LETTERS TO THE EDITOR

Reflux oesophagitis and acid exposure

EDITOR,—The interesting finding by Holloway *et al* is their pH findings of patients on omeprazole 20 mg compared with 40 mg (*Gut* 1996; **38:** 649–54). There seems to be a paradoxical rise in acid exposure in the face of an increased omeprazole dose. Their findings are not logical and have three possible explanations: firstly, a typographical error in their Table; secondly, unreliable pH recordings and thirdly, a genuine increase in acid exposure with higher doses of omeprazole. The actual numbers are not given and are likely to be small, making statistical significance dubious but the supine acid exposure rises from 24·9% on omeprazole 20 mg to 33·0% on the 40 mg dose. This is likely to represent 'rebound acid secretion' at night after the suppressive effects of the morning dose of omeprazole have worn off. This 'rebound acid secretion' effect is shown in their study with H_2 antagonists, which show higher pretreatment acid exposure. The 'rebound acid secretion' phenomenon is clinically important as it implies that 24 hour acid suppression is necessary to attain healing in severe oesophagitis. Cardiologists are aware that blood pressure control needs to be maintained over the complete 24 hours to be effective and gastroenterologists need to become aware that complete 24 hour control of acid suppression is important in reflux oesophagitis. Developments in proton pump inhibitors need to be towards increasing the half life and duration of action.

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Reply

EDITOR,—Dr Ransford has questioned the apparent increase in supine oesophageal acid exposure during treatment with omeprazole. He suggests that these findings are not logical and proposes three explanations. However, while we agree that at first glance the findings might appear paradoxical, we disagree with his interpretation and explanations.

Firstly, we believe that Dr Ransford has over interpreted the importance of the apparent increase in median acid exposure time. The value for supine acid exposure in the 40 mg omeprazole was not significantly different from that with 20 mg and we believe that it is more appropriate to conclude that supine acid exposure was not decreased in patients whose oesophagitis did not heal. Similar results were found with the 20 mg dose when compared with the pre-treatment levels in the patients who did not heal with 20 mg. While small patient numbers may have obscured a potential real increase in the patients who receive 40 mg, one cannot assume this is so and this explanation is highly unlikely in the case of the 20 mg dose where patient numbers were adequate.

Secondly, the findings cannot be explained on the basis of rebound hypersecretion as, in contrast with acid inhibition with H_2 antagonists, this does not occur with omeprazole.[1]

In our view the most plausible explanation for the findings is that there was no significant inhibition of supine oesophageal acid exposure in the patients who failed to heal, and that the higher median value represents intrasubject variability in supine acid exposure, which is known to be greater than in total or upright acid exposure.[2 3]

We agree that adequate control of acid secretion throughout the 24 hour period is important to heal oesophagitis. However, whether or not the answer lies in the development of proton pump inhibitors with a longer half life and duration of action is debatable. The duration of action of omeprazole is unrelated to its plasma half life. Increasing the duration of action might increase the adverse effects of prolonged acid secretion. There is some evidence that patients who appear refractory to omeprazole have more rapid metabolism of omeprazole[4 5] and perhaps this would be a more productive field for development of new proton pump inhibitors. An even better approach, however, would be to develop drugs that would inhibit reflux by improving control of lower oesophageal sphincter function.

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5 Van de Mierop F, Flockhart D, Gallagher J, *et al.* Omeprazole metabolsim in refractory GERD: pharmacokinetics and pharmacodynamics. *Gastroenterology* 1995; **108:** A249.

Microvascular disease in the human large bowel

EDITOR,—I read with interest the paper by Fawcett *et al* (*Gut* 1996; **38:** 714–8) concerning the presence of microvascular disease in human large bowel and its relation to smoking, hypertension, and anastomotic healing after colorectal resection.

These authors examined material histologically from 147 patients who had undergone colectomy for a variety of diseases. They recorded the presence (or absence) of intimal hyperplasia, medial degeneration, and atherosclerotic plaque formation but do not mention how they assessed the incidence of these lesions in the sections examined or the criteria used to decide whether any microvascular lesions noted were significant or not. Furthermore, the authors make no mention of any other morphological vascular change, such as medial hypertrophy, which has been shown to be present in the intramural vessels in patients with systemic hypertension.[1] Not withstanding these findings, direct statistical comparisons (χ^2) between the presence of microvascular lesions and other parameters, such as smoking, hypertension, and anastomotic failure were made. The authors found that smoking and systemic hypertension were significantly associated with microvascular disease, mainly in the form of intimal hyperplasia.

Although sporadic lesions of the distal mesenteric and intramural vessels have been noted by several authors,[2–5] it was our group who first systematically examined these changes quantitatively in human gut using vascular morphometry.[1 6–8] In these studies the medial and intimal thicknesses of small extramural and intramural arteries (>100 μm in external diameter) and arterioles (<100 μm in external diameter) were measured under light microscopy; these indices being expressed as a percentage of external vessel diameter.[1] The incidence of intimal thickening (intimal fibrosis and intimal longitudinal smooth muscle) was also calculated by dividing the number of vessels with intimal thickening by the total number of measured vessels. Using these techniques, 2760 vessels from 53 patients were analysed. A positive correlation between the degree of medial hypertrophy of both small mesenteric arteries and intramural arterioles and the level of diastolic blood pressure was observed. Taken in conjunction with reduplication of the internal elastic lamina, which is a common feature of hypertrophied vessels, our results indicate that small arteries and arterioles of the gut undergo the same changes as vessels in other organs in response to chronic hypertension. These changes may be regarded as adaptive and prevent overdistension of vessels in response to raised intravascular pressure. With respect to intimal disease, a direct relation between the level of diastolic blood pressure and the degree and incidence of intimal fibrosis of intramural arteries and arterioles was shown.[1] Important age related changes were also observed in that the incidence of intimal fibrosis increased progressively with age in both extramural and intramural arteries and arterioles. The mean (SD) intimal thickness was 6 (1·9)% of external vessel diameter and the mean number of small arteries and arterioles affected was 16·7 (15·7)%, (mean age=63·4 years; range=11 to 82). In contrast with Fawcett *et al,* we were unable to demonstrate any statistically significant correlations beween smoking and medial or intimal thickness of extramural or intramural vessels.[1] We concluded that any microvascular disease of the gut in smokers is probably the result of associated hypertension. Most of the vascular changes in our material were seen in the submucosal layer of the bowel wall.

There has been much speculation about the significance of these vascular lesions. In distal mesenteric arteries it is probable that structural alterations reduce vascular compliance, impair the ability of vessels to dilate, and contract and interfere with the regulation of regional blood flow. Moreover, both medial hypertrophy and intimal fibrosis cause a decrease in internal vessel diameter[1] and increase resistance to blood flow. Furthermore, because blood flow is inversely related to the fourth power of internal vessel radius, even minor degrees of medial hypertrophy and intimal hyperplasia could be expected to significantly reduce flow within the gut microcirculation.

Fawcett *et al* make an unreferenced statement in the discussion section of their paper that the submucosa derives its blood supply from the serosal plexus. This conclusion is not in keeping with the findings from several microradiographic studies,[1 8–13] which show that the submucosa is the most vascular layer of the bowel wall and that the mucosa, mus-