Ann. Rev. Nutr. 1987. 7:91–116

NUTRITIONAL REQUIREMENTS OF LOW AND VERY LOW BIRTHWEIGHT INFANTS

O. G. Brooke

St. George's Hospital Medical School, Cranmer Terrace, London SW17 ORE, England

CONTENTS

0199-9885/87/0715-0091$02.00

INTRODUCTION

As the survival of very immature infants is made increasingly commonplace by improvements in neonatal intensive care, a new jargon has evolved with its appropriate acronyms. Hence, where once there were only "low birthweight" infants (LBW), for those infants born below 2.5 kg in weight, we now have "very low birthweight" for infants between 1000 and 1500 g, and "extremely low birthweight" for those under 1000 g. Most of the serious nutritional problems of these diminutive infants arise in the very and extremely low birthweight categories, in which the great majority are very immature (generally less than 30 weeks gestation), and the problems are most often the result of immaturity rather than small size per se. This chapter deals mainly with such infants. However, it is important to distinguish between those low birthweight infants whose main problem is immaturity and those who are mature (or relatively so) but undergrown, since their nutritional needs are different. For example, the mature but small-for-gestation infant has much less difficulty with nutrient absorption or metabolic intolerance to feeds than the very immature infant, but nevertheless has high energy requirements for catch-up growth and increased vulnerability to hypoglycemia. It is worth emphasizing that the nutrient requirements for growth in *all* low birthweight infants are greater than in normal mature neonates and older babies, since their weight gain is relatively greater: about 15 g/kg/day between 28 and 35 weeks postconceptional age, more than at any other time in the human lifespan.

Special Nutritional Problems of the Very Immature

QUANTITATIVE AND QUALITATIVE REQUIREMENTS To meet the needs of rapid growth, requirements of all nutrients are greater in the very immature than in full-term infants. This almost goes without saying, but the situation is less straightforward than it seems. It is impossible, even with intravenous feeding, to reproduce the transplacental provision of nutrients, which is under continuous physiologic control. Thus, although one can estimate the nutrient needs of the prematurely born infant by reference to the nutrients acquired by the fetus in utero, there are many factors that may make it difficult or impossible to put these estimates into practice. For example:

1. The immature function of the gut may not allow sufficient enteral intake to meet the estimated requirements.

2. Water requirements are high because of evaporation and immature renal function, so attempts to circumvent "mechanical" problems, such as poor gastric emptying and feed aspiration into the lungs, by giving small volumes of concentrated feed are likely to lead to dangerous systemic hyperosmolarity.

3. Nutrient absorption from the gut is universally impaired in immature infants, especially the digestion and absorption of fat, calcium, fat-soluble vitamins, and some of the trace elements, and it may be impossible to absorb sufficient quantities of these nutrients to mimic the fetal condition. These problems are dealt with later in the chapter.

4. Energy needs are variably affected in ways that are difficult to estimate in clinical practice by factors such as intermittent cold stress, infection, medication, steatorrhea, and so on.

5. The immature brain and other organs, such as the liver, are vulnerable to the damaging effects of high plasma concentrations of some of the amino acids, for example tyrosine, phenylalanine, methionine. High protein feeds may be hazardous for this reason, and it is possible that even apparently well-tolerated protein intakes may become too high under conditions of stress, such as infection. Little is known about protein tolerance in the smallest infants capable of survival (500–600 g).

METABOLIC IMMATURITY Many of the difficulties in nourishing prematurely born infants are the result of immaturity of enzyme systems and other biochemical functions, especially in the gastrointestinal tract, liver, kidneys, and brain.

Gastrointestinal tract The main problem is with fat absorption. Whatever type of fat is given, some preterm infants show a degree of fat malabsorption that is sufficient to compromise their energy balance (16). Deficiencies have been identified in pancreatic lipase secretion and bile salt secretion, and there has been recent interest in lingual lipase secretion.

1. Pancreatic lipase secretion. In comparison with mature infants, preterm infants have low pancreatic response to secretin and pancreozymin-cholecystokinin (151), low lipase activity in the duodenal juice (47, 71), and high duodenal concentrations of triglycerides (65).

2. Bile salt secretion. Duodenal bile acid concentrations in preterm infants are often well below the critical micellar concentration (86, 122). This is probably due to reduced bile acid pool size and synthesis rate (142), which may be as low as 30% of values found in term infants. Infants fed breast milk have mainly taurine-conjugated bile acids, whereas the bile acids in formula-fed infants are mainly glycine-conjugated (21), cows' milk being a poor source of taurine. However, this does not seem to be an important factor in the steatorrhea of prematurity since supplementation of formula with taurine does not improve fat absorption (141).

3. Lingual lipase. Saliva contains a powerful lipase secreted by the lingual serous glands. It is stimulated by sucking (54) and some preterm infants appear to be deficient in it (55). There is evidence that dummy-sucking during tube-feeds ("nonnutritive sucking") results in increased weight gain (8), but it has recently been shown (33) that this practice does not increase fat absorption, so the role of lingual lipase in preterm infants remains uncertain.

Liver The pathways of intermediary metabolism of several amino acids in the liver of the preterm infant are incomplete or function inadequately. This results in potential problems that affect protein intake. For example, the last enzyme in the transsulfuration pathway, cystathionase, is absent from the fetal liver and it appears only slowly after birth in preterm infants (92). As a result, the synthesis of cyst(e)ine is greatly reduced, and this amino acid must be considered essential in such infants. The absence of cystathionase also limits the tolerance to methionine, which should normally be converted to cyst(e)ine if given in excess. Preterm infants fed high protein diets are vulnerable to hypermethioninemia (67), which is potentially damaging. Other examples of problems due to hepatic immaturity are to be found in the deficiency of enzymes essential for the oxidation of tyrosine, leading to hypertyrosinemia if a high tyrosine intake is given (73, 83), and various other deficiencies in pathways of amino acid catabolism causing high concentrations of several amino acids, hydrogen ion, and ammonia (46, 93, 135). All these have important implications for permissible protein intake.

Brain The immature brain is vulnerable to the toxic effects of raised concentrations of certain amino acids for example phenylalanine, methionine, histidine, and the branched-chain amino acids. It is likely that such effects will be more severe the more immature the infant. Thus hepatic immaturity and cerebral immaturity are linked problems for preterm infant nutrition.

Kidneys Immature renal function also affects nutritional management. Preterm infants given a standard acid load can only increase their urine titratable acidity by about 60% of the values found in term infants (133). This is an important factor in the development of "late metabolic acidosis," which results from a disproportion between the daily load of nonvolatile acid generated in the body (much of which is of dietary origin) and the kidneys' ability to excrete it. The incidence of late metabolic acidosis is directly related to protein intake (134).

Another problem of immature renal function impinging on nutrition is the low renal threshold for glucose that results in persistent glycosuria in spite of normal blood sugar concentrations in some very preterm infants. This limits glucose intake in intravenous feeding and may cause osmotic polyuria with disturbance of water balance.

"MALNUTRITION" IN PRETERM INFANTS In case there should be any doubt that nutritional problems are of the greatest importance in the management of premature infants, it is worth remembering that this group of individuals is vulnerable to more specific nutritional disorders than any other. Thus deficiencies of protein (30, 106, 107), sodium (98, 132), vitamin D and calcium (68, 74), phosphorus (20, 99), vitamin E (52, 97), folic acid (130), iron, zinc (2, 10), copper (11, 108), and essential fatty acids (44) have all been described. Some of these have only been seen on certain types of (unsuitable) feeding, for example copper deficiency on low-copper formulas. Others are likely to occur on all types of feeding, for example calcium depletion and osteopenia (20). It is also important to bear in mind that brain cell multiplication and differentiation are proceeding apace between 25 and 35 weeks of postconceptional age, and prolonged periods of poor growth due to inadequate nutrition may well interfere with the critical processes involved and lead to later developmental difficulties. There is some evidence that this may be the case (139).

WATER REQUIREMENTS

Water as a Major Nutrient

Water is quantitatively the most important nutrient, and the volume of water required in daily feedings is the basis for the nutritional management of premature infants. From 26 to 36 weeks of gestation water comprises 70-80% of body weight gain (150), but there is evidence (91, 96) that the prematurely born infant grows with a less watery body composition during the same postconceptional age period. From the available evidence, and assuming a growth rate of 15 g/kg/day, the amount of water deposited during growth will be about 10 ml/kg/day, a relatively small amount. The major part of the water requirement is determined by water losses from the body.

Water Losses in the Very Immature

Water is lost in evaporation (insensible loss), in obligatory renal losses (related to the osmolar load to be excreted), and in the feces. Insensible water losses (IWL) are very variable, but in general they are higher the younger and more immature the infant because of the extreme thinness of the skin. They are increased by high ambient temperature and low humidity, by increased activity, and by respiratory distress. Estimates of total IWL vary between 30 and 60 ml/kg, depending on the conditions (38).

