LETTERS TO THE EDITOR

When is a coeliac a coeliac?

EDITOR,—We read with interest the Science Alert comment by Mäki (*Gut* 1997;**41**:565–6) on Dieterich *et al*'s paper[1] identifying tissue glutamine (tTG) as the antigen for endomysial antibody (EMA). Unfortunately, Dr Mäki's comments were somewhat speculative and severely biased towards his own view that gliadin somehow (but how?!) reveals neoepitopes which, by inducing antibodies to connective tissue, apparently provide the key to the central pathogenic mechanism for gluten sensitivity. It is hardly useful to read that ". . . coeliac disease is indeed self-perpetuating and irreversible if the environmental trigger, gliadin, is not removed . . .": that information has been around since Dicke's era.

That there have been exciting findings from Sollid and colleagues from Oslo regarding the in vitro response of cloned (CD4+) mucosal T lymphocytes to gliadin and its derivative peptides with the production of interferon γ and other Th1-type cytokines,[2] seems to have escaped Dr Mäki's pen.

Moreover, it seems certain that, over the next few years, the Oslo group is set to define the qualitative T lymphocyte responses underlying mucosal damage in gluten sensitivity, and the gliadin peptides which evoke such changes. It is important to stress that these experiments underpin the drift of clinical research over the years which again has led to the inevitable conclusion that gluten sensitivity depends on T lymphocyte responses and not on B (humoral) immunology.[3 4] That gluten sensitivity with all its clinical and immunopathological findings can occur without demonstrable antibody[5] should amply inform Dr Mäki (and others) that a theory of pathogenesis for gluten sensitivity, based solely on antibodies, will not do[5]; that idea has already been dismissed by others.[6 7]

More importantly, at present there is no discussion in the literature about EMA negative patients. It is important to avoid a self-fulfilling prophecy—that is, taking biopsy samples only from EMA positive individuals. A recent editorial (*Lancet* 1991;**337**:590) notes the disparity between diagnosis and serology. In most studies, the sensitivity of serological markers has been evaluated in terms of severe (flat) mucosal lesions, or alternatively, a biopsy had only been performed when serological markers were positive.[8–10]

In contrast, we showed when using tTG that sensitivities and specificities for a subgroup of patients fulfilling the ESPGAN criteria with partial villous atrophy at presentation, initially tested by the Berlin group (Dieterich, Schuppan), gave disappointing values of 44% and 88% respectively.

Again, in two independent, prospectively studied groups of coeliac patients,[11 12] the overall sensitivity and specificity of EMA was 50%, and 90–95% respectively. Clearly, EMA is not exclusively positive in every gluten sensitised individual. However, when EMA positivity is related to the severity of the proximal mucosal biopsy, then sensitivity for EMA is about 90% for total villous atrophy, but only 30% for the milder infiltrative-hyperplastic lesions with partial villous atrophy.[13] Thus whether the EMA test is positive or not depends entirely on the presence of a severe lesion and possibly on the length of intestine involved. This point needs to be remembered in population studies, especially when a flat, severe lesion is taken as sole manifestation of coeliac disease.

Much more needs to be learned about effective screening for gluten sensitised individuals. Endomysial antibodies alone fail to predict all such cases and clearly, therefore, do not constitute the universal panacea for this disease as Dr Mäki wants us to believe. Gluten sensitivity is not due exclusively to endomysial antibody production.

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Gastric bacterial overgrowth is a cause of false positive diagnosis of *Helicobacter pylori* infection using ^{13}C urea breath test

EDITOR,—We read with interest the paper by Dominguez-Munos *et al* (*Gut* 1997;**40**:459–62) describing an optimal test drink in the ^{13}C-urea breath test (^{13}C UBT) for the diagnosis of *Helicobacter pylori* infection. In this study all *H pylori* negative subjects (adults with dyspeptic symptoms) had a negative result with the ^{13}C UBT (specificity 100%) after different meals. In other studies, using ^{13}C UBT to document *H pylori* infection both in adults and children, the sensitivity of the test ranged from 92 to 100% whereas specificity was usually above 92%.[1 2] However, no explanation has been given for the occurrence of false positive tests. Methodological bias and problems in defining the cut off value are possible reasons. However, there are no explanations for some false positive tests.[3 4] Here, we report two children with a positive ^{13}C UBT resulting from the presence of urease positive bacteria other than *H pylori* in the stomach.

