

Diet formulation and choice of enteral diet

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Once it has been decided to provide nutritional support via the enteral route the best formulation to meet the nutritional needs of the individual patient must be selected. A large number of enteral diets are now commercially available, and Table 1 summarises the different categories available. Until recently, controversy existed as to whether enteral feeds formulated and prepared in the hospital dietetic department should be used instead of their commercially prepared counterparts: problems caused by infection have now been well documented with "home brew" diets,¹ and there are now controlled data which show that the incidence of diarrhoea is higher when "home brew" rather than commercial diets are used for enteral feeding.² Knowledge gained about the processes entailed in the physiology of nutritional absorption and subsequent metabolism both in normal and disease states continues to influence the formulation of enteral diets, and this review will outline recent advances in those areas that are influencing diet formulation.

Fat absorption

Over the past two years there have been few research findings that have actually influenced diet formulation. The importance of preventing essential fatty acid deficiency needs emphasising, particularly as it may occur when gut function is particularly impaired and long chain triglycerides are poorly assimilated.³ As previously outlined,⁴ medium chain triglycerides are probably not as well assimilated in the presence of bile salt deficiency, exocrine pancreatic insufficiency, and intestinal resection as many would believe,⁵ and at least in the cases of exocrine pancreatic insufficiency and intestinal resection pancreatic supplements will greatly enhance energy assimilation from medium chain triglycerides and reduce steatorrhoea.⁶

Carbohydrate

The physiology of digestion and absorption of

dietary carbohydrate in relation to formulation of enteral diets has been reviewed.⁷ Although the early chemically defined "elemental" diets administered to man contained glucose as the sole source of carbohydrate energy,^{8,9} the glucose content was soon replaced in part by sucrose,¹⁰ and later by glucose polymer mixtures derived from the hydrolysis of starch by α -amylase.⁷ Although the potential carbohydrate forms used in enteral diets have been categorised,¹¹ Jones *et al*¹² characterised in detail the composition of starch hydrolysates commonly used as the carbohydrate energy source of enteral diets. Using gel permeation chromatography, they found that most consist of a very heterogenous mixture of glucose polymers—with about 50% of the glucose content being present as polymers, with less than and 50% more than 10 glucose molecules.¹²

Table 1 *Categorisation of enteral diets*

Type	Comment
1 <i>Polymeric diets</i>	Whole protein nitrogen source, for use in patients with normal or near normal gastrointestinal function
2 <i>Predigested chemically defined elemental diets</i>	Predigested nutrients: most diets have a low fat content, for use in patients with severely impaired gastrointestinal function
3 <i>Specially formulated predigested diets</i> Cirrhosis, Portosystemic encephalopathy	Amino acid nitrogen source High concentrations branched chain amino acids, low concentrations aromatic amino acids; indications still disputed
Stress	Amino acid nitrogen source High concentrations branched chain amino acids; may contain more than 1 kcal/ml energy Indications still disputed
4 <i>Diets containing fibre</i>	Concept for the future At present fibre containing polymeric diets marketed, fibre containing predigested diets may follow; indications still under investigation

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Intestinal perfusion studies performed in normal human volunteers in the absence of luminal α -amylase activity showed differential handling of the glucose polymers by the jejunum. The higher molecular weight glucose polymers (containing ≥ 10 glucose molecules) were assimilated slower than the lower molecular weight glucose polymers. It seemed that the lower weight polymers could be conferring a kinetic advantage on the transport of glucose.¹² This was confirmed in a further study,¹³ in which purified high and low molecular weight polymer fractions were perfused. Although the α -amylase hydrolysate of the low molecular weight glucose polymer fraction (< 10 glucose molecules) conferred the expected kinetic advantage on the transport of glucose, the high molecular weight fraction (osmolality one fifth of the starting material) was surprisingly well absorbed, even in the absence of α -amylase.¹³ The authors concluded that the energy content of enteral diets could be increased at the same time as diet osmolality was lowered, by substituting the commonly used heterogenous starch hydrolysates with purified high molecular weight fractions. So far this concept been used in only one diet (Vivonex TEN, Norwich Pharmaceuticals), with a subsequent lowering of osmolality from 830 to 630 mosmol/kg.

