

Reply

SIR,—The comments of Drs Colombel, Janin, and Torpier are of interest. We agree that the immune processes which may contribute to the mucosal lesion of coeliac disease may be multifactorial. The eosinophil is a major component of the inflammatory infiltrate in coeliac disease, although this is frequently not emphasised in descriptions of the lesion. We have recently produced additional evidence that eosinophils and polymorphs are present in increased numbers in the coeliac mucosa: using monoclonal antibodies to Fc receptors (for the gamma chain of IgG) types II and III, which are found on eosinophils and polymorphs, a marked increase in reactive cells was found. The evidence of Dr Colombel and colleagues that many of these eosinophils have degranulated and the associated finding of increased release of granule components points to mechanisms whereby eosinophils might mediate damage. The possibility that IgA, produced in large quantities in the damaged intestine, may be involved in eosinophil degranulation through interaction with IgA Fc receptors should also be considered.

The finding that many coeliac patients react rapidly to gluten challenge (both symptomatically and histologically) is in keeping with more immediate mechanisms of damage also participating in the development of the lesion. Eosinophils are good candidates for such a mechanism.

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Omeprazole in H₂ blocker non-responders

SIR,—The results of the study by Delchier *et al*¹ on the similar effectiveness of omeprazole 20 mg mane and ranitidine 150 mg twice daily in H₂ receptor blocker non-responders are very interesting, but also the comments by Bate² on this paper are important. We fully agree with Bate's opinion that a six week treatment cannot be judged sufficient to define resistance to H₂ blockers, because ulcer healing rates further increase by continuing therapy with these drugs to eight weeks.³ It must also be emphasised that the adoption of unstandardised definitions of ulcer refractoriness continues to generate confusion in this field and prevents a useful comparability of findings pertaining to different studies.

Even though Delchier and colleagues adopted patient selection criteria which may have greatly influenced their final results, it is worth pointing out that the reduced efficacy of omeprazole in their trial is a relevant factor in determining the lack of significant difference between this drug and ranitidine in healing resistant ulcers. As the authors discussed in their paper, the well known variability of individual response to single daily doses of omeprazole 20 mg^{4,5} may be the most reasonable explanation for the low efficacy of this dosage regimen in their study compared with the impressive one obtained in other trials which tested single daily doses of omeprazole 40 mg.⁶⁻⁸ Some of our recent data seem to sustain their supposition. We used 24 hour continuous pH-metry⁹ to study two patients with endoscopically proven duodenal ulcers on the fifth day of treatment with omeprazole 20 mg mane. As reported in the Figure, the

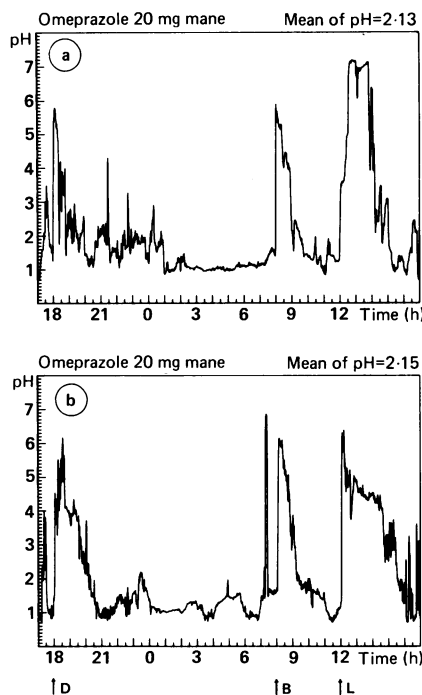


Figure: 24 hour gastric acidity profiles of two duodenal ulcer patients on the fifth day of treatment with omeprazole 20 mg mane. (D=dinner, B=breakfast, L=lunch.)

circadian profile of gastric acidity of both patients resulted poorly influenced by the drug. These findings show that the antisecretory effect of omeprazole 20 mg is very low in some subjects and the variability in acid suppression with this dosage can be even higher than previously reported.^{4,5} The reasons for this are at present unclear, but a derangement in the pharmacokinetic pathways of the drug might be involved.¹⁰ As regards patients' compliance, we could check daily drug intake because they were hospitalised.

