

Assessment of Growth of Formula-Fed Infants: Evolutionary Considerations

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Despite the general acknowledgment that breastfeeding is the most desirable means of feeding normal infants, it is evident that many infants are currently fed infant formulas and that evaluation of the adequacy of such formulas is an important topic in the field of pediatrics. During early infancy, growth is the most sensitive index of health, and growth is therefore a critical component in evaluation of the adequacy of a new infant formula. To use growth as a component of formula evaluation, it is necessary to select a reference population, and there is an ongoing debate about which of several reference populations is most suitable.

On first consideration, the breastfed infant may seem a logical choice as a reference. It can be pointed out that the lactation process has been modified by evolutionary forces over millions of years, and human milk is generally agreed to be the model for development of infant formulas. Nowhere is the superiority of human milk over infant formula more clearly evident than in protection against infection. The major antiinfective components of human milk have not been incorporated into currently available infant formulas, and there is little likelihood that this will occur in the future. Nevertheless, based on an argument that will be presented, the overwhelming evidence that breastfeeding is the preferred way to nourish infants does not logically lead to the conclusion that data on growth of breastfed infants are suitable for assessment of growth of formula-fed infants.

GROWTH OF BREASTFED AND FORMULA-FED INFANTS

Growth of infants fed a new formula needs to be tested over an interval that includes a substantial portion of the neonatal growth spurt (ie, from 8 to 42 days of age). Data are available for intervals of 8 to 112 days, 14 to 112 days, and 28 to 112 days.¹ Intervals beginning after 28 days of age will not include a substantial part of the neonatal growth spurt and therefore will miss the interval when the requirement for several nutrients per unit of energy intake is greatest. In a study conducted some years ago,² we obtained data suggesting that a formula that was

judged to be fully adequate for infants >56 days of age was probably inadequate for infants from 8 to 56 days of age. Thus, in judging whether data on growth of breastfed infants are suitable as a reference for growth of infants fed a new formula, the relevant age interval is the first few months of life.

It is generally accepted that the growth of breastfed infants does not conform with the most commonly used reference data,^{3,4} and it has been proposed that a new set of reference data be assembled based on growth of breastfed infants living in advantageous circumstances. Because suitable reference data on growth of breastfed infants beyond the first few months of life are not available, this effort can only be applauded. Nevertheless, reference data on growth of breastfed infants, however valuable and necessary for assessment of growth of breastfed infants, may not be suitable for assessment of growth of formula-fed infants.

On a gender-specific basis, from 8 to 42 days of age, gains in weight and length of breastfed and formula-fed infants are similar, whereas from 42 to 112 days of age, formula-fed infants grow more rapidly than do breastfed infants (Table 1). Greater (but not significantly greater) gains by formula-fed than by breastfed infants were also reported by Dewey et al⁵ from 1 to 3 and 2 to 4 months of age (lack of significance is possibly the consequence of small numbers of subjects and large standard deviations).

I do not find it acceptable to pass over the greater gains of formula-fed infants by noting that "bigger is not necessarily better" or by concluding that "formula-fed infants are overfed." Formula-fed infants grow more rapidly than do breastfed infants not only in weight but in length, and gain in length is directly associated with gain in fat-free mass. Recognizing that fat-free body mass is an abstraction and that each cell requires lipid for structure and function, it is nevertheless useful in considerations of growth to distinguish between growth of fat mass and fat-free mass.⁶ Growth of fat-free mass is regulated quite differently from growth of fat (much of which is in adipose tissue). I have previously⁷ offered the hypothesis that each infant has a genetically determined potential for growth of fat-free mass. If infants remain relatively free of illness and receive adequate intakes of energy and essential nutrients, they will meet their growth potential. According to this hypothesis, the ideal growth rate for infants is that which permits achievement of their potential for growth in fat-free mass, a rate of growth that cannot

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TABLE 1. Gains in Weight and Length of Breastfed and Formula-Fed Infants From 8 to 42 and 42 to 112 Days of Age

