LETTERS TO THE EDITOR

Osler's disease is not a telangiectasia but a tumour

SIR,—I have read with great interest the instructive article by Zentler-Munro *et al*¹ about an association of vascular abnormalities and hepatic fibrosis in Osler's disease. Above all, I was impressed by their photographs. In Figure 3, there are dilated vascular spaces practically devoid of erythrocytes and still other ones full of red blood cells. I covered the latter by white stain and looked with astonishment how few hepatocytes remained from original hepatic tissue. To all appearances, a tissue of hepatic lobules was almost destroyed by vessels the aggressive character of which reminds of tumoral growth instead of telangiectases.

As we believe that hyperplastic capillaries are involved in a pathogenesis of fibrosis, I looked for them in the article of Zentler-Munro *et al*.^{1,2} Having been unable to identify them, I turned to other articles concerning Osler's disease. I found them in an article by Tedesco *et al*³ who had described an angioma in the submucosa of a stomach and telangiectases associated with fibrosis in the liver.

Further, I was attracted by an article by Nödl⁴ who had studied cutaneous telangiectases. His outstanding photographs of pathological vessels surrounded by nonhaematopoietic mesenchymal cells (Figs 2, 3, 4, 5, 6, 7, 8) reminded me immediately of similar vessels that I had observed when I studied cutaneous vascular tumours.^{5,6} At that time, I described hyperplastic capillaries composed of epithelioid undifferentiated endothelial cells and situated in the vicinity of a capillary haemangioma, a haemangiopericytoma, and an angioleiomyoma. The capillaries were so similar to sweat glands that a careful morphological analysis was needed in order to distinguish these two structures. These hyperplastic capillaries could give rise: (a) to long narrow strips of smooth muscle tissue by an *in situ* differentiation of their cells into smooth muscle cells; (b) to pathological muscular vessels by a short distance centrifugal migration and a differentiation of their cells into vascular wall muscular cells; and (c) to ectatic capillaries surrounded by fibroblast-like cells by a migration of their cells into the extravascular space and their differentiation there.¹

A similarity between the vessels described by Nödl⁴ and the vessels I have observed suggests that Nödl described in reality tumoral lesions. I looked, therefore, for hyperplastic capillaries in his article. I found them in Figs 3, 4, 6c, 6d, 7, 8. Nödl does not mention them because he considers them to be sweat glands. Why I believe that at least some of these structures are hyperplastic capillaries: (1) a number, a location, and a morphology of pathological muscular vessels indicate that they are not formed by remodelling pre-existing normal vessels; (2) some of them are collapsed and undergoing involution suggesting their high turnover; (3) there are structures clearly recognisable as mesenchymal but similar to sweat gland tubules (Figs 3, 4, 6d—in the middle, 7—a large tubule on the right side, 8—on the right side); (4) referring to my previous observation,⁵

endothelial cells in the 'sweat glands' often degenerate, most probably because of hypoxia, and their nuclei form clusters leaving empty space in their vicinity (Fig 7—in the upper right corner); (5) endothelial cell nuclei often possess an elongated form. When they are oriented longitudinally hyperplastic capillaries manifest histopathological patterns incompatible with genuine sweat glands (Fig 7—in the upper right corner). Finally, there is a remnant of an original hyperplastic capillary composed of several layers of undifferentiated epithelioid endothelial cells (Figs 9, 10). Because there is no other pathological process present, the remnant is not a reactive hyperplasia but a manifestation of tumoural growth.

If Osler's disease is a vascular tumour anti-angiogenesis¹⁰ may be tried in its therapy. This proposition is supported by a successful treatment of this disease by medroxyprogesterone acetate,¹¹ an angiostatic steroid.¹²

There are several other diseases which present themselves as telangiectases but derive from hyperplastic tumoural capillaries. They are the senile haemangioma, *Cutis marmorata telangiectatica*,⁵ the vascular spider,¹³ and generalised essential telangiectasia (unpublished personal observation).

