Infant formula, past and future: opportunities for improvement\textsuperscript{1,2}

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ABSTRACT Infant formulas provide nutritional support to healthy infants that promotes growth and development equivalent to that in healthy infants fed human milk. Formula-fed infants are not as well protected against infections, and there remain infants whose health, growth, and development may not be supported optimally by either the formulas currently available or human milk. Some infants may be better supported by genetically engineered formulas that contain immunity-enhancing antibodies or antigens. Formulas that contain cytokines promoting epithelial cell growth and integrity may be protective against necrotizing enterocolitis. Formulas containing proteins with genetically excluded allergenic epitopes or formulas with tolerogenic peptides may be useful in treating allergic diseases or suppressing the development of autoimmune disorders later in life. Formulas with genetically engineered biologically active substances might increase the absorption of nutrients in infants with compromised absorption or digestion, enhance host immunity and mucosal integrity, and, potentially, mitigate or protect against the risk of disease. Am J Clin Nutr 1996;63:646S–50S.

KEY WORDS Genetic engineering, antibodies, cytokines, growth factors

INTRODUCTION

Since before the days of Hippocrates, diet has been linked to prevention and treatment of disease. Nonetheless, throughout most of human history infant mortality rates have averaged 15–25\% and have been as high as 90\% in orphans who did not have ready access to a wet nurse. As recently as 100 y ago, one-quarter of all infants in the United States died before reaching their first birthday. Many of these deaths were due to malnutrition and infectious diarrheal diseases associated with the poor sanitary conditions that were endemic in poor urban immigrants (1). Thus, until the 20th century, breast-feeding was almost a life-or-death proposition for newborns. In fact, attempts to simulate human milk by making various adjustments to cow milk were the basis for early American pediatric theory and practice. The founders of American pediatrics, such as Holt, Rotch, and Jacobi, devoted much of their careers to defining the nutritional needs of infants and developing safe infant feedings by modifying cow milk with water, sugar, and cream.

From the late 1950s through the 1960s, the greater availability, ease of feeding, high safety, and relatively low cost of infant formulas in the United States and other developed countries led to most infants being fed artificially from birth (2). The trend reversed in the 1980s, and now, particularly during the past 5 y, more mothers are initially breast-feeding. However, with the increasing numbers of mothers who must return to work 2–3 mo after giving birth, infant formula has continued to play a major role in infant nutrition. Indeed, although the use of evaporated milk and whole cow milk has decreased because of recent recommendations to avoid them before 1 y of age (3), the use of infant formulas has increased (4, 5).

DIFFERENCES IN OUTCOMES BETWEEN FORMULA- AND BREAST-FED INFANTS

Infections

In many developing countries the early introduction of infant formulas had unfortunate consequences if clean water was not ensured or if the cost of formula led the mothers to dilute it and thus provide inadequate nutrition to their infants. Many nonnutritional proteins that are present in human milk but absent from artificial feedings play a role in host defense, including secretory immunoglobulins to such pathogens as rotaviruses, giardia, \textit{Haemophilus influenzae}, campylobacter, enteropathogenic Escherichia coli, shigella, and poliovirus (6–12). The protective effects of human milk against otitis media that were reported in some studies, for example, may be due to specific secretory immunoglobulin \( \Lambda \) (IgA) that prevents nasopharyngeal colonization by \textit{H. influenzae} (13). Similarly, secretory IgA to intestinal pathogens protects against gastroenteritis in infants in developing countries, with campylobacter diarrhea being 3.2 times more common in non-breast-fed infants in one prospective study (9).

