The goal of feeding regimens for low-birth-weight infants is to obtain a prompt postnatal resumption of growth to a rate approximating intrauterine growth because this is believed to provide the best possible conditions for subsequent normal development. This statement reviews current opinion and practices as well as earlier reviews1-5 of the feeding of the low-birth-weight infant.

Caloric Requirement

The basal metabolic rate of low-birth-weight infants is lower than that of full-term infants during the first week of life, but it reaches and exceeds that of the full-term infant by the second week. Daily caloric requirements reach 50 to 100 kcal/kg by the end of the first week of life and usually increase to 110 to 150 kcal/kg in subsequent active growth.

A partition of the daily minimum energy requirements is shown in Table 1.6 There are considerable variations from these average values, depending on both biological and environmental factors. Infants who are small for gestational age tend to have a higher basal metabolic rate than do premature infants of the same weight.2 The degree of physical activity appears to be a characteristic of the individual infant. Environmental factors may have a greater influence than biological variation in determining the total caloric requirements. The maximal response to cold stress can increase the resting rate of heat production up to 2½ times.6 Calories expended for specific dynamic action and for fecal losses are dependent on the composition of the milk or formula fed, as well as on individual variations in absorption of nutrients, particularly fat.

In practice, caloric intakes of 110 to 150 kcal/kg/day enable most low-birth-weight infants to achieve satisfactory rates of growth. If infants fail to gain satisfactorily, a higher caloric intake may be offered.

Caloric Density of the Formula—Water Requirement

Although human milk or formulas that provide 67 kcal/dl (20 kcal/oz) are recommended for term infants, more concentrated formulas are often used for low-birth-weight infants to facilitate increased caloric intakes in infants with limited gastric capacity. Several studies have shown that feeding low-birth-weight infants formulas with higher caloric densities results in faster rates of growth.4-13 Some nurseries now feed formulas of 81 kcal/dl (24 kcal/oz) and in some instances 91 kcal/dl (27 kcal/oz). The 81-kcal/dl concentration supplies most of the water required by the infant (150 ml/kg)14 and provides 120 kcal/kg.

The increased protein and mineral levels in these more concentrated formulas increase the renal solute load. With the limited capability of the immature kidney for concentrating urine, sufficient water may not be supplied if the formula is too concentrated. Infants consuming less than a normal volume of formula are particularly vulnerable because, under constant conditions of extrarenal water loss, the lower the formula intake the greater the proportion of water required for renal excretion.15 Infants whose water balance is threatened (e.g., infants exposed to heat, phototherapy, or cold stress, and those with infection or diarrhea) should have formulas of low renal solute load and should not be fed formulas of caloric density greater than 81 kcal/dl.
TABLE I

<table>
<thead>
<tr>
<th>Item</th>
<th>kcal/kg/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting caloric expenditure</td>
<td>50</td>
</tr>
<tr>
<td>Intermittent activity</td>
<td>15</td>
</tr>
<tr>
<td>Occasional cold stress</td>
<td>10</td>
</tr>
<tr>
<td>Specific dynamic action</td>
<td>8</td>
</tr>
<tr>
<td>Fecal loss of calories</td>
<td>12</td>
</tr>
<tr>
<td>Growth allowance</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
</tr>
</tbody>
</table>

*Data from Sinclair et al.

kcal/dl (24 kcal/oz). Preterm infants excrete sodium well, and late metabolic acidosis seen in low-birth-weight infants may be related to low mineral intake. Lactic acid-containing formulas should not be fed because they may produce acidosis.

Alternate Feeding Procedures

When conventional feedings every few hours do not result in the attainment of a adequate nutrient intake, alternate methods of feeding such as continuous nasogastric drip, intravenous (IV) administration of nutrients supplemented by oral feeding, and total IV alimentation may be tried. However, the hazards and complexities of IV administration preclude its use in routine practice. Parenteral administration of (1) 20% glucose and 2.5% amino acid solution; (2) 12% glucose with 2.5% amino acids and 10% soybean oil emulsion; and (3) 12% glucose, 2.5% amino acids, and 1% alcohol in a volume of 125 to 150 ml/kg/day all provided positive nitrogen balance. Glucagon levels were lower and growth hormone levels higher in infants given the fat-free mixtures. Parenteral feedings appear to increase water retention.

In a controlled study of the feeding of low-birth-weight infants by continuous nasogastric drip, satisfactory growth and clinical progress were reported with the feeding of human milk and a simulated human milk formula (67 kcal/dl). Feeding was started at the fourth hour of life at the rate of 60 ml/kg/day and increased to 300 ml/kg/day (200 kcal/kg/day) by the ninth day. In practice, the latter intake is difficult to achieve.

