Enteral nutrition as primary therapy in short bowel syndrome

I W Booth

Abstract
The spectacular success of parenteral nutrition in supporting patients during small intestinal adaptation after massive resection, tends to obscure the prolonged periods often needed for such adaptation to take place. After neonatal small intestinal resection for example, it may take more than five years before adaptation is complete. There is therefore a strong argument for examining ways in which adaptation can be facilitated, in particular, by the addition of novel substrates to enteral feeds. Pectin is completely fermented by colonic bacteria to short chain fatty acids. In the rat, addition of pectin to enteral feeds led to a more rapid adaptive response in both the small and large intestine after massive small intestinal resection, although faecal nitrogen losses were increased. In a similar rat model, the provision of 40% of non-protein energy as short chain triglycerides facilitated the adaptive response in the jejunum, colon, and pancreas. The importance of glutamine as a metabolic substrate for the small intestine makes it another potential candidate and some, but not all animal studies, have suggested a therapeutic effect: increasing the glutamine content of feeds to 25% of total amino acids produced enhanced jejunal and ileal hyperplasia, even on a hypocaloric feed, and an improved overall weight gain. Studies in humans are very limited, but such promising results in the experimental animal suggest that this is probably a fruitful area for further study.

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Resection of more than 50% of the small intestine is probably associated with important nutritional sequelae, and when 25% or less remains, nutritional support, often by the parenteral route initially, is essential. This review summarises recent experience in optimising the constituents of enteral feeds to enhance postresection intestinal adaption.

Prognosis
The outlook for patients with short bowel syndrome (SBS) has changed considerably. The prognosis for neonates having extensive small bowel resection has improved steadily over the last 15 years, mainly because longterm parenteral nutrition permits affected children to grow and develop normally during the period of intestinal adaptation. One recent study reported an increase in the survival of children with less than 40 cm of small intestine from 42% before 1980 to 94% in the decade since.1 When 40–80 cm of small intestine remain, current longterm survival is 97%.1 This success story, however, obscures the time needed for full intestinal adaptation to take place, and some children have to receive parenteral nutrition for six years before eventually stopping treatment. Even the mean time to adaptation when less than 40 cm of small intestine remains varies from 18 to 45 months, depending on whether the ileo-caecal valve is present.1 It is therefore appropriate to examine those factors that regulate adaptation so they can be manipulated to accelerate this process.

Control of postresection adaptation
After small bowel resection, the remaining intestine dilates, and crypt depth and villus height increase, leading to enhanced segmental absorption of many nutrients. In the rat, mucosal DNA synthesis increases within 24 hours, leading to villus hyperplasia, which is fully established by one month. In humans, however, the adaptive response seems to be slower and often takes over a year to reach maximal effect. The finding that total parenteral nutrition leads to a more muted mucosal hypoplasia in humans than in the experimental animal is consistent with a comparatively less important role for luminal nutrients in maintaining normal intestinal function in humans and a longer period for adaptation.

Three main factors are responsible for promoting intestinal adaptation: pancreatic-biliary secretions, hormonal factors, and luminal nutrients. Clearly, only the last is of direct relevance to the role of enteral nutrition as primary therapy in SBS.

LUMINAL NUTRIENTS
A number of strands of evidence support the role of luminal nutrients in promoting adaptation. Jejunal resection by bypass, or ileojejunostomy transposition, all lead to hyperplastic changes in the segment exposed to increased nutrients. Similarly, mucosal growth may be stimulated by cold induced hyperphagia in the rat, or by luminal perfusion of nutrients into Thiry-Vella fistulas in the dog.

It has been recognised for some time that the adaptive response can be influenced by dietary components. For example, disaccharides seem to be more trophic than monosaccharides, provided the disaccharides are hydrolysed; a high protein diet leads to
increased peptide hydrolase and alkaline-phosphatase activities, and dietary starch leads to increased disaccharidase activities. Long chain triglycerides seems to be a more potent trophic stimulus than protein, starch or median chain triglyceride.

More recently, the role of a number of dietary components not normally included in postresection enteral feeds has been examined: dietary fibre, free fatty acids, and short chain triglycerides and glutamine. To date, they have been studied almost exclusively in the rat, although preliminary data suggest a potential role in reducing the duration of postresection adaptation in humans. In addition, changing composition of carbohydrates in enteral feeds may also be helpful in preventing recurrent D-lactic acidosis complicating massive small bowel resection.

**Specific nutrients as primary therapy**

**ENHANCED ADAPTATION**

**Pectin**

Pectin is a water soluble, non-cellulosic dietary fibre, which is completely fermented by colonic bacteria, leading to an increase in stool fatty acid concentrations without an increase in bulk. Interest in pectin in the context of intestinal adaptation followed the finding that pectin supplementation of an elemental diet was associated with improved healing of colonic anastomoses in the rat: pectin treated animals had higher bursting pressure and a higher hydroxyproline content at the anastomotic site.