Lactose

Lactose deficiency is common in certain racial and ethnic groups, particularly Blacks, Orientals, Indians, and Jews, with an incidence as high as 60-100%.¹⁴ On account of this it is perhaps hardly surprising that it is now considered to be commercially wise to minimise the lactose content of new enteral products. Walike and Walike¹⁵ were the first to suggest that the lactose content of blenderised formulae was one cause of diarrhoea occurring during enteral feeding. Certainly the recent study of O'Keeffe *et al*¹⁶ showed that if patients with biochemically confirmed lactose malabsorption are bolus fed with enteral diets containing lactose then diarrhoea will occur with stool volumes in excess of 1l/24 hours. It must be said, however, that it is far from certain that it is the lactose content that causes gastrointestinal symptoms when milk is ingested by normal subjects with biochemically confirmed lactose intolerance.

Two studies failed to show that the ingestion of 480 ml lactose containing milk by healthy normal subjects with biochemically confirmed lactose malabsorption resulted in a higher incidence of gastrointestinal side effects than when the same subjects ingested the same quantity of lactose free milk.^{17 18} In a recent study by Keohane *et al*¹⁹ enterally fed patients with biochemically confirmed

lactose malabsorption did not have a higher incidence of gastrointestinal side effects when fed a lactose containing enteral diet (20.9 ± 5.3 g lactose/24 hours) compared with the effects of a lactose free formulation. What then is the explanation for the discrepancy in these findings? The answer lies in the load (concentration \times rate) of lactose that is administered to lactose "intolerant" patients. Lactase, or β -galactosidase, is a brush border hydrolase whose specific activity is reduced but not absent in patients and subjects with lactose malabsorption. If 2-3 litres of diets containing lactose are infused constantly over 24 hours then the load of lactose administered per unit time is low, and symptoms, as shown by Keohane *et al*,¹⁹ will not occur. Symptoms will develop, however, as shown by O'Keeffe *et al*¹⁶ if high loads of lactose are administered by the bolus technique. The commercial pressures are now such that it is unlikely that any of the new enteral diets will contain appreciable quantities of lactose.

Sucrose

In patients with a very short bowel syndrome the factors that will limit uptake of glucose from glucose polymer mixtures will usually include intraluminal and brush border saccharide hydrolysis, and in a few instances when these do not limit the rate, the capacity of the membrane carrier to mediate uptake the released monosaccharide. Jejunal perfusion studies have shown that if transport of glucose from glucose polymers is saturated sugar absorption can be enhanced if disaccharide sucrose is added.²⁰ This is because sucrose is hydrolysed by the sucrase moiety of the hybrid brush border hydrolase sucrase-isomaltase²¹ to glucose and fructose, fructose absorption then being mediated by a carrier that is different from that used during glucose uptake.²²

Protein absorption

The digestion and absorption of dietary protein in relation to the formulation of enteral diets has been recently reviewed.²³ While it remains clear that patients with normal gastrointestinal function should be fed diets containing whole protein as the nitrogen source, controversy still remains as to whether the nitrogen source of enteral diets for use in patients with severely impaired gastrointestinal function should consist of free amino acids or oligopeptides, and if oligopeptides are used, what the most rational formulation should be. Intestinal perfusion studies in our laboratory have consistently shown more efficient absorption of α -amino acid nitrogen from partial enzymic hydrolysates of whole

protein than equivalent equimolar free amino acid mixtures.²⁴ On the basis of these physiological studies we proposed theoretical reasons for using peptides rather than free amino acids as the nitrogen source is predigested chemically defined "elemental" diets.²⁵ Other benefits, which include effects on osmolality, cost, and palatability, have also been discussed.^{23, 25} I have been struck by the variability in handling of the different partial enzymic hydrolysate of whole protein studied,²⁴ and in recent studies I investigated the influences that starter protein composition, hydrolysis method,²⁶ and peptide chain length²⁷ have on absorption profiles of partial enzymic hydrolysates of whole protein.

One of the most interesting observations was the finding that subtle increases in peptide chain length from 2–3 to 3–5 amino acid residues have a deleterious effect on α -amino acid nitrogen absorption.²⁸ If a peptide based nitrogen source is considered to be desirable, evidence now points to the fact that mixtures of dipeptides and tripeptides rather than higher peptides will result in the most efficient rates of α -amino acid nitrogen absorption per unit length of intestine.

