PROGRESS REPORT

Enteral nutrition and the small intestine

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It is now accepted that, whenever possible, nutritional support should be given enterally, reserving parenteral nutrition for patients with intestinal failure. This is partly because of the many problems associated with parenteral feeding, such as complications of central line insertion and metabolic derangements,¹ but recently it has also been appreciated that enteral feeding may have a positive advantage over parenteral feeding by maintaining small intestinal mucosal structure and function. Thus it may improve intestinal recovery and adaptation after gastrointestinal surgery, especially after small bowel resection. In addition, maintaining the barrier function of the intestinal mucosa may be an important consequence of enteral nutrition, for, in the critically ill, early enteral feeding may reduce translocation of bacteria and endotoxin from the gut lumen into the portal circulation,² thus decreasing the incidence of septicaemia.³

Recently, it has also been found that enteral nutrition influences the secretory function of the small intestine. In experimental animals starvation results in intestinal hypersecretion to neurotransmitters and secretagogues⁴⁻⁶ and such a response may contribute to the life threatening diarrhoea that can occur in patients with severe malnutrition.⁶ This review will focus, however, on the effects of enteral nutrition on small intestinal mucosal proliferation, with particular emphasis on the actions of individual nutrients.

Background

Most studies of small intestinal adaptation have been performed in experimental animals and of these the rat has been the most commonly used species. The experimental data reviewed here are derived from studies in laboratory rats, unless otherwise stated.

During starvation the small intestinal mucosa rapidly atrophies,⁷⁻⁹ with a reduction in cell proliferation being noted within hours of food withdrawal,¹⁰ and this occurs even when the overall nutritional state of the animal is maintained by total parenteral nutrition (TPN).^{11 12} Conversely, refeeding increases mucosal cell proliferation again, with even an initial rebound effect when cell proliferation increases above pre-starvation values.¹³

Studies in the dog as well as the rat have shown that luminal nutrients may stimulate this mucosal proliferation by a local direct action at their site of absorption.^{14 15} This direct effect, surprisingly, does not result from

the use of the nutrients as sources of energy by mucosal cells, as, in rats, non-metabolisable absorbed substrates, such as galactose and 3-O-methyl-D-glucose, can also promote mucosal cell proliferation.^{16 17} This has led to the interesting concept that the 'workload' of absorption determines the proliferative response.^{16 17} Luminal nutrients may also stimulate mucosal cell proliferation indirectly by releasing an enterotrophic hormone from the distal small intestine and colon.¹⁸⁻²¹ The identity of such a hormone(s) remains uncertain, and although there is circumstantial evidence from studies in humans as well as animals in favour of enteroglucagon,²²⁻²⁴ some recent *in vivo* and *in vitro* data have questioned this hypothesis.²⁵⁻²⁸ A third mechanism by which luminal nutrients may increase mucosal cell proliferation is by stimulating release of pancreaticobiliary secretions, which are themselves trophic to the small intestinal mucosa.²⁹⁻³¹

At the cellular level both direct and indirect enterotrophic effects of luminal nutrients seem to be mediated by induction of ornithine decarboxylase (ODC) and subsequent increases in cellular levels of polyamines.³²⁻³⁵ *In vitro* and *in vivo* studies suggest that induction of ODC occurs largely at the post-transcriptional level,^{36 37} in contrast with enteroglucagon synthesis, which results mainly from increased DNA transcription.³⁸

Adaptive changes in small intestinal mucosal mass are generally accompanied by parallel changes in segmental absorptive function,³⁹⁻⁴³ but the magnitude of induction of individual transport processes can be selectively influenced by the specific nature of the nutrients within the lumen. Thus in rats receiving TPN, infusion of D-glucose, but not the unmetabolised 3-O-methyl-D-glucose, into the small intestine increases specific transport capacity for glucose,¹⁷ while substituting protein isocalorically for carbohydrate in the diet increases amino acid transport capacity and reduces the transport capacity for galactose.⁴⁴

INTESTINAL ADAPTATION IN HUMANS

Although most studies of adaptation have been in experimental animals, available data in humans provide good evidence for functional adaptation in response to changes in food intake. Thus starvation or total parenteral nutrition cause a fall in brush border enzyme activity in humans^{45 46} and reduced absorption

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of ingested mannitol and D-xylose.^{47 48} The evidence, however, for structural adaptation of the human small intestine in response to food withdrawal is less clear cut. In patients who have previously had jejunoileal bypass operations for obesity, atrophy has been noted in the bypassed segment at a subsequent operation,⁴⁹ but this finding has not been universal.⁵⁰ Although a fall in protein content of jejunal biopsy specimens has been noted after a prolonged fast,⁴⁵ standard histological examination of the biopsy specimens in such patients or in patients who have received TPN for a prolonged period has shown no evidence of mucosal atrophy.^{45 46 51}

Only small samples from a limited number of intestinal sites can be taken in humans and this may in part explain the relatively poor evidence for structural adaptation in response to changes in food intake. Recently an interesting method has been used to give an indirect measure of total levels of small intestinal mucosal mass in humans. This method has relied on displacement of the enzyme diamine oxidase from endothelial binding sites in the lamina propria by intravenous heparin. This enzyme is confined almost exclusively to the small bowel mucosa and the post-heparin plasma concentrations may therefore reflect levels of mucosal mass. In subjects receiving TPN there was a reduction of post-heparin plasma concentrations that was reversed on refeeding.⁵²