Although early administration of fluids is generally considered beneficial to prevent dehydration, excessive weight loss, hypoglycemia, and excessive jaundice, use of 10% glucose parenterally may cause reactive hypoglycemia when the IV fluid is discontinued or hyperglycemia and hyperosmolality, which may be difficult to control. Serum glucose levels should be regularly monitored and glucose infusion rates lowered to 0.4 g/kg/hr, or less if the serum glucose level exceeds 125 mg/dl. The first feeding should be distilled water to avoid excessive damage to the lungs if vomiting occurs.

Protein Requirement

The optimal protein intake for the low-birthweight infant has not been precisely defined; however, it is between 2.25 and 5 g/kg/day for cow’s milk formulas. Human milk contains about 1.1 g of protein or less per deciliter, or 1.65 g/100 kcal. When fed at intakes of 120 kcal/kg/day, human milk supplies almost 2 g of protein per kilogram per day. The feeding of human milk to premature infants was the preferred practice until 25 years ago when Gordon et al. demonstrated that premature infants gained more weight and retained more nitrogen when fed cow’s milk formulas of higher protein content. Subsequent reports have confirmed this, but in some reports the increased weight gains with the higher protein cow’s milk formulas were attributed in part to increased electrolyte intake and subsequent water retention. However, Babson and Bramhall found no increase in weight gain when only minerals were added to formula providing 1.8 g of protein per 100 kcal.

In studies designed to determine the protein requirement of low-birth-weight infants, protein has been given at levels ranging from 1.7 to 9 g/kg/day. The feedings have consisted of human milk and cow’s milk formulas, with the protein content varied by dilution with carbohydrate or by the addition of casein or deionized milk or whey. Because of the many variables in the formulas, including types and levels of fat and carbohydrate and levels of vitamins and minerals, it is difficult to assess the nutritional adequacy of the various formulas used in the studies or to attribute the findings solely to dietary protein level.

Infants fed 1.7 to 2.25 g of protein per kilogram per day either from human milk or a cow’s milk formula did not increase in weight or length as rapidly as those fed higher intakes, and some developed low levels of serum proteins.

The feeding of relatively high levels of protein (6 to 9 g/kg/day) was associated with hyperpyrexia and lethargy, high BUN levels, diarrhea, high urinary excretion of phenols, clinical edema, late metabolic acidosis, and

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[Link to original publication]
increased mortality.39 The weight gains obtained with the feeding of the high intakes of protein did not exceed those obtained by the feeding of moderate levels.36,39,40 Elevated plasma amino acid levels in low-birth-weight infants fed high-protein formulas suggest that the high protein intake may present an amino acid load that exceeds the metabolizing capability of the immature enzyme systems. Elevated levels of plasma tyrosine and phenylalanine are not uncommon, a finding related to late maturing of p-hydroxyphenylpyruvic oxidase.32,44 High plasma levels of proline and methionine are also associated with high protein intake.45

The amino acid composition of formulas for premature infants deserves special attention. Low-birth-weight infants require some amino acids that are not essential for the term infant. In the balance studies of Snyderman,46 the removal of either cystine or tyrosine from the diet resulted in an impairment of growth and nitrogen retention, and a depression of the level of that particular amino acid in the plasma. Infants requiring cystine also failed to show an increase in plasma cystine level after a methionine load, a finding in accord with the lack of cystathionase in the livers of fetuses and premature infants reported by Sturman el al.47,48 The high levels of cystathionine in the plasma49 and urine50 of premature infants fed high-protein formulas also suggest that conversion of methionine to cystine is not efficient until some time after birth.

Raiha et al.51,52 fed low-birth-weight infants five formulas, including pooled breast milk. The breast milk supplied approximately 1.7 g of protein per kilogram per day, two formulas supplied 2.25 g of protein per kilogram per day, and two formulas supplied 4.50 g/kg/day. One formula at each protein level had a 60:40 ratio of whey/casein proteins, and the other two had an 18:82 ratio of whey/casein proteins. All infants grew equally well when fed 117 kcal/kg/day; statistically, the breast-fed group gained at a slightly lower rate. Significant differences in plasma amino acid and ammonia levels were noted. The lower ammonia, tyrosine, and phenylalanine levels were found in infants fed whey/casein of 60:40, and the highest levels were in those fed the high-protein formula with casein predominant. Those fed the high-protein, casein-predominant formula developed late metabolic acidosis. Serum protein levels were lowest in infants fed breast milk.

A major difference between the formulas was the higher content of cystine in the breast milk and high-whey protein formula. In addition, the breast milk had higher taurine levels than the other formulas. This suggestive study requires confirmation.

A review of the literature led Cox and Filer53 to conclude that, with an adequate caloric intake, most low-birth-weight infants will grow satisfactorily on cow's milk formulas supplying 2.25 to 5.0 g/kg/day of cow's milk protein. Fomon and co-workers estimated from hypothetical considerations that the premature infant requires 3.0 g/kg/day or 2.54 g of protein per 100 kcal, assuming an intake of 120 kcal/kg/day.54

If further studies confirm these findings, consideration of protein quality along the lines discussed here may be important in defining the optimal protein quantity for low-birth-weight infants. With adequate intakes, human milk may be the superior feeding for low-birth-weight infants.

