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Malnutrition in very low birth-weight, pre-term infants

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When a very low birth-weight, pre-term infant is compared with a foetus of equivalent gestational age in utero it becomes apparent that he is suffering from malnutrition, and is at times close to death from starvation. There is evidence for this from a variety of sources and it is my purpose to present some of this evidence and to consider the problems we have encountered with pre-term babies while trying to improve their nutrition.

When, at birth, the umbilical cord is cut, very low birth-weight, pre-term infants face a period of complete starvation. This period is generally very short but if there is any impediment to oral feeding—and there frequently is—then they may have to rely on an intravenous dextrose drip for a number of days. Table 1 gives the survival time in days for premature and full-term infants compared with an adult (Heird, Driscoll, Schullinger, Grebin & Winters, 1972). These values are based on the estimated energy reserves of these infants and their rate of energy expenditure, and illustrate the urgent need to introduce adequate nutrition as soon after birth as possible. Metabolic balance studies (Nicolopoulos & Smith, 1961; Auld, Bhanganada & Mehta, 1966) performed during the first 48 h of life have demonstrated negative nitrogen balance which, though minimized by a dextrose infusion (100 g/l), may nevertheless be equivalent to a loss of 3·5% of body protein in the first 48 h of life. Such a situation may be innocuous for a full-term infant provided with adequate body stores, but may be very damaging for a low birth-weight infant, who should be embarking on a rapid phase of exponential growth at a time when his body stores are trivial. In experimental animals, malnutrition at such a time permanently reduces the brain in size and cell number and this effect cannot be reversed by a period of liberal feeding later on (Elliott & Knight, 1972). Such drastic

Table 1. *Calculated survival times (d)* for premature and full-term infants, and adults, with intakes of water only or dextrose solution*

	Water only	Dextrose solution†
Small premature infant	4	11
Large premature infant	12	30
Full-term infant	35	80
Adult	90	350

*From Heird, Driscoll, Schullinger, Grebin & Winters (1972).
†100 g dextrose/l; 75 ml/kg body-wt per d for infants, 3 l/d for adults.

changes have yet to be demonstrated in low birth-weight infants but the incidence of mental handicap, though diminishing, is still unacceptably high, and it is possible that malnutrition at this time may have an adverse effect on subsequent intellectual development.

Fig. 1 shows the intrauterine growth of the human foetus obtained from the birth weights of live-born infants of different gestational age. Between 24 and 36 weeks gestation, growth in utero is exponential and there is surprisingly little difference between the two sets of results shown. The specific growth rate between 24 and 36 weeks gestation is 14·4 g/kg per d. Fig. 2 compares the measured growth velocity of two groups of infants weighing less than 1·5 kg at birth with the intrauterine growth velocity curve derived from the values in Fig. 1. It shows the severe weight loss that occurs immediately after birth, and that only rarely did these infants equal or exceed intrauterine growth rates in the first 40–50 d of life. This indicates a substantial degree of malnutrition persisting well beyond the immediate postnatal period. Weight gain, however, gives only the sum of the increments of the different components of body growth, and one can obtain from this no information about the quality of growth. Obviously, if the postnatal growth of the low birth-weight infant both quantitatively and qualitatively resembled the growth of the foetus of equivalent gestational age in utero, we would be satisfied with his standard of nutrition. But by considering the individual components of foetal