A 14 month old girl operated on just after birth for a congenital diaphragmatic hernia and presenting with severe gastro-oesophageal reflux associated with oesophageal dilatation and swallowing dysfunction was referred because of gastro-oesophageal haemorrhage. Endoscopy revealed oesophageal dilatation, severe oesophagitis and gastric stasis. The gastric and duodenal mucosa appeared normal. She was treated for two months with H_2 receptor antagonists. Antral and fundal biopsy samples (n=5) showed mild gastritis and were *H pylori* negative on histology (Giemsa staining). Direct examination and culture of gastric biopsy specimens were both negative for *H pylori*. Serum specific antibodies against *H pylori* (ELISA) were also negative. ^{13}C UBT was abnormal (5.63 $\delta\%_o$; normal values <3 $\delta\%_o$). Culture of gastric secretions revealed gastric bacterial overgrowth with colonic bacteria known to have urease activity (that is, *Proteus mirabilis*).

An 8 year old boy operated on just after birth for gastroschisis was referred because of a six month history of abdominal pain. Physical examination was normal. Endoscopy revealed moderate gastric stasis. Examination and culture of both antral and fundic biopsy specimens (n=5) were negative for *H pylori* as were serum specific antibodies against *H pylori* (ELISA). ^{13}C UBT was slightly abnormal (3.25 $\delta\%_o$, normal values <3 $\delta\%_o$). Culture of gastric secretions revealed gastric bacterial overgrowth with species, including micrococcus, with urease activity.

These two cases demonstrate that hydrolysis of urea as a result of bacterial metabolism can occur in the stomach of *H pylori* negative subjects, and that ^{13}C-urea can be hydrolysed in the presence of urease from bacterial species other than *H pylori*. Several bacteria—for example, *P mirabilis*, *Escherichia coli, Yersinia enterocolita*, *Klebsiella pneumoniae, Staphylococcus aureus*, have urease activity, but they do not usually colonise the stomach. Gastric bacterial overgrowth was probably favoured by prolonged antisecretory treatment in the first case and by gastric emptying abnormalities in the second (intestinal malrotation associated with gastroschisis). Urease activity associated with *H pylori* infection usually causes greater excretion of ^{13}C than that observed in our two patients (5.6 and 3.25 $\delta\%_o$ respectively). As the cut off value of 3.00 $\delta\%_o$ has been validated in both adults and children[2 3] and no technical bias occurred, false positive resuts can be ruled out in our patients.

In summary, the ^{13}C UBT is a sensitive and specific method for the non-invasive detection of *H pylori* infection, but gastric bacterial overgrowth may lead to a false positive

diagnosis. These patients may be wrongly considered to be *H pylori* positive if a single, non-invasive test is used. In some circumstances (long term use of antisecretory drugs or abnormalities of gastric motility) a low positive ^{13}C UBT without other evidence of *H pylori* infection (serology, bacteriology, histology) may be suggestive of gastric bacterial overgrowth.

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The Maastricht Consensus Report

Treating young dyspeptic patients

EDITOR,—The Maastricht Consensus Report (*Gut* 1997;**41**:8–13) is a welcome benchmark summarising current opinion and scientific evidence regarding the role of *Helicobacter pylori* in gastroduodenal disorders. Whereas the management of peptic ulcer disease is no longer controversial and is very evidence-based the same is not yet true for the syndrome of non-ulcer dyspepsia and the management of the uninvestigated dyspeptic patient. The recommendation of the Maastricht Report reflects this uncertainty. They recommend that at the specialist level, eradication therapy for *H pylori* infected non-ulcer dyspepsia is "advisable", based on supportive scientific evidence, but only after "full investigation" including endoscopy, ultrasound and other tests. However, in the management algorithm for the uninvestigated dyspeptic in primary care, non-invasive testing (with a breath test) and treatment is recommended for patients who are at a low risk of gastric carcinoma. Why such a difference? If it is recommended that a breath test is investigation enough of dyspepsia in primary care then an endoscopy and biopsy should be adequate in specialist practice if there are no other clinical indicators of another diagnosis (such as biliary colic) and the patient is at low risk of malignancy. The difficulty is that non-ulcer dyspepsia will remain a hard target and even several studies of symptom response after eradication therapy due to be reported shortly will not resolve the issues as there will be perennial debate about inclusion and exclusion criteria in such trials and these will have a great bearing on outcomes. Moreover, the ability to quantitate the lifetime risk reduction of peptic ulcer disease and perhaps even gastric carcinoma in patients who have eradication therapy will remain contentious. Medico-legal issues and patient preferences will also continue to be important factors influencing the decision to investigate and treat. At present the suggested test and treat strategy of uninvestigated patients seems reasonable for well-informed, low-risk patients with endoscopy the recourse if needed. Further investigation and the decision to test and treat for *H pylori* in uninvestigated dyspeptics and investigated dyspeptics who fit the criteria for non-ulcer dyspepsia will no doubt remain a decision that is assessed on a "case by case" basis as suggested in the recent report of the American Digestive Health Initiative.[1]