Importantly, changes have also been found in the small intestine. Addition of pectin to the diet in the rat resulted in an increase in small intestinal length and weight and an increase in crypt depth in the mid jejunal and ileal segments. The migration rate of enterocytes up the villus was also increased by pectin feeding, leading to a reduction in cell transit time.

**Studies in the experimental animal** – Koruda et al have investigated the effects of a pectin supplemented elemental diet on intestinal adaptation to massive small bowel resection in the rat. After an 80% small bowel resection and anastomosis, animals were allocated to receive gastrostomy feeds of an elemental diet, with or without the addition of citrus pectin (2 g/100 ml). Animals were killed 15 days postoperatively, after eight days on the full diet. Control animals were gastrostomy fed but not resected. As expected, resection led to increases in bowel weight/unit length, but this hypertrophy was significantly increased in the ileal and colonic segment by pectin supplementation. In the resected animals, pectin significantly increased mucosal weight (Fig 1) and DNA, RNA, and protein content by 1:3–2–0-fold in jejunal, ileal, and colonic segments. Pectin feeding also increased villus height, crypt depth, and mucosal thickness in both jejunal and ileum, although with the exception of mucosal depth, these improvements were only significant in the ileum (Table I). Mitotic activity/crypt was significantly greater in the jejunal and colon of the pectin group than the non-pectin animals. Interestingly, weight loss in the resected animals was significantly reduced by pectin supplementation, even though nitrogen balance was reduced by pectin as a result of increased faecal nitrogen losses. After resection, and in the absence of pectin supplementation, ileal segmental sucrase, maltase, and lactase activities were increased in the ileum but only maltase activity in the jejum. Pectin supplementation, however, led to significant increases in the segmental activity of all three disaccharidases in the jejunum (Table II).

**Experience in humans** – There has been only one case report so far of the effects of pectin supplementation of enteral feeds, in a 3 year old boy with only 18 cm of jejunum after a small bowel volvulus. In contrast with studies in the experimental animal, pectin did not have

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**TABLE I**  Pectin and postresection adaptation in the rat

<table>
<thead>
<tr>
<th></th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight/length</td>
<td>↑</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mucosal weight</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DNA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RNA</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Protein</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Villus height</td>
<td>−</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Crypt depth</td>
<td>−</td>
<td>+</td>
<td>N/A</td>
</tr>
<tr>
<td>Mucosal thickness</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A= Not applicable

**TABLE II**  Pectin and postresection adaptation in the rat

<table>
<thead>
<tr>
<th>Segmental activity</th>
<th>Jejunum</th>
<th>Ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrase</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Malatase</td>
<td>↑↑</td>
<td>−</td>
</tr>
<tr>
<td>Lactase</td>
<td>↑↑</td>
<td>−</td>
</tr>
</tbody>
</table>
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Figure 2: The effects on mucosal protein (mg/cm) for each intestinal segment of resected and transected (control) rats fed chemically defined (CD), medium chain triglyceride (MCT) or short chain triglyceride (SCT) diets. Resected groups with different letters differ significantly (in the jejunum, p<0.05; in the colon p<0.01). *Significantly different from the respective transected control p<0.01.

an adverse effect upon nitrogen balance, in fact, nitrogen absorption improved somewhat. Pectin supplementation was associated with prolongation of stomach to anus transit time, and there were no adverse effects on electrolyte balance. Mineral balances, a potentially adverse effect of pectin, were not studied.

Mechanisms – There are a number of possible mechanisms whereby pectin might influence intestinal adaptation after resection. An effect in the colon is not surprising; pectin fermentation produces short chain fatty acids, the preferred oxidative substrate for colonicocytes, metabolism of which leads to colonic mucosal proliferation. An effect in the small intestine may be related to an increase in transit time and consequently more contact with luminal nutrients, stimulation of pancreatic secretion, or entero-glucagon release, glutamine and ketone production, or increased gut blood flow.

Soy polysaccharide
In a short term six hour study in six patients with SBS, the addition of soy polysaccharide to an enteral feed delayed transit but was associated with increased stool wet weight and sodium output, together with decreased energy absorption.

Short chain triglycerides
Short chain triglycerides are handled in the small intestine like medium chain triglycerides. They are hydrolysed by pancreatic and gastric lipase and are well absorbed in both the hydrolysed and esterified form. In contrast with medium chain triglycerides, the component short chain fatty acids of short chain triglycerides are absorbed by the colonic epithelium as well as in the small intestine and stimulate intestinal mucosal growth in the rat.