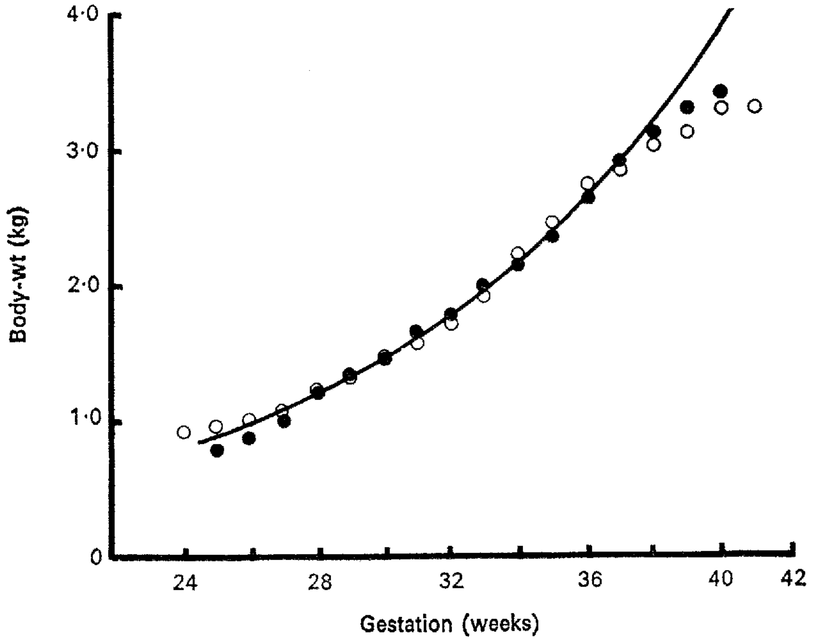

Fig. 1. Comparison of two intrauterine growth curves obtained from infants born at sea level (Kloosterman, 1970) and at 1 mile above sea level (Lubchenco, Hansman, Dressler & Boyd, 1963). The growth of the foetus between 24 and 36 weeks gestation is similar in both places and is exponential in character: $y=y_0.e^{kt}$; $y_0=70\cdot5$ g, $k=0\cdot0144$/d. ○, Lubchenco *et al.* (1963); ●, Kloosterman (1970).

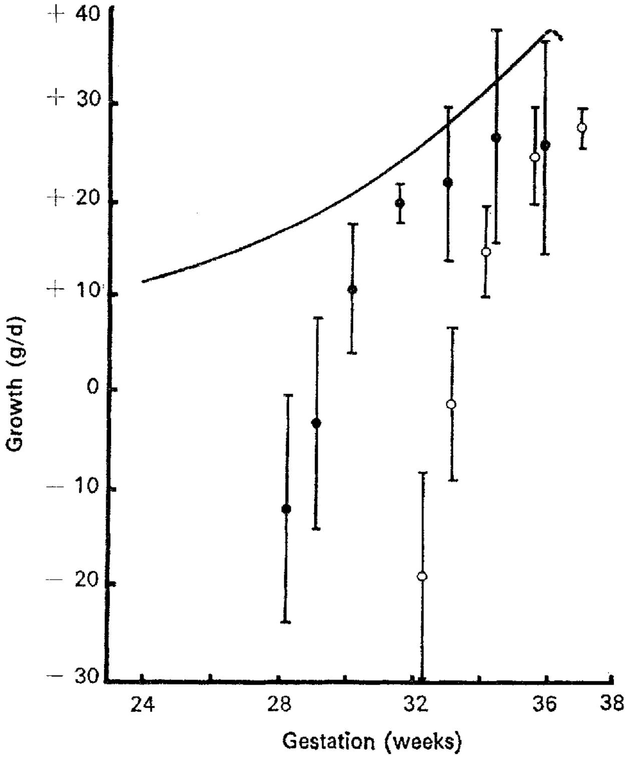

Fig. 2. Comparison of postnatal growth of two groups of infants born at University College Hospital in 1969, who weighed less than 1·5 kg at birth, with an intrauterine growth velocity curve obtained from the data in Fig. 1. ○, modal gestation 32 weeks; ●, modal gestation 28 weeks; vertical bars indicate the standard deviation.

growth it is possible to show that the postnatal growth of the low birth-weight infant differs strikingly in some respects from the growth of the foetus in utero. Fig. 3 gives the results of all the analyses of foetal bodies for N performed over the last 80 years (Kelly, Sloan, Hoffman & Saunders, 1950; Widdowson & Dickerson, 1964). Between 16 and 40 weeks gestation the accumulation of this element can be described by a simple exponential equation, as can the accumulation of calcium and all the other substances that have so far been analysed in foetal bodies. From these body-composition data it is easy to calculate rates for all the substances studied and these are shown in Fig. 4. These rates provide a valuable tool for determining the nutritional requirements of low birth-weight infants and for evaluating their postnatal growth. It is also worth noting that they are the best estimate that we have of the net flux of these substances across the placenta from mother to foetus, and it will be interesting to see how they compare with values obtained by direct measurement when this becomes possible.