Effects of individual nutrients on mucosal growth

CARBOHYDRATE AND AMINO ACIDS

Weser *et al*⁵³ compared the effects of individual carbohydrates and found that disaccharides promote greater mucosal growth in rats than do isocaloric amounts of monosaccharides. This requires the hydrolysis of the disaccharide and absorption of its monosaccharide components, because the effect of sucrose on mucosal cell proliferation is largely abolished by the alpha glucosidase inhibitor, acarbose. Different hydrolysable disaccharides have similar effects on small intestinal mucosal mass,⁵³ as do different monosaccharides,^{15 17} but a mixture of amino acids stimulates mucosal growth and ODC concentrations more than an isocaloric amount of glucose.^{18 54} Dietary supplementation with ornithine (as its alpha ketoglutarate salt) causes small intestinal mucosal growth, perhaps as a result of increased polyamine production,⁵⁵ but other individually administered amino acids may also stimulate mucosal cell proliferation to varying degrees.⁵⁶

Attention has recently focused on the role of the amino acid glutamine in small intestinal growth. Glutamine is an important metabolic substrate for small intestinal mucosal cells⁵⁷ and its deficiency causes mucosal atrophy.⁵⁸ Glutamine is unstable in solution and so is often omitted from regimens for parenteral nutrition. This may in turn contribute to the mucosal atrophy associated with TPN, as

supplementation with parenteral glutamine can reduce, though not completely reverse, the atrophy in animals.⁵⁹ Glutamine is, therefore, essential for small intestinal epithelial cell growth and thus may have an important role in the diet of patients with small intestinal disease, as, at least in animals, inclusion of glutamine in the diet enhances mucosal proliferation after small bowel resection, or cytotoxic or radiation induced injury.⁶⁰⁻⁶² It is not clear, however, whether supplementing this amino acid above minimum requirements further enhances mucosal growth.

DIETARY LIPIDS

Initial reports raised the exciting possibility that dietary fat may exert a greater trophic stimulus to the small intestinal mucosa than other nutrients. Thus Morin *et al*⁶³ found that intragastric infusion of long chain triglycerides enhanced the adaptive response to partial small intestinal resection in the rat more than protein, carbohydrate or medium chain triglycerides, and subsequently it was shown that long chain free fatty acids have an even greater effect than long chain triglycerides.⁶⁴ Nevertheless, although others have also shown a potent enterotrophic effect for long chain triglycerides,⁶⁵⁻⁶⁹ this has not been a universal finding. For example, Thomson *et al*⁷⁰ using a number of different measures of mucosal mass found little consistent evidence for an enhanced enterotrophic action of a high fat diet compared with laboratory chow, while in two other studies long chain triglycerides substituted for carbohydrate alone in the diet even seemed to cause jejunal mucosal atrophy.^{71 72}

Recent findings suggest, however, that the method by which long chain triglycerides are given itself profoundly influences the proliferative response of the small intestinal mucosa, as boluses increase small intestinal mucosal mass and cell proliferation compared with the same daily dose of fat consumed more gradually as part of a mixed diet.⁷³ This may be because bolus doses of fat enhance release of enteroglucagon from the distal small intestine and colon.⁷³ In a mixed diet substituting long chain triglycerides for glucose does not affect the overall mucosal mass of the small intestine, but does change the distribution of mucosal mass along the small intestine.⁷⁴ With increasing proportions of long chain triglycerides (and decreasing amounts of glucose) mucosal mass falls in the proximal small intestine and correspondingly rises in the mid small intestine.⁷⁴ These changes may reflect differences in the sites of absorption of glucose and lipid, with mucosal cells proliferating locally in response to the 'workload' of absorption.¹⁵⁻¹⁷ This finding now also explains why some earlier studies have suggested that dietary fat causes mucosal atrophy in comparison with carbohydrate,^{71 72} for in those studies mixed diets were used and measurements were confined to the jejunum and did not include the mid small intestine. By contrast with long chain triglycerides, medium

chain triglycerides, which are more rapidly hydrolysed and absorbed,⁷⁵ maximally stimulate mucosal proliferation in the proximal small intestine when given in mixed diets.^{76 77}

Essential fatty acids may have an important role in mucosal proliferative responses, as deficiency of this dietary component attenuates the adaptive response of the small intestinal mucosa to partial small intestinal resection⁷⁸ and also reduces the regenerative response of the mucosa to methotrexate induced injury.⁷⁹ Such effects might result from decreases in mucosal concentrations of prostaglandins, which are products of essential fatty acid metabolism and are themselves trophic to the small intestinal mucosa.⁸⁰ There is little evidence, however, that supplementing the omega 6 fatty acid, linoleic acid above minimum requirements is trophic to the small intestinal mucosa⁶⁷ and a diet containing 10% by weight of safflower oil (rich in linoleic acid) does not enhance any parameters of mucosal mass during recovery from methotrexate induced mucosal injury over a diet containing 1% by weight safflower oil.⁷⁹ The essential fatty acids, however, in fish oil (the omega 3 family) may have special properties. Thus, an oil rich in eicosapentaenoic acid improved mucosal recovery after methotrexate induced injury⁸¹ and also stimulated mucosal growth after partial small intestinal resection when compared with other long chain fatty acids.⁸²