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Oesophageal carcinoma in Sri Lanka

SIR,—With reference to the article by Sagar (*Gut* 1989; **30**: 561-4), I wish to add that Sri Lanka was a transit point in the old silk route between China and Rome. Marco Polo also stopped over in Sri Lanka (then identified by him as Seilan) on his return from China.^{1,2} On the diet of the natives of the northern region of Ceylon, seven centuries ago, Marco Polo wrote,

'They have no grain other than rice. They have sesame, from which they make oil. They live on milk, flesh and rice and have wine made from trees'.

The wine he referred to, is known as 'kallu' in Tamil language, and is produced from the palmyrah palm *Borassus flabellifer*.

Stephen and Urugoda³ have reported that cancer of the oesophagus is the commonest among the patients admitted to thoracic units in Ceylon, and Ceylon is one of the few countries with a high incidence of both oral and oesophageal carcinoma. In China,⁴ the male-female ratio of patients with oesophageal cancer is reported as 2:1. But in Sri Lanka, the incidence of oesophageal carcinoma is higher among women than men.⁵

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Ranitidine nocte (Rhs) v ranitidine mane and nocte (Rbid)

SIR,—We wish to comment on the abstract by Dobrilla *et al* (*Gut* 1989; **30**: A726) stating that there is no significant difference between Rhs and Rbid healing rate at two weeks but the authors did not mention which statistical test and significance level they used.

We found, however, using the χ^2 test, without Yates correction, a significant difference between the two treatments at two weeks ($\chi^2 = 5.2$ resulting in a p value < 0.05).

It would be interesting to know why according to the authors the difference in healing rate was not significant at two weeks.

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Reply

SIR,—With regard to the letter of VanWilder and Jan Plas, the comment of these authors is correct but there is an error in our abstract.

In fact, while the reported ranitidine bid healing percentage by week two is correct (64.2%), the absolute figures are 102/159 and not 107/159, as indicated. Using the χ^2 test on the correct number of patients, the difference between the two treatment groups proves to be statistically not significant.

Further details can be found in the full paper which now has been published. (*Clin Trial J*) 1989; **26**: 153-62.

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H pylori and duodenal ulcer

SIR,—Dr Carrick and colleagues are to be congratulated on quantifying in their 137 subjects the strength of the risk factor for duodenal ulceration (relative risk = 51) of duodenal infec-

tion with *H pylori* (69/70=99%) compared with the smaller risk (RR=8) with antral infection with *H pylori* (85/96=89%).¹

In our series^{2,3} the frequency of duodenal ulcer in patients with *H pylori* in their duodenum was double the frequency of ulcers in the duodenums of patients with *H pylori* in their antra, which is why we suggested 'that duodenal *H pylori* may be more closely correlated with duodenal ulceration than is antral infection'.²

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Influence of treatment with pancreatic extracts on pancreatic enzyme secretion

SIR,—The article by Mossmer and colleagues (*Gut* 1989; 30: 1143-9) is a carefully conducted attempt to study the possible negative feedback regulation of pancreatic enzyme secretion. The authors point out a possible flaw in their design, in that they perfused the jejunum with enzymes, rather than the duodenum. Nevertheless they failed to show any negative feedback of pancreatic enzyme secretion. In fact their results are consistent with stimulation of CCK release from the jejunum by the protein load, with consequent increased pancreatic enzyme secretion. Similar results were obtained by two groups independently^{1,2} in studies in the dog. Duodenal perfusion with pancreatic juice in the basal state stimulated rather than inhibited pancreatic enzyme secretion.

Mossmer and colleagues cite the evidence for negative feedback inhibition of pancreatic enzyme secretion in the rat, pig, and chicken.

Their study emphasises once again the difficulties of extrapolating into man from results obtained in other species. Recommendations for expensive treatment with pancreatic extracts that are based on such experimental studies must be viewed with caution. If a clinical benefit for these treatments is demonstrated, this study suggests that a mechanism other than negative feedback inhibition might be involved.

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- 1 Magee DR, Naruse S. Effect of pancreatic juice on basal pancreatic and gastric secretion in dogs. *J Physiol* 1982; 330: 489-96.
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Helicobacter pylori infection in Meckel's diverticula

SIR,—We were interested to read that Dr Morris and colleagues found *Helicobacter pylori*

colonisation of gastric mucosa in a resected Meckel's diverticulum (*Gut* 1989; 30: 1233-5). We have recently published a similar study of 69 Meckel's diverticula, in which four of 13 diverticula containing gastric mucosa were colonised by organisms indistinguishable from *H pylori*.¹ There was an active histological 'gastritis' present in all four cases containing the bacteria, while four others showed 'gastritis' but no organisms. In one case where organisms were present there was a perforating ulcer within the focus of heterotopic mucosa, while in the other cases the bacteria were clearly not related to the patient's symptoms. Bacteria were scanty in three of the four cases.