In our laboratories, Ca and fat absorption in ten low birth-weight infants of 28–31 weeks gestation and of birth weight 1110–1390 g have been studied by metabolic balance techniques continuously for periods of 20–60 d. We undertook this investigation because it was apparent from the amount of Ca in breast milk and SMA

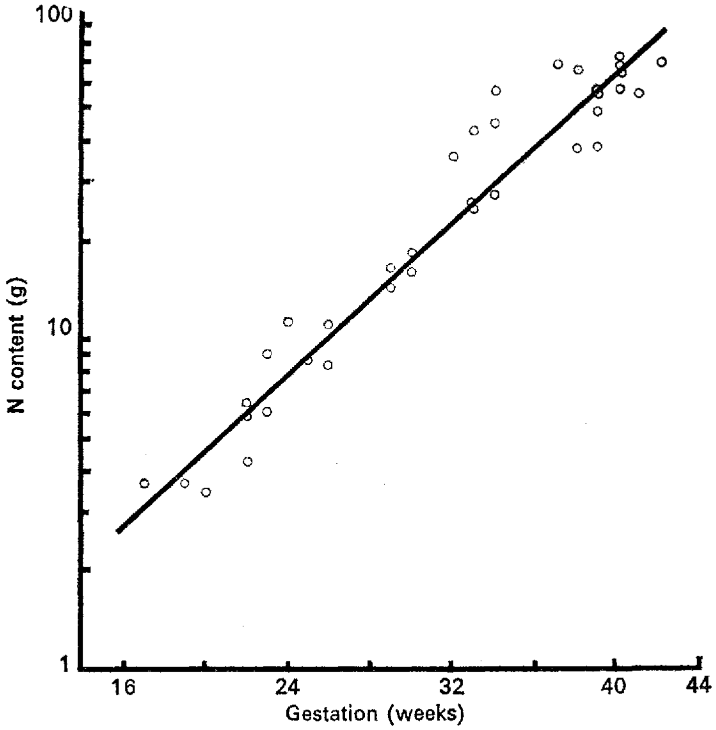

Fig. 3. Results of analyses of foetal bodies for nitrogen at different periods of gestation, showing that the accumulation of N between 16 and 40 weeks gestation is exponential in character: $y = y_0.e^{kt}$; $y_0 = 0{\cdot}346$ g, $k = 0{\cdot}0186/d$ ($r = 0{\cdot}97$).

(John Wyeth Ltd, Maidenhead, Berks) that these milks could never meet the requirements of low birth-weight infants which had been calculated from the data on body composition. The fat balances were performed to see if altering the fat content of the milk would materially influence Ca absorption. An example of such a balance is shown in Fig. 5. From such values it is possible to compare the amount of Ca retained over the whole balance period with the amount that would have been accumulated by a foetus of equivalent gestational age in utero. The results of ten such balances are summarized in Fig. 6. The infants given the cow's milk preparations retained only one-third of their estimated requirement and those given breast milk and SMA retained less than one-fifth of their estimated requirement. Since metabolic balance studies tend to over-estimate body retentions (Wallace, 1959), one can safely assume that these data do not exaggerate the actual situation and they explain the clinical observation that the skull bones of these infants become remarkably soft after a few weeks and that their bones are unusually translucent on X-ray. Since this state of affairs exists for Ca it seems likely that it exists for other substances as well and further deficits may be revealed as systematic investigations of this sort are pursued. The results of the fat balances are summarized in Table 2. They confirm the severe degree of fat malabsorption that occurs when these infants are given fat other than breast-milk fat, a fact that has been known since the work of

Table 2. *Results of fat balance tests in ten low birth-weight infants given different milks*

Fat source	% Absorption	
	Mean	Range
Full-cream cow's milk	48	36–61
Half-skimmed cow's milk	60	46–73
SMA*	60	33–77
Breast milk	85	69–99

*John Wyeth Ltd, Maidenhead, Berks.

