THE LOW BIRTH WEIGHT INFANT AND PARENTERAL NUTRITION

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INTRODUCTION

The need for physiological independence is thrust upon the new baby at birth; developmental maturity, morbidity, source and supply of nutrients are critical in determining outcome, in the short and long term. Infants born significantly preterm have limited energy reserves; in these infants feeding regimens need to provide nutrients for tissue growth and development, and also the energy and catabolic cost of any morbidity;

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Table 1. *Daily nutritional requirements of the low birth weight infant*

	Intra-uterine accretion, 26–36 week gestation	AAP†	ESPGAN‡	TPN (feasible)
Energy				
(kcal/kg)	43	120	120–130	50–90
(kJ/kg)	180	500	500–545	210–375§
Protein (g/kg)	2·0	2·5–5·0	4·0 (< 1200 g)	2–3–5§
Lipid (g/kg)	2·9	3·0	4·5	1–3–4§
Water (ml/kg)	11	150	150–200	65–180
Zinc (μg/kg)	250	700	720	100–300
Copper (μg/kg)	51	117	117	20
Calcium (mg/kg)	116	210	70–140	40‖
Phosphorus (mg/kg)	75	140	50–90	40‖

† Recommendation for enterally fed infants (Mauer *et al.* 1985).
‡ Recommendation for enterally fed infants (Wharton, 1987).
§ TPN (total parenteral nutrition) introduced in stepwise progression (see text).
‖ See MacMahon *et al.* 1990(a).

seriously sick infants have lower protein synthesis (Mitton *et al.* 1991); the onset of bacterial infection, for example, leads to a two-fold increase in total urinary nitrogen excretion (Raiha & Boehm, 1987). Parenteral feeding may be more appropriate than enteral feeding in the very low birth weight (VLBW) infant, this better simulating intra-uterine feeding. The period of 30 weeks' gestation to 6 months of life is critical for brain development; nutritional compromise in this period may cause permanent impairment of brain development (Dobbing, 1974).

A reasonable aim is to provide nutrients and energy to match accretion and growth seen in the equivalent postconceptional age-matched fetus (Zlotkin *et al.* 1981; Wharton, 1987); most published recommendations on need are based on infants fed enterally (Wharton, 1987). The daily recommended allowances for the parenterally fed infant should be less overall, as intravenous feeding bypasses the gut; the American Academy of Pediatrics (Mauer *et al.* 1985) and the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN; Wharton, 1987) statements, however, provide useful guidelines (Table 1).

Clinical indications for parenteral feeding in the newborn include an inability to tolerate enteral feeding due to gut immaturity, illness, established gut pathology such as necrotizing enterocolitis (NEC), and the need for surgery. The route, type of feeding and time of introduction of nutrients (protein and lipid) is in practice determined both by clinical need and personal preference; the early introduction of intravenous amino acids and lipids has been shown to be safe and efficacious in the sick, ventilator-dependent, VLBW infant (Saini *et al.* 1989; Gilbertson *et al.* 1991). In many infants mixed enteral and parenteral feeding is possible after the first few days as morbidity lessens.

The prescription of an appropriate intravenous solution mix is facilitated by use of the microcomputer; allowances are determined by gestation, weight, regular clinical assessment and daily monitoring of blood chemistry (Marshall & Mitchell, 1987). Various routes for vascular access may be used to provide intravenous feeding; peripheral, central via a silastic catheter inserted percutaneously or surgically, or through an umbilical arterial catheter (Yu *et al.* 1979). Metabolic, technical and other complications associated with parenteral feeding are well recognized (Table 2); equally enteral feeding of these infants is not without potential risk (Vidyasagar *et al.* 1987).

Table 2. *Complications of parenteral nutrition, modified from Kovar & Morgan, 1990*

Technical	Metabolic	Other	Nutritional deficiency
Pharmaceutical solution stability component incompatibilities	Laboratory error (calcium, bilirubin, sodium)	Cholestasis	Osteopenia and rickets
Insecure vascular access	Glucose intolerance	Cholelithiasis	Essential fatty acid deficiency
Superior vena cava thrombosis	Hyperphenylalaninaemia (abnormal aminogram)	Fat embolism	Carnitine
Hydrocephalus	Hyperammonaemia	Blood film changes (eosinophilia, thrombocytosis, thrombocytopenia)	Zinc
Pericardial tamponade	Acidosis	Potential later coronary artery disease	Copper
Coronary sinus thrombosis	Intralipid		Trace elements
Infection			
Chylothorax			
Pulmonary embolism			
Cardiac arrhythmia			
Accidental subcutaneous infusion (tissue necrosis, later contractures)			

