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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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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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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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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- 1 Hamer DH. Metallothionein. *Ann Rev Biochem* 1986; 55: 913-951.
- 2 Danielson KG, Ohi S, Huang PC. Immunochemical detection of metallothionein in specific epithelial cells of rat organs. *Proc Natl Acad Sci USA* 1982; 79: 2301-4.

Some possible pathological consequences of peptic ulcer therapy

SIR,—The past 25 years have produced

pharmacological agents of high potency and long duration of action, which when given to animals in large doses for their natural life spans may produce changes difficult to interpret in terms of potential risk for man. Such is the case with powerful inhibitors of gastric acid secretion where the finding of ECL cell hyperplasia and gastric carcinoids in rodents has caused concern. Any logical attempt at the extrapolation of these findings to the clinical situation must involve an exercise in which relevant similarities and differences between animal and man are weighed.

Studies designed to display carcinogenic hazard are usually conducted in mice and rats treated for their natural life spans with high daily doses. Unlike man spontaneous tumours of the glandular stomach are rare in rodents which, as they are experimentally susceptible, must mean that they do not normally come into contact with significant quantities of environmental gastric carcinogens. Simply expressed it is evident that rodents kept under controlled laboratory conditions do not get stomach cancer whereas man in his uncontrolled environment does. Acid suppression in the rodent produced by H_2 blockade or proton pump inhibition has been particularly studied in the rat where hypergastrinaemia is followed by hyperplasia of the fundic neuroendocrine ECL cells.¹ Potent antisecretory agents such as omeprazole and loxidine have further been associated with malignant changes of such cells in the form of gastric carcinoid tumours.^{2,4} Whereas the hyperplastic response is predictable and occurs in many animals, however, in only some were malignant carcinoids seen. Because the studies were designed to last for the natural life span of the rodents and as hypergastrinaemia and ECL cell hyperplasia occur shortly after the commencement of treatment it is surprising that if, as proposed, hyperplasia slips inexorably into microcarcinoidosis and carcinoid formation then more do not show malignancy. There must surely have been enough time for such changes to develop. Other factors may be involved. It is possible that over the relatively long periods of time involved the achlorhydric state has encouraged the formation of carcinogens which act on the already hyperplastic ECL cells to render them neoplastic. In this event it would not be too surprising if in the rat the first indication of a malignant change consequent upon marked acid suppression was the development of a carcinoid and not an adenocarcinoma.

Further evidence that the achlorhydric environment might present a risk was seen in mice given loxidine,⁴ an unsurmountable H_2 receptor antagonist, where in addition to the marked atypical hyperplasia and carcinoid formation in the gastric fundus there also appeared signs of early incomplete metaplasia; a change which is, in man, regarded as a precancerous condition. Are all the pathological changes seen in the stomachs of mice and rats attributable to hypergastrinaemia?

A simple extrapolation from gastric carcinoid tumours in rodents to similar tumours in man cannot be done without an understanding of the nature of gastric tumours, especially important are the differences and similarities between carcinoids and carcinomas, both of which are malignant tumours of gastric epithelial cells. If the tumour is of glandular origin it is a carcinoma; if it is of neuroendocrine origin it is a carcinoid. As it is now accepted, however, that the stomach stem cell is pluripotent it is perfectly acceptable to refer to a gastric carcinoid as a gastric neuroendo-

crine carcinoma and some authors do this. Further as the stem cell is pluripotent it is not surprising that many human gastric adenocarcinomas contain neuroendocrine cells and that composite tumours composed of adenocarcinoma and carcinoid are recognised. Although clinically different carcinoma and carcinoid may be regarded as poles of a spectrum of gastric neoplasia. This was well illustrated in a rat given loxidine where the obvious malignant carcinoid in the mucosa took on a decided glandular form as it infiltrated below the muscularis mucosa.

It is necessary before consideration is given to the clinical use of omeprazole or other compounds producing considerable periods of achlorhydria to ask what other changes may be present in the gastric mucosa of patients having peptic ulcer disease. As we age, atrophic gastritis becomes common and in this condition the epithelial cells fail to repress DNA synthesis and undergo abnormal maturation as they migrate through the gastric mucosa. Further, atrophic gastritis is accompanied by pseudopyloric metaplasia of body glands or by metaplasia towards an intestinal type of epithelium with its associated histological and histochemical features. In fact intestinal metaplasia occurs only in epithelium which is already the seat of chronic gastritis or gastric atrophy.⁵ When it is appreciated that intestinal metaplasia has been recognised as a precancerous condition since 1955⁶ it is pertinent to ask if it is likely to be present in ulcer disease. As it is known that duodenal ulcer, hyperacidity and antral gastritis are commonly associated⁷ and also that in gastric ulcer atrophic gastritis is present in both fundus and antrum,⁸ it is apparent that the gastric mucosae of such patients may already be in a precancerous condition, in that metaplastic changes will be present. Of special concern is incomplete metaplasia because various studies strongly suggest a close relationship to gastric carcinoma.⁹ It may well be injudicious to produce profound and long lasting suppression of gastric acid particularly in patients whose stomachs already show precancerous conditions.

Direct comparison of omeprazole 20 mg om and ranitidine 150 mg bid shows marked differences in median hourly intragastric acidity in duodenal ulcer patients observed for 24 hours after a total of 28 days of treatment. With ranitidine acidity reached 60 mmol/l whereas with omeprazole values were usually nil rising no higher than 10 mmol/l on one occasion.¹⁰ In a separate study¹⁰ it was found that ranitidine treatment given in the same way was associated with significant positive correlations among pH, nitrate concentration and bacterial counts but that despite these changes, an acid tide at some point in each 24 hours prevented persistent bacterial colonisation of the stomach. Even after nine to 12 months of maintenance ranitidine (150 mg nocte) there was no significant effect on the concentrations of nitrite or N-nitroso compounds. The analysis of the N-nitroso compounds was performed by C L Walters who also participated in a further study¹¹ in which 30 mg of omeprazole per day was given for two weeks. As expected omeprazole had a considerably more potent antisecretory effect than ranitidine. The highest acidity recorded reached just over 20 mmol/l. Twenty two hours after the last dose of omeprazole there were significant increases in the bacterial count and also, in contrast with ranitidine, significant increases in the nitrite and N-nitrosoamine concentrations. As the N-nitroso

group is associated with carcinogenicity the effect of sustained treatment with omeprazole must cause concern.

The rodent studies performed with new antisecretory compounds must be considered in relationship to man. Malignant changes, if found, must be evaluated, simple extrapolation to man considering only carcinoid tumours is not enough. Powerful compounds such as omeprazole and loxidine may produce enough acid suppression to allow bacterial overgrowth and the formation of N-nitroso compounds. Such compounds are known to be associated with carcinoma and their effect on precancerous gastric changes may well be of significance.

I believe that physicians should only use powerful antisecretory agents which produce persistent effects on parietal cells, for conditions unresponsive to established therapy.

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Dr Poynter was formerly the Director of Pathology at Glaxo Group Research; he is now retired but is retained by that company as a consultant.

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NOTES

European Digestive Disease Week

This meeting of the European Association for Gastroenterology and Endoscopy will be held in Vienna, Austria from 5-9 June, 1990. Further information may be obtained from Univ Doz Dr H Pristautz, Medizinische Universitätsklinik Graz, Auenbruggerplatz 15, 8036 Graz, Austria.