Feeding Group	Gender	Number of Subjects	8–42 days				42–112 days			
			Gain in Weight, g/d		Gain in Length, mm/d		Gain in Weight, g/d		Gain in Length, mm/d	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Breastfed	Male	203	38.9	9.7	1.29	0.22	25.4	6.2	0.96	0.17
Formula-fed	Male	380	39.8	7.7	1.33	0.22	28.5	6.4	1.03	0.12
Breastfed	Female	216	33.8	9.3	1.24	0.22	22.6	6.3	0.89	0.13
Formula-fed	Female	340	33.3	7.4	1.25	0.19	24.7	5.2	0.94	0.11

Gains in weight and length from 8 to 42 days of age were similar for breastfed and formula-fed infants; gains from 421 to 112 days were greater ($P < .001$) by formula-fed than breastfed infants. SD indicates standard deviation. The table was modified from Nelson et al.¹

be exceeded but one that may not be met under circumstances in which intake of energy or specific nutrients is limited.

It may seem heretical to suggest that at least some breastfed infants fail to meet their potential for growth of fat-free tissue. However, as stimuli to evolutionary change, other factors are considerably more important than rate of growth. An understanding of the effect of evolutionary factors on the composition of human milk requires acceptance of 2 major considerations: 1) the forces driving evolution are focused on the mother-offspring unit rather than on the infant; and 2) changes in living conditions can occur in 100 years, whereas evolutionary adaptation requires thousands of years.

MOTHER-OFFSPRING UNIT

Many authors^{8–13} have pointed out that evolutionary forces are not focused on survival of the infant; rather, they are focused on survival of the mother-offspring unit, and “offspring” in this sense must be thought of in the plural. The survival of the species requires investment by the parent in the offspring to the extent that will maximize the number of offspring surviving to reproduce. This goal could not be achieved if provision of milk ideally suited to the needs of the infant resulted in excessive depletion of the mother’s nutritional reserves. For the infant to survive, the mother who nurses the infant must survive and remain in a state of health sufficient to permit her to care for the infant, including providing his food. The investment by the mother in the infant should result in a high likelihood of survival of the infant without unduly decreasing the mother’s ability to invest in other offspring, including those not yet born. Thus, evolutionary processes can be expected to work out a compromise between the mother’s welfare, that of the infant, and that of the infant’s siblings or potential siblings.

As stated by Dugdale¹¹: “Simple arithmetic shows that where there is a conflict of interests, the welfare of the mother outweighs that of the infant. The dyad hypothesis suggests that maximum evolutionary gain is obtained when protein and energy levels in breast-milk are just high enough to prevent prohibitive infant mortality rates, but low enough to spare the mother. The anti-infective constituents of breast-milk are very small in bulk, so they place a minimum metabolic load on the mother but have a large benefit for the child.”

Animals with short gestation periods are likely to

resolve a conflict between the welfare of the mother and that of the offspring in favor of the mother. Thus, when food supply is short, a rodent dam may kill all or part of the litter, presumably choosing to sacrifice the present offspring in favor of maintaining her health to be able to invest in the next litter. In animals with long gestation periods, the investment in the current offspring is quite high, and the mother may continue to invest her nutritional resources to support her infant despite some personal short-term disadvantage. In this context, the milk produced by undernourished Gambian women was reported to be of the same quantity and quality as that produced by well-nourished women in the United Kingdom.¹⁴ Nevertheless, although a short-term disadvantage to the mother may be acceptable in promoting the welfare of the species, it is clear that a long-term disadvantage to the mother is unacceptable.

PROTEIN

From 1 to 2 million years ago until 30 000 to 15 000 years ago, there is evidence that meat accounted for a large percentage of human energy intake.¹⁵ Subsequently, as the ready availability of big game decreased, the subsistence pattern changed to reliance on small game, shellfish (in some areas), and an increased amount of plant foods.¹⁵ This change undoubtedly began at different times in different areas, but, in at least some sites, it seems to have occurred between 30 000 and 15 000 years ago.^{16,17} The first agricultural revolution began 10 000 to 12 000 years ago¹⁸ and for many years did not seem to be very successful in improving the lot of the people. There is a popular notion, well summarized by Cassidy,¹⁹ that hunter-gatherers must be nomadic to take advantage of sparse wild-food resources, have little spare time, often go hungry, and live harried, short, simplified, and rough lives, whereas agriculturalists have a stable food supply, even an excess of food that can be used to feed full-time artisans and other non-farming specialists. A stable food supply has been believed to permit the building of complex societies.