GROWTH

Expected growth *in utero* is the usual standard against which nutritional regimens for the preterm infant are referenced and compared (Shaw, 1988); *ex utero* growth rarely matches intra-uterine ideal, regardless of whether fed enterally or parenterally. Growth *per se* is too crude a measure against which to make estimates of specific nutritional requirements; data on nutrient accretion *in utero* provide useful estimates of requirements for some nutrients, although practical delivery and apparent postnatal need may not follow these estimates, e.g. calcium, phosphorus. A factorial method does not take into account the varied maturity of the infant – so, for example, protein requirements are based mainly on growth rate: the higher the rate in theory the higher the requirements – but this alone does not allow for the maturity of biosynthetic pathways. Fig. 1 illustrates *in utero* growth curves, described by a single exponential equation from which specific growth rates can be calculated. Daily estimates (Shaw, 1988) of growth rates of fetuses based on published data between 24 and 36 weeks are 16·6 g/kg, 16·2 g/kg and 15·9 g/kg on the 10th, 50th and 90th centile respectively. Male fetus growth rate tends to be more rapid than female; fetuses of multiparae tend to grow more rapidly than those of primiparae (Shaw 1988). By way of comparison, the daily growth rate of full term infants is about 6 g/kg in the first month of life. Nutritional requirements will thus be greater in fetus (and by inference the premature infant) when compared with the full term infant.

ENERGY

Energy needs in the premature infant in infancy have been well reviewed (Brooke, 1986; Wharton, 1987). Energy requirement components are shown in Table 3; the major component is for resting metabolism (about 50%); requirements for growth (synthesis of new tissue and storage) represent the second major component, particularly in the very young premature infant where intake should theoretically provide sufficient energy to

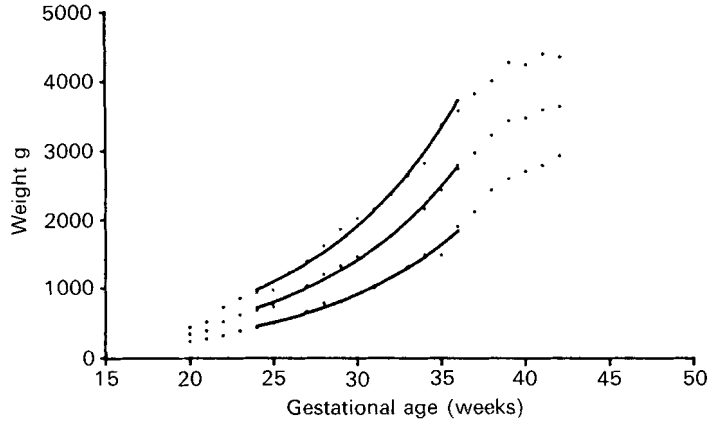

Fig. 1. Intra-uterine growth data, to which a single exponential curve has been fitted (24–36 weeks) using least squares linear regression analysis (modified from Shaw, 1988).

Table 3. *Components of energy requirements in enterally fed low birth weight infants, modified from Brooke, 1986*

Component	Energy (kcal (kJ)/kg per day)
Intake	100–165 (420–690)
Excretion	10–30 (40–125)
Expenditure	
Resting metabolism	45–60 (190–250)
Activity	5–10 (20–40)
Thermoregulation	10 (40)
Growth: Synthesis	10–35 (40–145)
Growth: Storage	20–30 (85–125)

facilitate the equivalent of intra-uterine gain ($\sim$ 15 g/kg daily; see this page). Values vary for the energy cost of growth and tissue synthesis of 1 g wet tissue—this is in the region of 5–7 kcal (20–30 kJ)/g; any variation is likely to be related to the type of composition of the tissue laid down, the impact of dietary induced thermogenesis (Morgan & Mumford, 1981) or the variation in the provision of amino acids (Weinstein *et al.* 1987). The day-to-day variation in energy expenditure of the low birth weight (LBW) infant (sick and well) may explain the widely varying growth rates reported in premature infants receiving similar energy intakes (Marks *et al.* 1987).

The data from which the component of energy requirements (Table 3) was derived were from well infants fed on formula milk or human milk. The energy requirements of the LBW infant fed parenterally may vary from the enterally fed in that there is little faecal excretion (less than 1 g/d) because of the nature of the regimen which bypasses the gut and the liver; this is equivalent to 2 kcal (8 kJ)/d (Kovar *et al.* 1989). In addition, activity levels in these infants are often minimal; energy costs of morbidity vary and cost of thermoregulation is small as the infants are usually nursed in a thermoneutral environment. Acceptable growth and nitrogen retention can be achieved on parenteral regimens of 90 kcal (375 kJ)/kg daily; this level of intake, however, can be difficult in practice to achieve (Saini *et al.* 1989; Kovar & Morgan, 1990). Morbidity in the infant (e.g. respiratory distress, patent ductus arteriosus, necrotizing enterocolitis, renal disease) may limit fluid intake and thus restrict overall energy and nutrient delivery.