Renal water losses are considerably greater than in mature infants because of impaired renal concentrating ability (4, 132). Very low birthweight infants cannot concentrate their urine much above 500 mOsmol/kg, even with maximal vasopressin secretion (94), so these infants are vulnerable to dehydration if their feeds yield too high an osmolar load. In practice, urine

osmolalities in the range of 100–200 mOsmol/kg are the norm for most premature infants fed human milk or formula (111), so there is some scope for compensation if other water losses increase. Assuming a renal solute load of about 15 mOsmol/kg/day (which would be expected from a formula containing 2.0 g protein, 1.2 mmol sodium, and 2.0 mmol potassium per 100 ml fed at an intake of 175 ml/kg/day), renal water losses will be about 90 ml/kg/day.

Fecal water losses are almost constant except during diarrhea, and average 15 ml/kg/day in infants fed breast milk and 10 ml/kg/day in formula-fed infants (88a).

From the above data it can be calculated that the minimum water requirement of a growing preterm infant nursed in optimum conditions is likely to be about 130 ml/kg/day. Maximum permissible intake is determined by the ability of the immature kidney to eliminate water, which is limited mainly by low glomerular filtration rate (4, 132), but premature infants have been fed on intakes as high as 250–300 ml/kg/day without apparent problems (140). In clinical practice such very high intakes would rarely be used, an upper limit of about 200 ml/kg being the norm. The most important thing to monitor is water depletion, and this can be done by regular clinical examination and measurement of urine specific gravity, body weight, and the concentration of plasma electrolytes.

ENERGY REQUIREMENTS

Energy requirements are higher in immature than in mature infants for the following reasons: 1. The energy needs of growth are greater; 2. The resting metabolic rate may be higher; 3. The needs of incidental cold stress are higher (for example, the transient fall in environmental temperature that occurs during all nursing procedures); 4. Losses of unabsorbed nutrients are greater.

Energy Needs for Growth

The energy cost of growth (E_{cg}) is the sum of the energy content of the tissue laid down and the energy cost of synthesizing it. The net cost of deposition of both fat and protein is about 12 kcal/g (the cost of synthesis being much higher for protein than for fat while the enthalpy is of course much higher for fat (66). Thus the E_{cg} does not vary very much according to the composition of tissue being laid down unless there is a major variation in water content. The figure generally taken for growing infants is 5 kcal/g weight gain. Direct measurements of the E_{cg} in preterm infants, however (16, 53, 95), have produced values that vary from 3.0 to 5.7 kcal/g. The explanation for these differences is uncertain, but they may be related to the energy intakes of the infants studied, and it appears that the E_{cg} increases with increasing energy intake (i.e. growth takes place with reduced efficiency):

Source	Energy intake (kcal/kg/d)	E_{cg} (kcal/g)
Gudinchet et al, 1982 (53)	130	3.0
Reichman et al, 1982 (95)	149	4.9
Brooke et al, 1979 (16)	181	5.7

From these data and assuming an average weight gain of 15 g/kg/day, the range of the energy requirement for growth is 10–25 kcal/kg/day.

Resting Metabolic Rate

Resting metabolic rate (energy expenditure at rest and in thermoneutrality, at least one hour after the previous feed) is the most important component of energy expenditure. It incorporates the basal metabolic rate, which is difficult to measure in preterm infants because they cannot be fasted for long enough, and any additional energy expenditure arising from postprandial metabolism still lingering after the last feed. The latter includes the oxidative cost of growth. There is evidence (14) that both resting and postprandial metabolic rates rise as energy intake increases, implying an increased contribution from synthesis. Resting metabolism is extremely variable in preterm infants, depending on their size and postnatal age; mean values in various studies range from 36 to 51 kcal/kg/d (1, 15, 60, 84, 105). It tends to be low in very immature infants in the early neonatal period and high in infants who are growing on high energy intakes.

Needs of Incidental Cold Stress

Requirements of energy to meet demands of incidental cold stress are always greater in low birthweight infants than in larger ones. Premature infants nursed just below thermoneutrality increase their energy expenditure by 7–8 kcal/kg/d (48), and it has been shown that neonatal nurses tend to maintain incubator temperatures slightly lower than optimal for minimal energy expenditure (125). Frequent handling increases thermal losses. For these various reasons it has been suggested that about 10 kcal/kg/d should be allowed to cover thermoregulatory requirements (123).

Losses of Unabsorbed Nutrients

Some reference to the loss of unabsorbed nutrients has already been made above. Energy losses in the feces consist mainly of fat, but there may be an important loss of unabsorbed protein as well. Energy excretion varies from about 10 kcal/kg daily to as much as 70 kcal/kg (16, 95), but by 2–3 weeks of age most preterm infants can be expected to absorb between 80 and 90% of the dietary energy. The various components of energy balance in preterm infants are shown in Table 1.

Table 1 Energy expenditure and storage in a preterm infant receiving energy intake of 130 kcal/kg/day

	Mean (kcal/kg/day)	Range (kcal/kg/day)
Energy expenditure: Resting metabolism	52	45–60
Activity	8	5–10
Thermal stresses	8	5–10
Synthesis	17	10–25
Energy excreted (feces and urine)	20	10–30
Energy intake (*a*)	130	
Total expenditure and losses (*b*)	105	
Energy stored ($a - b$)	25	

Provision of Dietary Energy

Careful attention to the composition of dietary energy is important because in this way fecal losses can be minimized. Fat absorption is readily influenced by the type of fat given. Thus there is general agreement that human infants absorb long-chain fatty acids best if they are unsaturated (137, 143), which probably accounts for the relatively good absorption of raw human milk fat (in which about 65% of the fatty acids are C18:1 and C18:2) in comparison with bovine milk fat, which has a much higher proportion of C16:0 (62). Medium-chain fatty acids (C8–10) are better absorbed than long-chain ones by preterm infants (101, 136) and, although they cannot be regarded as physiological nutrients since they are present in very minute quantities in natural foods, they have been used with success as constituents of formulas for preterm infants, replacing up to 40% of long-chain fatty acids.

Human milk fat is much better absorbed when fed raw than when heated (5, 146), a characteristic that is likely due to the inactivation of bile-salt-stimulated human milk lipase by heating. Thus the virtues of human milk in relation to fat digestibility are not entirely due to its fatty acid composition. A well-designed formula containing a suitable blend of vegetable and animal fats can equal the performance of raw human milk in this respect, and is considerably better than pasteurized human milk (5). Human milk fat also forms an unstable emulsion, and so tends to separate when given by continuous gavage infusion and to adhere to the walls of containers (17).

The other main source of dietary energy is of course carbohydrate, which in most milk-fed mammals means lactose. Intestinal lactase activity is induced rapidly after birth (41), and there seems no reason to substitute other carbohydrates in any quantity. However, there is the occasional infant who does not tolerate the 7% lactose found in human milk, so some formulas substitute 1–2% maltodextrins, which appear to be well digested.

The optimal energy density of feeds for preterm infants has yet to be established. It is generally considered sensible, when designing a preterm formula, to provide a rather higher energy density than is found in pooled human milk (67 kcal/100 ml), but the limits of osmotic tolerance must not be exceeded. Furthermore, it has been shown that feeds of very high energy density may induce the formation of lactobezoars (34) and, if hyperosmolar, may predispose to the development of necrotizing enterocolitis (12). For these reasons energy densities exceeding 90 kcal/100 ml are not recommended.

PROTEIN REQUIREMENTS

Protein requirements for low birthweight babies are determined by the needs for growth, by the energy supply, by the quality of protein given, by the development of amino acid metabolism, and by the maturation of renal function. The last two of these have been discussed above.

Needs for Growth

Values for the protein requirements for growth have been determined in several different ways that have not always given the same results. These include the factorial method (149), which relates postnatal requirements to what is known about changing body composition in utero (which is very little, since few preterm fetuses have been subjected to dissection and complete analysis); dynamic studies of nitrogen retention and changing body composition (96, 112); labelled amino acid turnover (32, 58); and postnatal growth rates (30, 93). Values obtained by the factorial method suggest that about 3.7 g of protein per kg/day is required for infants under 1500 g weight, which is considerably more than the amount of protein supplied by mature breast milk when fed at a reasonable volume (2.0–2.6 g/kg). However, the changes in body composition of the premature infant during postnatal growth may not be the same as those of the fetus during the same postconceptional age period, and satisfactory quality of growth may well be obtained on a substantially lower protein intake. In spite of this it should not be forgotten that there are data to show that many preterm infants, especially those fed on donor breast milk, have evidence of protein undernutrition (30, 106, 107).

Protein Requirement and Energy Intake

The metabolizable energy intake is very important in determining the rate of protein synthesis during growth, and hence the protein requirement (147). When a high protein intake is given with inadequate additional dietary energy, surplus protein is metabolized and stresses the immature pathways of protein degradation. Conversely, an excess of energy over protein results in relative protein deficiency and growth is qualitatively abnormal. In general it is

unwise to provide less than 10% of the dietary energy as protein in low birthweight infants.