**Fat**

The ability of low-birth-weight infants to absorb fat, particularly saturated fat such as butterfat, is relatively poor.55-58 This limitation is associated with liver immaturity and decreased bile salt synthesis,59 and it is found to a lesser extent in full-term infants during the first few weeks of life.60,61 When palmitic acid—a long-chain saturated fatty acid—is present in fat, its absorption depends on its position in the triglyceride molecule.62,63 Early recommendations for the feeding of low-birth-weight infants included the feeding of low-fat formulas.64,65 However, the recognition that the vegetable oils were much better absorbed than butterfat and other saturated fats led to use in formulas of vegetable oils, or blends of vegetable oils and animal fats. These are absorbed well, as is human milk fat.66

Including medium chain triglycerides as part of the fat in the formula has been shown to improve fat absorption in low-birth-weight infants.67-70 Medium-chain triglycerides have also been shown to increase weight gain70 and to enhance calcium absorption69 and nitrogen retention.68

Fat in human milk supplies a major proportion of the caloric content. Formulas with 40% to 50% of calories from fat are recommended for the feeding of low-birth-weight infants because formulas of a lower fat content may contain higher levels of protein which increase renal solute load.

To meet the normal infant's requirement for essential fatty acids, it is recommended71 that infant feedings supply 3% of the total calories in the form of linoleic acid or 300 mg of linoleic acid per 100 kcal. Proprietary infant formulas with
their high content of unsaturated fat supply a generous allowance of linoleic acid.

**Carbohydrate**

The utilization of carbohydrate by the low-birth-weight infant differs slightly from that of the full-term infant. Intestinal disaccharidases develop early in fetal life; maltase and sucrase reach mature values by the sixth to eighth month, and lactase reaches it at term. These data suggest that the low-birth-weight infant can adequately digest disaccharides, although there is some evidence that lactose digestion may not be fully efficient for the first few days of life. Low-birth-weight infants develop satisfactorily when fed formulas in which the lactose of the milk has been augmented with sucrose and when fed lactose-free formulas (i.e., formulas based on soy isolates, meat or protein hydrolysates and containing sucrose and/or dextrose, maltose, and dextrins as the carbohydrate). Lactose, sucrose, and maltose oral tolerance tests conducted on 2-week-old, low-birth-weight infants previously fed formulas containing either lactose or sucrose as the sole carbohydrate revealed no significant differences in the utilization of these three disaccharides, despite the presence or absence of the substrate sugar in the diet for the two weeks preceding the test. In another study of dietary sugars, infants grew equally well on soy-isolate formulas containing sucrose or dextrose, and a slightly lesser rate with lactose.

Lactose, as the natural sugar of human milk, has been the usual choice for addition to a cow’s milk formula to increase the carbohydrate content up to that of human milk. However, a recent study with cow’s milk formulas found that the addition of sucrose rather than lactose to the milk base resulted in a lower incidence of diarrhea and metabolic acidosis, which appears to support the findings of Boellner et al. Thus, the slight delay in the maturation of intestinal lactase may be of physiological consequence in some infants. Usually lactose enhances calcium absorption in the small intestine and reduces the incidence of constipation.

**Minerals**

Two thirds of the mineral content of the body of the full-term infant is deposited during the last two months of gestation. The amounts of minerals the preterm infant must retain from the diet to achieve the mineral composition of the full-term infant might be estimated from the differences in mineral contents of the bodies of premature and term infants. Body composition data can provide a rough estimate, at best, of the increase in minerals that the low-birth-weight infant would have accrued had he remained in utero.

Because infants with low stores may retain 50% to 70% of the nutrients they are fed, the levels of nutrients supplied by formula must be 1.3 to 2 times those required to meet their needs. It appears that minimal levels in formula designed for full-term infants could probably satisfy requirements of the low-birth-weight infant for sodium, potassium, chloride, and zinc; would probably be borderline in copper; and would probably be deficient in iron, calcium, and phosphorus. Based on these calculations, some changes in mineral composition might be made in formulas intended for use by premature infants to achieve a mineral retention equivalent to that in utero.

**Calcium and Phosphorus**

Balance studies and roentgenographic findings in low-birth-weight infants suggest that formulas made from cow’s milk with higher calcium and phosphorus levels provide greater retention of calcium and phosphorus and increased mineralization of the skeleton than does human milk. Although earlier studies suggested that the low phosphorus content of human milk was the limiting factor in skeleton mineralization, work by Day et al. suggests that the undermineralization of bone observed in premature infants fed human milk may also be caused by an inadequate calcium intake. In the Day et al. study of low-birth-weight infants (less than 1,300 g), infants fed a proprietary formula supplemented with calcium lactate (total calcium, 154 mg/100 kcal) showed a better-defined bone texture and wider cortices than infants fed unsupplemented formula containing 63 mg of calcium per 100 kcal. Fomon et al. have calculated that premature infants require 132 mg of calcium per 100 kcal.