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GUIDELINES FOR ENERGY REQUIREMENTS

There are no universally accepted guidelines on the intravenous fluid, energy and nutrient intakes for (sick) preterm infants. The ESPGAN guidelines for the nutritional requirements of preterm infants fed enterally (Wharton, 1987) make no specific recommendations for the nutritional management of infants fed by the parenteral route. The values (Table 1) for total parenteral nutrition (TPN) are estimates based on recent published studies and on the authors' experience. The usual practice is to establish full parenteral feeding (both in volume and nutrient concentration) in a stepwise progression over a number of days (Saini *et al.* 1989; Gilbertson *et al.* 1991) in an attempt to minimize metabolic overload in the physiologically immature infant. Energy is primarily provided in the form of glucose and lipid emulsion.

PROTEIN

There are a number of ways in which protein (amino acid) requirements in the LBW infant on TPN can be estimated, including the factorial approach; fetal accretion rates (whole body analysis; Widdowson & Dickerson, 1964), and protein balance and turnover studies. Protein requirements suggested by various sources are given in Table 1. The effect of type of feeding route on protein metabolism in the neonate has been extensively reported elsewhere (Duffy & Pencharz, 1986; Pencharz *et al.* 1989).

GUIDELINES FOR PROTEIN REQUIREMENTS

Accumulation data indicate that 252 mg/kg and 320 mg/kg of nitrogen is laid down *in utero* daily at 24 weeks and 36 weeks respectively; this is equivalent to 2·0 g protein/kg daily. Once feeding of parenteral nutrition is established, retention of parenterally infused amino acids is about 70% (Table 4, Kovar *et al.* 1989); these and other data suggest that requirements in the LBW infant are in the region of 3·2 g/kg daily. Adequate energy intake is essential if nitrogen retention is to be optimal. Few studies have been undertaken which examine nitrogen balance in the LBW infant within a few hours after birth; recent evidence, however, has indicated the importance of adequate nitrogen and energy intake in achieving nitrogen retention (deposition of lean tissue) and growth early in life (Saini *et al.* 1989; Kandil *et al.* 1991) (Fig. 2).

In a recent review, Micheli & Schutz (1987) showed that protein metabolism and growth varied in LBW infants, whether healthy, sick or undernourished *in utero* (intra-uterine growth retardation). The rate of protein synthesis, net protein gain and the energy cost of growth varied depending on severity of illness or gestation; the more sick the infant and the lower the gestation, the greater the overall requirement for protein.

AMINO ACID PROFILE

The amino acid requirement for the parenterally fed infant differs from that of enterally fed infants (Stegink, 1986); this is in part because the gastrointestinal tract and the liver are bypassed when intravenous amino acid solutions are administered directly to tissues. Differences include the mix of non-essential to essential amino acids and the fact that additional amino acids may be essential in the parenterally fed infant, e.g. cystine/cysteine, tyrosine and glycine (Jackson *et al.* 1981).

Taurine depletion has been demonstrated in a prospective controlled trial on VLBW infants receiving TPN for 32–49 days (Zelikovic *et al.* 1990); they concluded that taurine supplementation may prevent retinal damage.

The essentiality of taurine is supported by others (McIntosh & Mitchell, 1990); in a

Table 4. *Mean nitrogen intake, nitrogen retention and nitrogen retained (%) in four balance periods, compared with fetal accretion rates at comparable postconceptional ages, modified from Kovar et al. 1989*

Balance (postconceptional age)	No. of infants	Nitrogen intake (mg/kg daily)	Nitrogen retention (mg/kg daily)	Nitrogen retained (%)	Fetal accretion values (mg/kg daily)†
1 (177–208)	8	291	155	48	323
2 (190–214)	8	487	340	69	301
3 (198–228)	6	481	323	67	284
4 (221–246)	4	495	335	68	260

† Widdowson, E. M., personal communication.