However, several writers^{20,21} have examined evidence about hunter-gatherers and primitive agricultural societies and point out that, in such societies, protein intakes are likely to be marginal and energy intakes may be erratic because of variable climatic conditions and variable success in food preservation and storage. Moreover, congregations of persons living in fixed locations without adequate sanitation facilities contribute to the spread of infectious dis-

eases. Perhaps for these reasons, early European *Homo sapiens*, who enjoyed an abundance of animal protein (and, presumably, experienced fewer infectious diseases), were an average of 6 inches taller than their descendants who lived after the development of farming.²¹ Although we have no data on the protein concentration of human milk during the long interval of time when diets were high in protein, it seems reasonable to speculate that the protein content of human milk was greater than at present.

One might ask whether subsistence on diets much lower in protein over a period of 15 000 to 30 000 years could be sufficient to result in a decrease in the protein concentration of human milk, a change that would benefit the mother. Based on the discussion by Smith²² concerning spread of a favorable gene, it may be calculated that in 250 generations (ie, in ~5000–6000 years), a gene present in 1% of a population might spread to 67% of the population. The best example of rapid spread of a favorable gene is the development of lactose tolerance of the adult, which presumably developed as a genetic adaptation to milk drinking.^{23,24} In times of food shortage, the ability to tolerate milk consumption probably had major survival value. A similar genetic change that permitted a lactating woman to limit the protein content of her milk would also be expected to enhance her survival. From the evolutionary point of view, it is irrelevant that, in a number of industrialized countries, abundant supplies of protein have been present in the diet for ≥ 100 years. It is obvious that our genetic pool, modified during at least 15 000 to 30 000 years of subsistence on marginal protein intakes, could not yet have responded to such a recent change.

OTHER NUTRIENTS OF INTEREST

Breastfed infants are known to be at risk of deficiencies of vitamin K, vitamin D, and iron. Occurrence of these deficiencies is important in demonstrating that a woman's milk may not fully meet the needs of her infant. However, there is reason to believe that the prevalence of these deficiencies in breastfed infants was much less during most of human history than it is now, and it seems likely that the current prevalence of these deficiencies is a consequence of changes in living conditions.

Vitamin K

It is well known that the microorganisms of the gastrointestinal tract produce menaquinones, which, if ingested, exert vitamin K activity. A synthetic menaquinone (menaquinone-4) is used in Japan rather than phylloquinone (vitamin K₁) for administration to the newborn to prevent vitamin K-deficiency bleeding.²⁵ However, the extent of absorption of menaquinones from the site of their formation in the intestinal tract (ie, if not ingested) seems to be low. Thus, menaquinones cannot be counted on for meeting the needs for vitamin K for individuals living under current conditions of sanitation in industrialized countries. With what we would now consider poor environmental sanitation and poor personal hygiene, one can imagine that through all

but the last hundred years or so of our evolutionary history, menaquinones produced by fecal microorganisms were widely available in the infant's environment, and in fact the infant was likely to receive, inadvertently, a substantial oral dose of menaquinones during the birth process and was likely to receive supplements of menaquinones from contamination of the immediate environment, including the surface of his mother's breasts.

Vitamin D

Over all but the last 100 or 200 years of human history, the great majority of human infants met their needs for vitamin D by converting (with the aid of sunlight) 7-dehydrocholesterol in the skin to previtamin D₃ and then to vitamin D₃. Currently, vitamin D deficiency in breastfed infants, especially dark-skinned breastfed infants, is not uncommon²⁶ and reflects the inadequate exposure of some infants to sunlight because of seasonally low availability of sunlight, atmospheric pollution, or purposeful avoidance of exposure.

