LETTERS TO THE EDITOR

Towards a better assessment of reflux oesophagitis

SIR,—We read with interest the exhaustive and balanced overview by Dr Colin-Jones on gastro-oesophageal reflux.¹ We were particularly pleased to see that an authoritative reviewer has at last officially suggested an adaptation of the notorious endoscopic classification of oesophagitis by Savary and Miller.² For reasons which are beyond our understanding, the oesophageal mucosa is the only one in the digestive system (or, better, in the whole body), the lesions of which were graded starting from erosions. Thus, in clinical practice, when patients with symptoms of gastro-oesophageal reflux have endoscopic evidence of erythematous areas in the distal oesophagus the term of 'grade 0 oesophagitis' is often used. In our opinion mild (non-erosive) oesophagitis should be graded from longitudinal red streaks to circumferential erythema, but any attempt to include non-erosive lesions within the concept of 'oesophagitis' is welcome.

On the other hand in clinical trials the endoscopic evaluation criteria are often at variance with Savary and Miller's classification and tend to include non-erosive forms as well, in order to obtain a more realistic approach to the problem.³⁻⁵

As for the possibility of improving the results of H₂ receptor blockers in the treatment of reflux oesophagitis, we believe that the time of administration can also play a major role. Contrary to that reported in the past,⁶ daytime reflux has been claimed to be an important factor in the pathogenesis of the disease.⁷ Therefore a single dose of a H₂ blocker at night might not be ideal in some subjects. The results of a recent cooperative study performed in northern Italy⁸ seem to support this view.

A group of 33 healthy controls was initially examined by means of 24 hour ambulatory pH-metry to determine the upper normality limit, on the basis of De Meester's criteria⁹ (mean $\pm$ 2SD) of the percentage of time with pH below 4. Accordingly, 112 consecutive subjects with abnormal pH-metry were detected and could be divided in upright (53%) or supine (11%) refluxers and in patients with reflux in both positions (36%).⁸ These figures differ from De Meester's findings and in particular the number of upright refluxers is substantially higher (53% *v* 9%). The reasons for those discrepancies are unclear. It must be noted, however, that the Italian study was carried out in outpatients and not subjected to dietary restrictions, whereas DeMeester examined only hospitalised patients on a standard diet. At any rate, the high number of upright refluxers in the Italian series makes the habit of indiscriminately treating reflux oesophagitis with a single bedtime dose of a H₂ receptor blocker questionable.

To achieve better results, the choice of administering the drug in the morning and at bedtime or only at night should be based on the results of 24-hour pHmetry. For practical reasons we cannot expect that each and every subject with reflux oesophagitis can have previously been submitted to the test in order to obtain a 'personalised' therapy. On the other hand, at least in patients who fail to respond to treatment, the time of administration of H₂-

blockers should be adjusted to the results of pHmetry. This does not apply to omeprazole, the long lasting action of which makes it irrelevant the time of administration. The superior results observed with omeprazole, including healing of most cases resistant to H₂-blockers, possibly rely not only upon its greater antisecretory effect, but also upon its ability to suppress the acidity of refluxate throughout the whole day.

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Macrophage activity in inflammatory bowel disease

SIR,—I read with interest the recent article by Mahida and coworkers.¹ They clearly showed that macrophages isolated from inflamed colonic or ileal mucosa in Crohn's disease show an enhanced respiratory burst compared with those isolated from normal mucosa.

I disagree, however, with their conclusion that the respiratory burst capacity of macrophages isolated from normal colonic and ileal mucosa is downregulated compared with inflamed bowel.

It is well recognised (since the original observation by Metchnikoff that macrophages in infected hosts respond more vigorously to the introduction of phagocytic particles²) that tissue macrophages exist as two distinct populations;^{3,4} (i) Resident/basal (poorly active) state. (ii) Primed/transformed (activated) state. Macrophages in both states can produce free radicals and release lysosomal enzymes. Those macrophages which are in the primed (transformed) state, however, will react much more vigorously.^{4,5} A number of stimuli will provoke this transformation—for example, prostaglandin E₂, lipopolysaccharide, C5a, tumour necrosis factor, gamma interferon and fMLP (N-formylmethionyl-leucyl-phenylalanine), BCG vaccination, corynebacterium parvum inoculation, and low concentrations of A23187 (calcium ionophore).^{4,6}

Thus those macrophages isolated from inflamed mucosa in inflammatory bowel disease have been upregulated (activated) into a primed state as a consequence of the inflammatory process.

The authors were able *in vitro* to show a response with IFN- γ but not lipopolysaccharide upregulating macrophages isolated from normal colonic mucosa, and it may be that

other factors are important *in vivo* in enhancing this response.