Tidwell, Holt, Farrow & Neal (1935). Many low birth-weight infants in this country, however, are still fed on full-cream cow's milk and as a result they may be expected to lose about 125 kJ (30 kcal)/kg per d in their stools, and also presumably a proportionate amount of fat-soluble vitamins. No significant effect of fat malabsorption

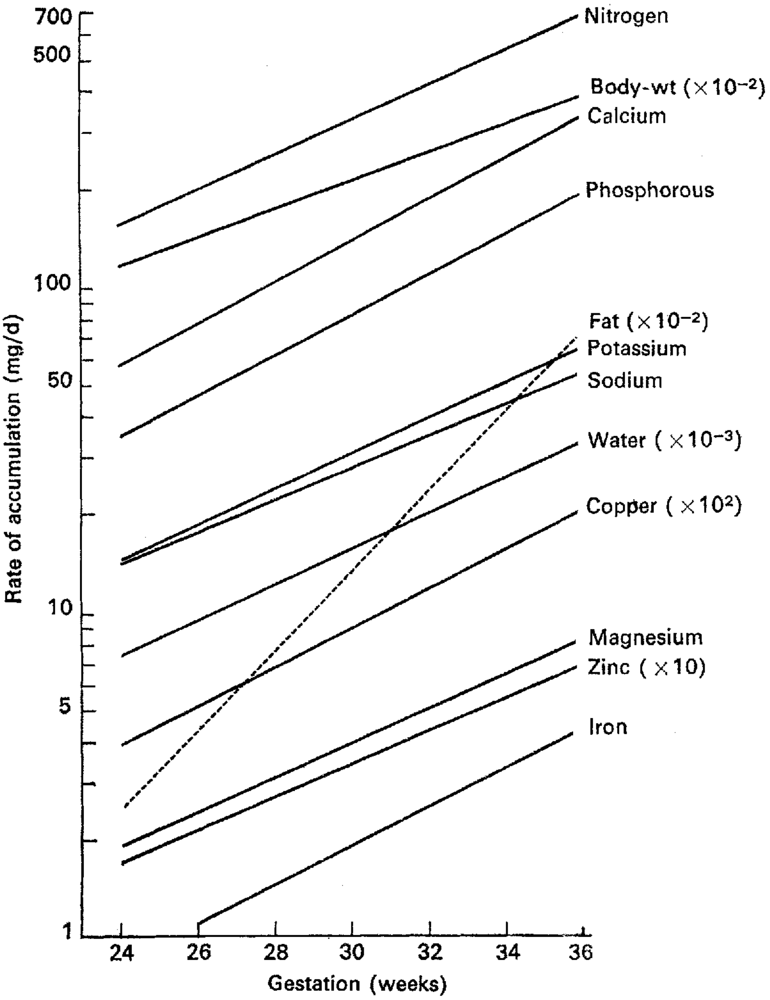

Fig. 4. Rates of accumulation of different substances by the human foetus in utero between 24 and 36 weeks gestation.