Iron

Iron ranks among the most abundant elements in our environment. Although it occurs primarily in highly insoluble forms, in some soils it occurs in forms soluble enough to be toxic to plants.²⁷ Hallberg and Björn-Rasmussen²⁸ found that ~30% of contamination iron in some diets was exchangeable with the remainder of iron in the diet (ie, was bioavailable). As stated by Hallberg²⁹: "Considering the high iron content of many soils. . . the intake of soil iron must be considered in human nutrition, especially in the diets in developing countries where the intake of soil iron may be quite considerable." The concentrations of iron in milks of many precocial mammals (those whose young are relatively mature at birth) are low. The young of these animals generally have ready access to iron in the environment. It is well known that piglets suckled in clean environments without access to soil develop iron deficiency. Such deficiency can be prevented by providing supplements of iron or putting dirt in the pen.³⁰

On the other hand, concentrations of iron in milk of altricial mammals (those whose young are quite immature at birth) are greater. A young marsupial remains attached to its mother's nipple for weeks or months and would be unlikely to ingest iron from sources other than milk. Iron concentration of milk of the tamar wallaby ranges from ~10 to >20 mg/L during the period before the young marsupial emerges from the pouch.³¹ When the young marsupial emerges from the pouch (and presumably has access to iron in the environment), the iron concentration of the milk rapidly decreases to ~5 mg/L. Concurrently, the energy concentration of the milk increases ~2.7-fold, indicating that the iron content per unit of metabolizable energy has decreased remarkably.

During most of our human history, the infant, even during the early months of life, was exposed to an environment in which dirt, and therefore iron, was ingested from the environment: from the skin

and clothing of the mother and other caretakers, from the bedding on which the infant slept, and, by 3 to 5 months of age, directly from the floors of living quarters. Thus, it is reasonable to speculate that infants were able to achieve adequate iron intake despite the quite limited intake of iron from human milk. However, in industrialized countries during the last 100 years or so, improvements in sanitation have been successful in excluding contamination iron from the diet.

The observation that iron deficiency is common in infants in developing countries should not be assumed to indicate lack of bioavailability of iron inadvertently consumed from environmental sources. Studies of iron nutritional status in developing countries have been conducted primarily in areas in which the population density exaggerates the problems of sanitation with high rates of infection and parasitic infestation. Even areas now classified as rural have greater populations than was the case during most of human history. Living conditions were quite different when the human population was sparse.

FINAL COMMENTS AND SPECULATION

As we puzzle over the evolutionary events that have led to the composition of human milk, it is well to reflect that we know little of the infant feeding customs of our ancestors. In several nonindustrialized societies today, the mother offers the infant prechewed food. This practice, although unappealing to many people in industrialized societies today, would seem to be a reasonably safe means of supplementing the energy and nutrient intakes of the breastfed infant. Thus, it is entirely possible that, even during the early months of life, the infant did not solely depend on human milk for energy and nutrients. If such a practice existed, it would require the infant to digest a variety of foods from the maternal diet, including starches. Perhaps this is the explanation for the presence of amylase, an enzyme that has been shown to be resistant to digestion in the stomach,^{32,33} in human milk and may permit adequate digestion of starch at an age when pancreatic amylase is inadequate. It has been estimated³⁴ that, during the early months of lactation, amylase activity of 100 mL of human milk is sufficient to digest 20 g of starch in 1 hour. One can speculate that genetic selection would favor women whose milk contained appreciable amounts of amylase, because the infants nursed by these mothers could tolerate ingestion of starch and therefore could thrive with a lesser drain on the energy and nutrient stores of the mother.

Although intakes of protein were luxurious during most of human history, the increase in the human population and concurrent decrease in the biomass greatly decreased protein intake beginning 30 000 to 15 000 years ago. I speculate that evolutionary change since 30 000 years ago has been responsible for a nutritional compromise that favored survival of the mother through limiting the drain on her body reserves during lactation. The lactating woman was therefore able to conserve body protein by limiting its concentration in her milk.

According to my speculation, some breastfed infants fail to meet their potential for growth of fat-free tissue because of marginal intakes of energy, protein or other nutrients. The more-rapid growth of formula-fed than of breastfed infants may merely reflect the more-generous intakes of energy and essential nutrients by formula-fed infants. In the absence of evidence that the lesser gain in fat-free tissue by breastfed infants is advantageous, it seems unsound to select the gains of breastfed infants as our reference for growth of formula-fed infants. If one were to accept the conclusion that the growth of breastfed infants is the most suitable reference for growth of formula-fed infants, it would seem logical to require the infant-formula industry to devise formulas that would result in lesser gains in fat-free tissue than are now observed with formula-fed infants. In my view, this course of action is unacceptable. Adequate reference data on growth of formula-fed infants are available,³ and I believe they should be used for evaluation of growth of infants fed a new formula.

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