Free radical production by activated macrophages may be an important mechanism of tissue injury in inflammatory bowel disease.

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Helicobacter associated gastritis in patients with duodenal ulcer: the influence of various drugs

SIR,—We read with great interest the study reported by Loffeld *et al*¹ on the effects of colloidal bismuth subcitrate (CBS) on Helicobacter associated gastritis in patients with non-ulcer dyspepsia.

We report here our preliminary results of a study, concerning the influences of CBS, sucralfate and ranitidine on Helicobacter associated gastritis in patients with active duodenal ulcer (DU).

Thirty one patients with active duodenal ulcer who fulfilled the following criteria were included in the study: all patients were subjected to upper GI endoscopy and biopsy twice that is, before any therapy started as well as six weeks afterwards; biopsies were taken from the gastric antrum for HLO test (1-2) and histological examination (2-3); thus, the presence of helicobacter associated gastritis was initially confirmed and subsequently followed up in all the patients. Sections for histological detection of helicobacter like organisms (HLO's) were stained with Giemsa stain.

HLO test results were arbitrarily classified into four grades, as follows: grade 3: positive within the first 20 min of inoculation; grade 2: positive within the first two hours; grade 1: positive within the first 24 hours; grade 0: negative.

Antral gastritis was classified histologically into four grades (1, 2, 3, 4) according to Hafter and Siebenmann² by one pathologist (PD); semi-quantitative estimation of HLO's presence on biopsy material was made by the same pathologist 'blindly'—that is, without any information on the HLO test results. There was, however, reasonable correlation between his semiquantitative estimation and the HLO test results. If HLO test was positive and the histology failed to show HLOs, or *vice versa*, the HLO test was considered to be positive, grade 1.

The patients were divided into three groups (a, b, c) according to the medication given: Patients in group a (12) were given CBS, 240 mg/bid, in group b (13) sucralfate, 2 g/bid, and

in group c (6) ranitidine, 150 mg/bid. χ^2 with Yates' correction and Wilcoxon's test for pair differences were used for statistical analysis.

Our results show there was a reduction in the percentage of patients with gastritis grade 4 and 3 put together, by the end of six weeks. The difference was substantial but not significant, in patients treated with CBS (before treatment: 50%, after treatment: 17%). The small number of patients in group c does not guarantee any relevant suggestion for this group. No differences were found in gastritis grading in any one of the studied group, before and after treatment.

There was a substantial but insignificant reduction in the percentage of HLO positive, grade 3 and 2 patients by the end of six weeks treatment with CBS or sucralfate; 25% of CBS and 15% of sucralfate treated became HLO test negative. On the contrary, all the patients treated with ranitidine became HLO positive, grade 2 and 3, by the end of six weeks.

No significant differences were found in HLO test grading in any group of patients before and after treatment.

None of the drugs studied significantly improved gastritis, although CBS reduced substantially the percentage of patients with gastritis grade 4 and 3. Others have found CBS to significantly improve *Helicobacter* associated gastritis in patients with non-ulcer dyspepsia¹ as well as in a mixed population of patients suffering from duodenal ulcer, gastric ulcer and non ulcer dyspepsia, by the end of four weeks treatment.² This discrepancy could be caused by the rather small number of patients in our study. Another interesting finding was that two patients on sucralfate therapy became *Helicobacter pylori* negative, by the end of six weeks treatment. Others³ have found no influence of sucralfate on *Helicobacter pylori*. Our finding could be due to sampling error or perhaps the concomitant use of some other drugs that is, amoxicillin or metronidazole by these two patients.

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Lectin binding sites in the jejunal mucosa of patients with gluten sensitive enteropathy

SIR, — We have read with interest the article by Vecchi *et al* (*Gut* 1989; 30: 804-10) concerning the histochemical distribution of glycoconjugates investigated by lectins in the jejunal mucosa of patients with gluten sensitive enteropathy and subtotal villous atrophy. Four patients with coeliac disease and 10 patients

with dermatitis herpetiformis were studied; in addition 10 jejunal biopsies taken from patients with irritable bowel syndrome, showing normal morphology were used as controls. Although our experience has been reported in a previous study¹ this was not cited by Vecchi *et al*. In our study we have investigated the lectin binding sites in duodenojejunal mucosae from 119 coeliac children (67 with subtotal villous atrophy and 52 with partial villous atrophy after gluten free diet for 12 months) (age range 1-12 years); moreover, 16 biopsies obtained from infants with short stature and normal intestinal mucosa and nine specimens obtained from infants suffering from postenteritis syndrome were also utilised as normal and pathological controls respectively.

