

### 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 (*Gut* 1994; 35: 1765–9). 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 paradoxes that exist in our understanding of gut growth.

The first paradox concerns the divergent reported actions of pancreaticobiliary secretions. The authors quote work by Altmann that suggests that pancreatic secretions are trophic to the small intestine.<sup>1</sup> Some recent articles show, however, that the predominant trophic effect of pancreaticobiliary diversion is seen in the proximal (enzyme free) section.<sup>2,3</sup> These regional specific changes in intestinal growth, and those following ileojejunum transposition also argue against a circulating hormone being the sole agent responsible for these particular adaptive changes, as a circulating hormone would be 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 enteroglucagon (correlation with 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.<sup>4,5</sup>

The second paradox is why intact proteins but not elemental diets can maintain gut growth.<sup>6</sup> This is difficult to explain in terms of differences in direct enterocyte 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 preserved by the presence of competitive substrates for the digestive enzymes. In favour of this idea is our finding that luminal concentrations of epidermal growth factor (EGF) seem to be modulated by this mechanism.<sup>3</sup> Nevertheless, subsequent studies have raised a further paradox, as there is evidence that EGF may not be the effector molecule, as almost all studies have shown that the EGF receptor is only present on the basolateral membrane. This suggests that the presence of EGF in the intestinal lumen may be to act in a 'surveillance' or repair role.<sup>7</sup> However, this general mechanism may still apply to other luminal trophic agents, for example, IGF-1.

Finally, we would like to point out that the Goodlad/Johnson debate on the proliferative effects of fibre has (almost) been resolved by a collaborative study using germ free and conventional mice,<sup>8</sup> which has shown that guar gum has both direct effects in the small bowel and indirect (fermentation related) effects in the distal bowel. Moreover, in this study we showed that lipid also has direct and fermentation related effects on both the small intestine and the colon.

In summary there is a great need to examine these paradoxes and inconsistencies so that we can hope to understand this complex system of intestinal physiology and devise new strategies to prevent clinically relevant atrophy.

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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 could be that the diverted secretions, and also poorly digested food, stimulate release of a trophic peptide from the distal gut that causes mucosal hyperplasia proximally in the small intestine. Nevertheless, infusion of harvested pancreaticobiliary secretions into isolated intestinal loops shows that these secretions do themselves have a direct trophic action to the mucosa.<sup>1</sup>

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.<sup>2</sup> 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 parenteral nutrition. This implies that 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 fibre in the elemental diet and its 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.<sup>3,4</sup>

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 mucosal growth through direct and hormonally mediated mechanisms. However, we know of 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.<sup>5</sup> This proposal cannot, though, explain why mucosal hyperplasia after pancreaticobiliary diversion is itself much reduced by maintaining the animals on total parenteral nutrition.<sup>6</sup>

We agree that many issues remain to be resolved about the mechanisms that mediate the enterotrophic effects of luminal nutrients and hope that our article will stimulate further interest in this important area.

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### Duodenogastric reflux and pancreatic growth

EDITOR,—In their interesting paper (*Gut* 1995; 36: 137–41), Dr Gasslander *et al* 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 trophic effect of duodenogastric reflux may contribute to the increased incidence of pancreatic cancer reported after gastric operations in humans. In our own study,<sup>1</sup> 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 the same hypothesis – that hyperplasia promotes neoplasia – we further showed an appreciable increase in premalignant pancreatic lesions in rats receiving azaserine.