Protein Quality

Protein requirement is influenced by the quality of dietary protein. Preterm infants are unlikely to receive feeds containing much protein derived from sources other than human or cows' milk, both of which are of high biologic value, but there is some evidence (7) that whey-predominant feeds are associated with the best net protein utilization in the immature infant, and protein requirements may be a bit higher if unmodified cows' milk proteins are given (casein:whey 70:30) than if the ratio is modified to resemble human milk (casein:whey 40:60).

The quality of protein precursors supplied in parenteral nutrition solutions is obviously very important, since concentrations of amino acids that can be utilized perfectly well by an adult may be toxic for a preterm infant.

Minimum and Maximum Intakes

There is evidence that low birthweight infants fed 2.25 g protein per kg/day in a casein-predominant formula grow as fast as babies fed breast milk (93). There is, however, little doubt that infants given more protein grow faster (29), so a case can be made for setting the minimum at a higher level, perhaps even over 3.0 g/kg/d (148). However, this would preclude many infants from receiving their mothers' breast milk and it ignores the large variability in individual requirements (148). Thus a value of 2.25 g per kg for *minimum* intake may be reasonable. Maximum intake is determined by metabolic tolerance. Intakes above 4.0 g/kg/d are associated with metabolic disturbances in many infants (46, 83, 93) and with later developmental problems (50); hence they are not advised.

CALCIUM AND PHOSPHORUS HOMEOSTASIS

The requirement for calcium, phosphorus, and vitamin D is an important aspect of the nutrition of low birthweight babies since metabolic bone disease is one of the most common forms of nutritional deficiency seen in these infants. Chemical analysis of fetal bodies shows that the daily rate of accumulation of calcium between 26 and 36 weeks gestation is about 130 mg/kg, and of phosphorus 75 mg/kg (40, 115). These amounts are never provided by human milk, and calcium is poorly absorbed from the immature gut (116).

Metabolic Bone Disease of Prematurity

Metabolic bone disease is now a very well-recognized condition (20) and has been called "osteopenia" and "rickets of prematurity." It encompasses a range

of radiologic and clinical appearances, from mild undermineralization to severe rachitic bone disease with fractures. The reported incidence varies from center to center (69, 79, 80, 109), but in infants under 1000 g in weight, frank radiologic rickets has been described in up to 57% of cases (80). Infants less than 1500 g in weight almost always have reduced bone mineralization because they have poor calcium retention for several weeks after birth, whatever their calcium intake (31, 116). There are no clear guidelines on when this possibly physiologic event should be considered pathologic, and this probably accounts for the variation in recorded incidence of bone disease.

ROLE OF VITAMIN D Although vitamin D deficiency is well known to occur in preterm infants not given supplements (74), severe metabolic bone disease is not prevented by vitamin D intakes as high as 2000 IU/day (80), despite normal or elevated plasma concentrations of 25-hydroxyvitamin D (78, 80). There is thus little evidence that vitamin D deficiency is the primary problem, neither is there any convincing evidence that hepatic or renal hydroxylation of vitamin D are impaired (20).

ROLE OF SUBSTRATE DEFICIENCY There is increasing evidence that deficiency of calcium and phosphorus is the main cause of the metabolic bone disease syndrome (20). It is commonest in infants fed on breast milk, which only provides a fraction of the Ca and P requirement (128), and there are well-documented reports of rickets developing in preterm infants fed diets specifically low in calcium or phosphorus (68, 99). It is likely that P deficiency plays the most important role. Thus infants with severe bone disease may have lower intakes of phosphorus than infants without bone disease, but not of calcium (81); and infants fed breast milk may have extremely low plasma phosphate concentrations and raised urinary calcium excretion, despite a concurrently low calcium intake (77, 113, 114). This can be explained by the overriding need of the body for phosphorus for soft tissue growth and metabolism. When P intake is inadequate, plasma reserves fall and P is withdrawn from the skeleton. Calcium cannot be used for bone growth without phosphorus, so is lost in the urine. When P supplements are given there is an immediate fall in urine Ca excretion (113). From the available data it is not easy to assess the independent role of Ca deficiency in the pathogenesis of bone disease, but it is likely to be important as well. At least one study has shown that preterm infants may benefit from both calcium and phosphorus supplementation (128).

Vitamin D, Calcium, and Phosphorus Requirements

VITAMIN D About 800–1000 IU of vitamin D are required daily to ensure adequate hepatic 25-hydroxylation and optimum calcium absorption in preterm infants (113). This should be regarded as the minimum requirement.

CALCIUM Although factorial analysis (149) shows the calcium requirement of the preterm infant to be as high as 210 mg/kg/d, it is not at all certain whether this amount should be provided in the diet. Decreased bone density and bone remodelling may well be physiologic events after birth, and high calcium feeds have been associated with lactobezoar formation (18), impaired fat absorption (31, 65, 114), precipitation of calcium salts (9), and metabolic acidosis (127). There is no evidence that intakes greater than 140 mg/kg/d are likely to result in any further improvement in bone mineralization, so it is reasonable to take this as an upper limit, while ensuring that the lower limit is appreciably higher than that normally recommended for full-term infants (about 80 mg/kg/d). The problem of supplementing human milk is dealt with at the end of the chapter in the section on the approach to feeding and nutrition.

PHOSPHORUS Phosphorus retention and hence requirement is related to both calcium retention and nitrogen retention according to the equation (127)

$$\text{P retention (mg)} = \frac{\text{Ca retention}}{2} + \frac{\text{N retention}}{17.4}.$$

Thus when calcium intake is low, the ratio of phosphorus to calcium in the diet must be relatively high to ensure that there is adequate provision for soft tissue growth, but when calcium intake is high the ratio may be lower. In practice Ca:P ratios between 1.4 and 2.0 are usually satisfactory. Phosphorus is well absorbed, in contrast to calcium, and excessive intakes lead to hyperphosphatemia and hypocalcemia (138). An intake of 120 mg/kg should not be exceeded (13). Phosphorus supplements should be provided when human milk is used to feed extremely and very low birthweight infants (see below).

ELECTROLYTE NUTRITION

Sodium, potassium, and chloride are required in amounts exceeding the requirements of full-term infants because of poor renal economy and to some extent because of deposition in new tissues. In practice, specific deficiencies of potassium and chloride are rare, but sodium deficiency is very common.

Sodium Requirements

Sodium accumulation in the fetus is about 1.0 mmol/kg/day in the second and third trimesters (115, 144), but because of renal sodium losses this figure cannot be used as a guide to sodium requirements in preterm infants. There is no doubt that sodium economy is poor in premature infants, especially those born before 30 weeks gestation (98), and that it leads to the common

syndrome of late hyponatremia, which may interfere with growth and, if extreme, may cause convulsions. Gross (51) found hyponatremia (plasma Na <130 mmol/liter) after the first week in 50% of preterm infants fed donor breast milk providing 1.3 mmol/kg/d; in 20% of infants fed formula providing 1.9 mmol/kg/d; and in 15% of infants fed preterm breast milk providing 2.2 mmol/kg/d. There is evidence (98, 131) that renal tubular sodium reabsorption increases more slowly than glomerular filtration rate in the early postnatal weeks, and negative sodium balance is common. However, postnatal maturation of tubular function appears to be faster in the more mature preterm infants, and it has been shown (42) that by 34 weeks gestation infants were able to maintain normal plasma sodium concentrations on intakes as low as 1.2 mmol/kg/d. Less mature infants can usually, but not always, maintain plasma sodium above 130 mmol/liter on intakes of 2.3 mmol/kg/d (51); to prevent hyponatremia developing in all infants, intakes between 3.0 and 5.0 mg/kg are required (13). Thus infants fed donor breast milk will almost always require sodium supplements, and those fed on preterm breast milk or formula will sometimes need them. Regular monitoring of plasma sodium is essential.

Potassium and Chloride Requirements

Potassium depletion is rare in preterm infants and it appears that the amount present in breast milk, which is normally sufficient to provide an intake greater than 3.0 mmol/kg when fed at 180 ml/kg/d, is enough for most infants, who retain about 1.0 mmol/kg (118). Chloride deficiency has only been described in infants fed a very low chloride formula (<3 mmol/liter) (100).

TRACE NUTRIENT REQUIREMENTS

Vitamins

Although it can be assumed that the requirement for all vitamins is likely to be somewhat higher than in term infants because of the needs of rapid growth and variably poor gastrointestinal absorption, in practice deficiencies have only been described for vitamins D, E, and K and for folic acid. There is some evidence of suboptimal vitamin A and riboflavin nutrition and a good case can be made for supplementary vitamin C.

VITAMIN D Requirements for vitamin D were discussed above in the section on calcium and phosphorus homeostasis.