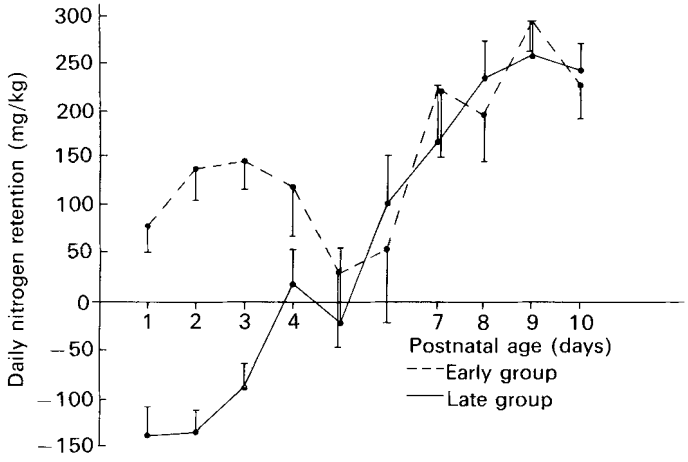

Fig. 2. Daily energy intake (kcal/kg) and nitrogen retention (mg/kg) for a group of preterm infants in which the amino acid solution was given within 24 h (above, r = 0·35, $P < 0·001$) and for that in which it was given at 72 h (below, r = 0·66, $P < 0·001$). Each point represents a 24 h balance period (Saini *et al.* 1989).

double-blind randomized, controlled trial, Vamin 9 glucose (Kabi Pharmacia, Milton Keynes, UK) with no taurine was compared to a newly designed intravenous preparation of crystalline amino acids (MB233G, Cernep Synthelabo, France) where the amino acid concentration was based on cord blood amino acid concentrations and contained taurine; plasma aminograms of the neonates were within the reference range of normal newborn infants. In the Vamin 9 glucose group some infants had extremely low plasma taurine levels; no such findings were reported in the other group.

At issue is whether solutions should be designed to achieve plasma amino acid profiles as seen in human milk-fed infants or whether the amino acid profile of fetal lean body tissue (or cord blood) is the ideal model. Stegink (1986) highlighted the many unsolved problems, and detailed the technical difficulties in the preparation of tailormade VLBW amino acid solutions. For example, tyrosine and cystine may not be sufficiently soluble to add to TPN solutions in necessary quantities. A similar problem exists with calcium salts.

EARLY PARENTERAL FEEDING OF AMINO ACIDS

In LBW infants fed enterally, a protein source (human or cows' milk) is usually introduced within a few hours of birth; in the sick infant who needs to be fed parenterally there is no

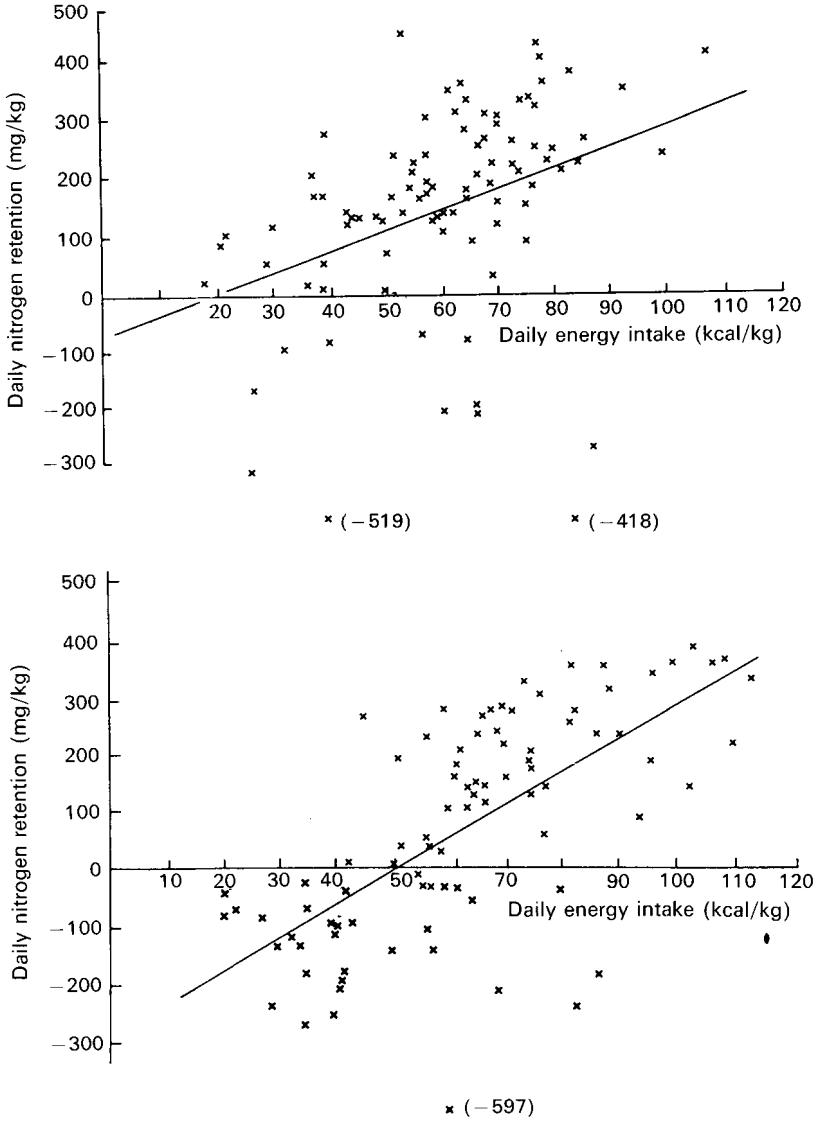

Fig. 3. Mean 24 h nitrogen retention (mg/kg) for 2 groups of preterm infants over a ten day study period. Bars indicate SEM. Significant differences were recorded at days 1, 2 and 3 ($P < 0{\cdot}001$). In the 'early' group the amino acid solution was given within 24 h and in the 'late' group it was given at 72 h (modified from Saini *et al.* 1989).