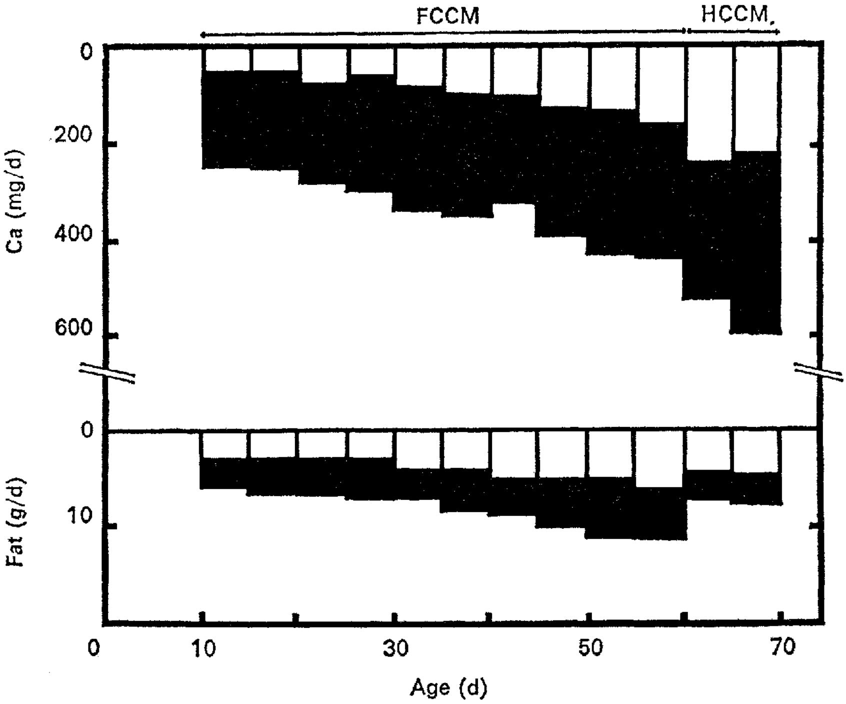

Fig. 5. Example of serial 5 d metabolic balances performed on a low birth-weight infant (gestation 28 weeks, birth weight 1200 g) between the 10th and the 70th day of life. The total height of each column represents intake of calcium or fat. ■, Faecal and urinary excretion of Ca, or the faecal excretion of fat; □, the retention of Ca, or the absorption of fat. FCCM, fed on full-cream cow's milk; HCCM, fed on half-skimmed cow's milk.

on Ca absorption could be demonstrated in this study and the principle determinant of the Ca absorbed was the postnatal age of the infant, and the amount of Ca in the diet.

I will now briefly consider some problems associated with total intravenous nutrition. In order to avoid having to rely so heavily on oral feeding in the immediate postnatal period, we have adapted the techniques of intravenous nutrition, pioneered by Wilmore & Dudrick (1968), to low birth-weight infants. It involves the continuous infusion of a hypertonic solution of amino acids, glucose, minerals and vitamins into the right atrium of the heart, through a silicone-rubber catheter. The technique has been described in detail elsewhere (Shaw, 1973). One concern of fundamental importance is the composition of the infusate. If substances are infused at a rate that exceeds their rate of utilization, dangerously high blood levels may result. Because of this we have adopted the prudent course of limiting the intake of certain nutrients, principally the amino acids and Ca. Table 3 compares the daily allowances of some substances with their rate of accumulation in utero. The amino acid allowance is 2·5 g/kg body-weight per d (320 mg N/kg per d). There is a modest surplus of sodium, potassium and magnesium but the allowance of Ca is only one-third of the estimated requirement. This amount of Ca is sufficient to maintain normal levels of serum Ca and to allow skeletal mineralization to proceed at a rate

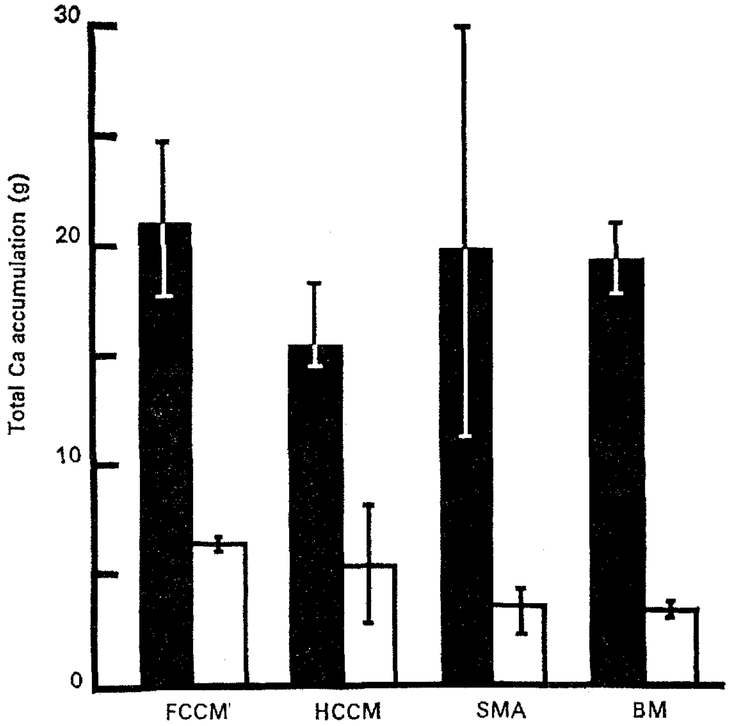

Fig. 6. Summary of the results of ten metabolic balances performed on low birth-weight pre-term infants weighing less than 1·5 kg at birth. □, Mean calcium retained over the whole period studied for the different groups of infants; ■, Ca that would have been accumulated by a foetus of equivalent gestation age in utero. FCCM, full-cream cow's milk; HCCM, half-skimmed cow's milk; SMA, proprietary artificial milk (John Wyeth Ltd, Maidenhead, Berks.); BM, breast milk. Vertical bars indicate the range.