VITAMIN E Vitamin E (α-tocopherol) protects polyunsaturated lipids in cell membranes from oxidation, and the daily requirement is related to the dietary content of polyunsaturated fatty acids. Although it was established some years

ago that preterm infants could develop clinical illness due to vitamin E deficiency (97), the resurgence of recent interest in the vitamin has been due mainly to reports that damage caused by oxygen toxicity might sometimes be prevented or modified by pharmacological dosage (25, 61, 64, 102).

Vitamin E deficiency causes hemolytic anemia and sometimes edema (87, 97). It was relatively common in North America at a time when premature infants were often fed on formulas very rich in polyunsaturated fatty acids (57). It now appears to be rare, but there is evidence that biochemical signs of deficiency occur by six weeks of age in some VLBW infants who have been given iron supplements in the early weeks of life (52). These could be prevented by giving 5 mg of α-tocopherol daily from the end of the first week. It therefore seems reasonable to offer vitamin E supplements at this level to all very and extremely low birthweight infants at least until discharge from hospital.

Pharmacologic doses of vitamin E, given from the first day of life, have been suggested and used in immature infants in order to ameliorate or prevent damage caused by oxygen toxicity, specifically retinopathy of prematurity (61, 64) and bronchopulmonary dysplasia (35, 102); they have also been used in the prophylactic treatment of intraventricular hemorrhage (25, 126), to which oxygen might contribute by causing damage to capillary endothelial membranes (25). On present evidence it seems that such treatment is ineffective at preventing or treating bronchopulmonary dysplasia (82, 102), of only marginal effectiveness in preventing intraventricular hemorrhage (90, 126), and clearly effective at preventing or modifying retinopathy of prematurity (61, 64). While there remains the possibility that very large doses of α-tocopherol could have harmful effects (63), it is prudent to be cautious about recommending the wholesale use of megadoses of the vitamin. Retinopathy of prematurity has a wide variation in incidence from center to center, and prophylaxis should probably be reserved for those centers specially troubled by the problem.

VITAMIN K There is no doubt about the need for supplementary vitamin K at birth in all LBW infants (39), because stores of the vitamin are low and synthesis in the gut deficient. Hemorrhagic problems are common in very and extremely low birthweight infants and every effort should be made to ensure that these are not aggravated by vitamin K deficiency. An intramuscular dose of 0.5–1.0 mg of a water-soluble preparation is adequate to prevent hemorrhagic disease of the newborn (70), and a case could be made for repeating this on a weekly basis in infants <1500 g, especially those being fed mainly on breast milk, which is deficient in the vitamin.

FOLIC ACID Folic acid is very important for growth (45). Limited reserves at birth together with the needs for rapid growth will increase the requirement

for the vitamin in the preterm neonate (26, 36). Megaloblastic anemia due to folate deficiency has been described in immature infants (130), and morphological changes in the formed elements of the blood are said to be common (130). A test dose of folic acid disappears from the blood more rapidly in premature infants than in full-term infants without a corresponding increase in urinary excretion (121), which probably implies an increased need for the vitamin. The clinical and hematologic effects of routine supplementation have not been impressive (22, 129), but they have not been examined in very and extremely low birthweight infants. It is probably time for a reevaluation. Since folic acid is completely without toxicity, it is sensible to recommend supplementation (37) at a level of about 50 μg/d.

VITAMIN A Although overt signs of vitamin A deficiency have not been described in preterm neonates, there is evidence (19, 120) of biochemical deficiency in extremely and very low birthweight infants who are very sick or have bronchopulmonary dysplasia. It is usual to give oral supplements of vitamin A to preterm babies, but there may be a case for giving more than the usual 4000 IU/day, parenterally, in such infants. This needs further evaluation.

RIBOFLAVIN It was recently shown (75) that biochemical riboflavin deficiency is common in preterm infants. There are as yet no studies showing improved growth or health when riboflavin supplements are given, but riboflavin is thought to enhance the effect of phototherapy (89) and has no known toxicity. It should therefore be given in routine vitamin supplementation programs for preterm infants to ensure a reasonable excess (say 400 μg/d, the daily requirement being less than 60 μg/100 kcal).

VITAMIN C Scurvy has not been described in premature infants but vitamin C has very important effects on amino acid metabolism, being involved in the oxidation of tyrosine. The hypertyrosinemia that sometimes occurs in very low birthweight infants fed high protein diets is responsive to vitamin C therapy (73). The protein content of preterm breast milk may be quite high (76) and there is no guarantee that the ascorbic acid concentration in the milk will always be at a level to facilitate optimal tyrosine metabolism. furthermore it is degraded by heating. Thus all breast-milk-fed infants should receive ascorbic acid supplements (about 20 mg/day), and formulas for premature infants should contain added vitamin C.

Iron and the Trace Elements

The increased requirement for iron by LBW infants is well known, and there are also reports of zinc and copper deficiency. These nutrients are discussed in this section. However, it should not be forgotten that a deficiency of other

essential trace elements (manganese, selenium, molybdenum, chromium, iodine) may be lurking in the background and may emerge with the occasional, at present unrecognized, deficiency syndrome in extremely low birthweight infants.

IRON Iron stores are low in all LBW infants, who will inevitably become deficient if fed on milks with low iron content without supplementation. The stores become exhausted at 6–8 weeks in infants weighing less than 1400 g and at 8–12 weeks in larger LBW infants (110). Frequent blood sampling further depletes stores. Supplementation of the diet with iron is mandatory, the only additional consideration being when to start giving it. Iron given to preterm infants in the first 4–6 weeks is partly absorbed (27) but not utilized for hematopoiesis because of the low erythropoietin production at this time. There are potentially harmful effects of supplementary iron as well, for example gram-negative sepsis (6), and a high iron intake may induce lipid peroxidation of red cell membranes and hemolysis if vitamin E intake is marginal (145). Iron supplements are thus best started between four and eight weeks, and probably not before eight weeks in infants who have had multiple blood transfusions, since these infants may have temporary iron overload (119). Various authoritative reports (3, 23) recommend 2.0–2.5 mg iron per kg daily for preterm infants, which is enough to prevent late iron deficiency anemia. However, supplementation will have to be based on the level of iron provision in the feed, and an infant fed on an iron-fortified formula may need no additional iron at all.

ZINC Zinc is present in many enzymes and is an important growth-promoting nutrient. Several reports of cases of clinical zinc deficiency in preterm infants, with features similar to acrodermatitis enteropathica, have been published in the last few years (2, 10). In all cases the infants were fed almost exclusively on breast milk, and it seems that some breast milks are very low in zinc, especially after the first few weeks of lactation. Zinc economy in preterm infants is not as good as it is in term infants, and positive zinc balance is not achieved until 40 days or more after birth (28). Thus requirements are certainly higher than in term infants, probably in the range 1.0–1.6 mg/kg/day to ensure an early resumption of the intrauterine accumulation rate of about 0.25 mg/kg (117). There is as yet no evidence to suggest that all extremely and very low birthweight infants should receive zinc supplements as a routine.

COPPER Copper deficiency is well described in preterm infants, with bone lesions, anemia, neutropenia, prominent scalp veins, and fish odor (11, 108), but has only been reported in infants fed on formulas with low copper content.

Negative copper balance is not uncommon in the early weeks of life (28). Precise requirements are not known but deficiency has never been described in infants fed breast milk, so it can be assumed that the amount present in pooled breast milk is sufficient (90–120 μg/100 kcal, or 120–150 μg/kg/day when fed at usual volumes). Formula must be supplemented with copper at least to this level.

Carnitine and Essential Fatty Acids

CARNITINE Carnitine is a quarternary amine that plays an important role in facilitating the transport of long-chain fatty acids across mitochondrial membranes. Preterm infants have been reported to have low plasma and tissue concentrations, especially when fed by total parenteral nutrition (103), and carnitine deficiency may be a cause of low rates of clearance of parenteral fat emulsions from the plasma (104). Severe carnitine deficiency has been described in a full-term infant presenting with nonketotic hypoglycemia (124), but this syndrome has not yet been seen in a preterm infant. Carnitine is present in both human and cows' milk, and plasma concentrations of orally fed infants rise after birth. There seems to be no indication to provide carnitine as a supplement in premature infants, except possibly in parenteral nutrition solutions.

ESSENTIAL FATTY ACIDS (EFA) EFA are a group of naturally occurring unsaturated fatty acids of chain length 18, 20, or 22 carbon atoms containing two to six double bonds in *cis* configuration. Their essential nature is related to their role as components of phospholipids and as precursors of prostaglandins and leukotrienes. Various workers have studied EFA requirements in neonates (43, 56, 88) and it appears that both clinical (skin changes) and histologic evidence of EFA deficiency may occur when linoleic acid (C18:1) forms less than 1% of the total dietary energy. Requirements are likely to be higher in infants growing fast on a high energy intake (43). To be on the safe side it has been recommended that preterm infants should receive not less than 4.5% of total dietary energy as linoleic acid, i.e. about 500 mg/100 kcal, and not less than 0.5% as linolenic acid (13).