Diarrheal morbidity is related to many factors and contaminated supplemental foods are as likely to cause problems, as is the absence of antiinfective factors that are provided by breast milk (14). However, in most developed countries infant mortality rates have dropped by 10- or 20-fold to as low as 5–10 deaths per 1000 live births, and there seem to be no significant differences in long-term growth, morbidity, or mortality in infants fed formula and those fed human milk. Some early studies showed significant differences in the rates of respira-

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tory infections, diarrhea, and hospital admissions in formula-fed infants (15). However, difficulties in completely controlling for socioeconomic factors such as social class, smoking, and other siblings and reporting bias suggest that the difference in the severity of infections is much less than the difference in hospitalizations and that in industrialized countries breastfeeding has at most a minimal protective effect (16, 17). Subsequent prospective cohort studies showed no significant differences in the overall incidence of gastroenteritis or respiratory illness, but there may be a slightly lower incidence of specific infectious illnesses such as otitis media in breast-fed infants (18). Thus, it appears that the major goals of providing safe, effective, and affordable alternatives for mothers who cannot continue breast-feeding have largely been met. It should be recognized, however, that the outcomes measured between breast-fed and formula-fed infants remain crude.

**Growth**

Formula- and human milk–fed infants grow at similar rates in the first 3–4 mo of life. Thereafter, breast-fed infants grow more slowly. Formula-fed infants are on average slightly taller and heavier in later infancy than their breast-fed counterparts, but studies vary somewhat in their conclusions (19–22). There has been much discussion about the effects of breast-feeding in mitigating the risk of later obesity, but this has been difficult to establish in a good prospective trial in which socioeconomic, genetic, and cultural factors are controlled for. In two large prospective studies in which infants were followed up from birth to 5–8 y of age there was no difference in obesity according to the mode of feeding during infancy (23, 24). Furthermore, most obese infants do not become obese adults and most obese adults were not obese as children (25). In any event, the nutritional adequacy of the standard infant formulas currently available in the United States is well established.

**CONDITIONS REQUIRING SPECIALIZED NUTRITIONAL SUPPORT IN INFANCY**

Specialized formulas are available for supporting immature infants and those with allergic, inflammatory, and metabolic disorders. In many circumstances, advances in our understanding of mucosal immunity and epithelial growth and function will lead to improved formulas for the support of these infants.

**Prematurity**

Low-birth-weight infants have unique nutritional needs, some of which can be met by human milk instead of placental transfer. However, not all of their nutrient requirements can be met by human milk, and this along with the immaturity of their gastrointestinal function has led to the development and use of specialized formulas for premature infants. These usually contain additional proteins, glucose polymers, and medium-chain triglycerides as well as increased concentrations of calcium and other minerals. Although these formulas appear to realize the normal intrauterine growth rates in enterally nourished infants, they may not be completely ideal. For example, incomplete oxidation of 6:0 to 12:0 fatty acids may not result in increased growth or nitrogen retention in premature infants who are fed formula (26).

Biochemical engineering of specific nutrients and early enteral feeding have been successful approaches to promoting the growth and development of gastrointestinal function in premature infants. Genetically engineered immunoprotective and growth factors, as described below, may supplement these approaches and may decrease the risk of intestinal disease and infectious illnesses that compromise the outcome in many very premature infants. Genetically engineered pulmonary growth factors, packaged in a way that promotes absorption into the circulation or carried by lymphocytes that migrate to distant mucosal surfaces from the gut, could in theory be added to formulas to promote lung maturation.

Achieving adequate growth and weight gain is a common problem in premature infants who are compromised by chronic illnesses such as bronchopulmonary dysplasia (27). Concentrated formulas that provide 3820–4260 kJ/L (113–126 kJ/fluid oz) are often used to meet the reported increased energy requirements of these infants. Supplements with vitamin A and inositol have been proposed to reduce morbidity in infants with lung injury (28, 29). Premature infants may also benefit from the addition of long-chain unsaturated n–3 and n–6 fatty acids such as docosahexaenoic acid and arachidonic acid (30).

Necrotizing enterocolitis is still a major problem in premature infants. It is not clear whether immaturity of the gut, susceptibility to infection, or ischemia is most important, but the sometimes catastrophic consequences can lead to high mortality from perforation and sepsis, or to long-term disability from intestinal resection and short-gut syndrome. The nutritional support of infants with chronic intestinal disease from inflammation, infection, ischemia, or surgical resection, as occurs in necrotizing enterocolitis or short-gut syndrome, often proves exceptionally challenging. Elemental formulas are useful for providing nutrients to these infants, many of whom require extended parenteral nutrition. Modular formulas are also helpful later in the course of these disorders.