The odds would seem to be stacked against *H pylori* successfully colonising what is often only a tiny focus of gastric mucosa at this site. Studies on reflux gastritis have shown that colonisation of gastric mucosa is inhibited in the presence of alkaline duodenal contents.^{2,3} Furthermore, the organism does not colonise small intestinal mucosa,⁴ and in some diverticula the heterotopic tissue is situated beneath the normal surface epithelium, where colonisation could presumably not occur. In view of these adverse factors, the finding of even infrequent colonisation of Meckel's diverticula by *H pylori* is significant, as it suggests that large numbers of bacteria are likely to be traversing the length of the bowel while still remaining viable. If this is so, transmission of *H pylori* from person to person by the faecal-oral route is entirely feasible.

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- 1 De Cothi GA, Newbold KM, O'Connor HJ. *Campylobacter*-like organisms and heterotopic gastric mucosa in Meckel's diverticula. *J Clin Pathol* 1989; 42: 132-4.
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Acrodermatitis enteropathica with normal zinc concentrations

SIR,—I was extremely interested to read of the abnormalities of Paneth cells characteristic of acrodermatitis enteropathica aiding the diagnosis in a child with normal serum zinc concentrations¹. I must comment on the statement 'that the high zinc content of the normal Paneth cell renders it particularly vulnerable to zinc deficiency'.

The belief that human Paneth cells contain high concentrations of zinc is based on the histochemical findings in rat small intestine using dithizone and the concentration of zinc^{2,3} by these cells. We have shown that human Paneth cells are dithizone negative and that human and rat Paneth cells on x ray microanalysis contain no more zinc than other intestinal cells⁴ and that in man Paneth cells had lower zinc levels than goblet cells, stem cells, and enterocytes in jejunum and ileum.⁴

Our study on Paneth cell abnormalities in acrodermatitis enteropathica and the effect of zinc therapy is cited by Dr Mack and colleagues. We agree that zinc deficiency is associ-

ated with Paneth cell abnormalities. Rat Paneth cells have been reported to contain the zinc binding protein metallothionein (MT)⁵ and we have done some preliminary immunohistochemical studies on human Paneth cells using a monoclonal antibody raised in mice to horse MT1 and MT2.

Paneth cells were strongly positive but both goblet and crypt epithelial cells showed punctate positivity as well.

We conclude that present evidence does not indicate that the Paneth cell has an exceptionally high zinc content when compared with other intestinal epithelial cells, but do not disagree with the suggestion that it may be sensitive to changes in body zinc status.

The role played by metallothionein in zinc metabolism of intestinal epithelial cells including Paneth cells needs further investigation.

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- 1 Mack D, Kolatzko B, Cunnane S, Cutz E, Griffiths A. Acrodermatitis enteropathica with normal serum zinc levels: diagnostic value of small bowel biopsy and essential fatty acid determination. *Gut* 1989; 30: 1426-9.
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Reply

SIR,—We thank Dr Elmes for her interest in our recent paper. We are also grateful for her comments regarding her work on x ray microanalysis of zinc in intestinal tissues which adds further to the discussion in our case report. Dr Elmes also raises an interesting topic with regards to the metallothionein content of Paneth cells.

Although there has been speculation that metallothionein plays a homeostatic role in the metabolism of zinc, the true role remains unknown. Metallothioneins are inducible by a number of agents, including the heavy metals.¹ It appears that Paneth cells contain greater levels of metallothioneins than other cells in the small intestine.²

Whether this increased metallothionein level is a primary event and in some way responsible for greater susceptibility of the Paneth cell to changes in body serum zinc status when compared with other markers, or whether this is secondary to increased synthesis will be an interesting relationship to explore.

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Some possible pathological consequences of peptic ulcer therapy

SIR,—The past 25 years have produced