APPROACH TO FEEDING AND NUTRITION

The feeding of very and extremely low birthweight infants has two phases: first there is the period of instability and often of illness during which intragastric feedings may not be well tolerated, but when the critical condition of the infant demands the closest attention to energy and nitrogen intake; and second is the period of rapid growth during which enteral feedings are usually well tolerated.

Early Management

It is mandatory to have access to a blood vessel in any infant <1000 g weight and in very low birthweight infants who are ill with respiratory distress or infection. This allows part or all of the early nutrient needs to be given parenterally, and the use of small-bore silicon rubber catheters has simplified management considerably (115). Extremely low birthweight infants should not be allowed to go for more than 24 hours without receiving a source of nitrogen to prevent excessive catabolism, so an amino acid solution should be started within this period. It may not be necessary to provide total parenteral nutrition (TPN), since many infants will tolerate small amounts of fresh human milk intragastrically at this time, especially if their airway is protected by the presence of an endotracheal tube. Such feeding encourages bile flow and enterocyte development. Critically ill infants who are not being ventilated must receive TPN until stable, as must infants who have just been extubated. Many small but otherwise well babies will tolerate breast milk from the start, but often not in sufficient volume to meet their water requirements, so an IV infusion is needed in them too. It is reasonable to follow the hallowed procedure of 60/90/120/150 ml/kg/day for total fluid intake in the first four days, and then to increase to 180 ml/kg as tolerated, but remembering that water losses may be variably quite high in extremely low birthweight infants due to the extremely thin skin and any additional requirement generated by phototherapy, so a careful watch must be kept on the state of water balance by regular clinical assessment and measurement of plasma electolytes and urine specific gravity. It is also essential at all stages of management not to persist with high enteral feed intakes that are not adequately tolerated, because unabsorbed food residues are likely to contribute to the development of necrotizing enterocolitis (49).

Later Management

Once the infant is stable and tolerating at least 150 ml/kg/day of enteral feed he has entered the second phase of nutritional management. At this time it is necessary to decide whether the infant should be fed on breast milk or formula. Many neonatologists have strong views on this subject and insist that a suitable "premature" formula adapted to the needs of very low birthweight infants be used. These formulas perform well and allow very good growth (5, 42, 139). They have the great advantage over breast milk that their composition is known and intakes can be calculated precisely. However, the case for breast milk rests on different foundations. In spite of its variable and often inadequate composition, it has the undeniable advantage that it empties well from the stomach (24) and hence is more readily tolerated by the smallest infants. Furthermore, the whole emphasis of neonatal intensive care has shifted and is still shifting toward more maternal involvement, at a time when

there has also been a marked trend to increased breast feeding in all Western societies. This has resulted in strong pressure being put on mothers and neonatal staff to promote breast feeding in premature infants. While such a policy may be essential for the survival of such infants in Third World countries (85), it is by no means certain that it is necessarily the right policy in the West, where concerns about poor growth and the later effects of inadequate early nutrition may be of greater significance than infection and immediate survival. However, it does seem a good thing to involve the mother as much as possible in the care of her prematurely born infant, and it is undeniable that "preterm" milk can provide a very satisfactory source of nutrition.

BREAST MILK FOR PRETERM INFANTS It has been shown in several studies that the milk of mothers of preterm infants is qualitatively different from the milk of full-term mothers, having more protein and sodium (59, 72). It is quite variable in composition (59), but has generally been found to support growth well (5, 96). Another advantage of preterm milk over donor milk is that it can generally be given fresh; this avoids the damaging effects of heat, particularly the degradation of fat absorption from pasteurized donor milk (146).

All breast milk given to extremely low birthweight infants (and perhaps also to very low birthweight infants but less certainly) should be supplemented with phosphorus, say 10 mg/100 ml of breast milk as buffered sodium phosphate, which can be mixed with the feed without fear of precipitation; and also with calcium (which should be given separately between feeds to avoid problems of precipitation) in amounts that will not result in the overall daily Ca:P intake ratio exceeding 2.0. Calcium should not be given without phosphorus in these circumstances since, in the presence of the inevitable phosphate deficiency, calcium cannot be utilized adequately for bone formation and will be lost in the urine, thereby causing potentially damaging hypercalciuria. Sodium supplements are also usually required, especially in infants fed donor milk, and the amount given can be monitored by plasma sodium concentration, with a starting schedule of 2–4 mmol/kg/day.

Infants who do not thrive on breast milk pose a particular problem if the mother is determined to continue breast feeding. Under these circumstances it is reasonable to supplement the mother's milk with whole preterm formula in a 50:50 ratio, which usually results in improved growth while maintaining maternal involvement with the baby's nutrition. This also allows her the opportunity to maintain lactation, with the ultimate aim of discharging a breast-feeding infant.

The best way to feed these very small infants is still unknown, and the

results of multicenter studies with long-term follow-up are needed. One of these studies is approaching completion in England. They will have to evaluate the potential nutritional disadvantages of breast milk against the possibly very considerable advantages of greater maternal involvement, the potential reduction of various types of infection (including necrotizing enterocolitis), and the later occurrence of allergic disease.

CONCLUSION

Very low and extremely low birthweight infants pose particular problems of nutrition. They are liable to a greater variety of specific nutritional deficiency disorders than any other group of individuals and there are formidable difficulties in providing adequate nutrient intakes in the smallest babies. The major problems are related to the need to maintain water and energy balance, particularly in infants who are very sick, to provide enough but not too much protein, and to maintain calcium and phosphorus homeostasis. Breast feeding, while the undoubted goal for all full-term infants, may be far from ideal in very small preterm babies because of the milk's variable composition and deficient content of several essential nutrients. Nevertheless there are reasonable doubts as to whether infants <1000 g weight can always tolerate formulas of apparently ideal composition without metabolic stress; for some of these breast milk may be safer. The problem remains of how to identify which infants will be most suited to which feeding regimen. The ideal may be to use adequately supplemented preterm breast milk. This demands cheap and reliable side-room equipment for the analysis of the milk's macronutrient composition, so it can be adjusted to suit the needs and intolerances of the infant.

Literature Cited

1. Abdulrazzaq, Y. M., Brooke, O. G. 1984. Respiratory metabolism in preterm infants: the measurement of oxygen consumption over prolonged periods. *Pediatr. Res.* 18:928–31
2. Aggett, P. J., Atherton, D. J., More, J., Davey, J., Delves, H. T., et al. 1980. Symptomatic zinc deficiency in a breast-fed preterm infant. *Arch. Dis. Child.* 55:547–50
3. American Academy of Pediatrics: Committee on Nutrition. 1985. Nutritional needs of low birthweight infants. *Pediatrics* 75:976–86
4. Aperia, A., Broberger, O., Herin, P., Thodenius, K., Zetterstrom, R. 1983. Postnatal control of water and electrolyte homeostasis in preterm and full-term infants. *Acta Paediatr. Scand. Suppl.* 305:61–65
5. Atkinson, S. A., Bryan, M. H., Anderson, G. H. 1981. Human milk feeding in premature infants: protein, fat, and carbohydrate balances in the first 2 weeks of life. *J. Pediatr.* 99:617–25
6. Barry, D. M. J., Reeve, A. W. 1977. Increased incidence of gram negative neonatal sepsis with intramuscular iron administration. *Pediatrics* 60:908–12
7. Berger, H. M., Scott, P. H., Kenward, C., Scott, P., Wharton, B. A. 1979. Curd and whey proteins in the nutrition of low birth weight babies. *Arch. Dis. Child.* 54:98–104
8. Bernbaum, J. C., Pereira, G. R., Watkins, J. B., Peckham, G. J. 1983. Nonnutritive sucking during gavage feeding enhances growth and maturation in premature infants. *Pediatrics* 71:41–45
9. Bhatia, J., Fomon, S. J. 1983. Formulas