In the diseased or resected small bowel addition of long chain triglycerides to the diet might cause steatorrhoea. The more rapidly hydrolysed and absorbed medium and short chain triglycerides may be better tolerated when small intestinal absorptive capacity is reduced. It is thus of considerable interest that Kripke *et al*⁸³ found that substituting short chain triglycerides for carbohydrate in a diet enhances the small intestinal adaptive response to distal small bowel resection. Direct infusion of short chain fatty acids into the ileum also stimulates mucosal cell proliferation both in the caecum and in the more proximal jejunum, perhaps by release of a trophic gut peptide.⁸⁴ Interestingly, intravenously administered short chain fatty acids may stimulate small intestinal mucosal proliferation both in intact animals⁸⁵ and after partial small intestinal resection.⁸⁶

The nature of ingested fat may also influence the absorptive function of the small intestine, perhaps as a result of changes in the nature of lipid incorporated into the cell membrane of the enterocyte. Thus Thomson *et al* have found that a number of specific intestinal transport properties can be varied according to the nature of ingested triglycerides,^{72 87 88} while Sagher *et al*⁸⁹ showed that, compared with a diet rich in fully saturated fatty acids, a diet rich in polyunsaturated fat significantly improved jejunal absorption of water and electrolytes. This second study raises the possibility that changing the nature of ingested lipid may offer a simple means of improving absorptive function for water and electrolytes in acute diarrhoeal illnesses.

DIETARY FIBRE

Non-absorbable, inert bulk such as kaolin has no trophic effect on the small intestinal mucosa,^{90 91} but dietary fibre may provide a potent enterotrophic stimulus. Ecknauer *et al* showed that supplementing an elemental diet with alpha cellulose increases small intestinal weight and cell proliferation compared with the same elemental diet alone,⁹² and others have confirmed that dietary fibre is trophic to the small intestine and colon,⁹³⁻⁹⁵ with the increases in small intestinal cell proliferation being most noticeable distally.⁹⁶

Dietary fibre can be fermented by lower gut bacteria to release short chain fatty acids⁹⁷ and Goodlad *et al*⁹¹ showed that small intestinal and colonic mucosal proliferation was maximally increased by the most fermentable fibres and that the enterotrophic effects were abolished in germ free animals.⁹⁸ Short chain fatty acids may exert a direct trophic action on the colonic epithelium,⁹⁹ perhaps because colonic enterocytes use them as a metabolic fuel.^{100 101} In addition, as already described, infusion of short chain fatty acids into the ileum can stimulate cell proliferation more proximally,⁸⁴ perhaps by releasing a trophic gut peptide; in the study of Goodlad *et al*⁹¹ enteroglucagon release was stimulated by the most fermentable fibre. The role of enteroglucagon was questioned, however, by the finding that concentrations of this hormone were high in fibre fed germ free animals,²⁸ even though mucosal proliferation was not increased.⁹⁸

The role of bacterial fermentation in mediating the enterotrophic effect of dietary fibre has itself also been disputed. In two studies, the trophic effects of a number of different non-digestible polysaccharides showed little correlation with their fermentability by gut bacteria,^{27 102} and in rats fed increasing amounts of haricot beans there was no increase in duodenal or caecal cell proliferation, despite increases in short chain fatty acid production in the caecum.¹⁰³ Johnson *et al*^{27 104} have suggested that the viscosity of the diet may be important as, in their studies, only the most viscous diets increased cell proliferation in the terminal ileum perhaps because these viscous polysaccharides delayed absorption of nutrients and increased their delivery to the terminal ileum. In keeping with this hypothesis, this group has subsequently produced evidence for synergism between the enterotrophic effect of corn oil and a viscous non-starch polysaccharide, guar gum.¹⁰⁵

While the stimulatory effects of dietary fibre on small intestinal mucosal proliferation may prove to be beneficial, it is interesting to speculate that, conversely, the therapeutic efficacy of elemental and polymeric diets in Crohn's disease¹⁰⁶⁻¹⁰⁸ may result from the lack of fibre in these diets. In experimental animals such diets cause mucosal atrophy, especially in the ileum and colon, in relation to standard laboratory diets^{109 110}; this effect could result from the absence of a trophic stimulus to the distal gut that is normally provided by dietary

fibre. It is therefore conceivable that the therapeutic efficacy of these enteral feeds in Crohn's disease is related to such local 'bowel rest' in the distal gut.

Discussion

By stimulating mucosal cell proliferation, enteral nutrition may provide clinical advantages to patients after gastrointestinal surgery, especially small bowel resection. In the rat and dog it has been shown that enteral nutrition is essential for stimulating adaptive hyperplasia in the remnant^{111 112} after partial small intestinal resection, and so a diet that has a potent enterotrophic action might provide great benefit in the short bowel syndrome. In our view, the data suggesting that short chain triglycerides and fatty acids are potent stimulants of mucosal growth hold great promise. The observed enterotrophic effects of intravenously given short chain fatty acids and glutamine also suggest that supplementing parenteral fluid regimens with these nutrients may preserve small intestinal mucosal integrity and function in patients who cannot receive enteral nutrition.