Infant formulas fed to low-birth-weight infants in the United States (Table II) contain higher levels of calcium and phosphorus than those supplied by human milk, but they are generally lower than the level used by Day et al. or that recommended by Fomon et al. In clinical studies in which low-birth-weight infants were fed current proprietary formulas or earlier formulas of comparable calcium and phosphorus content, no apparent abnormalities of calcium/phosphorus metabolism were noted, offer-
### TABLE II
**Nutrient Composition of Human Milk and Proprietary Infant Formulas and Recommended Levels for Full-Term and Low-Birth-Weight Infants**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Minimum Level Recommended†</th>
<th>Human Milk 100%</th>
<th>Enfamil</th>
<th>PM60/40</th>
<th>Premature Formula</th>
<th>Similac</th>
<th>SMA</th>
<th>Similac (13, 24, or 27 Calories/oz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, g</td>
<td>1.8‡</td>
<td>1.3-1.6</td>
<td>2.3</td>
<td>2.3</td>
<td>2.8</td>
<td>2.3</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Fat, g</td>
<td>3.3§</td>
<td>5</td>
<td>5.5</td>
<td>5.2</td>
<td>5.1</td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Carbohydrate, g</td>
<td>...</td>
<td>10.3</td>
<td>10.3</td>
<td>11.1</td>
<td>11.5</td>
<td>10.6</td>
<td>10.7</td>
<td>10.3</td>
</tr>
<tr>
<td>Ash, mg</td>
<td>...</td>
<td>300</td>
<td>530</td>
<td>320</td>
<td>680</td>
<td>530</td>
<td>370</td>
<td>580</td>
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<tr>
<td>Vitamin A, IU</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>370</td>
<td>250</td>
<td>370</td>
<td>370</td>
<td>370</td>
</tr>
<tr>
<td>Vitamin D, IU</td>
<td>40</td>
<td>3</td>
<td>63</td>
<td>60</td>
<td>63</td>
<td>60</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Vitamin E, IU</td>
<td>0.3(0.7)</td>
<td></td>
<td></td>
<td>0.3</td>
<td>1.9</td>
<td>2.2</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Vitamin K, µg</td>
<td>4</td>
<td>2</td>
<td>9</td>
<td>4</td>
<td>9</td>
<td>14</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>8</td>
<td>7.8</td>
<td>8.1</td>
<td>8.1</td>
<td>8.0</td>
<td>8.1</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Thiamin, µg</td>
<td>40</td>
<td>25</td>
<td>78</td>
<td>96</td>
<td>78</td>
<td>96</td>
<td>105</td>
<td>96</td>
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<tr>
<td>Riboflavin, µg</td>
<td>60</td>
<td>60</td>
<td>94</td>
<td>147</td>
<td>94</td>
<td>147</td>
<td>156</td>
<td>147</td>
</tr>
<tr>
<td>Niacin, µg</td>
<td>250</td>
<td>250</td>
<td>1,250</td>
<td>1,074</td>
<td>1,250</td>
<td>1,030</td>
<td>780</td>
<td>1,000</td>
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<tr>
<td>Vitamin B₆, µg</td>
<td>35†</td>
<td>15</td>
<td>63</td>
<td>49</td>
<td>63</td>
<td>60</td>
<td>63</td>
<td>60</td>
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<tr>
<td>Folic acid, µg</td>
<td>4</td>
<td>4</td>
<td>16</td>
<td>7.3</td>
<td>16</td>
<td>7.3</td>
<td>8</td>
<td>7.3</td>
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<tr>
<td>Pantothenic acid, µg</td>
<td>300</td>
<td>300</td>
<td>470</td>
<td>440</td>
<td>470</td>
<td>440</td>
<td>310</td>
<td>440</td>
</tr>
<tr>
<td>Vitamin B₁₂, µg</td>
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<td>0.15</td>
<td>0.3</td>
<td>0.22</td>
<td>0.3</td>
<td>0.22</td>
<td>0.16</td>
<td>0.22</td>
</tr>
<tr>
<td>Biotin, µg</td>
<td>1.5</td>
<td>1.0</td>
<td>2.5</td>
<td>1.7</td>
<td>2.5</td>
<td>1.5</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Inositol, mg</td>
<td>4</td>
<td>20</td>
<td>5</td>
<td>7.5</td>
<td>6</td>
<td>5.0</td>
<td>5.5</td>
<td>...</td>
</tr>
<tr>
<td>Choline, mg</td>
<td>7</td>
<td>13</td>
<td>7</td>
<td>18.8</td>
<td>7</td>
<td>15</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>50</td>
<td>50</td>
<td>80</td>
<td>60</td>
<td>156</td>
<td>75</td>
<td>66</td>
<td>102</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>25#</td>
<td>25</td>
<td>70</td>
<td>30</td>
<td>78</td>
<td>57</td>
<td>49</td>
<td>79</td>
</tr>
<tr>
<td>Magnesium, mg</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>0.15**</td>
<td>0.1</td>
<td>0.2††</td>
<td>0.4</td>
<td>0.2</td>
<td>Trace††</td>
<td>1.9</td>
<td>Trace††</td>
</tr>
<tr>
<td>Iodine, µg</td>
<td>5</td>
<td>4-9</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>15</td>
<td>10</td>
<td>15</td>
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<tr>
<td>Copper, µg</td>
<td>60</td>
<td>60</td>
<td>100</td>
<td>62</td>
<td>100</td>
<td>60</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>Zinc, µg</td>
<td>0.5</td>
<td>0.5</td>
<td>0.65</td>
<td>0.59</td>
<td>0.65</td>
<td>0.74</td>
<td>0.55</td>
<td>0.74</td>
</tr>
<tr>
<td>Manganese, µg</td>
<td>5</td>
<td>1.5</td>
<td>160</td>
<td>5</td>
<td>160</td>
<td>5</td>
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<td>5</td>
</tr>
<tr>
<td>Sodium mg</td>
<td>20#</td>
<td>24</td>
<td>42</td>
<td>23</td>
<td>40</td>
<td>32</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>mEq</td>
<td>0.9#</td>
<td>1.0</td>
<td>1.8</td>
<td>1.0</td>
<td>1.7</td>
<td>1.6</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Potassium mg</td>
<td>80</td>
<td>81</td>
<td>102</td>
<td>85</td>
<td>110</td>
<td>103</td>
<td>83</td>
<td>126</td>
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<tr>
<td>mEq</td>
<td>2.1</td>
<td>2.1</td>
<td>2.6</td>
<td>2.2</td>
<td>2.8</td>
<td>2.5</td>
<td>2.1</td>
<td>3.2</td>
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<td>Chloride mg</td>
<td>55</td>
<td>55</td>
<td>80</td>
<td>66</td>
<td>85</td>
<td>79</td>
<td>55</td>
<td>94</td>
</tr>
<tr>
<td>mEq</td>
<td>1.6</td>
<td>1.6</td>
<td>2.3</td>
<td>2.0</td>
<td>2.4</td>
<td>2.3</td>
<td>1.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Renal solute load, mOsm</td>
<td>...</td>
<td>11.3</td>
<td>16</td>
<td>14.3</td>
<td>18.1</td>
<td>16.2</td>
<td>13.6</td>
<td>18.4</td>
</tr>
</tbody>
</table>