Amino acid v peptides:clinical studies

Three recent studies^{29–31} compared the efficacy of Vivonex HN, whose nitrogen source is composed of free amino acids, and Criticare HN, whose nitrogen source is composed of partially hydrolysed protein (peptides and amino acids). Smith *et al*²⁹ showed higher blood urea, nitrogen, and urinary urea excretion values in patients with inflammatory bowel disease who had been fed Vivonex HN. Similarly, increased blood urea nitrogen values were also observed in patients with pancreatic insufficiency who had been both fed with diets.³⁰ A weight gain was seen only in the patients who had been fed Criticare HN.³⁰ In malnourished patients with head and neck cancer greater weight gains, higher serum albumin concentration, and lower rises in blood urea nitrogen were seen in the patients fed Criticare HN.³¹ Contrary to some unpublished suggestions, the differences noted in these three trials do not indicate a superiority of peptides over amino acids.

The quantitative differences in the amino acid composition between the two diets are many,³¹ particularly with regard to glutamine, an amino acid known to stimulate directly the urea cycle.³¹ Ureagenesis, with subsequent increases in excretion of urinary urea nitrogen and impairment of nitrogen balance, would thus be expected to occur with Vivonex HN rather than with Criticare HN. In my

unit higher urinary urea excretion values in patients who had been fed Vivonex HN compared with those fed with Clinifed 400, a whole protein polymeric diet were also noted.³² The question as to whether peptides have a specific advantage over free amino acids can only be answered if patients with severely impaired gastrointestinal function are fed peptide and free amino acid diets of identical amino acid composition.

Vitamin and trace elements

The mineral, trace element, and vitamin contents of enteral diets have traditionally been based on recommended dietary allowances (RDA), which are the levels judged by the various national boards and the World Health Organisation to be adequate to meet the nutritional needs of practically all healthy persons. It had already been pointed out³³ that the RDA do not cover therapeutic nutritional needs, so that vitamin and trace element requirements, affected by disease or pharmaceutical preparations, may not be met in all enteral feeds.³³ Vitamin requirements have been comprehensively reviewed.³³ Of the trace elements, zinc has received the most attention, and two to three times the RDA has been recommended for hypermetabolic patients.³⁴ Requirements of other trace elements for hypermetabolic patients are unknown, and deficiencies of magnesium, copper, chromium, and selenium have all been reported in patients receiving parenteral nutrition.^{35–37} Recently Bunker and Clayton³⁸ reported discrepancies between concentrations of zinc, copper, iron, and manganese in enteral diets stated by the manufacturers and those found on analysis. Several feeds even produced less than the United States' recommended daily allowance.

Electrolytes

Table 2 summarises the approximate mean quantities of water and electrolytes handled by the gut in 24 hours by normal subjects. Despite the fact that nearly 9 litres of water and in excess of 1000 mmol sodium is ingested, secreted, and absorbed little emphasis has been placed, until recently, on water and electrolyte absorption during enteral feeding. Small intestinal disease or resection results in an increased colonic inflow of water and electrolytes. As a consequence of the large absorptive capacity of the colon,³⁹ however, severe diarrhoea and depletion of water and electrolytes usually only occur in the presence of coexisting colonic disease or resection. It follows that the diarrhoea, which occurs in enterally fed patients with normal or near normal

Table 2 Approximate mean quantities of water and electrolytes handled by the gut in 24 hours by normal subjects

	Water (ml)	Sodium (mmol)	Chloride (mmol)	Potassium (mmol)
Input				
Diet	1500	150	150	80
Gut secretions	7500	1000	750	40
Total	9000	1150	900	120
Absorption				
Small intestine	7500	950	800	110
Colon	1350	195	97	-3
Output				
Faeces	150	5	3	12

gastrointestinal function in up to 24% of cases,³² is either due to a hormonally induced colonic secretion of water and electrolytes, a hypothesis currently unsubstantiated,⁴⁰ or to other causes such as a synergistic action between enteral feeding and concomitant treatment with antibiotics.⁴¹ In patients with the short bowel syndrome, however, the situation is quite different. Here, large segments of small bowel are diseased or have been resected, often with coexisting colonic disease or resection. In the absence of the reserve absorptive capacity of the colon³⁹ it becomes imperative that fluid and electrolyte absorption from residual small gut is maximised during enteral feeding. I was disturbed to find, therefore, that a net secretion of fluid and electrolytes were observed during in vivo steady state perfusion of segments of normal jejunum with isotonic Vivonex.²⁰ Further studies have been performed using a range of solutions containing the amino acid and glucose polymer components of Vivonex.⁴² Results showed that for all the nine nutrient solutions studied there was a linear correlation between initial sodium concentration and net sodium absorption, so that if the initial concentration exceeded 90 mmol/l net sodium absorption occurred, while at concentrations below this, net secretion of sodium was observed. Water absorption was linearly related to net absorption of osmotically active particles, a substantial proportion of which was accounted for by the movement of sodium and its anions. Thus jejunal sodium secretion observed during perfusion of Vivonex²⁰ is not a unique feature of this diet, but will occur during jejunal perfusion of any low sodium containing diet. The sodium content of four widely used predigested chemically defined "elemental diets," Vivonex, Vivonex HN, Nutrel, and Flexical is 39.2, 36.3, 20.1, and 30.1 mmol/l, respectively, at recommended dilutions, values which are substantially lower than would be required to promote net