Table 3. *Comparison of daily intravenous (IV) allowances of some substances with their rates of accumulation by the human foetus in utero (mg/kg body-wt per d)*

	IV allowance	Rate of accumulation in utero
Nitrogen	320	319–350
Sodium	92	23–30
Potassium	101	29
Magnesium	7	4
Calcium	45	116–152
Phosphorus	23	70–86

comparable to that occurring in orally fed infants. Infusing much larger amounts may result in metabolic acidosis. The incorporation of Ca into bone mineral can be described by the following equation:

$$10\,Ca^{2+} + 4{\cdot}8\,HPO_4{}^{2-} + 1{\cdot}2\,H_2PO^-{}_4 + 2\,H_2O \rightleftharpoons (Ca_3(PO_4)_2)_3 .\,Ca(OH)_2 + 9{\cdot}2\,H^+,$$

and it has been calculated that for each g of Ca laid down in the skeleton, 20 mmol of hydrogen ions are released into the extracellular fluid and would have to be excreted in the urine (Kildeberg, 1968). Infusing the full requirements of these infants would increase the endogenous H^+ production by an estimated 2–3 mmol/kg body-weight per d, and might be dangerous for those infants who are ill and whose acid-base homeostasis is often already compromised.

For the administration of trace minerals, most workers have relied upon blood and plasma transfusions. Table 4 compares the allowances of trace minerals recommended by various authors with the rate of accumulation in utero; the difference is very striking. Copper is largely stored in the liver (Widdowson & Dickerson, 1964) and may not be required in such large amounts for normal postnatal growth, but Cu deficiency has been reported in a premature infant on long-term parenteral nutrition (Karpel & Peden, 1972), and when we begin to study trace mineral metabolism in more detail it is likely we shall find evidence of further deficiencies.

Table 4. *Comparison of suggested allowances of trace elements with their rate of accumulation by the human foetus in utero (mg/kg body-wt per d)*

	Wilmore *et al.* (1969)*	Filler *et al.* (1969)†	Daily increments in utero
Iron	0·020	0·008	1·6–2·0
Copper	0·022	0·006	0·078–0·092
Zinc	0·040	0·007	0·272–0·337
Manganese	0·040	0·0006	—
Cobalt	0·014	0·002	—
Iodine	0·015	0·0004	—

*Wilmore, Groff, Bishop & Dudrick (1969).
†Filler, Eraklis, Rubin & Das (1969).

We have only encountered a severe nutritional deficiency in one case: she was an infant who was maintained on total parenteral nutrition until the 39th day of life, because each attempt to introduce oral feeding resulted in severe apnoea. During her period of intravenous feeding her specific growth rate was 12·5 g/kg per d, which was 15% below the intrauterine rate of 14·4 g/kg per d. Between day 35 and 39 she developed a severe exfoliative skin condition. This might have been due to a number of deficiencies, but because she had been maintained on a virtually fat-free diet and because her total body reserves of fat at birth were probably about 5–10 g, we think it was due to essential fatty acid deficiency. The condition cleared rapidly when breast milk was introduced. We now routinely supply essential fatty acid as ethyl linoleate orally or as Intra-Lipid (Paines & Byrne Ltd, Greenford, Middx) intravenously. It is clearly important to presume that such infants possess no stores of nutrients to subsidize their exceptionally rapid growth rate and we should attempt in future to provide everything they require in the infusion.

Conclusions

There have been tremendous advances in the care of low birth-weight infants in recent years. The survival rate is rising and the incidence of mental handicap is falling. Nevertheless, when the low birth-weight infant is judged by the standard of the normally grown foetus in utero he appears to be suffering from malnutrition.

If we can deal effectively with this problem we may be able further to improve the prognosis of these infants.

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