*Per 100 kcal.
†Committee on Nutrition recommendations for formula for full-term infants per 100 kcal.
‡Committee on nutritional quality equivalent to casein.
§Including a minimum of 300 mg of essential fatty acids.
||Committee on Nutrition recommendation different for low-birth-weight infants; also 1.0 IU/g linoleic acid.
¶Minimum of 15 µg of vitamin B₆ per gram of protein.
#Some evidence for higher requirement for low-birth-weight infant.
**1.0 mg in iron-fortified formula.
††1.5 mg in iron-fortified formula.
‡‡Calculated by the method of Ziegler and Fomon.13
ing some assurance that current ranges of concentrations are not grossly inadequate for the feeding of low-birth-weight infants.

The hypocalcemia-hyperphosphatemia syndrome seen in normal term neonates fed undiluted cow's milk has been attributed to immature homeostatic control of serum phosphate. This suggests that formulas for low-birth-weight infants should have a calcium/phosphorus ratio approaching that of human milk (2.0:1), or at least between 1.1:1 and 2.0:1, as recommended for formulas fed to full-term infants.71

**Magnesium**

The recommended minimum requirement for magnesium in formula for the term infant was based on the amount present in human milk, 6 mg/100 kcal.71 Clinical experience suggests that this amount also suffices for the low-birth-weight infant. Average serum magnesium levels of the neonatal, low-birth-weight infant are similar to adult values.89 Low levels are not uncommon in the first few days of life, particularly in the small-for-gestational-age group, but they rise to adult values within days after feeding of conventional formulas.

Magnesium depletion has been observed in infants suffering from the gross malnutrition of kwashiorkor,91 and hypomagnesemia, as is true with hypocalcemia, may result from high phosphate feedings.92 But, there have been no reports of magnesium deficiency in healthy, low-birth-weight infants fed formulas of magnesium content equal to or in moderate excess over that in human milk. Low-birth-weight infants have been maintained for prolonged periods on IV feeding containing 2 mg of magnesium per 100 kcal.26 If the low-birth-weight infant can absorb 33% of the magnesium in the formula—a reasonable assumption—the 6 mg/100 kcal required in the formula would readily supply the 2 mg/100 kcal given intravenously.