It has also been proposed that maintenance of mucosal integrity may reduce bacterial translocation from the gut and so reduce the incidence of sepsis in critically ill and post-operative patients.^{2 3} A recent study in patients undergoing elective surgery has challenged this assertion by showing no increase in the incidence of bacterial translocation at the time of laparotomy in patients fed preoperatively by TPN compared with patients who were enterally fed.⁵¹ Comparatively fit patients undergoing elective surgery, however, may not be the most relevant group to study, as it is possible that the risk of bacterial translocation is in any case low in such patients. Any beneficial effect of enteral feeding might be more apparent in critically ill patients in whom the risk of bacterial translocation may be increased,² perhaps as a consequence of mucosal damage resulting from impaired mucosal blood flow.^{2 113} Indeed, another recent study in patients who had suffered multi-system trauma showed that, compared with TPN, enteral feeding reduced the incidence of sepsis only in severely injured patients.¹¹⁴ Nevertheless, it is debatable whether the protective effects of enteral feeding in such patients are caused by maintenance of mucosal integrity in itself, or whether another mechanism, such as stimulation of local immune function,¹¹⁵ could be more important. Deitch has shown that there is a poor correlation between the incidence of translocation and parameters of mucosal mass in rats and mice receiving various enteral and parenteral feeds.¹¹⁶

Further research might be directed at assessing further the benefits of enterotrophic dietary regimens in a clinical setting, with particular attention to the incidence of gut derived sepsis in the critically ill patient, to the efficacy of small intestinal adaptation after gastrointestinal surgery, and to amelioration of

cytotoxic or radiation induced intestinal injury. Little is known about the molecular mechanisms that mediate the direct enterotrophic actions of absorbed nutrients, and so research in this field may provide a method of further enhancing mucosal proliferative responses to enteral feeding and of adding to our knowledge of the factors that control epithelial cell growth.

