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.

CONLETH FEIGHERY
DONALD WEIR
ALEX WHELAN
St James's Hospital, PO Box 580, Dublin 8, Ireland

Omeprazole in H_2 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 H_2 receptor blocker non-responders are very interesting, but also the comments by Bate[2] 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 H_2 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-metry[9] 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

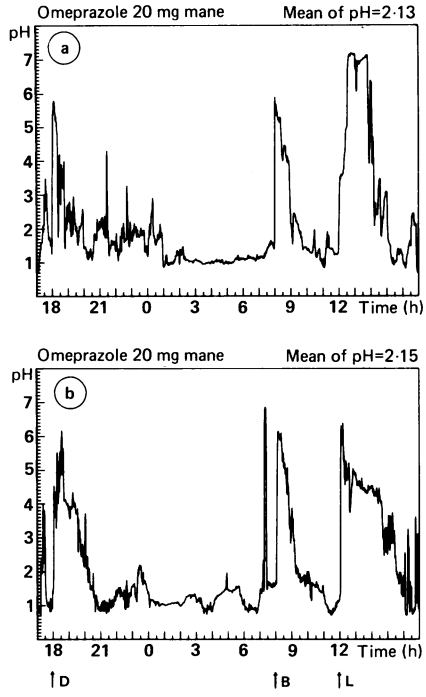

Figure: 24 hour gastric acidity profiles of two duodenal ulcer patients on the fifth day of treatment with omeprazole 20 mg mane. (D=dinner, B=breakfast, L=lunch.)

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 H_2 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.

V SAVARINO
G MELA*
A SUMBERAZ
G CELLE
ISMI—Cattedra di Gastroenterologia and Clinica Medica R Università di Genova, Italy*

1 Delchier J-C, Isal J-P, Eriksson S, Soule J-C. Double blind multicentre comparison of omeprazole 20 mg once daily versus ranitidine 150 mg twice daily in the treatment of cimetidine or ranitidine resistant duodenal ulcers. *Gut* 1989; **30**: 1173–8.
2 Bate CM. Omeprazole v ranitidine. *Gut* 1989; **30**: 1437–8.
3 Howden CW, Jones DB, Hunt RH. Nocturnal doses of H2 receptor antagonists for duodenal ulcer. *Lancet* 1985; i: 647–8.
4 Sharma BK, Walt RP, Pounder RE, Gomes M de FA, Wood EC, Logan LH. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. *Gut* 1984; **25**: 957–64.
5 Lanzon-Miller S, Pounder RE, Hamilton MR, *et al*. Twenty-four hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine and omeprazole. *Aliment Pharmacol Ther* 1987; **1**: 239–51.
6 Tytgat GNJ, Lamers CBHW, Hammeeteman W, Jansen JMBJ, Wilson JA. Omeprazole in peptic ulcers resistant to histamine H2-receptor antagonists. *Aliment Pharmacol Ther* 1987; **1**: 31–8.
7 Brunner G, Creutzfeldt W, Harke U, Lamberts R. Therapy with omeprazole in patients with peptic ulcerations resistant to extended high-dose ranitidine treatment. *Digestion* 1988; **39**: 80–90.
8 Bardhan KD, Naesdal J, Bianchi Porro G, *et al*. Omeprazole (OM) in the treatment of refractory peptic ulcer (RPU). [Abstract] *Gastroenterology* 1988; **94**: A22.
9 Savarino V, Mela GS, Zentilin P, *et al*. Gastric aspiration versus antimony and glass pH electrodes. A simultaneous comparative in vivo study. *Scand J Gastroenterol* 1989; **24**: 434–9.
10 Howden CW, Merdith PA, Forrest JAH, Reid JL. Oral pharmacokinetics of omeprazole. *Eur J Clin Pharmacol* 1984; **26**: 137–9.
11 Clissold SP, Campoli-Richards DM. Omeprazole. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. *Drugs* 1986; **32**: 15–47.

Reply

SIR,—I read with interest the comments by Bate[1] 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 H_2 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*[2] suggest that 24 h-gastric pHmetry could be helpful to select patients requiring maintenance treatment with high doses of omeprazole.

J DELCHIER
Unité INSERM 99 et Service d'Hépatogastroentérologie Hôpital Henri MONDOR, 94010 CRETEIL CEDEX, France

1 Bate CM. Omeprazole versus ranitidine. *Gut* 1989; **30**: 1437–8.
2 Delchier JC, Isal JP, Eriksson S, Soulé JC. Double-blind multicenter comparison of omeprazole 20 mg once daily versus ranitidine 150 mg twice daily in the treatment of resistant duodenal ulcers. *Gut* 1989; **30**: 1173–80.
3 Tytgat GNJ, Lamers CBHW, Hammeeteman W, Jansen JMBJ, Wilson JA. Omeprazole in peptic ulcers resistant to histamine H2-receptor antagonists. *Aliment Pharmacol Ther* 1987; **1**: 31–8.
4 Bardhan KD. Treatment of duodenal ulceration: reflections, recollections, and reminiscences. *Gut* 1989; **30**: 1647–55.

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