**Iron**

The low-birth-weight infant is especially susceptible to the development of iron deficiency anemia because its stores of iron are much smaller than those of a full-term infant, and they are insufficient to last over a prolonged period when growth must be rapid. Erythrocyte and hemoglobin levels are high at birth; the hemoglobin iron released by destruction of old RBCs is salvaged and stored for future use. Active erythropoiesis resumes between 1 and 2 months of age, and rapidly decreases the size of the iron reserve. Without supplemental iron, the body stores of iron will be depleted sometime after 2 months of age rather than after 4 to 6 months of age, as in the normal, full-term infant.93 Orally administered iron is well absorbed.94

Although the greater need for iron by the low-birth-weight infant has been interpreted to indicate that iron-fortified formulas be given as early as possible, recent findings show that iron-supplemented formulas increase the susceptibility of infants to vitamin E deficiency and hemolytic anemia, especially when formulas are high in polyunsaturated fatty acids.5,95 (See discussion of vitamin E.) These studies leave unresolved the question of whether supplementary iron should be started at 2 months of age or shortly after birth.93 They also suggest that formulas for low-birth-weight infants containing more than 1 mg of iron per 100 kcal should contain moderate amounts of polyunsaturated fats (and ample vitamin E in an absorbable form), and that those with higher amounts of polyunsaturated fats should contain about 0.1 mg of iron per 100 kcal, which is roughly equivalent to the iron present in breast milk.

Another, more speculative reason for temporarily delaying the use of iron-fortified formula in low-birth-weight infants comes from recent evidence that two iron-binding proteins in human milk (lactoferrin and transferrin) lose their bacteriostatic action when saturated with iron.93 The bacteriostatic properties of these proteins may be especially important to low-birth-weight infants in the early weeks of life.

Thus, even though the Committee on Nutrition continues to recommend that low-birth-weight infants receive 2 mg of iron per kilogram per day starting at age 2 months or earlier, one cannot categorically require that formulas provide this level of iron from birth. Thus, formulas for low-birth-weight infants may provide either 0.1 mg or 1.5 mg of iron per 100 kcal. If they provide the higher level of iron, they should contain ample vitamin E and a moderate level of polyunsaturated fatty acids.

**Copper**

The recommended level of copper in infant formulas is 60 μg/100 kcal.71 This level is based on early data on human milk. Although copper deficiency has not been noted in normal infants on customary feedings, several reports96-98 have indicated that copper deficiency may develop in small infants fed formulas not supplemented with copper. Recent data suggest that an intake of 90
µg/100 kcal is desirable for low-birth-weight infants.99

Iodine

The recommended minimum requirement of normal infants (5 µg of iodine per 100 kcal)71 was also based on the iodine content of human milk. The uptake of radioactive iodine by the thyroid gland of premature infants has been found to be in the normal range for children and adults100; therefore, we can assume that 5 µg of iodine per 100 kcal is also adequate for the low-birth-weight infant.

Zinc and Manganese

The Committee on Nutrition has recently proposed that infant formulas for full-term infants supply 0.5 mg of zinc and 5 µg of manganese per 100 kcal.71 There is no basis for modifying these recommended levels for low-birth-weight infants.

Other Trace Minerals

Although other minerals (such as cobalt, molybdenum, selenium, and chromium) are probably essential in trace amounts for infants, there is no information on which to base recommendations at this time. Fluoride is usually provided in supplements or as fluoridated water.

Sodium, Chloride, and Potassium

The daily requirements of low-birth-weight infants for sodium, chloride, and potassium can only be roughly estimated from tissue composition (Table II), because obligatory losses in the urine and feces and from the skin vary considerably.

Minimum levels of sodium, chloride, and potassium recommended by the Committee on Nutrition for new formula standards were based on levels in human milk and should be sufficient for low-birth-weight infants. There have been a few reports101-102 of hypernatremia in low-birth-weight infants fed a formula with a concentration of sodium similar to that in human milk. Fomon et al.34 also suggest that the level of sodium in human milk is not sufficient for the premature infant; they recommend 30 mg of sodium per 100 kcal.

The Committee on Nutrition recommends that, to prevent dehydration and disturbances of acid-base balances, minimum and maximum levels of sodium, chloride, and potassium in formulas for low-birth-weight infants be the same as those recommended for full-term infants71 until further work confirms a higher, suggested need.

Vitamins

Table II shows the levels of vitamins recommended by the Committee as minimum levels for infant formulas for full-term infants.71 These apply to formulas based on milk and milk substitutes. The Committee recommends that the same levels apply to formulas for low-birth-weight infants, except for vitamin E.