for premature infants: fate of the calcium and phosphorus. *Pediatrics* 72:37–40
10. Blom, I., Jameson, S., Krook, F., Larsson-Styme, B., Wranne, L. 1981. Zinc deficiency with transitory acrodermatitis enteropathica in a boy of low birth weight. *Br. J. Dermatol.* 104:459–64
11. Blumenthal, I., Lealman, G. T., Franklyn, P. P. 1980. Fracture of the femur, fish odour, and copper deficiency in a preterm infant. *Arch. Dis. Child.* 55: 229–31
12. Book, L. S., Herbst, J. J., Atherton, S. O., Jung, A. L. 1975. Necrotizing enterocolitis in low-birth-weight infants fed on an elemental formula. *J. Pediatr.* 87:602–6
13. Bremer, H. J., Brooke, O. G., Orzalesi, M., Putet, G., Räihä, N. C. R., et al. 1987. Nutrition and feeding of preterm infants. *Acta Paediatr. Scand. Suppl.* In press
14. Brooke, O. G. 1985. Energy expenditure in the fetus and neonate: sources of variability. *Acta Paediatr. Scand. Suppl.* 319:128–34
15. Brooke, O. G., Alvear, J. 1982. Postprandial metabolism in infants of low birthweight. *Hum. Nutr. Clin. Nutr.* 36C:167–75
16. Brooke, O. G., Alvear, J., Arnold, M. 1979. Energy retention, energy expenditure, and growth in healthy immature infants. *Pediatr. Res.* 13:215–20
17. Brooke, O. G., Barley, J. 1978. Loss of energy during continuous infusions of breast milk. *Arch. Dis. Child.* 53:344–45
18. Brooke, O. G., Gentner, P. R., Harzer, G., Spitz, L. 1982. Milk fat bolus obstruction in a preterm infant. *Acta Paediatr. Scand.* 71:691–92
19. Brooke, O. G., Howells, D. 1984. Plasma vitamin A and E in very immature infants: relationships with fat absorption and dietary intake. *Pediatr. Res.* 18:1049
20. Brooke, O. G., Lucas, A. 1985. Metabolic bone disease in preterm infants. *Arch. Dis. Child.* 60:682–85
21. Brueton, M. J., Berger, H. M., Brown, G. A., Ablitt, L., Iyngkaran, M., et al. 1978. Duodenal bile acid conjugation patterns and dietary sulphur amino acids in the newborn. *Gut* 19:35–39
22. Burland, W. L., Simpson, K., Lord, J. 1971. Response of low birthweight infants to treatment with folic acid. *Arch. Dis. Child.* 46:189–93
23. Canadian Paediatric Society: Committee on Nutrition. 1981. Feeding the low birthweight infant. *J. Can. Med. Assoc.* 124:1301–11
24. Cavell, B. 1979. Gastric emptying in preterm infants. *Acta Paediatr. Scand.* 68:725–30
25. Chiswick, M. L., Johnson, M., Woodhall, C. 1983. Protective effect of vitamin E (DL-α-tocopherol) against intraventricular haemorrhage in premature babies. *Br. Med. J.* 287:81–84
26. Dallman, P. R. 1974. Iron, vitamin E and folate in the preterm infant. *J. Pediatr.* 95:742–45
27. Dauncey, M. J., Davies, C. G., Shaw, J. C. L., Urman, J. 1978. The effect of iron supplements and blood transfusions on iron absorption by low birthweight infants fed pasteurized human breast milk. *Pediatr. Res.* 12:899–904
28. Dauncey, M. J., Shaw, J. C. L., Urman, J. 1977. The absorption and retention of magnesium, zinc and copper by low birthweight infants fed pasteurized human breast milk. *Pediatr. Res.* 11:991–97
29. Davidson, M., Levine, S. Z., Bauer, C. H., Dann, M. 1967. Feeding studies in low-birth-weight infants. I. Relationships of dietary protein, fat, and electrolyte to rates of weight gain, clinical courses, and serum chemical concentrations. *J. Pediatr.* 70:695–713
30. Davies, D. P. 1977. Adequacy of expressed breast milk for early growth of preterm infants. *Arch. Dis. Child.* 52:296–98
31. Day, G. M., Chance, G. W., Raddle, I. C., Reilly, B. J., Park, E., et al. 1975. Growth and mineral metabolism in very low birthweight infants. II. Effects of calcium supplementation on growth and divalent cations. *Pediatr. Res.* 9:568–75
32. de Benoist, B., Abdulrazzaq, Y. M., Brooke, O. G., Halliday, D., Millward, J. 1983. The measurement of whole-body protein turnover in the preterm infant with intragastric infusion of L-[1-13c]leucine. *Clin. Sci.* 66:155–64
33. De Curtis, M., McIntosh, N., Ventura, V., Brooke, O. G. 1986. Effect of non-nutritive sucking on nutrient retention in preterm infants. *Pediatrics.* In press
34. Duritz, G., Oltorf, C. 1979. Lactobezoar formation associated with high density caloric formula. *Pediatrics* 63: 647–50
35. Ehrenkranz, R. A., Ablow, R. C., Warshaw, J. B. 1979. Prevention of bronchopulmonary dysplasia with vitamin E administration during the acute stages of respiratory distress syndrome. *J. Pediatr.* 95:873–78
36. Ek, J. 1980. Plasma and red cell folate values in newborn infants and in their

mothers in relation to gestational age. *J. Pediatr.* 96:288–94
37. Ek, J. 1985. Folic acid and vitamin B_{12} requirements in premature infants. In *Vitamin and Mineral Requirements in Preterm Infants,* ed. R. C. Tsang, pp. 23–38. New York: Dekker
38. Fanaroff, A. A., Wald, M., Gruber, H. S., Klauss, M. H. 1972. Insensible water loss in low birthweight infants. *Pediatrics* 49:236–45
39. Farrell, P. M., Zachman, R. D., Gutcher, G. R. 1975. Fat soluble vitamins A, E and K in the premature infant. See Ref. 37, pp. 63–98
40. Forbes, G. B. 1976. Calcium accumulation by the human fetus. *Pediatrics* 57:976–77
41. Fosbrooke, A. S., Wharton, B. A. 1975. Added lactose and added sucrose cows' milk formulae in nutrition of low birthweight babies. *Arch. Dis. Child.* 50:409–18
42. French, T. J., Colbeck, M., Burman, D., Spiedel, B., Hendy, R. A. 1982. A modified cows' milk formula suitable for low birthweight infants. *Arch. Dis. Child.* 57:507–10
43. Friedman, Z. 1979. Polyunsaturated fatty acids in the low-birth-weight infant. *Semin. Perinatol.* 3:341–52
44. Friedman, Z., Damon, A., Stohlman, M., Oates, J. 1976. Rapid onset of essential fatty acid deficiency in the newborn. *Pediatrics* 58:640–44
45. Gandy, G., Jacobson, W. 1977. Influence of folic acid on birth weight and growth of the erythroblastic infant. II. Growth during the first year. *Arch. Dis. Child.* 52:7–14
46. Gaull, G. E., Rassin, D. K., Räihä, N. C. R., Heinonen, K. 1977. Milk protein quantity and quality in low-birth-weight infants. III. Effects on sulfur amino acids in plasma and urine. *J. Pediatr.* 90:348–55
47. Geschwind, Von R. 1950. Das Verhalten der Pancreasenzyme bie Fruhgebornen. *Ann. Paediatr.* 157:176–80
48. Glass, L., Silverman, W. A., Sinclair, J. C. 1968. Effect of the thermal environment on cold resistance and growth of small infants after the first week of life. *Pediatrics* 41:1033–46
49. Goldman, H. I. 1980. Feeding and necrotizing enterocolitis. *Am. J. Dis. Child.* 134:553–57
50. Goldman, H. I., Goldman, J. S., Kaufman, I., Liebman, O. B. 1974. Late effects of early dietary protein intake on low-birth-weight infants. *J. Pediatr.* 85:764–69
51. Gross, S. J. 1983. Growth and biochemical response of preterm infants fed human milk or modified infant formula. *N. Engl. J. Med.* 308:237–41
52. Gross, S. J., Gabriel, E. 1985. Vitamin E status in preterm infants fed human milk or infant formula. *J. Pediatr.* 106:635–39
53. Gudinchet, F., Schutz, Y., Micheli, J.-L., Stettler, E., Jéquier, E. 1982. Metabolic cost of growth in very low-birth-weight infants. *Pediatr. Res.* 16: 1025–30
54. Hamosh, M. 1979. The role of lingual lipase in neonatal fat digestion. In *Development of Mammalian Absorptive Processes,* Ciba Found. Symp. No. 70. Amsterdam: Excerpta Medica
55. Hamosh, M., Sivasubramanian, K. N., Salzman-Mann, C., Hamosh, P. 1978. Fat digestion in the stomach of premature infants. *J. Pediatr.* 93:674–78
56. Hansen, A. E., Wiese, H. F., Boelsche, A. N. 1963. Role of linoleic acid in infant nutrition: clinical and chemical study of 428 infants fed on milk mixtures varying in kind and amount of fat. *Pediatrics* 31:171–83
57. Hashim, S. A., Asfour, R. 1968. Tocopherol in infants fed diets rich in polyunsaturated fatty acids. *Am. J. Clin. Nutr.* 21:7–14
58. Heine, W., Plath, C., Richter, I., Wutzke, K., Töwe, J. 1983. ^{14}N-Tracer investigations into the nitrogen metabolism of preterm infants fed mother's milk and a formula diet. *J. Pediatr. Gastroenterol. Nutr.* 2:606–12
59. Hibberd, C., Brooke, O. G., Carter, N. D., Wood. C. 1981. Comparison of protein concentrations and energy in breast milk from preterm and term mothers. *J. Hum. Nutr.* 35:189–98
60. Hill, J. R., Robinson, D. C. 1968. Oxygen consumption in normally grown, small-for-dates and large-for-dates newborn infants. *J. Physiol.* 199:685–703
61. Hittner, H. M., Godio, M. D., Rudolph, A. J. 1981. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. *N. Engl. J. Med.* 305:1365–71
62. Jensen, R. G., Hagerty, M. M., McMahon, K. E. 1978. Lipids of human milk and infant formulas: a review. *Am. J. Clin. Nutr.* 31:990–1010
63. Johnson, L., Bower, F. W., Abbasi, S. 1985. Relationship of prolonged pharmacological serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birthweight

