Luminal nutrition and gut growth

EDITOR,—We read with considerable interest the article by Jenkins and Thompson on the influence of enteral nutrition on the growth of the small intestine (J Pediatr Gastroenterol Nutr 1994; 18: 176-7). We agree that the elucidation of the mechanisms by which the intestinal mucosa interacts with nutrients is a very important area of research. This may be of particular relevance when it is considered that bacterial translocation through the atrophic bowel is an important cause of morbidity and mortality. We would, however, like to have seen more emphasis placed on some of the current paradigms that exist in our understanding of gut growth.

The first paradox concerns the divergent reported actions of pancreaticcirccitary secretions. The authors quote work by Altman that suggests that pancreatic secretions are trophic to the small intestine. Some recent articles, however, show that the predominant trophic effect of pancreaticobiliary diversion is seen in the proximal (enzyme free) section.3,4 Though the precise changes in intestinal growth, and those following jejunal transposition also argue against a circulating hormone being the sole agent responsible for these particular adaptive changes, as a circulation of bile and nutrients is expected to affect all regions in a similar way. As the authors point out, the only hormone seriously left ‘in the running’ is enteroglucagon, and unfortunately most of the evidence in favour of enteroendocrine cell production and distal location) can also be applied to peptide YY (which is coproduced with enteroglucagon) and which has subsequently been shown not to be trophic to the bowel.

This would explain why intact proteins but not elemental diets can maintain gut growth.4 This is difficult to explain in terms of differences in direct enteroocyte nutrition or luminal workload, and leads us to suggest that a semilabile luminal trophic agent may be responsible for adaptive changes to diet. In our model, this agent would be digested by luminal proteases in the fasting lumen but could be protected by luminal secretions from proteolytic substrates for the digestive enzymes. In favour of this idea is the finding that luminal concentrations of epidermal growth factor (EGF) seem to be modulated by the presence of luminal secretions, and also poorly digested feed, stimulate release of a trophic peptide from the distal gut that causes mucosal hyperplasia proximally in the small intestine. Nevertheless, infusion of harvested jejunal secretions into isolated intestinal loops shows that these secretions do themselves have a direct trophic action to the mucosa.5

We agree that the effects of a circulating hormone alone cannot account for the changes seen in jejunoileal transposition, where the transposed ileum undergoes hyperplasia and the transposed jejunum hypoplasia.6 The direct effects of luminal nutrients may, however, be relevant to these changes. The transplanted ileum will be exposed to an increased luminal load and the jejunum to a correspondingly reduced luminal load. These changes may make a more important contribution to mucosal growth than hormonally mediated effects.

Although the study quoted by Dr Playford and colleagues (their reference 6) shows that an elemental diet does not maintain mucosal growth compared with a standard laboratory diet (chow), it also shows that the elemental diet stimulates growth in the proximal small intestine compared with total parental nutrition. Thus, the contents of the elemental diet do themselves have a trophic effect on the small intestine. It is true that this trophic action may be less than that of the standard laboratory diet, but this may not be because the elemental diet contains pure amino acids while the laboratory diet contains whole protein. The diets differ in many other ways, not least of these being the absence of mucosal growth in the elemental diet and the presence in the standard laboratory diet. Moreover, studies quoted in our article prove that amino acids do themselves have trophic effects on the small intestinal mucosa.

The suggestion by Dr Playford and colleagues that a semilabile luminal trophic agent may be responsible for adaptive changes to diet is interesting and is not incompatible with the proposal that luminal nutrients also stimulate the mucosal growth through hormonally mediated mechanisms. However, we have little direct evidence to support their hypothesis. It has been proposed by Playford et al that the presence of undigested growth factors in the proximal intestinal lumen may cause the proximal mucosal hyperplasia seen after pancreaticobiliary diversion.7 This proposal cannot, though, explain why mucosal hyperplasia after pancreaticobiliary diversion is reduced by maintaining the animals on total parenteral nutrition.8 We agree that many issues remain to be resolved about the mechanisms that mediate intestinal growth and, in particular, the luminal influences and how we will stimulate further interest in this important area.

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REFERENCES
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REPLY

EDITOR,—We are interested to receive the comments of Dr Playford and colleagues and would like to respond to the points they make. We accept that pancreaticobiliary diversion causes trophic changes in the proximal (enzyme free) section of intestine, as well as distal to the site of diversion. One explanation for this phenomenon is the presence of undigested secretions, and also poorly digested feed, stimulate release of a trophic peptide from the distal gut that causes mucosal hyperplasia proximally in the small intestine. Nevertheless, infusion of harvested jejunal secretions into isolated intestinal loops shows that these secretions do themselves have a direct trophic action to the mucosa.1

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REFERENCES

Duodenogastric reflux and pancreatic growth

EDITOR,—In their interesting paper (Gut 1995; 36: 137-41), Dr Gaskell and colleagues describe an increase in pancreatic wet weight and serum gastrin at two weeks and six weeks after split gastrojejunostomy in rats, an operation that produces complete duodenogastric reflux. They speculate that the tropic effect of duodenogastric reflux may contribute to the increased incidence of pancreatic cancer reported after gastric operations in humans. In our own study,1 which the authors do not cite, we showed an increase in pancreatic wet weight and serum gastrin six months after exactly the same operation in rats. Pursuing this hypothesis that reflux promotes neoplasia – we further showed an appreciable increase in premalignant pancreatic lesions in rats receiving azaserine.2

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The important difference between these two studies is that Gaslander et al found a raised plasma cholecystokinin concentration in rats with duodenogastric reflux (at two weeks and six weeks), whereas we found a normal plasma cholecystokinin concentration (at six months) in a cholecystokinin receptor antagonist deoxepamide did not completely inhibit the tropic effect of the operation, they suggest that gastrin may also be important as an intermediary, our own data clearly support this interpretation. In the context of promoting neoplasia, the longterm hypergastrinaemia may be at least as relevant as the more transient hypercholecystokinaemia. That cholecystokinin alone could play a part in the induction of pancreatic cancer in patients with previous gastrectomy is confirmed by another study (again not cited) showing enhanced pancreatic carcinogenesis in rats with distal gastrectomy, an operation that lowers serum gastrin.