sodium and water absorption. There are therefore corroborative experimental data for suggesting that the sodium concentration of the predigested diets, whose use is recommended in the early postoperative management of the short bowel syndrome, should be raised to 80–90 mmol/l.

Choice of enteral diet

PATIENTS WITH NORMAL OR NEAR NORMAL GASTROINTESTINAL FUNCTION

In our experience cumulative positive nitrogen balance in enterally fed patients has not always been achieved.^{32 41 43} Several factors are responsible for this, including an underestimate of energy and nitrogen requirements, use of starter regimens, inadvertent removal of feeding tubes⁴⁴ and poor administration techniques.⁴³ As yet there seems to be no easy answer to the problem of inadvertent removal of feeding tubes.⁴⁴ In a recent study, however, we showed that the use of starter regimens reduces nutrient intake but not the incidence of gastrointestinal symptoms, so that cumulative nitrogen balance can be improved by administering undiluted polymeric diet from the outset of feeding.⁴¹ In my experience it has been rather difficult to administer routinely more than 2l feed/24 hours,^{41 43} but despite this cumulative positive nitrogen balance was achieved when starter regimens were abandoned in a heterogeneous group of patients who had nitrogen requirements of less than 12 g/24 hours. A case can be made, therefore, for recommending the routine use of a polymeric diet of energy density 1 kcal/ml for non-hypermetabolic patients with normal or near normal gastrointestinal function, the composition of which would accord with recommendations outlined in Table 3. It seemed that one way of circumventing the problems that exist in achieving positive nitrogen balance in some of the non-hypermetabolic, or modestly hypermetabolic patients (nitrogen losses 10–15 g/24 hours) would be to use routinely a more energy dense (1.5 kcal/ml) polymeric diet containing higher concentrations of nitrogen (9–10 g/l). By definition, the osmolality of such a diet would be higher than the 1 kcal/ml diets, but if the carbohydrate energy moiety was rationalised according to the concepts proposed by Jones *et al*¹³ the osmolality could be lowered. Clinical trials are currently being performed in my laboratory to determine the efficacy of this approach.

For extremely hypermetabolic patients – for example, those with burns and multiple trauma – normal gastrointestinal function polymeric diets are available with an energy density of 2.0 kcal/ml and nitrogen contents of up to 14 g/l. These are

Table 3 Choice and formulation of enteral diets

	<i>Polymeric diets for patients with normal or near normal gastrointestinal function</i>			<i>Predigested diets for patients with severely impaired gastrointestinal function</i>
	<i>Non-hypermetabolic to moderately hypermetabolic</i>			
	<i>Current</i>	<i>Proposed</i>	<i>Hypermetabolic</i>	
Nitrogen source (g/l)	Protein (5-7)	Protein (9-10)	Protein (11-13)	Purified low molecular weight peptide mixtures (5-10)
Carbohydrate	Glucose polymers	Glucose polymers ± sucrose	Purified glucose polymers (now > 10 glucose molecules) ± sucrose	Glucose polymers
Fat source	Long chain triglycerides	Long chain triglycerides	Long chain triglycerides	Medium chain triglycerides linoleic acid
Energy (%)	32-36	32-36	34-41	?
Kcal/ml	1.0	1.5	2.0	1.0
Electrolytes (mmol/l)				
Sodium	30-70	30-70	30-70	70-90
Potassium	30-70	30-70	30-70	30-70
Chlorine	30-70	30-70	30-70	70-90
Minerals (fraction RDA)	1.0	1-1.5	1.5-2.0	1.0-1.5
Vitamins (fraction RDA)	1.0	1-1.5	1.5-2.0	1.0-1.5
Osmolality (mosmol/kg)	300-400	Up to 500	Up to 600	450-650

hypertonic diets, and I have no personal experience of their use. It should be borne in mind that there may be a real risk of infusing excess carbohydrate to these patients, some of whom already have insulin resistance. Furthermore, excessive carbohydrate loads could also have a deleterious effect on respiratory function.⁴⁵ Modular formulae, whereby the composition of a diet is formulated in the diet kitchen according to the needs of the individual patient, have been proposed for these difficult patients.⁴⁶