universal agreement as to timing of the introduction of amino acids. In many cases protein feeding is delayed for up to 72 h postnatally; this practice may have serious effects on the deposition of lean tissue. Concerns about fibrin and casein hydrolysate solutions has led to this delay in the introduction of an amino acid source, because of various metabolic complications including hyperammonaemia and acidosis. Today crystalline L-amino acid solutions are widely used in the UK as they are better utilized compared with the fibrin and casein hydrolysates and have fewer complications.

Early introduction of an amino acid source to sick VLBW infants has been shown to be clinically and biochemically safe and, although nitrogen retention is initially lower in the

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early days of life compared with fetal accretion rates, fetal accretion can be matched after 240 postconceptional days (Kovar *et al.* 1989; Table 4). There is, however, wide individual variation in nitrogen retention at any age. A study conducted by Saini *et al.* (1989) investigated the introduction of amino acids 3 days postnatally. These VLBW infants had significant negative nitrogen balance until intravenous nitrogen was introduced (Fig. 3); this loss was equivalent to 2·5 g protein over the first 3 postnatal days (3% of the body's protein each day), whereas those in the early group were in positive nitrogen balance from d 1. In neither group of infants were energy intakes of greater than 210 kJ/d (50 kcal/d) achieved in the postnatal period (Fig. 2), which is well below the current recommendations (Table 1). The difficulties in achieving both energy and protein targets in the early stages of life in this and other studies are well documented. Often metabolic complications preclude any further increase in protein load; increased phenylalanine concentrations are well recognized in infants infused with Vamin 9 as the amino acid solution (Puntis *et al.* 1986). With the introduction of amino acid solutions more tailored to the newborn, these abnormalities in plasma amino acid profiles should be prevented.

The development of stable isotope techniques as applied to preterm infants permits definition of protein turnover, synthesis and breakdown (De Benoist *et al.* 1984; Stack *et al.* 1989; Mitton *et al.* 1991). Mitton *et al.* (1991) examined two groups of infants prior to TPN; in the group which subsequently went on to receive TPN, protein turnover was lower than in the less sick group; further studies are required to confirm these results.

LIPID

In the enterally fed LBW infant lipid in milk provides approximately 50% of the total energy intake. Fat malabsorption can be a problem for the immature infant (Friedman *et al.* 1976) because of lack of lipase, lingual, gastric and pancreatic, required for the digestion of lipid and for the absorption of essential fatty acids (EFA). Lipids are required to provide non-protein energy, as integral structural components of cell membranes, and for brain development. Important issues to consider in the provision of parenteral lipid to the LBW infant include requirements for EFA and the timing of provision of lipids.

Intralipid (Kabi Pharmacia, Milton Keynes, UK) is the standard lipid source; this is isotonic, rich in EFA and has a high energy density (1 kcal (4 kJ)/ml 10% solution compared with < 1 kcal (1 kJ)/ml 10% dextrose). It is not, however, tailormade for the special nutritional needs of the LBW infant. In addition there are concerns regarding the clinical safety of infusing lipids into a sick infant; these have been discussed in detail elsewhere (Kovar & Morgan, 1990).

FATTY ACID PROFILE

The relatively low amounts of 18:3n-3 and the lack of docosahexaenoic acid (DHA) in Intralipid are theoretical limiting factors in the long term use of Intralipid in preterm infants. There is evidence that a dietary source of DHA is essential in premature infants, as they appear to have limited Δ-4-desaturase activity (Carlson *et al.* 1986). DHA is an important component of the main phospholipids of the brain and liver. Martinez & Ballabriga (1987) studied five infants between the age of 35 and 43 weeks' gestation who received TPN (with Intralipid) for between 4 days and 12 days, and who died because of major surgical problems; the fatty acid compositions of the ethanolamine and choline phosphoglycerides in brain and liver were compared with a control group of 18 infants aged between 20 and 44 weeks' gestation who died within the first 48 h of life. They found a higher liver phosphatidylethanolamine DHA content for infants at 36 weeks gestational

age in the control group (mean ± S.E.M., 17·7 ± 3·5; weight %) compared with the intravenously fed group (9·1 ± 2·6). The main developmental changes in the brain and liver in the control group were related to an increase in DHA and a linear decrease in arachidonic acid in red blood cell phospholipids. However, for infants fed TPN there was a reported decrease in DHA in liver phospholipids. The authors speculated that the n-6 sequence of fatty acids was preferentially metabolized over the n-3 sequence because of the high dose of linoleic acid in the TPN regimen.