However, even with proprietary formulas containing adequate levels of vitamins, premature and low-birth-weight infants often consume much less than 120 kcal/kg/day during the early weeks of life, and they may not receive sufficient vitamins to prevent deficiency. For example, rickets has been found in premature infants fed proprietary formulas containing 400 IU of vitamin D per liter,104 and folate and vitamin B12 deficiencies have also been noted105-108 when the infants consumed a small volume of formula. Therefore, the Committee recommends that low-birth-weight infants receive an intramuscular injection of 1 to 2 mg of vitamin K at birth and a daily, oral, multivitamin supplement providing the recommended daily allowance of vitamins for infants as established by the Food and Drug Administration.109

The vitamin E requirement of low-birth-weight infants merits special consideration.

1. Absorption of vitamin E by these infants is poor; Gordon et al.110 showed that the levels of vitamin E usually found in formulas—which are adequate to maintain normal serum tocopherol levels in term infants—were not sufficient to do so in premature infants. Recently, it was shown that water-soluble forms of vitamin E improve absorption and result in higher serum tocopherol levels.111

2. The requirement for vitamin E increases as the level of polyunsaturated fats in the diet increases.93 Thus, when formulas are high in polyunsaturated fats, the infant needs more vitamin E.

3. When iron levels in the formula are high, the requirement for vitamin E by low-birth-weight infants also increases. For example, low-birth-weight infants receiving a formula supplemented with iron (12 mg/liter) and high in polyunsaturated fats have a greater incidence of RBC hemolysis and lower serum tocopherol levels than infants receiving formula that has a low level of iron and is low in polyunsaturated fats.94 Therefore, the Committee on Nutrition recom-
mends that formula fed to premature infants should provide 0.7 IU of vitamin E per 100 kcal and at least 1.0 IU of vitamin E per gram of linoleic acid. In addition, the multivitamin supplement given to low-birth-weight infants should provide 5 IU of vitamin E, preferably in water-soluble form.

**Formula Compositions**

Table II shows the composition of major proprietary formulas available for feeding full-term and low-birth-weight infants, the average composition of human milk, and the recent recommendations of the Committee on Nutrition\(^1\) for proposed standards for infant formula. This information is presented in units per 100 kcal—which relate specific nutrient needs to caloric requirements—and is particularly useful in discussing formulas for low-birth-weight infants because it allows easy comparison of formulas of differing caloric densities.

In many instances, formulas for term infants are used for feeding low-birth-weight infants, and, in other instances, special formulas are available for premature and low-birth-weight infants.

Discussions in this statement suggest that levels of some nutrients in formulas for low-birth-weight infants should be somewhat higher than the minimum levels proposed by the Committee for full-term infants; however, all of these recommendations can be met within the proposed standards for infant formulas.\(^1\)

**Conclusions**

The optimal diet for the low-birth-weight infant may be defined as one that supports a rate of growth approximating that of the third trimester of intrauterine life, without imposing stress on the developing metabolic or excretory systems. Cell division and growth of all tissues in the infant should proceed at a rapid rate; undue delay in the resumption of growth may have serious and lasting consequences. The attainment of an adequate caloric intake is the primary requirement, and this may be facilitated by the feeding of formulas of caloric density greater than that of human milk. However, the feeding of this type of formula requires special attention to avoid too high an osmolar load and to provide sufficient water. The use of continuous intragastric or intrajejunal drip with formulas providing 67 or 81 kcal/dl also may be a safe and practical means of increasing caloric intake. Caloric intakes of about 120 kcal/kg/day in formula volumes of 150 to 200 ml/kg/day will support the desired weight gain in most infants.

An appropriate requirement for protein equivalent to casein for the low-birth-weight infant would appear to fall in the range of 2.5 to 5.0 g/kg/day, or 2.25 to 4.5 g/100 kcal. A more precise statement of optimal protein quantity awaits the definition of optimal protein quality for low-birth-weight infants. Evidence has been accumulating that some amino acids considered nonessential for the normal infant are indispensable to low-birth-weight infants. Thus, the apparent normal growth of infants fed breast milk supplying 1.7 g of protein per kilogram of body weight may be caused in part by its distribution of amino acids. For the larger low-birth-weight infant, recommendations similar to those for the term infant, including the desirability of breast feeding, apply.\(^1\)

Fat mixtures in formulas currently in use include unsaturated vegetable oils and/or medium-chain triglycerides, which are well absorbed. Although good absorption of fat is important—not only for energy requirements but also to enhance the absorption of fat-soluble vitamins and certain minerals—other aspects must be considered in the selection of ideal formula fat compositions for low-birth-weight infants. The fatty acid composition of the diet influences the composition of body lipids, especially in low-birth-weight infants who have meager stores of body fat. Fat mixtures should not be too saturated or too unsaturated.