PATIENTS WITH IMPAIRED GASTROINTESTINAL FUNCTION

In cases in which the rate of nutrient absorption is limited by impaired luminal hydrolysis, or reductions in mucosal absorption, or hydrolytic capacity the use of enteral diets containing predigested nutrients will result in more efficient nutrient repletion than the use of polymeric diets discussed above. Strictly speaking, the criteria for using the predigested or so called chemically defined elemental diets will usually occur only in patients with severe exocrine pancreatic insufficiency and those with an inadequate or short bowel syndrome. Although other indications for using predigested chemically defined elemental diets have been proposed,⁴⁷ there is very little controlled evidence to support most of the claims.⁴⁸

When nutrient assimilation is severely impaired there are theoretical reasons for believing that nutrients should be presented to the mucosa so that maximal absorption will occur in normal subjects. Table 3 summarises the suggested formulation of such a diet, and it is based on discussions of the physiology of nutrient absorption outlined at the beginning of this paper.

In practical terms, it may often be difficult to decide whether a polymeric or predigested diet should be used. In my opinion, the assimilatory capacity of the human gastrointestinal tract for nutrients is often underestimated. For example, there is no evidence that there is any clinically important impairment of exocrine pancreatic secretion or intestinal absorptive capacity in the post-operative period. Moreover, there is no clinical evidence to support a contention that the use of predigested diets in jejunostomy feeding results in more efficient nutrient repletion than that obtained by polymeric diets.

Little attention has been directed towards enteral feeding in patients with cholestatic jaundice. In the absence of other coexisting gastrointestinal disease these patients will be able to assimilate all the major classes of nutrients except fat and fat soluble vitamins. Diets for those patients should not contain long chain triglycerides, so most of the currently available diets are not indicated. A modular formula

based on whole protein, glucose polymers, medium chain triglycerides, linoleic acid (in the hope of preventing essential fatty acid deficiency), electrolytes, minerals, and water and fat soluble vitamins would be most appropriate. Assimilation of medium chain triglyceride by the jaundiced patient will depend on several factors, including the degree of jaundice, and the presence of coexisting gastrointestinal pathology. Although there are no data to support it, medium chain triglycerides should probably not contribute to more than 20% of the total energy content of these formulations.

CHRONIC PORTAL-SYSTEMIC ENCEPHALOPATHY

Patients with chronic portal-systemic encephalopathy are faced with a nutritional dilemma. They require dietary protein to maintain nitrogen balance, but the ingestion of protein often precipitates encephalopathy. Despite treatment with lactulose or antibiotics many patients with cirrhosis are unable to tolerate sufficient protein to prevent long standing negative nitrogen balance. As the plasma amino acid profiles of these patients are characterised by decreased values of branched chain amino acids and increased values of aromatic amino acids (phenylalanine, tyrosine, free tryptophan and methionine),⁴⁹ investigators have administered mixtures of amino acids rich in branched chain amino acids and deficient in aromatic amino acids.⁵⁰ Overall, it has not been easy to draw conclusions from the published data as the controlled trials evaluated different types and degrees of encephalopathy using different mixtures of branched chain amino acids administered in different ways, different end points, and they found different results. As far as enteral nutrition is concerned, one trial⁵¹ clearly shows that a branched chain amino acid enriched enteral diet low in aromatic amino acids induced positive nitrogen balance in protein intolerant cirrhotic patients, all of whom had had chronic portal-systemic encephalopathy, to about the same degree as an equivalent amount of dietary protein without inducing encephalopathy as often.⁵²

RESPIRATORY AND CARDIAC FAILURE

In one study respiratory, cardiovascular, and metabolic changes were monitored during balance studies in undernourished patients receiving continuous enteral feeding.⁴⁵ At increasing energy infusion rates oxygen consumption, carbon dioxide production and minute ventilation, heat production, heat release and heart rate increased on both a high carbohydrate and high fat diet. Rather disturbingly, increases in carbon dioxide production and minute ventilation were greater for the high carbohydrate relative to the high fat formula. In the

clinical setting care must be taken not to precipitate heart failure during continuous enteral feeding in compromised patients. Furthermore, these findings also suggest that the carbohydrate to fat ratio should be decreased in enteral diets administered to patients with respiratory failure. A new diet (Pulmocare, Ross) has been formulated along these lines.

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