Recently Kripcie et al. have investigated the effect of short chain triglycerides on intestinal adaptation during 60% small bowel and caecal resection in the rat. Animals were allocated to receive a low fat, chemically defined feed, or a feed in which part of the carbohydrate was replaced with either medium or short chain triglycerides (40% of non-protein energy). After 12 days the group receiving the short chain triglyceride had significantly greater segment and mucosal weight and protein content in the jejunum and colon, than the group receiving the medium chain triglyceride or low fat diets (Fig. 2). Resection increased the comparative weight of the pancreas compared with controls, and this was again increased maximally in the group receiving the short chain triglyceride diet.

Free fatty acids
Free fatty acids seem to be even more potent than long chain triglyceride, protein, starch or medium chain triglyceride in enhancing adaptation. After 50% small bowel resection in the rat, infusion of 10% of the total calories as fatty acids (50:50 wt/vol mixture of oleic and linoleic acid) resulted in enhanced small intestinal and colonic adaptation compared with an equivalent amount of long chain triglyceride.

Glutamine
Glutamine is a non-essential amino acid and is the most abundant amino acid in plasma, where it accounts for 20% of the total circulating pool. Nearly all tissues are capable of glutamine synthesis, but most is synthesised and stored in muscle, where its concentration is 30 times that of plasma. Glutamine is an important vehicle for nitrogen transport between tissues, a regulator of protein synthesis, the most important substrate for renal ammoniagenesis, and is an essential precursor for nucleotide synthesis. It is also an important metabolic fuel for rapidly dividing cells, including the small intestinal mucosa, and after small bowel resection, glutamine released from muscle stores is taken up by the gut.

Supplementing parenteral nutrition fluids with glutamine reduces the gastrointestinal atrophy seen during parenteral nutrition and the severity of the mucosal injury after chemotherapy or radiation treatment.

Glutamine provided enterally may enhance postresection adaptation. Increasing the glutamine content of enteral feeds so that it provided 25% of total amino acids instead of the usual 4–10%, resulted in enhanced hyperplasia in the jejunum and ileum. In pair fed animals, glutamine supplementation led to enhanced body weight, which was again maximal when glutamine provided 25% of total amino acid. Glutamine may also be capable of inducing postresection hyperplasia where the animals receive only 50% of their energy requirements enterally. These findings have not been confirmed by others. It seems then, that glutamine may have an anabolic effect on body tissues in addition to its effects on intestinal adaptation, although it is noteworthy that the requirement for dietary glutamine under these circumstances far exceeds the glutamine content of a normal diet.
PREVENTION OF D-LACTIC ACIDOSIS

Recurrent D-lactic acidosis is an uncommon complication of SBS. Carbohydrate that escapes small intestinal absorption enters the colon and is fermented to the D-L-isomers of lactates when lactobacilli are present in the colon. Although L-lactate can be metabolised by L-lactate dehydrogenase, no such pathway exists for D-lactate, and patients have severe acidosis and a considerable disturbance in the level of consciousness. Treatment is usually directed at changing the colonic flora by giving broad spectrum antibiotics orally. We recently described a child in whom it was possible to prevent recurrent symptoms by modifying the patient's enteral feed.

At the age of 9 the patient had a massive resection after a small bowel volvulus, which left her with 14 cm of jejunum. Superior venacaval obstruction prevented longterm parenteral nutrition, and the patient was dependent upon enteral feeds. Recurrent D-lactic acidosis occurred initially after sucrose binges, but continued despite strict adherence to a low sucrose diet in addition to enteral nutrition. Stool culture showed a pure growth of lactobacilli. Because this patient's colon represented a potentially valuable source of nutrient salvage, it was decided not to use broad spectrum antibiotics, but to attempt to reduce D-lactic acid production by modifying the nature of the carbohydrate substrate entering the colon. Test of fermentation by lactobacilli in vitro showed D-lactate production from a wide range of mono and disaccharides, but none from starch. The patient was therefore switched from a feed in which the carbohydrate was mainly oligosaccharide, to a feed in which over 75% of the carbohydrate was present as pentasaccharides or larger. The patient had no further episodes of acidosis and thrived.

It is now clear that dietary modification is capable of enhancing post resection adaptive hyperplasia in the experimental animal. In addition to conventional nutrients, supplementation of enteral feeds with pectin, short chain triglycerides, free fatty acids, and glutamine may be important in this respect, but there has been very little experience of similar dietary modification in humans. The difficulties of proving a beneficial effect in humans should not be underestimated. Patients with severe SBS, the group in whom enhanced adaptation will probably be of most benefit, are not common, and the nature of the disorder and of the intervention do not lend themselves readily to a cross over design. There is now sufficient evidence, however, in the experimental animal to support further studies in humans.

Finally, it should be remembered that modification of the composition of enteral feed composition may have a role in the primary treatment of recurrent D-lactic acidosis secondary to SBS.

26 Smith RJ, Wilmore DW. Glutamine nutrition requirements. JPEN 1990; 14: 94-95.
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