Clinical and pathological spectrum of coeliac disease

Editor,—In their article, Ferguson et al 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, after some period, has 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 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 and many others since, complete gluten withdrawal 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 there ever was intraluminal digestion of gluten, or nutrient deficiency, or episodes of increased permeability causing mucosal flattening?

Actually 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.)1

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. '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.1

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


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

M L MEARIN
Department of Pathology, Academisch University Hospital, Liden

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

Unfortunately, the views expressed in their leading article may bring confusion rather than clarity. We agree with Ferguson et al that the pathological spectrum of coeliac disease is generally accepted in the past, needed to be revised. We think, however, that this has already been done by Marsh in his excellent review. 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 infiltration (infiltrative lesion), and finally to the classic 'flat' mucosa (hypertrophic lesion). Marsh has shown 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) determines the clinical presentation of the disease, deserves further investigation.

We agree with Ferguson et al that a gluten free diet should be advised to all patients with histologically proven coeliac disease. 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 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.3

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 immunohistological 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.4

J S PENA
Department of Gastroenterology, Free University, Amsterdam, The Netherlands

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

Letters


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 mitotic rate, and crypt cell production rate have been found in coeliac disease by many workers using a variety of histological and biochemical techniques. This certainly 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 vertical single villi. Marshall 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 in hyperplasia is 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 biopsy tissue volumes in his studies of gluten challenge work, and in dermatitis herpetiformis patients. We are not persuaded that ‘infiltrative’ is the best way to describe this spectrum of small bowel changes. 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 permissive for the intraepithelial lymphocytes, 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 small bowel biopsies. More objective assessment of this 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, unariable, 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 fulfill 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 intoler-

ance 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 coeliaics’ in our day to day discussion of the clinical progress and research results for such patients. In fact we should have classified them as ‘possible’ or ‘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 coeliaics, 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 that it more convenient simply to use the term ‘potential coeliaics’ 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 ARRANG
University of Edinburgh, Department of Medicine, University General Hospital, Edinburgh EH14 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 who saddened 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 apthoid 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 to 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.

Gastrectic mucosal phospholipids and gastroduodenal diseases

EDITOR,—I was interested to read the study of Professor Budillon’s group on changes in gastrectic 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 ‘gastrectic mucosal barrier’ is still incompletely understood, of relevance, however, 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. In patients with duodenal ulcer rates of positivity for H pylori vary from 70 to 100%; and chronic gastritis, from 13–92%, depending on the amount of atrophy and activity in the biopsy specimen. 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 about gastric surfactant and the possible interaction between it and H pylori makes this oversight in patient selection even more problematic. 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

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Reply

D LESCU T
Clnique desMaladies de l’Appareil Digestif, Hopital Claude Huriez, L’Hôpital des Verdron, 59045 Lille Cedex, France

P J SHORVON
Central Middlesex Hospital, London NW10 7NS

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of gastric biopsy specimens in patients with 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 ‘gastrectic mucosal barrier’ is still incompletely understood, of relevance, however, 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. In patients with duodenal ulcer rates of positivity for H pylori vary from 70 to 100%; and chronic gastritis, from 13–92%, depending on the amount of atrophy and activity in the biopsy specimen. 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.

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