The Quest for the Perfect Infant Formula

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Breast milk provides the ideal nutrient composition for the newborn. In the past, if the biological mother did not breast-feed, a wet nurse was found to feed the infant. "And Pharaoh's daughter said unto her, take this child away, and nurse it for me, and I will give thee thy wages. And the woman took the child and nursed it" (Exodus: 2:9). Although many infants received animal milk as a substitute to human breast milk, satisfactory artificial feeding only became possible with the advent of analytical techniques for determining the components of milk. The correct chemical composition of both human and animal milk became known in the late 1880s [1]. The first infant formulas that attempted to emulate breast milk were based on diluted cows milk (to lower the casein content) with the addition of cream and sugar [2].

In recent years the food industry and the medical community have worked together in the attempt to produce commercial formulas that best replicate nature's formulation for infant nutrition. It is noteworthy that in this issue of *IMAJ* two articles are devoted to this topic. Lerner and Shamir [3] review the use of nucleotides in newborn nutrition, and Weisbrod and Mimouni [4] provide original research data investigating the tolerance levels to different infant formulas.

Taking breast milk as the "gold standard," and with improved technical ability to identify the numerous compounds in milk, infant formula composition is becoming increasingly similar to human breast milk. Despite significant advancements in the area of artificial feeding of babies, there is still widespread intolerance to infant formulas. Not all attempts at replicating the composition of breast milk have been successful. In their study, Lloyd et al. [5] compared two powdered infant formulas that differed in fat blend. Palm olein was added to one of the formulas to provide palmitic acid at the level similar to that found in breast milk. The infants fed the milk containing the palmitic acid had less frequent stools, fewer brown stools and more yellow stools than infants fed a fat blend from safflower, coconut and soy oils. The authors explained the tendency towards constipation by the fact that palm olein triglycerides are arranged differently from those of breast milk and are poorly absorbed. Unabsorbed palmitic acid may react with calcium to form insoluble soaps that are associated with stool hardness. This illustrates some of the difficulties encountered in artificially replicating the composition of human milk.

Macronutrients are only a small part of the overall picture, as milk also contains a variety of additional substances that may actively influence growth and development of the infant and stimulate neonatal protection against various diseases. These compounds in breast milk include hormones, growth factors, antibodies, cytokines, glutamine, lactoferrin and nucleotides [6].

As a mediator of biochemical messages sent from the mother to her newborn, breast milk has unique properties. The most recent theories connect both *in utero* exposures and breast-feeding to a wide range of diseases that occur in adulthood. It is thought that infant nutrition is involved in "programming" metabolism in later life. Work in rodent models supports this theory. In rats fed low protein diets during pregnancy or lactation, their offspring suffered from changes in liver metabolism including permanent changes in key hepatic enzymes involved in carbohydrate metabolism [7]. In our laboratory, evidence from studies in female mice fed high levels of fat from different sources supports this theory. In female offspring exposed to low levels of carcinogens, significant changes in the splenic lymphoid system were observed along with enhanced Fas expression in lymphocytes of offspring from mothers fed olive oil [8]. These studies accentuate the importance of the composition of breast milk or breast milk substitutes for the future health of children.

Nucleotides were isolated in human breast milk over 30 years ago and have been introduced into infant formulas around the world in the last 15 years. During this period no deleterious effects have been reported. In their review Lerner and Shamir [3] present data in favor of and against the addition of nucleotides to infant formula. The majority of the evidence shows a beneficial effect of adding these compounds to infant formula. Although the specific biological functions of the nucleotides have not yet been determined, the fact that they appear naturally in the human breast (at physiological concentrations) is highly unlikely that they are beneficial in promoting good health in newborns.

While the addition of nucleotides to formula attempts to make infant nutrition similar to human breast milk, the ready-to-use formulas, albeit more convenient and sterile,

are moving further from the "gold standard." In this issue, Weisbrod and Mimouni [4] present some interesting data on the use of these formulas in newborn infants, and emphasize the variable tolerance levels of different commercially available products. Although regurgitation is a mild form of intolerance, it may, or may not, reflect a greater overall intolerance to specific manufacturing methods and food additives found in the ready-to-use milk. The article discusses at length the numerous compounds added to ready-to-use formulas in order to stabilize and increase viscosity of the milk, as well as the differences in processing methods. Indeed, this may have an impact on the tolerance level of a specific commercial product.

For those of us involved in medical fields one of our primary goals is to provide the best neonatal care available to our children. Proper nutrition is critical for the growth and development of infants and may have meaningful long-term health implications for adulthood. Furthermore, the continuous evaluation of new commercially available products, as carried out by the doctors at the Laniado and Lis Maternity Hospitals, shows a commitment to maintaining high standards of care and providing the best nutrition possible for the next generation.

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