- Maynard ND, Bihari DJ. Postoperative feeding. Time to rehabilitate the gut. *BMJ* 1991; 303: 1007-8.
- Alexander JW. Nutrition and translocation. *J Parent Ent Nutr* 1990; 14 (suppl): 170-4S.
- Moore F, Feliciano D, Andrassy R, McArdle A, Booth F, Morgenstein T, et al. Enteral feeding reduces postoperative septic complications. *J Parent Ent Nutr* 1991; 15 (suppl): 22S.
- Carey HV, Tucker KE. Intestinal secretion is altered by the absence of luminal contents in piglets. *Gastroenterology* 1991; 100: A681.
- Carey HV. Effects of fasting and hibernation on ion secretion in ground squirrel intestine. *Am J Physiol* 1992; 263: R1203-8.
- Levin RJ. The diarrhoea of famine and severe malnutrition - is glucagon the major culprit? *Gut* 1992; 33: 432-4.
- Steiner M, Bourges HR, Freedman LS, Gray SJ. Effect of starvation on the tissue composition of the small intestine in the rat. *Am J Physiol* 1968; 215: 75-7.
- McManus JPA, Isselbacher KJ. Effect of fasting versus feeding on the rat small intestine. Morphological, biochemical and functional differences. *Gastroenterology* 1970; 59: 214-21.
- Altmann GG. Influence of starvation and refeeding on mucosal size and epithelial renewal in the rat small intestine. *Am J Anat* 1972; 133: 391-400.
- Aldewachi HS, Wright NA, Appleton DR, Watson AJ. The effect of starvation and refeeding on cell population kinetics in the rat small bowel mucosa. *J Anat* 1975; 119: 105-21.
- Levine GM, Deren JJ, Steiger E, Zinno R. Role of oral intake in maintenance of gut mass and disaccharidase activity. *Gastroenterology* 1974; 67: 975-82.
- Hughes CA, Dowling RH. Speed of onset of adaptive mucosal hypoplasia and hypofunction in the intestine of parenterally fed rats. *Clin Sci* 1980; 59: 317-27.
- Goodlad RA, Al-Mukhtar MYT, Gbatei MA, Bloom SR, Wright NA. Cell proliferation, plasma enteroglucagon and plasma gastrin levels in starved and refed rats. *Virchow Arch B Cell Pathol* 1983; 43: 55-62.
- Jacobs LR, Taylor BR, Dowling RH. Effect of luminal nutrition on the intestinal adaptation following Thiry-Vella by-pass in the dog. *Clin Sci* 1975; 49: 26P.
- Weser E, Vandeventer A, Tawil T. Non-hormonal regulation of intestinal adaptation. *Scand J Gastroenterol* 1982; 17 (suppl 74): 105-13.
- Clarke RM. 'Luminal nutrition' versus 'functional workload' as controllers of mucosal morphology and epithelial replacement in the rat small intestine. *Digestion* 1977; 15: 411-24.
- Richter GC, Levine GM, Shiau Y-F. Effects of luminal glucose versus nonnutritive infusates on jejunal mass and absorption in the rat. *Gastroenterology* 1983; 85: 1105-12.
- Spector MH, Levine GM, Deren JJ. Direct and indirect effects of dextrose and amino acids on gut mass. *Gastroenterology* 1977; 72: 706-10.
- Williamson RCN, Buchholtz TW, Malt RA. Humoral stimulation of cell proliferation in small bowel after transection and resection in rats. *Gastroenterology* 1978; 75: 249-54.
- Miazza BM, Al-Mukhtar MYT, Salmeron M, et al. Hyperenteroglucagonaemia and small intestinal mucosal growth after colonic perfusion of glucose in rats. *Gut* 1985; 26: 518-24.
- Appleton GVN, Bristol JB, Williamson RCN. Proximal enterectomy provides a stronger stimulus to intestinal adaptation than distal enterectomy. *Gut* 1987; 28 (suppl 1): 165-8.
- Gleeson MH, Bloom SR, Polak JM, Henry K, Dowling RH. Endocrine tumour in kidney affecting small bowel structure, motility and absorptive function. *Gut* 1971; 12: 773-82.
- Bloom SR. An enteroglucagon secreting tumour. *Gut* 1972; 13: 520-3.
- Bloom SR. Gut hormones in adaptation. *Gut* 1987; 28 (suppl 1): 31-5.
- Gregor M, Menge H, Stossel R, Riecken E-O. Effect of monoclonal antibodies to enteroglucagon on ileal adaptation after proximal small bowel resection. *Gut* 1987; 28 (suppl 1): 9-14.
- Gregor M, Stallmach A, Riecken E-O. Enteroglucagon does not stimulate proliferation in intestinal epithelial monocultures. *Gastroenterology* 1989; 96: A183.
- Johnson IT, Gee JM, Brown JC. Plasma enteroglucagon and small bowel cytokinetics in rats fed soluble non-starch polysaccharides. *Am J Clin Nutr* 1988; 47: 1004-9.
- Goodlad RA, Ratcliffe B, Fordham JP, Gbatei MA, Domin J, Bloom SR, et al. Plasma enteroglucagon, gastrin and peptide YY in conventional and germ-free rats refed and fibre-free or fibre-supplemented diet. *Q J Exp Physiol* 1989; 74: 437-42.
- Altmann GG, Leblond CP. Factors influencing villus size in the small intestine of adult rats as revealed by transposition of intestinal segments. *Am J Anat* 1970; 127: 15-36.
- Altmann GG. Influence of bile and pancreatic secretions on the size of the intestinal villi in the rat. *Am J Anat* 1971; 132: 167-77.
- Hughes CA, Ducker DA, Warren IF, McNeish AS. Effect of pancreatico-biliary secretions on mucosal structure and function of self-emptying jejunal blind loops in rats. *Gut* 1979; 20: A924-5.
- Luk GD, Yang P. Polyamines in intestinal and pancreatic adaptation. *Gut* 1987; 28 (suppl 1): 95-101.
- Dowling RH. Polyamines in intestinal adaptation and disease. *Digestion* 1990; 46 (suppl 2): 331-44.
- Tabata K, Johnson LR. Ornithine decarboxylase and mucosal growth in response to feeding. *Am J Physiol* 1986; 251: G270-4.
- Tabata K, Johnson LR. Mechanism of induction of mucosal ornithine decarboxylase by food. *Am J Physiol* 1986; 251: G370-4.
- Siedel ER, Ginty DD. Apparent post-transcriptional modification of ornithine decarboxylase accounts for its induction in IEC-6 cells in culture. *Digestion* 1990; 46 (suppl 2): 383-9.
- Taylor RG, Beveridge DJ, Fuller PJ. Expression of ileal glucagon and peptide tyrosine-tyrosine genes. Response to inhibition of polyamine synthesis in the presence of massive small bowel resection. *Biochem J* 1992; 286: 737-41.