1599 grams or less. *Pediatrics* 75:619–38
64. Johnson, L., Schaffer, D., Boggs, T., Quinn, G., Mathis, M. 1980. Vitamin E treatment of retrolental fibroplasia grade III or worsel. *Pediatr. Res.* 14:601–5
65. Katz, L., Hamilton, J. R. 1974. Fat absorption in infants of birthweight less than 1300 g. *J. Pediatr.* 85:608–11
66. Kielanowski, J. 1965. Energy metabolism. In *Proceedings of the Symposium on Energy Metabolism,* Troon, ed. K. L. Blaxter, pp. 13–20. London: Academic
67. Komrower, G. M., Robins, A. J. 1969. Plasma amino acid disturbance in infancy. I. Hypermethioninaemia and tyrosinemia. *Arch. Dis. Child.* 44:416–21
68. Kooh, S. W., Fraser, D., Reilly, B. J. 1977. Rickets due to calcium deficiency. *N. Engl. J. Med.* 297:1264–66
69. Kulkarni, P. B., Hall, R. T., Rodes, P. G. 1980. Rickets in very low-birthweight infants. *J. Pediatr.* 96:249–52
70. Lane, P. A., Hathaway, W. E. 1985. Vitamin K in infancy. *J. Pediatr.* 106: 351–59
71. Lebenthal, E., Lee, P. C. 1980. Development of functional response in human exocrine pancreas. *Pediatrics* 66: 556–59
72. Lemons, J. A., Moye, L., Hall, D., Simmons, M. 1982. Differences in the composition of preterm and term human milk during early lactation. *Pediatr. Res.* 16:113–20
73. Levine, S. Z., Marples, E., Gordon, H. H. 1941. A defect in the metabolism of tyrosine and phenylalanine in premature infants. II. Spontaneous occurrence and eradication by vitamin C. *J. Clin. Invest.* 20:209–13
74. Lewin, P. K., Reid, M., Reilly, B. J. 1971. Iatrogenic rickets in low birthweight infants. *J. Pediatr.* 78:207–14
75. Lucas A., Bates, C. 1984. Transient riboflavin depletion in preterm infants. *Arch. Dis. Child.* 59:837–41
76. Lucas, A., Hudson, G. J. 1984. Preterm milk as a source of protein for low birthweight infants. *Arch. Dis. Child.* 59: 831–36
77. Lyon, A. J., McIntosh, N., Wheeler, K., Brooke, O. G. 1984. Hypercalcaemia in extremely low birthweight infants. *Arch. Dis. Child.* 59:1141–44
78. Markestad, T., Aksues, L., Finn, P. H., Aarskog, D. 1983. Plasma concentrations of vitamin D metabolites in a case of rickets of prematurity. *Acta Paediatr. Scand.* 72:759–61
79. McCowen, C., Hey, E. N. 1983. Plasma 25-hydroxyvitamin D and rickets in low birthweight babies. *Arch. Dis. Child.* 58:476
80. McIntosh, N., Livesey, A., Brooke, O. G. 1982. Plasma 25-hydroxyvitamin D and rickets in infants of extremely low birthweight. *Arch. Dis. Child.* 57:848–50
81. McIntosh, N., Livesey, A., Brooke, O. G. 1983. Plasma 25-hydroxyvitamin D and rickets in low birthweight infants. *Arch. Dis. Child.* 58:476–77
82. McLung H. J., Backes, C., Lavin, A., Kerzner, B. 1980. Prospective evaluation of vitamin E therapy in premature infants with hyaline membrane disease. *Pediatr. Res.* 14:604–8
83. Menkes, J. H., Avery, M. E. 1963. The metabolism of phenylalanine and tyrosine in the premature infant. *Bull. Johns Hopkins Hosp.* 113:301–19
84. Mestyán, J., Fekete, M., Bata, G., Jarai, I. 1964. The basal metabolic rate of premature infants. *Biol. Neonate* 1: 11–25
85. Narayanan, I. 1985. Nutrition for preterm and growth retarded infants: developing country concerns. *Hum. Nutr. Appl. Nutr.* 39A:242–54
86. Norman, A., Strandvik, B., Ojamae, O. 1972. Bile acids and pancreatic enzymes during absorption in the newborn. *Acta Paediatr. Scand.* 61:571–76
87. Oski, F. A., Barness, L. A. 1967. vitamin E deficiency: a previously unrecognized cause of hemolytic anemia in the premature infant. *J. Pediatr.* 70: 211–20
88. Panos, T. C., Stinnett, B., Cross, E. 1961. Metabolic effects of low fat feeding in premature infants. *Fed. Proc.* 20:366–69
88a. Parma, V., Abdulrazzaq, Y. M., Brooke, O. G. 1986. Stool water in preterm neonates. *Arch. Dis. Child.* 61: 1136–37
89. Pascale, J. A. 1976. Riboflavin and bilirubin response during phototherapy. *Pediatr. Res.* 10:854–56
90. Phelps, D. L. 1984. Vitamin E and CNS hemorrhage. *Pediatrics* 74:1113–14
91. Putet, G., Senterre, G., Rigo, J., Salle, B. 1984. Nutrient balance, energy utilization and composition of weight gain in very low birthweight infants fed pooled human milk or a preterm formula. *J. Pediatr.* 105:79–85
92. Räihä, N. C. R. 1974. Perinatal development of some enzymes of amino acid metabolism in the liver. In *Scientific Foundations of Pediatrics,* ed. J. A.

Davis, J. Dobbing, I:95–104. London: Heineman
93. Räihä, N. C. R., Heinonen, K., Rassin, D. K., Gaull, G. E. 1976. Milk protein quality and quantity in low-birth-weight infants: I. Metabolic responses and effects on growth. *Pediatrics* 57:659–74
94. Rees, L., Brook, C. G. D., Shaw, J. C. L., Forsling, M. L. 1984. Causes of hyponatraemia in the first week of life in preterm infants. I. Arginine vasopressin secretion. *Arch Dis. Child.* 59:414–22
95. Reichman, B. L., Chessex, P., Putet, G., Verellen, G., Smith, J. M., et al. 1982. Partition of energy metabolism and energy cost of growth in the very low-birth-weight infant. *Pediatrics* 69: 446–51
96. Reichman, B., Chessex, P., Verellen, G., Putet, G., Smith, J. M., et al. 1983. Dietary composition and macronutrient storage in preterm infants. *Pediatrics* 72:322–28
97. Ritchie, J. H., Fisch, M. B., McMasters, V., Grossman, M. 1968. Edema and hemolytic anemia in premature infants: a vitamin E deficiency syndrome. *N. Engl. J. Med.* 279:1185–90
98. Ross, B., Cowett, R. M., Oh, W. 1977. Renal functions of low birthweight infants during the first two months of life. *Pediatr. Res.* 11:1162–64
99. Rowe, J. C., Wood, D. H., Rowe, D. W., Raisz, L. G. 1979. Nutritional hypophosphatemic rickets in a premature infant fed breast milk. *N. Engl. J. Med.* 300:293–96
100. Roy, A., Arant, B. S. 1979. Alkalosis from chloride deficient Neo-Mul-Soy. *N. Engl. J. Med.* 301:615
101. Roy, C. C., Ste-Marie, M., Chartrand, R. T., Weber, A., Bard, H., et al. 1975. Correction of the malabsorption of the preterm infant with a medium-chain triglyceride formula. *J. Pediatr.* 86:446–50
102. Saldanha, R. L., Ceped, E. E., Poland, R. L. 1980. Effect of prophylactic vitamin E on the development of bronchopulmonary dysplasia in high risk neonates. *Pediatr. Res.* 14:650–55
103. Schiff, D., Chan, G., Seccomb, D. Hahn, P. 1979. Plasma carnitine levels during intravenous feeding in the neonate. *J. Pediatr.* 95:1043–46
104. Schmidt-Sommerfeld, E., Penn, D., Wolf, H. 1982. Carnitine blood concentrations and fat utilization in parenterally alimented premature newborn infants. *J. Pediatr.* 100:260–63
105. Scopes, J. W., Ahmed, I. 1966. Minimum rates of oxygen consumption in sick premature newborn infants. *Arch. Dis. Child.* 41:407–12
106. Scott, P. H., Berger, H. M., Kenward, C., Scott, P., Wharton, B. A. 1978. Plasma alkaline ribonuclease and nitrogen retention in low birthweight infants. *Br. J. Nutr.* 40:459–64
107. Scott, P. H., Berger, H. M., Wharton, B. A. 1985. Growth velocity and plasma amino acids in the newborn. *Pediatr. Res.* 19:446–50
108. Seeley, J. R., Humphrey, G. B., Matler, B. J. 1972. Copper deficiency in a premature infant fed on iron-fortified formula. *N. Engl. J. Med.* 286:109
109. Seino, Y., Ishii, T., Shimotsuji, T., Ishida, M., Yabuuchi, H. 1981. Plasma active vitamin D concentration in low birthweight infants with rickets and its response to vitamin D treatment. *Arch. Dis. Child.* 56:628–32
110. Seip, M., Halvorsen, S. 1956. Erythrocyte production and iron stores during the first months of life: the anaemia of prematurity—aetiology, pathogenesis and iron requirements. *Acta Paediatr. Scand.* 45:600–17
111. Senterre, J. 1976. *Alimentation Optimale du Prématuré.* Liège: Vaillant Carmanne
112. Senterre, J. 1979. Nitrogen balances and protein requirements of preterm infants. In *Nutrition and Metabolism of Fetus and Infant,* ed. H. K. A. Visser, pp. 195–212. The Hague/Boston/London: Nijhoff
113. Senterre, J., Putet, G., Salle, B., Rigo, J. 1983. Effects of vitamin D and phosphorus supplementation on calcium retention in preterm infants fed banked human milk. *J. Pediatr.* 103:305–7
114. Senterre, J., Salle, B. 1982. Calcium and phosphorus economy of the preterm infant and its interaction with vitamin D and its metabolites. *Acta Paediatr. Scand. Suppl.* 296:85–92
115. Shaw, J. C. L. 1973. Parenteral nutrition in the management of the sick low birthweight infant. *Pediatr. Clin. North Am.* 20:333–58
116. Shaw, J. C. L. 1976. Evidence for defective skeletal mineralization in low birthweight infants. The absorption of calcium and fat. *Pediatrics* 57:16–25
117. Shaw, J. C. L. 1979. Trace elements in the fetus and young infant. I. Zinc. *Am. J. Dis. Child.* 133:1260–68
118. Shaw, J. C. L. 1982. Absorption and retention of sodium, potassium, magnesium and calcium by preterm infants. In *Meeting the Nutritional Goals for Low*

