

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 H₂ 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 H₂ 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 intra-subject 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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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 Notwithstanding 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 μ m in external diameter) and arterioles (<100 μ m 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 between 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 diameter¹ 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-

cularis, and serosa receive their blood supply by secondary branches from the submucosal plexus of vessels.^{1,8} Vasa recta have clearly been demonstrated passing through the bowel wall and joining the submucosal plexus.^{1,6} Hence it seems probable that reduced serosal perfusion stems from either extramural vascular disease or obliterative lesions within the submucosal plexus.

The colonic microcirculation represents the final common pathway for the delivery of oxygen and nutrients to the tissues of the bowel wall and we agree with Fawcett *et al* that its integrity is critical to successful anastomotic healing. However, the importance of the serosal plexus, as emphasised by these authors remains open to question. It is noteworthy that the distal two thirds of the rectum is devoid of serosa and hence it is untenable that the vascularity of this layer plays any part in the healing of anastomoses below the peritoneal reflection. Based on our own micro-radiographic and fluorescent x ray analysis studies,^{1,12-14} the submucosal region provides the cornerstone of perfusion of other layers of the bowel wall. We believe that preservation of the submucosal plexus by careful extramucosal appositional anastomosis provides the most favourable set of circumstances for uneventful anastomotic healing.

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In our study, the incidence of microvascular disease was assessed by examining all vessels apparent in at least two sections taken from the anastomotic margins. (Sections taken further away may not necessarily reflect the state of the vasculature at the anastomosis.) The incidence of the lesions can be easily assessed visually, particularly in the intima, which is normally only one to two cell thicknesses wide. Histological analysis was focused on intimal changes rather than others already well documented such as medial hypertrophy, because, as the discussion section of the paper indicates, our main interest is in the possible altered response to vasoactive substances that may occur in the presence of a diseased endothelium.

Mr Carr and his group were unable to show a correlation between smoking and microvascular disease in their research. We cannot explain this difference in results with any certainty, but would suggest that one reason for this discrepancy may be that this study, while examining fewer vessels overall than did Carr *et al*, involved nearly three times as many patients. Our study showed that not all smokers exhibit colonic microvascular disease. Thus the smaller the number of patients involved, the less likely it is one would find a significant correlation if it existed.

Our description of the submucosa 'deriving' its blood supply from the serosa is poorly phrased and we apologise for this. We accept that the serosa is principally supplied by recurrent branches arising from the submucosal plexus. Our intention was simply to point out that to reach the submucosal plexus, the vessels must pass through the serosa. If disease is present in the vessels as they traverse the serosa, this clearly may affect the distal circulation. We thus agree that submucosal perfusion may still be the critical factor in anastomotic healing, as we stated in the paper.

We would take issue, however, with Mr Carr's comments concerning the role of the serosal layer in anastomoses formed below the peritoneal reflection. While it is true that the distal two thirds of the rectum has no serosal covering, the proximal end of such anastomoses are formed by intraperitoneal colon, which does have a serosal coat. The significance of this serosal coat and its vascularity is open to question, but it is of interest to note that when a colorectal anastomosis breaks down as a consequence of ischaemia, it is more often than not the proximal end of the anastomosis that is at fault.

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There have been few advances in modern general surgery that have had such an impact on the management of a common problem as the introduction of laparoscopic cholecystectomy (LC). This book commemorates the first five years of its widespread use by reporting the details of an international meeting held in Bern, Switzerland in May 1995. It generally represents a European perspective but there is limited US input.

The volume begins with a general introduction to gall stone disease, which includes chapters on the pathogenesis of gall stones, the assessment of patients, the types of treatment modalities available, and concludes with a summary of the history of cholecystectomy and a comparison between open versus laparoscopic procedures. Subsequent sections report on various different countries' experiences with LC and has chapters from surgeons in Switzerland, UK, Austria, Berlin, Hungary, and Chile.

There is a section devoted to 'advanced techniques' with articles on LC and acute cholecystitis and pancreatitis, the use of intraoperative imaging of the biliary tree with cholangiography and ultrasonography, and three separate chapters on the management of bile duct stones. Unfortunately, the authors of these latter sections sit comfortably on the fence and fail to provide hard advice on whether operative cholangiography should be done and the best way of managing bile duct stones under varying circumstances. Expert guidance could have replaced a 'balanced' reflection of controversies.

Predictably the volume finishes with a section on the complications of LC and their management. This covers experiences with high risk patients, access related complications, bile duct injuries and ends rather incongruously for the section with a chapter on gall bladder cancer.

Generally the volume is very readable and well presented, allowing the reader to browse rapidly through its contents and yet it contains a great deal of information on recent published data with regards to not just LC but also gall stone disease and cholecystectomy in general. One could envisage this summary of information being a very useful source of references when researching into this area and this is the volume's main strength.

There is little in the way of novel concepts contained within the book and it is not the best source for detailed information about the management of bile duct injuries for example. The section on the management on the complicated LC was generally rather weak and would have benefited from more pages of text with less emphasis on the experiences from different countries, the selection of which seemed arbitrary and I suspect reflected the individual biases of their respective authors.

While the width of topics covered was good, there were a couple of general omissions, namely: the impact of this technique on the training of surgeons and also the comparison of LC with minicholecystectomy, which received much attention in the recent Royal College of Surgeons of England systematic review. It would be interesting to know of the European experience with these two operations and how it compares with the UK.

Ultimately, the book is a useful source of references and background data but contains little new information to the experienced general surgeon.

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BOOK REVIEWS

Five years of Laparoscopic Cholecystectomy: A reappraisal. Progress in Surgery. Vol 22. By M W Büchler, E Frei, Ch Kläiber, L Krähenbühl. (Pp 216; illustrated; \$159.25.) Basel: S Karger 1996. ISBN 3-8055-6271-3.

Reply

EDITOR,—The work by Mr Carr on the colonic microcirculation is well known and we are grateful for his comments. He raises several points that require clarification.