- 38 Taylor RG, Verity K, Fuller PJ. Ileal glucagon gene expression: ontogeny and response to massive small bowel resection. *Gastroenterology* 1990; **99**: 724-9.
- 39 Dowling RH, Booth CC. Structural and functional changes following small intestinal resection in the rat. *Clin Sci* 1967; **32**: 139-49.
- 40 Bury KD. Carbohydrate digestion and absorption after massive resection of the small intestine. *Surg Gynecol Obstet* 1972; **135**: 177-87.
- 41 Urban E, Pena M. In vivo calcium transport by rat small intestine after massive small bowel resection. *Am J Physiol* 1974; **226**: 1304-8.
- 42 Morita A, Pellegrini CA, Kim YS. Functional changes and protein composition in the brush border membranes following small bowel resection in the rat. In: Robinson JW, Dowling RH, Reicken E-O, eds. *Mechanisms of intestinal adaptation*. Lancaster: MTP Press, 1982: 363-8.
- 43 Goodlad RA, Plumb JA, Wright NA. The relationship between intestinal crypt cell production and intestinal water absorption measured in vitro in the rat. *Clin Sci* 1987; **72**: 297-304.
- 44 Scharer E, Wolfram S, Raab W, Amann B, Agne N. Adaptive changes of amino acid and sugar transport across the brush border of rat jejunum. In: Robinson JW, Dowling RH, Reicken E-O, eds. *Mechanisms of intestinal adaptation*. Lancaster: MTP Press, 1982: 123-37.
- 45 Knudsen KB, Bradley EM, Lecocq FR, Bellamy HM, Welsh JD. Effect of fasting and refeeding on the histology and disaccharidase activity of the human intestine. *Gastroenterology* 1968; **55**: 46-51.
- 46 Guedon G, Schmitz J, Lerebours E, Metayer J, Audran E, Hemet J, et al. Decreased brush border hydrolase activities without gross morphologic changes in human intestinal mucosa after prolonged total parenteral nutrition of adults. *Gastroenterology* 1986; **90**: 373-8.
- 47 Elia M, Goren A, Behrens R, Barber RW, Neale G. Effect of total starvation and very low calorie diets on intestinal permeability in man. *Clin Sci* 1987; **73**: 205-10.
- 48 Maxton DG, Menzies IS, Slavin B, Thompson RPH. Small-intestinal function during enteral feeding and starvation in man. *Clin Sci* 1989; **77**: 401-6.
- 49 Dudrick SJ, Daly JM, Castro G, Akhtar M. Gastrointestinal adaptation following small bowel bypass for obesity. *Ann Surg* 1977; **185**: 624-47.
- 50 Tompkins RK, Waisman J, Watt CM-H, Corlin R, Keith R. Absence of mucosal atrophy in human small intestine after prolonged isolation. *Gastroenterology* 1977; **73**: 1406-9.
- 51 Sedman PC, May J, Brooks SG, Saqar P, Johnson D, Tring I, et al. Total parenteral nutrition does not predispose to gut translocation in man [abstract]. *Gut* 1993; **34** (suppl 1): S64.
- 52 Rokkas T, Vaja S, Murphy GM, Dowling RH. Postheparin plasma diamine oxidase in health and intestinal disease. *Gastroenterology* 1990; **98**: 1493-501.
- 53 Weser E, Babbitt J, Hoban M, Vandeventer A. Intestinal adaptation. Different growth responses to disaccharides compared with monosaccharides in rat small bowel. *Gastroenterology* 1986; **91**: 1521-7.
- 54 Moore P, Swendseid ME. Dietary regulation of the activities of ornithine decarboxylase and S-adenosyl methionine decarboxylase in rats. *J Nutr* 1983; **113**: 1927-35.
- 55 Cynober L. Can arginine and ornithine support gut function? *Gut* 1994; **35** (suppl 1): 42-5.
- 56 Spector MH, Traylor J, Young EA, Weser E. Stimulation of mucosal growth by gastric and ileal infusion of single amino acids in parenterally nourished rats. *Digestion* 1981; **21**: 33-40.
- 57 Windmueller HG. Glutamine utilization by the small intestine. *Adv Enzymol* 1982; **53**: 201-37.
- 58 Baskerville A, Hambleton P, Benbough JE. Pathological features of glutaminase toxicity. *Br J Exp Pathol* 1980; **61**: 132-8.
- 59 O'Dwyer ST, Smith RJ, Hwang TL, Wilmore DW. Maintenance of small bowel mucosa with glutamine-enriched parenteral nutrition. *J Parent Ent Nutr* 1989; **13**: 579-85.
- 60 Wang XD, Jacobs DO, O'Dwyer ST, Smith RJ, Wilmore DW. Glutamine-enriched parenteral nutrition prevents mucosal atrophy following massive small bowel resection. *Surg Forum* 1988; **39**: 44-6.
- 61 Fox AD, Kripke SA, De Paula J. Effects of a glutamine-supplemented enteral diet on methotrexate-induced enterocolitis. *J Parent Ent Nutr* 1988; **12**: 325-31.
- 62 Klimberg VS, Salloum RM, Kasper M, Plumley DA, Dolson DJ, Hautamaki RD. Oral glutamine accelerates healing of the small intestine and improves outcome after whole abdominal radiation. *Arch Surg* 1990; **125**: 1040-5.
- 63 Morin CL, Grey VL, Garofalo C. Influence of lipids on intestinal adaptation after resection. In: Robinson JW, Dowling RH, Reicken E-O, eds. *Mechanisms of intestinal adaptation*. Lancaster: MTP Press, 1982: 175-84.