To our knowledge no studies have been undertaken to examine the beneficial effects to the premature infant of supplementing the parenteral lipid source with DHA. It would seem logical that the development of a lipid emulsion for premature infants should retain the lipid profile modelled on human milk, which naturally contains the longer chain and unsaturated fatty acids of the n-3 and n-6 series. The question regarding the ideal fatty acid profile for intravenous infusion remains unanswered; equally whether this profile should simulate human breast milk, or the serum profile of infants fed human breast milk, or indeed some other parameter, has yet to be resolved.

EARLY PARENTERAL FEEDING OF LIPID

The introduction of intravenous lipid is frequently delayed until 7 d postnatally. This is because of concern regarding possible adverse effects such as increased free bilirubin concentration or impaired oxygenation resulting from impaired lipid tolerance. However, there is now evidence that initial low infusion rates (less than 0·2 g/kg per hour) are well tolerated (Gilbertson *et al.* 1991).

CARNITINE

Carnitine is a quaternary amine (β-OH-γ-trimethyl amino-butyric acid) which is an essential cofactor in the transport of long chain fatty acids across the mitochondrial membrane. Deficiency of carnitine may have effects on lipid clearance, ketogenesis and thermoregulation. It is not commonly considered an essential nutrient as it is freely synthesized in the body; carnitine may, however, be essential in the premature infant (Penn *et al.* 1981).

Interest in carnitine in the parenterally fed LBW infant has followed reports that low rates of fat clearance are seen in these babies. A recent study by Sulkers *et al.* (1990) has reappraised the effect of carnitine supplementation on substrate utilization in a group of parenterally fed LBW infants compared with an unsupplemented group; in the supplemented group, carnitine in a dose of 2 g/l (the upper range of requirement) resulted in slower growth, higher metabolic rates, and higher nitrogen excretion compared with the unsupplemented group. There is, however, no consensus regarding the efficacy of routine carnitine supplementation in parenteral infusions (Coran *et al.* 1985; Helms *et al.* 1986).

CARBOHYDRATE OR LIPID AS THE ENERGY SOURCE

Carbohydrate and lipid infusions are essential energy sources in the sick newborn. There is now evidence that replacing 25% of glucose energy isocalorically with intravenous lipid has beneficial effects for the infant, including decreased energy expenditure and better growth (van Aerde *et al.* 1989). The protein sparing action of lipid in TPN regimens has been well recognized for many years in adults; this is equally important for the premature infant. Evidence for the beneficial effects of the early introduction of lipids, carefully monitored, is also accumulating (see this page).

CARBOHYDRATE

Unlike amino acids and fatty acids there is no absolute dietary requirement for glucose in the full term infant; although the metabolism of the central nervous system and haemopoietic tissue is dependent on glucose, this can be supplied endogenously via the gluconeogenic pathways. In the preterm infant, many metabolic pathways including the gluconeogenic system are decreased. Thus a dietary source of energy from carbohydrate is essential in these infants.

Glucose (dextrose) is the main source of energy (3·4 kcal (14 kJ)/g) in parenteral infusions for the LBW infant, providing up to 40–50% of total energy. In some cases there is impaired glucose tolerance and concentrations as low as 7·5% or 5% dextrose may be the maximum tolerated. Intolerance results in hyperglycaemia, leading to osmotic diuresis and dehydration; it may occur where there is excess glucose load, immature gluconeogenic and glycolytic hepatic enzyme systems, or where insulin receptors are abnormal in number or function.

The administration of glucose alone in the sick LBW infant dramatically increases survival (Shaw, 1988). The difficulty in achieving energy requirements with glucose alone, particularly in the early days of life in the neonate, is well illustrated in the study of Mitton *et al.* (1991) where parenteral feeding of glucose was monitored between 17 and 91 h postnatal age; daily energy intakes ranged from 17 kcal (71 kJ)/kg to 44 kcal (184 kJ)/kg with no infant reaching recommended levels on glucose alone; on average, intakes were 50% below requirement. As no net fat storage occurs until the parenterally fed neonate receives more than 77 kcal (322 kJ)/kg daily (Heim *et al.* 1981), none of the neonates in the study by Mitton *et al.* was laying down adipose tissue, or even lean tissue. Limitations of fluid intake (see p. 125) have a detrimental impact on energy intake, and a balance has to be struck between the two. Although insulin has been used to control glucose metabolism, in practice this is seen as a short term measure because of the risk of hypoglycaemia; prenatal hypoglycaemia is well recognized as a cause of later neurological deficit.