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1 Anonymous. The report of the Digestive Health Initiative International Update Conference on Helicobacter pylori. *Gastroenterology* (in press).

Functional dyspepsia in the young

EDITOR,—I read with interest the Maastricht Consensus Report on the diagnosis and treatment of *Helicobacter pylori* infection (*Gut* 1997;**41**:8–13). Whereas the role of *H pylori* in peptic ulcer disease, gastric carcinoma and mucosa associated lymphoid tissue type lymphoma is established, its role in functional dyspepsia is still controversial. Recent data indicate that *H pylori* positive patients with functional dyspepsia benefit from eradication therapy.

In 1989, we published a treatment algorithm in which serological screening had a key part in the decision whether or not to endoscope patients presenting with dyspepsia.[1] We suggested that endoscopy was not essential and advocated anti-*H pylori* treatment in seropositive dyspeptic patients. In our original algorithm there were several unanswered questions regarding coincidental non-helicobacter related disorders. These questions would have to be answered before serological screening could be used in routine practice. At that time this algorithm was refuted.[2] Nevertheless since then several papers have been published in which serological screening was used. However no data were available on non-helicobacter related disorders of the upper gastrointestinal tract and also real screening was not done as selected patient populations were used.[3–5]

Much to my surprise the Maastricht Consensus Report advocates anti-*H pylori* therapy in seropositive dyspeptic patients under 45 years of age without the need for endoscopy. Although, from a clinical point of view I fully agree with this statement, it is based on common sense and not on scientific evidence. To the best of my knowledge, no prospective studies have been done in which seropositive patients did not undergo endoscopy. Selected patient populations were studied in all of the references quoted in the report. Endoscopy should be omitted, in retrospective analysis, on seronegative cases.

If serology is used and endoscopy is not performed in selected cases, whether *H pylori* positive or negative, it is inevitable that some cases of non-helicobacter related disease will be missed, reflux oesophagitis being the most important. It is essential that a non-selected patient population is assessed to determine how many cases of reflux oesophagitis would be missed if endoscopy was not done. This is especially true as the clinical presentation of reflux oesophagitis is far from specific. We showed in a recent paper that the majority of dyspeptic patients with reflux oesophagitis were *H pylori* negative,[6] and that, at least in theory, the best screening strategy seemed to be to omit endoscopy in seronegative patients.

The statement that serological screening is cost effective and leads to more efficient use of endoscopy facilities has yet to be proved in prospective randomised studies. The only study published to date is unsuitable as a selected patient population was used.[7]

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Dual publication

EDITOR,—I was astonished, as I am sure many were, to see publication of the The Maastricht Consensus Report (1997;**41**:8–13) in *Gut*. Not only was this surprising, but to see it appear as a leading article was even more amazing particularly in an issue which carried an editorial by yourself on research misconduct, quite rightly condemning similar practices.

Under the circumstances, it does not appear unreasonable to enquire whether you were aware at the time that a synopsis of this event had previously been published in the *European Journal of Gastroenterology and Hepatology* (1997;**9**:1–2)? If so, no acknowledgement appears to have been included in this parallel report. Had you been informed that the meeting from which this report had its origins was organised "with an educational grant from Astra-Hässle" with accompanying documentation inferring that travel and hotel expenses were paid for participants and discussions limited to those who were paid for? If so, why is this not acknowledged in the leading article and it registered as a possible "conflict of interest" as seems to be the philosophy of your parent publishing group, and acceptance of financial support within the stated policy of your own journal. Perhaps your readers should further be aware that this publication is the result of discussions by a self-appointed group who have no mandate to represent any official bodies or organisations.