On the basis of our data, it seems advisable to take into consideration the authors' suggestions that omeprazole 40 mg is probably the optimal dosage for treating H₂ blocker non-responders and that 24 hour pH monitoring could be valid for verifying whether the clinically recommended dose of omeprazole 20 mg in duodenal ulcer disease,¹¹ is really appropriate in individual patients.

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Reply

SIR,—I read with interest the comments by Bate¹ and Savarino *et al* on our paper.² They both pointed out that duodenal ulcers cannot be regarded as truly 'resistant' after only six weeks of treatment with an H₂ blocker. I do not fully agree with their opinion. In 1990, a duodenal ulcer remaining unhealed after six weeks has to be considered a treatment failure. Indeed, the actual question is: What is the best strategy to accelerate ulcer healing? This is especially important in patients with persisting symptoms or/and at risk related to age, associated disease or anticoagulation. . . . Our results and those of Tytgat *et al*³ clearly suggest that the adequate dosage of omeprazole is rather 40 mg than 20 mg. As recently outlined by Bardhan,⁴ another problem is to determine both the adequate drug and dosage to be used in maintenance treatment once healing has been achieved in initially resistant patients. In this regard, results reported by Savarino *et al*⁵ suggest that 24 h-gastric pHmetry could be helpful to select patients requiring maintenance treatment with high doses of omeprazole.

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Epithelial dysplasia in Caroli's disease

SIR,—We read with interest the report by Fozard *et al*¹ of Caroli's disease complicated by dysplasia of biliary epithelium in the absence of invasive carcinoma. We recently saw similar changes in a 60 year old man presenting with recurrent episodes of epigastric and right upper quadrant abdominal pain associated with jaundice, pale stools, and dark urine. ERCP showed numerous calculi within a grossly dilated left intrahepatic ductal system but no proximal stricture or obstruction, changes consistent with Caroli's disease. A formal left hepatic lobectomy was performed. In the resected liver, parenchyma was largely replaced by dilated bile ducts containing

numerous calculi and showing fibrous thickening of their walls. The ducts were lined by normal and mildly to severely dysplastic biliary epithelium. Severe dysplasia was characterised by cellular crowding, stratified pleomorphic nuclei with prominent nucleoli, and a papillary surface (Figure). No invasive carcinoma was identified.

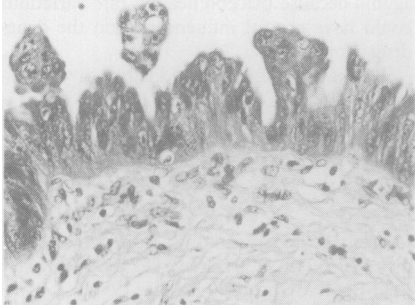


Figure: Severe dysplasia of epithelium in dilated bile duct.

Epithelial dysplasia is frequently seen adjacent to cholangiocarcinoma in the intra- and extrahepatic bile ducts and carcinoma of the gall bladder which has a similar epithelial lining.¹ Extensive severe epithelial dysplasia involving the gall bladder, cystic duct, and common bile duct, associated with adenocarcinoma of the common hepatic duct, was recently reported in a patient with primary sclerosing cholangitis and chronic ulcerative colitis,² diseases which, like Caroli's disease,³ are associated with an increased risk of cholangiocarcinoma. These findings, and that of epithelial dysplasia unassociated with carcinoma in Caroli's disease, provide evidence of the premalignant nature of biliary epithelial dysplasia. Because such dysplasia is usually detected only in surgical specimens, we agree that early resection of localised forms of Caroli's disease may be necessary to prevent late complication by cholangiocarcinoma.¹

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IgA class reticulin antibodies of human subtype in gluten sensitive enteropathy

SIR,—We read with interest the paper of Dr Hallström in the September issue (*Gut* 1989; 30: 1225-32) entitled 'Comparison of IgA-class reticulin and endomysium antibodies in coeliac disease and dermatitis herpetiformis'.