Birthweight Infants, Proc. 2nd Ross Clin. Res. Conf., pp. 97–103.
119. Shaw, J. C. L. 1982. Iron absorption by the preterm infant. The effect of transfusion and iron supplements on serum ferritin levels. *Acta Paediatr. Scand. Suppl.* 299:83–89
120. Shenai, J. P., Chytil, F., Stahlman, M. T. 1985. Vitamin A status of infants with bronchopulmonary dysplasia. *Pediatiatr. Res.* 19:185–88
121. Shojania, A. M., Hornaday, G. 1970. Folate metabolism in newborns and during early infancy. II. Clearance of folic acid in plasma and excretion of folic acid in urine by newborns. *Pediatiatr. Res.* 4:422–25
122. Signer, E., Murphy, G. M., Edkins, S., Anderson, C. M. 1974. Role of bile salts in fat malabsorption in premature infants. *Arch. Dis. Child.* 49:174–77
123. Sinclair, J. C., Driscoll, J. M., Heird, W. C., Winters, R. W. 1970. Supportive management of the sick neonate: parenteral calories, water and electrolytes. *Pediatr. Clin. North Am.* 17:863–90
124. Slonim, A. E., Borum, P. R., Tanaka, K. 1981. Dietary-dependent carnitine deficiency as a cause of non-ketotic hypoglycemia in an infant. *J. Pediatr.* 99:551–53
125. Smales, O. R. C. 1978. Simple method for measuring oxygen consumption in babies. *Arch. Dis. Child.* 53:53–57
126. Speer, M. E., Blifield, C., Rudolph, A. J. 1984. Intraventricular hemorrhage and vitamin E in the very low birthweight infant: evidence for efficacy of early intramuscular vitamin E administration. *Pediatrics* 74:1107–12
127. Stearns, G. 1931. The significance of the retention ratio of calcium: phosphorus in infants and in children. *Am. J. Dis. Child.* 42:749–55
128. Steichen, J. J., Gratton, T. L., Tsang, R. C. 1980. Osteopenia of prematurity: the cause and possible treatment. *J. Pediatr.* 96:528–34
129. Stevens, D., Burman, D., Strelling, M. K., Morris, A. 1979. Folic acid supplementation in low birthweight infants. *Pediatrics* 64:333–36
130. Strelling, M. K., Blackledge, D. G., Goodall, H. B. 1979. Diagnosis and management of folate deficiency in low-birth-weight infants. *Arch. Dis. Child.* 54:271–75
131. Sulyok, E., Nemeth, M., Tenyi, I., Csaba, I., Gyori, E., et al. 1979. Postnatal development of renin-angiotensin-aldosterone sustem, RAAS, in relation to electrolyte balance in premature infants. *Pediatr. Res.* 13:817–20
132. Sulyok, E., Varga, F., Gyory, E., Jobst, K., Csaba, I. F. 1979. Postnatal development of renal sodium handling in premature infants. *J. Pediatr.* 95:787–92
133. Svenningson, N. W. 1974. Renal acid base titration studies in infants with and without metabolic acidosis in the post neonatal period. *Pediatr. Res.* 8:659–72
134. Svenningson, N. W., Lindquist, B. 1973. Incidence of metabolic acidosis in term, preterm and small for gestational age infants in relation to dietary protein intake. *Acta Paediatr. Scand.* 62:1–10
135. Svenningson, N. W., Lindroth, M., Lindquist, B. 1982. Growth in relation to protein intake of low birth weight infants. *Early Hum. Devel.* 6:47–58
136. Tantibhedyangkul, P., Hashim, S. 1971. Clinical and physiological aspects of medium-chain triglycerides. *Bull. NY Acad. Med.* 47:17–30
137. Tidwell, H. C., Holt, L. E., Farrow, H. L., Neale, S. 1935. Studies in fat metabolism. *J. Pediatr.* 6:481–99
138. Tsang, R. C., Donovan, E. F., Steichen, J. J. 1976. Calcium physiology and pathology in the neonate. *Pediatr. Clin. North Am.* 23:611–26
139. Tyson, J., Lasky, R., Mize, C., White, R. 1981. Growth and development of infants less than 1500 g fed bank human milk or premature formula. *Pediatr. Res.* 15:549
140. Valman, H. B., Aitkens, R., David-Reed, Z., Garrow, J. S. 1974. Retention of nitrogen, fat and calories in infants of low birthweight on conventional and high volume feeds. *Br. Med. J.* 2:319–20
141. Watkins, J. B., Järvenpää, A.-L., Szczepanik, P., Klein, P. D., Räihä, N. C. R., et al. 1983. Feeding the low birthweight infant: Effects of taurine, cholesterol and human milk on bile acid kinetics. *Gastroenterology* 85:793–800
142. Watkins, J. B., Szczepanik, P., Gould, J. B., Klein, P., Lester, R. 1975. Bile salt metabolism in the human premature infant. *Gastroenterology* 69:706–10
143. Widdowson, E. M. 1974. Nutrition. In *Scientific Foundations of Paediatrics,* ed. J. A. Davis, J. Dobbing, I:44–55. London: Heinemann
144. Widdowson, E. M. 1982. Importance of nutrition in development with special reference to feeding low birth weight infants. See Ref. 118, pp. 4–11

145. Williams, M. L., Shott, R. J., O'Neal, P. L., Oski, F. A. 1975. Role of dietary iron and fat on vitamin E deficiency anemia in infancy. *N. Engl. J. Med.* 292:887–90
146. Williamson, S., Finucane, E., Ellis, H., Gamsu, H. R. 1978. Effect of heat treatment of human milk on absorption of nitrogen, fat, sodium, calcium and phosphorus by preterm infants. *Arch. Dis. Child.* 53:555–60
147. Young, V. R. 1981. Protein-energy interrelationships in the new-born: a brief consideration of some basic aspects. In *Textbook of Gastroenterology and Nutrition in Infancy*, ed. E. Lebenthal, I:257–63. New York: Raven
148. Ziegler, E. E. 1986. Protein requirements of preterm infants. In *Energy and Protein Needs during Infancy*, ed. S. J. Fomon, W. C. Heird, pp. 69–85. Orlando, Fl: Academic
149. Ziegler, E. E., Biga, R. L., Fomon, S. J. 1981. Nutritional requirements of premature infants. In *Pediatric Nutrition*, ed. R. M. Susskind, pp. 29–39. New York: Raven
150. Ziegler, E. E., O'Donnell, A., Nelson, S. E., Fomon, S. J. 1976. Body composition of the reference fetus. *Growth* 40:329–41
151. Zoppi, G., Andreotti, G., Pajo-Ferrara, F., Njai, D. M., Gaburro, D. 1972. Exocrine pancreatic function in premature and full-term neonates. *Pediatr. Res.* 6:880–84