OTHER CARBOHYDRATE SOURCES

Galactose, fructose, alcohol and maltose have all been used in TPN regimens, with mixed success. Galactose together with glucose may reduce hyperglycaemia (Avery, 1978). There are contra-indications in the use of fructose and alcohol; fructose infusions increase blood lactate to unacceptable levels (four or five times greater than after an equivalent load of galactose), while alcohol use has been queried because of the potential long term toxic effects on the developing central nervous system (Kerner, 1983).

Myoinositol, a C_6 sugar alcohol, is one of the most abundant sugars in the body. In a recent study by Pereira *et al.* (1990), serum myoinositol levels in infants receiving parenteral nutrition were compared with infants receiving human milk or cows' milk formula; results were 1840 *v.* 420 *v.* 100 μmol/l myoinositol in human milk, formula milk and parenteral solution respectively; serum levels of premature infants followed the same pattern. Although the authors did not claim that premature infants have a dietary requirement for this sugar, because of the close link between intake and serum concentrations an argument could be made for its addition to milk formula and TPN infusions.

WATER

For the LBW infant, water has been described as 'quantitatively and qualitatively the single most important nutrient' (Wharton, 1987). Individual requirements vary as much as for any other nutrient, and are dependent on insensible water loss, renal solute load, the

Table 5. *Minimal water requirements for a growing premature infant in a thermoneutral environment (relative humidity 50–80%), modified from Wharton, 1987*

	ml/kg daily	
Extra-renal water loss		
Insensible	30–60	
Gastrointestinal	5–10	
Renal water loss	90	
TOTAL WATER LOSS		125–160
Water for growth	10	
TOTAL REQUIREMENT		135–170
Water from endogenous sources	5–10	
MINIMAL WATER REQUIREMENT		130–160

Note: Not necessarily appropriate for the parenterally fed infant.

glomerular filtration rate and the renal concentration ability. All these variables differ with gestational age, postnatal age and environmental conditions. In a study of water and mineral balance conducted on ten infants fed parenterally the total mean evaporative water loss was calculated to be 26 g/kg daily – slightly higher than values for healthy newborn infants (Meurling, 1983). Comprehensive accounts regarding requirements for water have been provided by Wharton (1987) and Shaw (1988).

The VLBW infant consists of 80% water or more. Daily gain in body weight, at about 16 g/kg (70% water) represents 11 ml/kg of water. Insensible water losses vary greatly, from 2 to 6 ml/kg per hour (48–144 ml/kg per day). Shaw (1988) has proposed the following regimen for the parenterally fed infant: d 1 65–100 ml/kg (depending on potential evaporative water losses, whether nursed in closed or open incubator) increasing in a stepwise progression to 150–180 ml/kg daily (by d 5–7). Table 5 provides a guide for minimal requirements. Regular monitoring of body weight and plasma sodium are needed to reduce the likelihood of hyponatraemia; allowance needs to be made for excess losses, such as those due to the use of phototherapy lights to treat hyperbilirubinaemia.

Restriction of fluid is often required; nutritional intake of the infant is compromized in the provision not only of energy but also of amino acids, lipids, vitamins and minerals. Restriction to the region of 100–120 ml/kg daily is not uncommon, in conditions such as patent ductus arteriosus.

MINERALS

There is little information on the optimal requirement for minerals and other micronutrients in the LBW infant receiving TPN. However, because of the route of feeding, requirements are likely to be lower in these infants compared with the enterally fed. Conventionally *in utero* accretion values are used as the standard in evaluating requirements.

CALCIUM AND PHOSPHORUS

Guidelines for dietary intake of calcium and phosphorus are given in Table 1.

Metabolic bone disease (osteopenia and rickets) is common in premature infants. The cause is multifactorial; inadequate mineral substrate (calcium and phosphorus) intake is a major factor (Brooke & Lucas, 1985). It is well recognized in association with prolonged parenteral nutrition (The *et al.* 1983). The fetal skeleton acquires 80% of its calcium and phosphorus in the third trimester of pregnancy; daily *in utero* accretion of calcium and

phosphorus during this time is about 2·5–3·0 and 2·0–2·5 mmol/kg respectively (Ziegler *et al.* 1976). The amount of mineral which can be delivered in parenteral solutions varies according to their solubility product and the type of amino acid source (Fitzgerald & Mackay, 1986); the daily intake of these minerals is thus often restricted to about 1·0 mmol/kg (Aiken & Lenney, 1986). The calcium and phosphorus content can, however, be increased by using an acidic source of phosphorus during formulation (MacMahon *et al.* 1990*a*); this does not cause significant acidosis in the infant (MacMahon *et al.* 1990*b*). Increasing the substrate in this way has been shown to reduce the severity of bone demineralization (MacMahon *et al.* 1989). Positive calcium and phosphorus balance with net retention is seen in sick VLBW infants who are in positive nitrogen balance (Colonna *et al.* 1990); retention rates match those observed in well infants fed preterm formula.