It would be of interest to know the age of patients studied in the paper by Vecchi *et al*; in addition no information about the blood groups of patients is available in this study.

Comparisons can be made on the different results obtained by Vecchi *et al* with ours. Our findings show WGA and DBA in normal mucosae are different from those of Vecchi *et al*, in which a constant positivity at the tip of villi and in goblet cells was observed; the latter findings were similar to our pathological control mucosae. Moreover, Vecchi *et al* considered 10 normal patients suffering from chronic diarrhoea with a final diagnosis of irritable bowel disease; these patients are indeed comparable with our pathological controls. Therefore we contend that only patients without gastrointestinal symptoms and histologically normal intestinal mucosa must be chosen as normal controls, especially in studies assessing lectin binding sites in pathological tissues.

In pathological specimens, there is striking disagreement about the distribution of some lectins; in particular WGA was evident in our coeliac mucosae and pathological controls, whereas no reactivity was encountered in normal control mucosae. On the contrary, Vecchi *et al* reported no differences in the WGA pattern in pathological and 'normal control' mucosae. As regards DBA distribution, Vecchi *et al* observed an evident decrease of goblet cells reactivity in mucosae with subtotal villous atrophy in comparison with controls and they suggested an incomplete maturation of goblet cells; on the contrary we have documented the appearance of goblet cells reactivity in coeliac patients and pathological control mucosae. The DBA reactivity is considered to be a specific marker of human colonic mature goblet cells,^{2,3} as also outlined by Vecchi *et al*; it is noteworthy that colonic mature goblet cells contain acidic sulphated mucosubstances, which are absent in normal duodenojejunal mucosa. In coeliac mucosae, however, we have previously shown with high iron diamine - alcian blue pH 2.5 (HID-AB method), the presence of weak and strong acidic sulphomucins.⁴ This fact may be related to the DBA reactivity found in our coeliac mucosae, suggesting the appearance of new specific lectin binding sites. Additional evidence on the appearance of sulphated glycoproteins was the finding of the PNA expression in our coeliac mucosae in comparison with normal and pathological control mucosae. The latter datum is another divergent point with negative findings by Vecchi *et al* in their control and pathological mucosae.

Finally, Vecchi *et al* suggest that further studies about the lectin binding pattern in the jejunum of patients with GSE on a gluten free diet would be useful. In the aforementioned paper, we have extensively studied the lectin binding pattern in 52 treated coeliac patients on

a gluten free diet for at least 12 months; in particular, data concerning WGA, DBA and PNA obtained in these patients were similar to those found in untreated coeliac children. The hypothesis of a primary defect of the glycoconjugates metabolism in coeliac disease remains to be investigated in more extensive studies.

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Reply

SIR, — We appreciate the comments of Barresi and colleagues, who point out some very important matters of discussion on the use of lectin histochemistry. We feel, however, that the two studies cannot be considered fully comparable because of clinical and methodological differences.

First, while Barresi *et al* report the results obtained in a pediatric population,¹ our series consisted of adult patients only.² Although it is not known if age may induce changes in the lectin binding pattern in human subjects, this seems to be the case in animals.^{3,4} Indeed, the lectin binding pattern observed by Barresi *et al* differs not only from what we have observed but also from what has been observed by other authors.^{5,7}

In fact, as also mentioned by our colleagues, DBA has been shown to react with at least some of normal jejunal specimens studied by other authors.⁵ Furthermore, WGA reactivity of both epithelial and goblet cells is a common finding in normal jejunal mucosa, as described by other authors^{6,7} and is one of the most consistent findings in our experience.^{2,8} Staining with PNA has been reported to occur even in normal specimens by other authors⁹ but no evidence of staining was observed by us in either normal or pathological jejunal mucosa.^{2,8}

If these differences are indeed due to the fact that the only normal controls studied so far are those reported by Barresi *et al*,¹ as the authors suggest, is also not known. Their statement is based on the absence of any gastrointestinal symptom in their children of short stature. Short stature in children and chronic diarrhoea in adults, however, are both suggestive of coeliac disease. Thus, we believe that the presence of normal jejunal mucosa architecture, together with the negativity of other functional and serological evaluations (which were all performed in our patients) should be considered as sufficient evidence to rule out the disease in our patients with diarrhoea as well as in their children with short stature.

Lectin histochemistry is a useful and interesting tool for the study of tissue glycoconjugates. One should keep in mind, however, the fact that the use of different fixatives and of different tissue processing techniques may affect the presence and availability for staining