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Human milk, fatty acids, and the immune response: a new glimpse[1,2]

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Human milk contains cellular and "humoral" components that reduce the risk of intestinal and systemic infection during infancy and enhance the ontogeny of the immune system (1, 2). I use "humoral" because proteins, complex carbohydrates, nucleotides, and lipids participate in the immunomodulating activities of human milk. The possibility that lipids in human milk have an antiinflammatory effect emerged when it was shown that a diet supplemented with menhaden fish oil decreased eicosanoid production and improved the survival of newborn rats exposed to hyperoxia (3). This concept was strengthened when blood mononuclear cells obtained from adult subjects fed a diet enriched in polyunsaturated fatty acids (PUFAs) showed reduced proinflammatory characteristics (4). Both menhaden fish oil (3) and human milk (5) are enriched with docosahexaenoic acid (DHA).

An unanswered question in human neonatal nutrition is whether a diet must be supplemented with pharmacologic amounts of DHA to have antiinflammatory effects or whether a diet naturally rich in DHA is sufficient for this outcome. When suckling newborn rabbits were fed a diet supplemented with high-dose menhaden oil, pulmonary alveolar macrophages had an increased content of DHA and intrapulmonary killing of inhaled *Staphylococcus aureus* was impaired (6). No adverse effects were seen in pulmonary host defenses when neonatal rabbits had their diet supplemented with a low amount of menhaden oil.

In this issue of the Journal, Granot et al (7) provide new information about the effects of breast-feeding or formula feeding on the proinflammatory activity of blood mononuclear cells. These investigators cultured blood from human infants exclusively breast-fed or formula-fed until 2–4 mo of age. The blood was incubated with lipopolysaccharide for 24 h and thereafter culture supernates were analyzed and shown to have equivalent concentrations of interleukin 1 and tumor necrosis factor. Comparable concentrations of arachidonic and eicosapentaenoic acids were found in the red blood cells obtained from the breast-fed and formula-fed infants; however, the erythrocytes from the breast-fed infants had >2-fold more DHA. These findings support the concept that human milk increases the content of DHA in cell membranes. DHA was presumably elevated in the blood mononuclear cells of the breast-fed infants, but this phenomenon did not reduce their production of cytokines induced by endotoxin compared with that of similar cells from formula-fed infants.

Although the findings of Granot et al are reassuring regarding the immune responses of breast-fed and formula-fed infants, conclusions must be contemplated within the limitations of the study design. Infants were studied, on average, at 2.8 mo of age. Recent studies showed that the DHA content of erythrocytes is higher in breast-fed infants than in formula-fed infants shortly after birth (8). Thus, it is possible, although unlikely, that an analysis of blood mononuclear cells recovered from infants at <2 wk of age may have yielded different results.

Furthermore, no studies in exclusively breast-fed infants have ascertained the n−3 PUFA content of erythrocytes compared with that of blood monocytes, macrophages, B cells, T cells, or natural killer (NK) cells. This is important because DHA incorporation into NK cells reduces cytokine production, whereas incorporation of DHA into B cell and T cell membranes does not (9). Granot et al did not determine the proportions of monocytes, B cells, T cells, or NK cells in the blood used for culture and this information might have affected their interpretation of the results.

The amounts of interleukin 1 and tumor necrosis factor secreted by the cultured blood mononuclear cells were modest at best. The secretion of cytokines may have been diminished because the total numbers of mononuclear cells in the specimens were low, the absolute numbers of monocytes and NK cells present in the specimens were reduced, the duration of incubation was too long, or blood-related inhibitors of cytokine production were present. Mononuclear cells secrete interleukin 1 within hours of endotoxin exposure, and subsequent metabolism of interleukin 1 may have caused it to dwindle in culture supernates as the incubation time increased. Because only one endotoxin was used as the stimulus, one must also keep in mind that use of a wider range of proinflammatory stimuli might have produced different results.

Last, although increased incorporation of DHA into the cell membranes of immune cells may alter arachidonic acid metabolism, eicosanoid production, and cytokine secretion, Granot et al did not ascertain eicosanoid production in their cultured blood specimens. This information may have broadened our understanding of their study.

Despite these limitations, Granot et al offer a new glimpse into neonatal nutrition and its effects on the immune system. It

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is hoped that their investigation will initiate more studies of feeding practices and their influence on immunologic function during infancy.

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