- 64 Grey VL, Garofalo C, Greenberg GR, Morin CL. The adaptation of the small intestine after resection in response to free fatty acids. *Am J Clin Nutr* 1984; **40**: 1235-42.
- 65 Doffol M, Galluser M, Raul F. Effect of intravenous and intragastric fat infusion on intestinal brush border enzyme activities in rats. *Eur Surg Res* 1986; **18**: 107-11.
- 66 Weinberg LM, Pusateri JP, Levine GM. Comparison of different caloric substrates on intestinal adaptation in the rat. *Gastroenterology* 1989; **96**: 1514-20.
- 67 Maxton DG, Cynk EU, Jenkins AP, Thompson RPH. The effect of dietary fat on the small intestinal mucosa. *Gut* 1989; **30**: 1252-5.
- 68 Maxton DG, Cynk EU, Thompson RPH. Promotion of growth of the small intestine by dietary essential fatty acids. *Eur J Gastroenterol Hepatol* 1990; **2**: 131-6.
- 69 Jenkins AP, Thompson RPH. The trophic effect of Efamol on the rat small intestinal mucosa. *Clin Sci* 1989; **77**: 555-9.
- 70 Thomson ABR, Keelan M, Clandinin MT, Walker K. Dietary fat selectively alters transport properties of rat jejunum. *J Clin Invest* 1986; **77**: 279-88.
- 71 Jacobs LR. Effect of short-term dietary fat on cell growth in rat gastrointestinal mucosa and pancreas. *Am J Clin Nutr* 1983; **37**: 361-7.
- 72 Thomson ABR, McIntyre Y, Macleod J, Keelan M. Dietary fat content influences uptake of hexoses and lipids into rabbit jejunum following ileal resection. *Digestion* 1986; **35**: 78-88.
- 73 Jenkins AP, Ghatti MA, Bloom SR, Thompson RPH. The effects of bolus doses of fat on small intestinal structure and on release of gastrin, cholecystokinin, peptide tyrosine, tyrosine and enteroglucagon. *Gut* 1992; **33**: 218-23.
- 74 Jenkins AP, Thompson RPH. The effect of dietary fat on the distribution of mucosal mass and cell proliferation along the small intestine. *Gut* 1992; **33**: 224-9.
- 75 Greenberger NJ, Rodgers JB, Isselbacher KJ. Absorption of medium and long chain triglycerides: factors influencing their hydrolysis and transport. *J Clin Invest* 1966; **45**: 217-27.
- 76 Jenkins AP, Thompson RPH. Does the fatty acid profile of dietary fat influence its trophic effect on the small intestinal mucosa? *Gut* 1993; **34**: 358-64.
- 77 Galluser M, Czernichow B, Dreyfus H, Gossé F, Guérolld B, Kachelhoffer J, et al. Comparison of different lipid substrates on intestinal adaptation in the rat. *Gut* 1993; **34**: 1069-74.
- 78 Hart MH, Grandjean CJ, Park JHY, Erdman SH, Vanderhoof JA. Essential fatty acid deficiency and post resection mucosal adaptation in the rat. *Gastroenterology* 1988; **94**: 682-7.
- 79 Vanderhoof JA, Park JHY, Mohammadpour H, Blackwood D. Effects of dietary lipids on recovery from mucosal injury. *Gastroenterology* 1990; **98**: 1226-31.
- 80 Reinhart WH, Muller O, Halter F. Influence of long-term 16, 16-dimethyl prostaglandin E₂ treatment on the rat gastrointestinal mucosa. *Gastroenterology* 1983; **85**: 1003-10.
- 81 Vanderhoof JA, Blackwood DJ, Mohammadpour H, Park JHY. Effect of dietary menhaden oil on normal growth and development and on ameliorating mucosal injury in rats. *Am J Clin Nutr* 1991; **54**: 346-50.
- 82 Vanderhoof JA, Adrian TE, Blackwood DJ, Mohammadpour H, Herrington MJ, Park JHY. Effect of high fat diets on mucosal adaptation following massive bowel resection. *Gastroenterology* 1991; **100**: A552.
- 83 Kripke SA, De Paula JA, Berman JM, Fox AD, Rombeau JL, Settle RG. Experimental short-bowel syndrome: effect of an elemental diet supplemented with short-chain triglycerides. *Am J Clin Nutr* 1991; **53**: 954-62.
- 84 Sakata T. Stimulatory effect of short-chain fatty acids on epithelial cell proliferation in the rat intestine: a possible explanation for trophic effects of fermentable fibre, gut microbes and luminal trophic factors. *Br J Nutr* 1987; **58**: 95-103.
- 85 Koruda MJ, Rolandelli RH, Bliss DZ, Hastings J, Rombeau JL, Settle RG. Parenteral nutrition supplemented with short-chain fatty acids: effect on small-bowel mucosa in normal rats. *Am J Clin Nutr* 1990; **51**: 685-9.
- 86 Koruda MJ, Rolandelli RH, Settle RG, Zimmaro DM, Rombeau JL. Effect of parenteral nutrition supplemented with short-chain fatty acids on adaptation to massive small bowel resection. *Gastroenterology* 1988; **95**: 715-20.
- 87 Thomson ABR, Keelan M, Garg M, Clandinin MT. Spectrum of effects of dietary long-chain fatty acids on rat intestinal glucose and lipid uptake. *Can J Physiol Pharmacol* 1987; **65**: 2459-65.
- 88 Thomson ABR, Keelan M, Clandinin MT, Rajotte RV, Cheeseman CI, Walker K. Treatment of the enhanced intestinal uptake of glucose in diabetic rats with a polyunsaturated acid diet. *Biochim Biophys Acta* 1987; **905**: 426-34.
- 89 Sagher FA, Dodge JA, Moore R, McMaster C, McCaughey G. Modulation of fluid absorption and the secretory response of rat jejunum to cholera toxin by dietary fat. *Gut* 1990; **31**: 1256-61.