**Intestinal immaturity and inflammation**

Of recent interest is the use of nutrients that specifically promote intestinal epithelial cell growth. Glutamine is a conditionally essential amino acid that is present in high concentrations in the intestinal circulation and is a major intestinal fuel in stress. Providing as much as one-third of the protein requirement as glutamine was proposed as nutritional rehabilitation for patients with inflammatory disorders resulting in compromised intestinal epithelial regeneration (31, 32).

Human milk contains gastrointestinal regulatory peptides such as gastric inhibitory peptide, bombesin, cholecystokinin, and neuropeptide, which may be important for growth and maturation of the gastrointestinal tract in neonates (33). Factors such as growth hormone, insulin-like growth factor I, granulocyte-macrophage colony-stimulating factor, and transforming growth factor-β have been shown to enhance intestinal function and mucosal defenses. There are several other growth factors that stimulate DNA synthesis, such as epidermal growth factor, many of which have yet to be characterized completely (34). Tumor necrosis factor ( cachectin) and other cytokines such as interleukins 1, 6, 8, and 10 and interferons may be produced by the stimulation of mononuclear cells in human milk (35, 36). If their safety and efficacy can be demonstrated, all these proteins could potentially be produced by genetic
engineering and be added to specialized formulas to support intestinal maturation or improve immunocompetence.

Lysozyme, lactoferrin, and other factors in human milk may also be important in growth or host defense (37). Lysozyme is an enzyme that hydrolyzes glycosidic bonds between N-acetylglucosamine and N-acetylmuramic acid, which are components of bacterial cell walls. Only trace concentrations of lysozyme are present in cow milk; the mean concentration in human milk ranges from 80 to 245 mg/L (37). By binding to ferric ions, the lactoferrin in human milk not only increases iron absorption but also deprives bacteria of iron and exerts a bacteriostatic effect (38). Although human milk has lower concentrations of most vitamins and minerals than do infant formulas, the bioavailability of these nutrients (in particular, iron, calcium, and zinc) is often much higher in human milk because absorption is facilitated by the presence of specific binding ligands. If these ligands, such as lactoferrin and metallothionein, could be produced safely and inexpensively, they could be added to formulas to increase nutrient bioavailability and further minimize the risks of enteric infections or specific trace element nutrient deficiencies.

Nucleotides, particularly inosine monophosphate, may contribute to greater iron absorption in breast-fed infants, may act as growth factors, and may have immunomodulating effects on host immune defenses (39). They are now being added to some infant formulas. Polyamines such as putrescine, spermine, and spermidine are known to be involved in cell proliferation and differentiation, and may be present in highly variable amounts in both human milk and formula (40). Enterally administered polyamines have also been shown to influence intestinal maturation in several animal models.

Immunocompromised infants

A growing number of infants are immunocompromised early in life, most notably from vertically transmitted human immunodeficiency virus. These infants are often beset by growth failure, susceptibility to infections, and gastrointestinal compromise within the first year of life. Early efforts to maintain adequate nutritional support by enteral feeding may retard the progression of these signs and symptoms, maintain the infants' quality of life (eg, fewer hospitalizations), and possibly extend their lives. Elemental formulas may be necessary if malabsorption becomes a problem, but the addition of growth factors and agents that enhance immunity may increase the efficacy of current formulas. Antiinflammatory substances such as catalase, lysozyme, and various protease inhibitors might also modify the progression of inflammation or provide cytoprotection to infants who have experienced insults to their gastrointestinal tract or immune defenses or who are at high risk for such problems.

Immunocompromised infants may be better supported by genetically engineered formulas with immunity-inducing antibodies or antigens that have been coupled to ligands with known gut epithelial cell receptors. For example, cytokines such as epidermal growth factor I and interleukin 11, which promote epithelial cell growth and integrity, can be added to formulas for protecting against the development or worsening of necrotizing enterocolitis. Interleukin 11 is a recently described cytokine that has pleiotropic growth effects on various tissues and can stimulate the proliferation of crypt stem cells in small intestine as well as hematopoietic cells, making it potentially useful in treating congenital and acquired thrombocytopenias, bone marrow failure, and intestinal diseases (41).

