in our day to day discussion of the clinical progress and research results for such patients. In fact we should have classified them as 'might be latent coeliac disease, we will know in 3-6 months time after the effects of gluten free diet or gluten challenge or gluten loading or all three have been monitored by biopsy'. In other words they were potentially latent coeliacs, which is still rather a mouthful. There are many symptomatic patients with normal mucosal architecture but a high count of total or gamma/delta intraepithelial lymphocytes, intestinal IgM anti-gliadin and other antibodies, serum anti-endomysial antibody or clinical wheat sensitivity. We, our clinical colleagues, and the patients understand and find it more convenient simply to use the term 'potential coeliacs' until we have unequivocally shown by dietary manipulations whether they are or are not gluten sensitive. If they are not, then other avenues of investigation and treatment must be pursued.

A FERGUSON  
E ARRANZ  
*University of Edinburgh,  
Department of Medicine,  
Western General Hospital,  
Edinburgh EH4 2XU*

### Perioperative endoscopy of the whole small bowel in Crohn's disease

EDITOR,—Lescut, *et al* (*Gut* 1993; 34: 647-9) are to be congratulated on their very interesting findings on the widespread nature of small bowel Crohn's disease when assessed by perioperative endoscopy.

As a radiologist, what saddens me is the repetition of the pattern of discrediting radiology by comparing it with endoscopic techniques without rigorous methodology. The barium meal has almost been discounted on remarkably little sound trial evidence. This study seems to be subjecting small bowel barium radiology to the same fate. At no point in the study are we told of the level of experience of the radiologist who performed the small bowel studies, whether these studies were 'double read', what type of investigation was performed (single contrast follow through, or single or double contrast small bowel enema), how lesions were scored, the interval of the studies before surgery, whether the studies were all performed in the same institution, whether a careful search for aphthoid lesions was made, etc.

While I realise that comparison with radiology was not the main thrust of the paper, it was nevertheless made. If radiological data are going to be included then the same careful scientific method should be applied to these as any other data recorded. If this is not done it will soon become dogma that radiology misses '54 per cent' of lesions without proper scientific validation.

P J SHORVON  
*Central Middlesex Hospital,  
Acton Lane,  
London NW10 7NS*

### Reply

EDITOR,—We are grateful to Dr Shorvon for his comments on our paper. The aim of our study was to assess silent lesions of Crohn's disease in patients being operated on and to compare those endoscopic findings with the ones provided by radiology before operation. We have insisted that almost all the important lesions of the small bowel were identified by single contrast follow through before perioperative enteroscopy. This technique could only recognise milder lesions, which did not appreciably influence treatment of patients. Single contrast follow through investigations were performed in the same institution, by senior radiologists, and double read. The interval between x ray and surgery was variable but never more than three months.

We would be sorry if the main conclusion of our study was that 54 per cent of lesions of small bowel would be missed by radiology. We think that a good radiological examination of small bowel remains a simple and efficient tool for identifying the clinically significant lesions of Crohn's disease.

D LESCUT  
A CORTOT  
*Clinique des Maladies de l'Appareil Digestif,  
Hôpital Claude Huriez,  
1 place de Verdun,  
59045 Lille Cedex, France*

### Gastric mucosal phospholipids and gastroduodenal diseases

EDITOR,—I was interested to read the study of Professor Budillon's group on changes in gastric mucosal phospholipids in various gastroduodenal diseases (*Gut* 1993; 34: 456-60). Despite progress in the understanding of mucosal blood flow, the mucous bicarbonate blanket, and the protective effects of prostaglandins in recent years, the phenomenal ability of the 'gastric mucosal barrier' is still incompletely understood; of relevance, however, is that phospholipids probably play a part because of their hydrophobicity. Progress has also been made on the other side of the peptic ulcer equation, with non-steroidal anti-inflammatory agents and *Helicobacter pylori* (*H pylori*) both clearly implicated in the causation of both ulcers and various forms of gastritis.<sup>1</sup> In patients with duodenal ulcers rates of positivity for *H pylori* vary from 70 to 100%; and in chronic gastritis, from 13-92% depending on the amount of atrophy and activity in the biopsy specimen.<sup>3,4</sup> It is on these grounds that I question the findings of their study, as we are told that all 28 of their apparently unselected patient group are *H pylori* negative, 12 with duodenal ulcer disease and eight with chronic atrophic gastritis (activity of inflammation not given). This makes them an unusual subgroup of both peptic ulcer disease and gastritis and the findings cannot therefore be generalised without further study.

Another recent report<sup>2</sup> about gastric surfactant and the possible interaction between it and *H pylori* makes this oversight in patient selection even more problematic. If, as Professor Hills proposes, surface active phospholipids play a key part in gastric cytoprotection, and if *H pylori*'s pathogenicity is related to ingesting surfactant and thus exposing the gastric mucosa to acid attack, the findings of Professor Budillon's group are distanced even further from any relevance to most patients with peptic ulcer disease. It would be therefore very interesting to see if the phospholipid composition of gastric biopsy specimens in patients