The occurrence of hemolytic anemia in low-birth-weight infants has been related to the polyunsaturated fat, vitamin E, and iron content of the formula. The fortification of infant formulas with vitamin E, related to the polyunsaturated fatty acid content, is particularly important for the low-birth-weight infant because poor absorption of naturally occurring vitamin E by low-birth-weight infants makes them more susceptible to a deficiency. This is especially important if iron-supplemented formulas are used in the early weeks of life.

Recent evidence indicates that some mineral requirements (e.g., calcium, sodium, copper) of the low-birth-weight infant may be greater per 100 kcal than for full-term infants. This suggests that slightly higher levels of these minerals be present in formulas for low-birth-weight infants than the minimum levels proposed by the Committee for full-term infants.

Low body stores of vitamins, possible defects in absorption (particularly of fat-soluble vitamins),
and low intakes of formula in the first weeks of life necessitate the use of vitamin supplements, even though a formula adequate for full-term infants is used. A single injection of vitamin K₁ at birth and daily oral supplements of vitamins A, C, D, E, and all the B group are recommended.

The long-term effects of early nutrition are important and challenging aspects of infant nutrition. Early feeding of low-birth-weight infants entails a special responsibility because this is a crucial period of development when inadequacies, excesses, or imbalances are most likely to influence permanent changes. Long-term studies, still in progress, are attempting to relate feeding practices in the premature nursery to subsequent neurologic development, learning ability, behavioral characteristics, and mental development in general. Other possible pathologic consequences of improper early nutrition that are legitimate areas of concern for the pediatric nutritionist include atherosclerosis, obesity, hypertension, and renal disease.

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TWO CASES OF SUDDEN AND UNEXPLAINED DEATH OF CHILDREN DURING SLEEP AS REPORTED IN 1834

Published case reports of unexpected deaths of infants during sleep prior to the early decades of the 20th century routinely attributed the infant’s death either to overlaying of the mother or wet-nurse, or after the 1840s, to suffocation by an enlarged thymus. The two cases in letter form reported below are of historic interest because they are among the first to infer that unexpected infant death during sleep might be due to natural causes.

To the Editor of THE LANCET.

Sir,—I have lately been called upon to examine two children, who, without having been previously indisposed, were found dead in bed.

In the first case the child was about six months old, and was lying in bed with its mother, who discovered in the middle of the night that it was dead. An inquest was held upon the body, and I was directed, in the absence of anything like testimony as to the cause of its dissolution, to make a post-mortem investigation. I should mention that the mother stated positively that the child had not lain near her, and that it was impossible it could have been suffocated, either from its mouth having been applied to any part of her person or to the bed linen.

I found nothing unusual in the cavity of the skull,—no engorgement of the vessels,—no sanguineous or serous effusion. The viscera of the belly were in every respect of healthy appearance, and there was nothing in the stomach to indicate that it had come by its death unfairly. In the chest, however, I found, upon the surface of the thymus gland, numerous spots of extravasated blood, similar spots upon the surface of the lower and back parts of each lung, and many patches of ecchymosis upon the margin of the right ventricle of the heart, and along the course of the trunk of the coronary vein. There was no engorgement, however, of the pulmonary vessels, of the coronaries, or of the vessels of the thymus.

In the second case the child was five months old. It had been pretty well, had been sucked by its mother, and laid in bed upon its side, and in about an hour and a half afterwards was discovered to be dead. There was some frothy matter in and about the mouth, and its hands were firmly clenched. From the position in which it was found it was impossible it could have been smothered.

The appearances exhibited in the autopsy were strikingly the same as in the first case. The contents of the skull and belly were in a perfectly natural condition. The extravasated spots upon the thymus gland were more numerous than in the first case, and those upon the heart and the surface of the lungs were fewer in number. There was about half an ounce of serous fluid in the pericardium.

In these cases one naturally asks,—what was the cause of death? The similarity of the post-mortem appearances would lead one to suppose that the cause must in each case have been the same.

In the first case I was strongly disposed to think, in spite of the evidence of the mother, that the child must have been destroyed by overlaying it; but after the occurrence of the last case, where, from all the testimony that could be obtained, it seemed impossible that the child could have been suffocated, as it was lying in bed by itself, and was not obstructed in its breathing by the bed-clothes, I confess that the opinion I had formed was a good deal shaken, and that I became almost entirely at a loss how to account for death in either. In both cases there seems to have been, from some cause or other, a sudden and violent action of the heart,—and numerous small vessels, from the increased force of its contraction, appear as a consequence to have given way. But so trifling a lesion could hardly, in either instance, be supposed to be of itself sufficient to produce death, and it is with the hope that some of your correspondents who may have seen similar cases, and who may be better able to offer an explanation of the phenomena they present than I am, will take the trouble of enlightening me upon the subject, that I am induced to forward you this communication.

Derby, Oct. 19, 1834

Saml W. Fearn
Noted by T. E. C., Jr., M.D.

Nutritional Needs of Low-Birth-Weight Infants

*Pediatrics* 1977;60;519

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*Pediatrics* 1977;60;519

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