In the discussion the author refers to our article 'IgA class antibody against human jejunum in sera of children with dermatitis herpetiformis' (*J Invest Dermatol* 1986; 87: 703-6), as follows: 'R₁-type of reticulin antibodies reacting with human liver and spleen has also been described previously and already Seah *et al*¹ and Eterman *et al*² showed that such antibodies can react with human jejunum, a finding recently confirmed also by Kárpáti *et al*.³ Here we described for the first time IgA type antibodies binding to human jejunum and that they may be related to reticulin antibodies. An IgG type reticulin antibody reacting with human small bowel was seen by Eterman *et al*². . . the IgG type of reticulin antibodies were reported of low frequencies (18-46%) and low specificity (75-85%) in coeliac disease. In contrast, IgA class reticulin antibodies seem to be more sensitive and specific'. (From the introduction of Dr Hallström's paper.)

Jejunal antibodies have distinctive characteristic signs compared with other IgA type reticulin antibodies: they bind to the small bowel, which is the damaged organ in gluten sensitive enteropathy and they bind at the site of gluten absorption which is the precursor of the disease. In addition, the binding site of IgA type jejunal antibody corresponds to or is very similar to the extracellular IgA deposition detected in the diseased jejunum of patients with gluten sensitive enteropathy. Because of the damaged structure of coeliac jejunum, this similarity can be ascertained by investigating the diseased small bowel of patients with almost normal villous structure: (a) in jejunal biopsy samples taken several hours to one to two days after gluten challenge in coeliac

patients who have recovered on gluten free diet'; (b) we found IgA deposits in the small bowel of dermatitis herpetiformis patients with almost normal jejunal structure.'

In the present work Dr Hallström found both the endomysium, and IgA type reticulin antibodies to be very important in the diagnosis of gluten sensitive enteropathy, and by absorption studies the endomysium antibody (substrate: monkey oesophagus) was related to the human subtype of reticulin antibodies and was distinguished from that of rat subtype. We think that if antihuman antibodies are important in considering the pathogenesis of coeliac disease, they must be related to the IgA type antibodies reacting with human jejunum.

We conclude that one of the reticulin antibodies category mentioned does not correspond to the pathological concept of the IgA type jejunal antibodies supplied in our study.

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BOOK REVIEWS

Common problems in gastrointestinal surgery. Vol 1. By Josef E Fischer. (Pp 451; illustrated; £36.) London: Wolfe Medical, 1989.

Common problems in gastrointestinal surgery is one of a series produced by Year Book Medical Publishers on a variety of surgical subjects. The contribution in question is edited by Joseph Fischer, chairman of surgery at the University of Cincinnati. The approach is refreshing and novel. Each chapter is introduced by a specific clinical problem: four to eight line case history, one or more consultant is then asked to comment. Most contributors are pithy and to the point. Their comment usually consists of a brief overview of the literature, some reference to pathophysiology followed by the contributors own view on management. The book is largely, I suspect, designed to assist the private practitioner in North America to provide optimum clinical management based upon the views of experienced clinicians. The layout, diagrams and artwork are pleasing. Only key references are provided. The contributors: 66 in all are household names in GI circles, a few have been retired from practice for a variable time but most are regarded as contemporary experts in their disciplines. Only three are not from the USA (two from the UK and one from Canada). The reader must therefore expect a strong USA perspective.

Surprisingly the section on oesophageal and thoracic problems does not include any contribution on oesophageal carcinoma which

some will find surprising with the development of endoscopic endoluminal ultrasonography, the growing recognition of early oesophageal cancer and the impact of low morbidity bypass, intubation and laser therapy on palliative therapy. I find it curious to come across two breast problems in the thoracic section.

The gastroduodenal section includes a single contribution on GI bleeding. The emphasis, as is prevalent throughout the book, is on surgical treatment without even reference to endoscopic assessment or the role of endoscopic therapy. The medical:surgical divide is a real one in North America and the concept of joint management is not one that flavours this book.

The hepatobiliary section is varied and interesting, but it is difficult to do justice to all that has occurred over the last decade in liver transplantation by reference to a single case report.

The endocrine section makes interesting reading, but the gastrointestinal component of many case reports is enigmatic.

There is some unfortunate duplication in the colorectal section particularly with reference to diverticular disease and regional enteritis. The important clinical problem of major colonic haemorrhage takes no account of rapid bowel preparation and therapeutic endoscopy or the impact of intraoperative panendoscopy on surgical strategy.

This is a bold and attractive approach to a surgical update. In gastroenterology it must include joint management with gastroenterologists. The experiment has been a good one