ZINC AND COPPER

Guidelines for dietary intake of zinc and copper are given in Table 1.

Zinc is essential for cell division and as an enzyme co-factor. Deficiency results in growth retardation and skin rashes (Harper *et al.* 1984). Copper is needed for collagen synthesis, erythropoiesis and as an enzyme cofactor. Symptoms of deficiency include anaemia, skeletal changes similar to scurvy, and neutropenia (Heller *et al.* 1978). Copper deficiency in the VLBW infant is well described (Sutton *et al.* 1985); a reference range for plasma copper in preterm infants of 29–34 weeks has been provided by the same group.

The importance of the provision of zinc and copper in parenteral regimens has been described (Zlotkin, 1985; Shulman, 1989). From balance study data, daily intakes of 1·5 μmol/kg of zinc and 0·16 μmol/kg of copper were suggested as appropriate for non-surgical infants fed TPN short term. Additional intakes would be necessary for infants with gastrointestinal losses, or who are postoperative.

VITAMINS

Premature infants are at greater risk of developing vitamin deficiencies than full term infants because of poor stores at birth, the high risk of infection, NEC, and developmental lags in absorptive and enzymic capacity.

Recent studies have examined aspects of metabolism and requirements of certain vitamins in premature infants receiving TPN (vitamin B_6, Raiten *et al.* 1991; vitamins A, D, E and riboflavin, Baeckert *et al.* 1988); in the latter study the authors highlighted the problem that vitamins are invariably provided as commercial multivitamin preparations based on national and adult recommendations. These preparations may be inappropriate for the premature infant receiving TPN; one study was 'prematurely discontinued because the infants showed consistently, and markedly, elevated blood concentrations of riboflavin and concentrations of retinol below the reference range' (Baeckert *et al.* 1988). Daily intakes of 4 μg/kg vitamin D and 2·8 mg/kg vitamin E were considered appropriate. Retinol at 280 μg/kg daily was considered an insufficient dose and riboflavin at 0·68 mg/kg daily was considered too high, and possibly even harmful.

Deficiency of vitamin A results in skin changes, night blindness, and may contribute to aetiology of bronchopulmonary dysplasia (Shenai *et al.* 1985); vitamin A is not stable in TPN solutions. Vitamin D deficiency results in rickets and osteopenia and deficiency in vitamin E in haemolytic anaemia. Vitamin E may protect variously against retinopathy of prematurity, bronchopulmonary dysplasia and intraventricular haemorrhage (see Greene *et al.* 1988).

Although the provision of amino acids, lipids and glucose has been extensively investigated over the last 10 years, resulting in a more specific basis for feeding the premature, this is not the case in the provision of vitamins. Ideally vitamins should be fed to individual requirements. At the very least, fat soluble and water soluble vitamins should be provided so that they can be added to the TPN infusion independently. Much greater knowledge is required in this field.

CONCLUSION

To provide safe intravenous feeding for the premature infant requires considerable expertise and experience among the clinical and nursing staff. The formulation of the infusion has been simplified with the aid of computer technology (MacMahon, 1984). It is costly: £67/infant daily at 1992 prices plus the cost of extra monitoring, compared with £1·5/infant daily when fed enterally. The complications of parenteral feeding should not be underestimated (Table 2). In principle TPN is safe and efficacious in LBW infants, leading to reduced morbidity and mortality. The decision as to when enteral feeding should be introduced is a clinical one, with no fixed rules. The gradual introduction of enteral feeding in a stepwise nature facilitates the natural introduction of milk (human or formula); regular provision of small volume oral feeding has important effects on gut enzyme and hormone metabolism (Lucas *et al.* 1981). Failure to provide milk can delay the onset or ability to fully feed enterally.

Parenteral nutrition for the preterm infant should theoretically simulate intra-uterine/placental feeding. Ideal solutions of amino acids and fatty acids for these infants remain to be determined; they will depend on the outcome of arguments as to what constitutes the ideal 'requirement'. Fetal lean body profile, breast milk profile and blood profile of infants fed breast milk all have their proponents. Further information is required on the long term outcome of infants fed by different regimens with survival and intact outcome being the gold standards. We believe, however, that it is safe and efficacious to feed sick preterm infants intravenously, early and completely, with amino acids and lipid.

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