LETTERS TO THE EDITOR

Resection of the gastric fundus in rats

EDITOR, — We were interested to read the paper by Dr Chu *et al* from Sweden and Denmark (*Gut* 1993; 34: 988–93), which showed that resection of the gastric fundus in rats causes both pancreatic hyperplasia and the development of premalignant lesions (acidophilic atypical acinar cell foci or AACF). These changes were even more noticeable in another group of animals that had received pancreaticobiliary diversion to mid small bowel. These new Scandinavian data complement or confirm a number of our own published findings, some of which were available to the authors at the time of submission^{1–6} but none of which were cited.

Dr Chu and his colleagues carried out gastric fundectomy alone, restoring continuity by direct anastomosis of the rumen to the antrum; this operation increased circulating gastrin concentrations but not cholecystokinin concentrations. We carried out a 60 per cent distal gastrectomy (with Roux en Y anastomosis) to include much of the fundus and all the antrum, thereby reducing serum gastrin. We too found increased pancreatic weight and a ninefold increase in AACF (after azaserine exposure), and we related these effects to raised cholecystokinin concentrations, both fasting and postprandial.¹ When split gastrojejunostomy was done to provide complete duodenogastric reflux, the same hyperplastic/neoplastic response was encountered in the pancreas, but on this occasion plasma gastrin was raised instead of cholecystokinin.² Thus gastrin and cholecystokinin seem to have independent tropic effects on the pancreas. We accept the additional possibility of endogenous nitrosation after gastric surgery with formation of a pancreatic carcinogen.

Like Dr Chu, we have shown that pancreaticobiliary diversion has a more pronounced effect on the pancreas than partial gastrectomy or, for that matter, massive enterectomy.³ Although 90 per cent proximal small bowel resection increases circulating concentrations of enteroglucagon as well as cholecystokinin,⁴ the cholecystokinin receptor antagonist CR-1409 (lorglumide) inhibits the associated pancreatic hyperplasia.⁵ The primacy of cholecystokinin is further shown by experiments using the pancreaticobiliary diversion model to stimulate pancreatic growth. Two weeks after this operation serum cholecystokinin concentration was twice as high as values in sham operated rats⁶; by six months there was a fourfold increase.⁷ CR-1409 completely blocked the hyperproliferative response, which was manifested by increases in pancreatic RNA, bromodeoxyuridine labelling and metaphase arrests after vincristine.⁶ It also abolished the effect of pancreaticobiliary diversion in enhancing pancreatic carcinogenesis among animals exposed to azaserine.⁷

Thus cholecystokinin emerges as the dominant candidate for the role for pancreatotropin, but certain other gastrointestinal peptides probably play a subsidiary part.⁸ In the pancreas, as in the colon, 'surgical' hyperplasia predisposes to neoplasia. The increased cell proliferation that is caused by cholecystokinin may occur partly in response to injury, because

we have recently found evidence of severe ultrastructural damage to rat pancreas 14 days after pancreaticobiliary diversion.⁹ Treatment with CR-1409 largely prevents degranulation, but vacuolation of acinar cells is still seen.

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Reply

EDITOR, — We are fully aware of and agree with the results of the excellent studies of Professor Williamson *et al* on pancreatic changes related to surgical procedures with hormonal aberrations in the rat. We apologise for not having cited any of them in our paper (*Gut* 1993; 34: 988–93). To keep the reference list at a reasonable size, however, and for the sake of interpretation and debate, our choice of references was rather specific and aimed at similar studies showing diverging results. Our paper primarily concerned effects of longstanding hypergastrinaemia after fundectomy, using pancreaticobiliary diverted animals with hypercholecystokinaemia as positive controls. In some aspects, fundectomy simulates severe atrophic corpus gastritis, which is not the case with distal gastric resection or split gastrojejunostomy. In another study in rats focusing on the effects of pancreaticobiliary diversion and fundectomy after azaserine exposure (*Pancreas* 1993; 8: 330–7), the studies of Professor Williamson *et al* are cited.

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Gall stones and gall bladder motility

EDITOR, — We have read with interest the leading article *Gall stones and gall bladder motility* (*Gut* 1993; 34: 440–3). We agree that vagal

cholinergic and cholecystokinin mediated hormonal mechanisms are the most important factors in controlling gall bladder emptying. With regard to gall bladder emptying after truncal vagotomy, we have recently shown impaired gall bladder emptying after truncal vagotomy, with a higher fasting and residual volume and a decreased ejection fraction.¹ In our subjects, we found gall bladder emptying to have a triphasic pattern with a distinct phase of refilling occurring between 15 and 45 minutes, which separated two contraction phases. Minimum volume was attained between 30 and 90 minutes after the meal.

It is true that drugs having a prokinetic effect may prove valuable in preventing bile stasis and cholelithiasis in a variety of circumstances.

The effect of cisapride we feel is controversial, however, as in a double blind, prospectively randomised, placebo controlled study we found no prokinetic effect of cisapride either in healthy volunteers or in vagotomised subjects.¹ Another possible prokinetic modality that promises to have clinical benefit is the effect of a rapid intravenous infusion of amino acids, which is believed to cause gall bladder contraction and increase cholecystokinin concentrations.² This may be potentially important in the prevention of gall bladder sludge in patients on total parenteral nutrition.

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Iron deficiency anaemia

EDITOR, — The comment is well made that the possibility of coeliac disease should be considered in all iron deficient patients, regardless of age (*Gut* 1993; 34: 1102–7), and this is true also of those who present with dyspepsia and abdominal pain, because these symptoms may be prominent in some patients with this condition.^{1,2} Therefore, if endoscopy proves negative for suspected peptic ulceration or gastric cancer, the diagnostic trap to avoid is that of attributing upper gastrointestinal symptoms to colonic disease without taking the precaution to rule out coeliac disease by means of endoscopic biopsy.

Additionally, to heighten the index of suspicion, endoscopists should routinely comment on the appearance of the duodenal folds, because these may be characteristically effaced in some patients with coeliac disease.³

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