- 90 Dowling RH, Reicken E-O, Laws JW, Booth CC. The intestinal response to high bulk feeding in the rat. *Clin Sci* 1967; **32**: 1-9.
- 91 Goodlad RA, Lenton W, Ghatti MA, Adrian TE, Bloom SR, Wright NA. Effects of an elemental diet, inert bulk and different types of dietary fibre on the response of the intestinal epithelium to refeeding in the rat and relationship to plasma gastrin, enteroglucagon, and PYY concentrations. *Gut* 1987; **28**: 171-80.
- 92 Ecknauer R, Sircar B, Johnson LR. Effect of dietary bulk on small intestinal morphology and cell renewal in the rat. *Gastroenterology* 1981; **81**: 781-6.
- 93 Jacobs LR. Effects of dietary fibre on mucosal growth and cell proliferation in the small intestine of the rat: a comparison of oat bran, pectin and guar with total fiber deprivation. *Am J Clin Nutr* 1983; **37**: 954-60.
- 94 Sigleo S, Jackson MJ, Vahouny GV. Effects of dietary fibre constituents on intestinal morphology and nutrient transport. *Am J Physiol* 1984; **246**: G34-9.
- 95 Jacobs LR, Lupton JR. Effect of dietary fibers on rat large bowel mucosal growth and cell proliferation. *Am J Physiol* 1984; **246**: G378-85.
- 96 Johnson IT, Gee JM. Gastrointestinal adaptation in response to soluble non-available polysaccharides in the rat. *Br J Nutr* 1986; **55**: 497-505.
- 97 Cummings JH. Dietary fibre. *Br Med Bull* 1981; **37**: 65-70.
- 98 Goodlad RA, Ratcliffe B, Fordham JP, Wright NA. Does dietary fibre stimulate intestinal epithelial cell proliferation in germ free rats? *Gut* 1989; **30**: 820-5.
- 99 Sakata T, Yajima T. Influence of short chain fatty acids on the epithelial cell division of digestive tract. *Q J Exp Physiol* 1984; **69**: 639-48.
- 100 Roediger WEW. Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology* 1982; **83**: 424-9.
- 101 Kripke SA, Fox AD, Berman JM, De Paula J, Settle RG, Rombeau JL. Short chain fatty acids and colonic mucosal growth: importance of butyrate. *Clin Nutr* 1987; **6** (suppl): 38.
- 102 Wyatt GM, Horn N, Gee JM, Johnson IT. Intestinal microflora and gastrointestinal adaptation in the rat in response to non-digestible dietary polysaccharides. *Br J Nutr* 1988; **60**: 197-207.
- 103 Key FB, Mathers JC. Effects on volatile fatty acid production and gut epithelial proliferation of adding haricot beans to a whole meal bread diet. *Proc Nutr Soc* 1989; **48**: 47A.
- 104 Johnson IT, Gee JM. Influence of soluble non-starch polysaccharides and food intake on mucosal cell turnover and some gastrointestinal peptides in the rat. *Proc Nutr Soc* 1991; **50**: 57A.
- 105 Pell JD, Gee JM, Wortley GM, Johnson IT. Dietary corn oil and guar gum stimulate intestinal crypt cell proliferation in rats by independent but potentially synergistic mechanisms. *J Nutr* 1992; **122**: 2447-56.
- 106 Sanderson IR, Udeen S, Davies PSW, Savage MO, Walker-Smith JA. Remission induced by an elemental diet in small bowel Crohn's disease. *Arch Dis Child* 1987; **61**: 123-7.
- 107 O'Morain C, Segal AW, Levi AJ. Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. *BMJ* 1984; **288**: 1859-62.
- 108 Rigaud D, Cosnes J, Le Quintrec Y, René E, Gendre JP, Mignon M. Controlled trial comparing two types of enteral nutrition in treatment of active Crohn's disease: elemental v polymeric diet. *Gut* 1991; **32**: 1492-7.
- 109 Young EA, Cioletti LA, Winborn WB, Traylor JB, Weser E. Comparative study of nutritional adaptation to defined formula diets in rats. *Am J Clin Nutr* 1980; **33**: 2106-18.
- 110 Maxton DG, Cynk EU, Thompson RPH. Small intestinal response to 'elemental' and 'complete' liquid feeds in the rat: effect of dietary bulk. *Gut* 1987; **28**: 688-93.
- 111 Levine GM, Deeren JJ, Yeidner E. Small-bowel resection. Oral intake is the stimulus for hyperplasia. *Dig Dis Sci* 1976; **21**: 542-6.
- 112 Feldman EJ, Dowling RH, McNaughton J, Peters TJ. Effects of oral versus intravenous nutrition on intestinal adaptation after small bowel resection in the dog. *Gastroenterology* 1976; **70**: 712-9.
- 113 Molyneux ME, Loareesuwat S, Menzies IS, Grainger SL, Phillips RE, Wattanagoon Y, et al. Reduced hepatic blood flow and intestinal malabsorption in severe falciparum malaria. *Am J Trop Med Hyg* 1989; **40**: 470-6.
- 114 Kudsk KA. Gut mucosal nutritional support - enteral nutrition as primary therapy after multiple system trauma. *Gut* 1994; **35** (suppl 1): 52-4.
- 115 Ferguson A. Immunological functions of the gut in relation to nutritional state and mode of delivery of nutrients. *Gut* 1994; **35** (suppl 1): 10-2.
- 116 Deitch EA. Bacterial translocation: the influence of dietary variables. *Gut* 1994; **35** (suppl 1): 23-7.