Metabolic diseases

Certain inborn errors of metabolism, such as the disorders of urea cycle enzymes, benefit from a reduction in the concentrations of all nonessential amino acids. For other metabolic diseases such as phenylketonuria, tyrosinemia, and homocystinuria, infants should be given formulas from which one or two amino acids have been deleted. Using specific inhibitors such as NTBC [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanediol] to inhibit 4-hydroxyphenylpyruvate dioxygenase and stop tyrosine degradation may be lifesaving by effecting normalization of both renal and liver function and preventing neurologic crises (42). Formulas with reduced concentrations of branched-chain amino acids (eg, valine, leucine, and isoleucine) are available for maple syrup urine disease. The current management of phenylketonuria favors continuing dietary restrictions throughout childhood to prevent deterioration of intellectual progress. The need for specialized formulas for infants with rare metabolic disorders who cannot metabolize certain amino acids should decrease as specific gene loci are identified and gene therapy becomes available. It may be possible someday to incorporate specific gene replacement sequences in formula if safe and effective vectors can be ensured.

Cow milk allergy

The reported prevalence of cow milk allergy ranges from < 1% to as high as 8%. Cow milk allergy may be manifested as gastrointestinal, respiratory, central nervous system, and dermatologic symptoms. The onset of cow milk allergy is usually in the first year of life. Its pathogenesis has not been completely elucidated and various immunologic mechanisms have been postulated, ranging from IgE-mediated reactions to delayed-type cell-mediated hypersensitivity. All of the major protein fractions of cow milk are potentially antigenic and allergenic. Cow milk allergy may result from early sensitization by antigens in formula or those transmitted in the breast milk of mothers who drink cow milk. Breast-feeding per se does not appear to prevent the subsequent development of allergy (43). Formulas not based on cow milk but made from soy protein are widely available and are relatively inexpensive; however, 8–35% of infants with cow milk allergy also have allergic reactions to soy protein (44). Hypoallergenic formulas made with extensively hydrolyzed proteins are available and are useful for most affected patients, but they are unpalatable to most young children.

It may be possible to introduce proteins into formula that, paradoxically, would reduce the potential for the later development of allergic reactions or autoimmune disease. The enteral introduction at crucial times early in life of antigens that have been coupled to specific genetically engineered ligands may result in the development of tolerance by anergy or suppression by regulatory cells. Adding antibodies to specific antigens or genetically manipulating the removal of specific epitopes that are responsible for antigenic stimulus from orally administered proteins are some of the possible strategies that may produce tolerance. Orally administered autoantigens have been shown to suppress disease in several experimental auto-
immune models and the potential for treating or preventing autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and diabetes mellitus may be an intriguing line to pursue with genetically engineered self-proteins (45).

SUMMARY

In summary, human milk remains the optimal source of nutrition for healthy infants in the first 6 mo of life and the standard to which infant formulas should aspire. However, when infants are weaned from breast milk, the current formulas do support healthy infants well. In developed countries there is little difference in growth or morbidity between infants who are fed breast milk and those who are fed formula. There are still many differences in the composition of formula and human milk with respect to several substances that may affect growth and host defense. Therefore, continued efforts to provide improved formulas that may aid in adaptation to gut injury or increased growth for infants who are premature, allergic, or under other pathophysiologic stresses may prove helpful in the future.

Modular formulas, with the individual nutritional components added in the proportions required, could be available for better controlling metabolic diseases, malabsorption syndromes, and allergic reactions or for preventing chronic diseases. There may not be a need to use cow milk, for example, as a basis of infant formulas, given the prevalence of allergic intolerance or occult blood loss.

Soon it may be possible to introduce genetically engineered proteins, ligands, or growth factors into specialized infant formulas. These approaches may also be beneficial for infants who are compromised with necrotizing enterocolitis, short-gut syndrome, or other diseases and who would benefit from greater growth, increased absorption of macronutrients and minerals, or improved intestinal mucosal integrity.

REFERENCES

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