Using a different surgical model, massive enterectomy, we found two candidate hormones for the role of pancreatotropin: enteroglucagon and cholecystokinin.1 Cholecystokinin may be the more important because the cholecystokinin receptor antagonist longlumide completely abolished the effect of this operation on pancreatic growth. We have previously speculated on the relation between these two hormones.2 The strongest stimulus to pancreatic growth and carcinogenesis in our experience has been pancreato-biliary diversion; here again cholecystokinin seems to be the key intermediary, and longlumide prevents the response.6

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Reply

EDITOR,—We appreciate the interest that Professors Williamson and Watanapa have shown in our paper and apologise for failing to reference the important contributions they have made in the field of pancreatic growth and carcinogenesis.

These authors suggest that an important difference between their study and ours is that we saw an increase in circulating cholecystokinin concentrations and they did not. In fact mean basal cholecystokinin concentrations in their study were 59% higher in animals with split gastrojejunostomy than controls, although this did not reach statistical significance (p = 0.065); in our larger series it is probable that this would have reached statistical significance. Furthermore, in their study of partial gastrectomy, basal cholecystokinin concentrations were only 46% above control and less than those seen in their split gastrojejunostomy group, but here they concluded that partial gastrectomy increases plasma cholecystokinin.2 It is interesting to note that humans with longstanding gastric hyperchlolecystokinin reflux have increased concentrations of cholecystokinin postprandially, although their gastrin concentrations are quite normal.3 Although gastrin concentrations were increased after gastrojejunostomy, we do not feel that this hormone alone is responsible for the pancreatic growth as the trophic effect is not mimicked by omeprazole treatment even though gastrin concentrations are higher than after split gastrojejunostomy in the patients studied.

We do not fully agree with the conclusion drawn that the study of distal gastrectomy in rats confirms that cholecystokinin may play a part in the increased incidence of pancreatic cancer after this operation, because in their study no trophic effect on the pancreas was seen. Furthermore, while we agree that these hormones are of importance for pancreatic growth and neoplasia in the rat, their role in human ductal adenocarcinoma, the common tumour type in humans, is controversial.4,5 The authors go on to state that they found two candidate hormones, enteroglucagon and cholecystokinin, for the pancreaticotrophic effect associated with the small bowel resection and pancreatobiliary diversion. However, the increase of cholecystokinin and enteroglucagon and pancreatic growth associated with these surgical procedures had been described earlier.6,7

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Expression of adhesion molecules in human Peyer's patches

EDITOR,—We became aware of a publication in Gut by Fujimura and Kihara on human Peyer's patches while reviewing our own papers (Gut 1994; 35: 46–50); the title of this paper was exciting because our laboratory has without success tried to show expression of intercellular adhesion molecule-1 (ICAM-1) on murine jejunal and ileal Peyer's patches in the mouse with or without carcinogenic diet or treated with fat-rich or diseased gut (unpublished findings). This is also in accordance with other reports.1,4 We were able to upregulate ICAM-1 expression in the human adenocarcinoma cell line HT-29, however, by treatment with TNF-α.1,4 Particularly the combination interferon γ (IFN-γ)/tumour necrosis factor α, and IFN γ/interleukin 1 in the presence of butyrate.6 It was therefore quite intriguing when the title of the article by Fujimura and Kihara suggested that the follicle associated epithelium of Peyer's patches expresses ICAM-1. Unfortunately, the study had been performed in rats rather than humans and the title was further misleading because the localisation described for ICAM-1 was restricted to a subepithelial layer of fibroblasts. Contrasting this finding, which was claimed to be related to the unique immunobiology of follicle associated epithelium, the authors the were able to demonstrate that ICAM-1 beneath the villus epithelium. They therefore speculated that the massive lymphocyte traffic between follicle associated epithelium and the lymphoid follicles of Peyer's patches might be explained by the topical ICAM-1 expression.

In our opinion this hypothesis is not plausible. Lymphocytes in follicle associated epithelium are unevenly distributed being particularly concentrated in small aggregates related to the 'membrane' cells; outside these foci the intraepithelial occurrence of lymphocytes is more similar to that seen in the villus epithelium in terms of numerical as well as phenotypic distribution.3,9 In humans the diffusely scattered intraepithelial lymphocytes are mainly CD8+ T cells8 of the T cell receptor αβ variety with a small (4–5%) proportion of T cell receptor γδ cells.7 Similarly, the only adhesion molecule suggested to be important for their homing to the epithelium is the integrin αEβ7 (detected by monoclonal antibody HML-1),10 which apparently binds to a special epithelial E-cadherin.6,11 The lymphocytes found in relation to the membrane cells might rather be ascribed to the antigen transporting capacity of these special enterocytes. In fact, in vitro 50% of such aggregated lymphocytes consist of B cells—apparently representing topical extensions of the underlying follicles— together with a comparatively high proportion of CD4+CD25+ T cells (memory helper phenotype),12 but without admixture of the T cell receptor γδ+ subset.8 It is indeed difficult
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