Role and Function of Long-chain Polyunsaturated Fatty Acids in Infant Nutrition

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The term “long-chain polyunsaturated fatty acids” (LCPUFAs) is generally used to refer to arachidonic acid (20:4n-6) and docosahexaenoic acid (DHA) (22:6n-3), which are derived from the two noninterconvertible dietary essential polyunsaturated fatty acids (PUFAs), linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3), respectively (1). Eicosapentaenoic acid (20:5n-3), the most common LCPUFA in marine oils, is popular for preventive purposes (2) but does not seem to play any role in tissue growth and development.

The supply of linoleic acid and α-linolenic acid modulates arachidonic acid and DHA synthesis (3). Endogenous LCPUFA synthesis from dietary $^{18}$C precursors occurs from the first days of extrauterine life (4). However, the contribution of endogenous synthesis from α-linolenic acid to blood and tissue pools of infants does not match that of diets with preformed DHA (5). Similarly, neither linoleic acid nor the intermediate omega-6 (n-6) fatty acid, γ-linolenic acid, can support plasma arachidonic acid levels as well as preformed arachidonic acid in preterm infants (6), whereas the data are controversial for term babies (7).

Both arachidonic acid and DHA are present in human milk, but it is still unknown whether they should be added to infant formulas. The tissues of breast-fed infants, including the brain, are richer in LCPUFAs than are those of formula-fed infants (8–10), but the functional significance of these observations is still speculative.

HUMAN MILK AND DEVELOPMENTAL ADVANTAGE

The history of LCPUFAs as possible “food for thought” (11) dates from the time when the superiority of breast feeding for the developmental outcome of children was first recognized. Positive associations between breast feeding and developmental achievement have been reported for >70 years. In a recent meta-analysis (12), 20 studies selected over a 30-year period (1966–1996) were assessed to determine the differences in cognitive function between breast-fed and formula-fed groups. Breast-fed subjects showed an overall adjusted advantage of 3 points in intelligence.
assessments. Low-birthweight infants showed a larger difference (5 points). In practical terms, an IQ increase from 100 to 103 would cause an individual to increase from the 50th to the 58th centile of the population. Longer-term effects in adulthood have been poorly explored. In one of the few reports available so far, being breastfed in infancy had no advantage for an older adult population, the use of a dummy (pacifier) in infancy having the major impact on performance scores (13).

In interpreting these data, the individual roles of the practice of breast feeding, of human milk as a food, and of the LCPUFAs derived from human milk or formulas should be clearly differentiated. Indeed, it is obvious that the environment also may strongly affect neurodevelopmental achievement. Factors favorably connected with breast feeding (such as a term pregnancy, higher socioeconomic status, and better maternal education) are usually associated with optimal nutritional conditions during pregnancy, and possibly also influence milk composition. An increased body mass index and weight in pregnancy may be associated with an increase in fat secretion into milk (14). A positive maternal attitude toward breast feeding could benefit a child’s mental development through improved bonding and nurturing behavior, as suggested by studies showing a positive effect on the psychomotor and mental development of infants when breast feeding is prolonged (15).

The isolated positive effects of human milk as a food have been explored in studies of the effects of human milk given by tube to preterm babies (16), benefits on development being most evident in the second year of life in small-for-gestational-age infants (17). In healthy term infants, it would be virtually impossible to isolate the effects of human milk as a food from those of the practice of breast feeding per se; it would require huge numbers to identify any independent influences, in view of the negligible developmental risks in these subjects compared with those in preterm and low-birthweight infants.

Even considering human milk as “food,” many nutrients could influence infants’ development, such as LCPUFAs, oligosaccharides, amino acids (either incorporated in complex compounds or supplied as free amino acids), trace elements, hormone-like molecules, and contaminants.

**LONG-CHAIN POLYUNSATURATED FATTY ACIDS IN HUMAN MILK**

The fat composition of human milk includes saturated and monounsaturated fatty acids, but PUFAs account for only 20% of the total. The polyunsaturated fraction, however, includes both essential fatty acids (linoleic acid and α-linolenic acid) and LCPUFA molecules of the n-6 and n-3 series, deriving respectively from linoleic acid and α-linolenic acid as in most animal fats. LCPUFA levels (as a percentage of total fatty acids) are usually high, even doubled, in colostrum. As far as their distribution is concerned, 85–90% are incorporated in triglycerides (98–99% of total fat) and 10–15% in phospholipids (1–2% of total fat). This peculiar pattern further contributes to the unique composition of human milk (18).

Maternal dietary factors during lactation may influence the fatty acid composition of milk by modifying maternal plasma lipids. Recent work using stable isotopes
LONG-CHAIN POLYUNSATURATED FATTY ACIDS showed that an estimated 30% of human milk fatty acids are derived directly from the maternal diet, whereas 70% are derived from the mother's body stores (19). Some protective mechanisms seem to be at work in the maintenance of the LCPUFA fraction of milk fat. The secretion of n-6 LCPUFAs into human milk does not appear to depend on maternal dietary intake of preformed LCPUFAs, as studies have shown that the milk of rural African women whose diets include minimal amounts of animal fats still has a substantial n-6 LCPUFA content (20). Human milk DHA is more variable, and the influence of dietary intake on milk content is greater than that observed with arachidonic acid (21). Whereas the total PUFA content of milk does not vary significantly from colostrum to mature human milk or during the rest of lactation, both arachidonic acid and DHA levels decrease in weight percentages of total fatty acids during the first 3 months of lactation. There is little published information on the absolute LCPUFA content of human milk through the course of lactation. In a recent follow-up study, we observed that the hind milk of 10 mothers showed a stable and progressive increase in the total fat and essential fatty acid content through 12 months of lactation, whereas arachidonic acid and DHA levels remained relatively stable, in the range of 7–8 mg/dl for DHA and 12–17 mg/dl for arachidonic acid (22). Thus the supply of LCPUFAs appears to be more continuous and less prone to time-dependent changes in human milk composition when it is expressed as a percentage of the milk fatty acids.

LONG-CHAIN POLYUNSATURATED FATTY ACIDS AND DEVELOPMENTAL ADVANTAGE: BIOLOGIC AND EXPERIMENTAL EVIDENCE

The anatomic evidence linking breast feeding to higher IQ scores lies in the higher DHA levels found in neuronal structures of breast-fed infant victims of sudden infant death syndrome compared with those in their formula-fed counterparts (8,9). This is not limited to brain, as in vivo observations in infants undergoing minor orthopedic surgery have shown that the dietary LCPUFA supply affects the fatty acid composition of skeletal muscle membrane phospholipid as well (10).

It is generally accepted that the biologic effects of fatty acids are mediated through modifications of the physical properties of membranes, leading to different membrane-linked enzymatic activities (23). Thus DHA could play a key role in the structural development of neural and synaptic networks by imparting particular fluid properties to the membrane bilayers. In the disc membrane of retinal photoreceptors, DHA contributes 50% of total fatty acids and accounts for 75–100% of the fatty acids at the sn-2 position of phosphatidylethanolamine. It is claimed that this biologic phenomenon is strictly connected to rhodopsin metabolism (24). Cell-to-cell interactions also may be influenced by the LCPUFA composition of circulating and membrane lipids. In particular, arachidonic acid seems to have possible neurotransmitter roles as second messenger and even as primary messenger in the synaptic cleft of the brain (25).

In nonhuman primates, a subnormal accumulation of retinal and brain DHA leads
to abnormal retinal physiology and poorer visual acuity, as revealed by tests of visual fixation, stereotyped behavior, and locomotor activity. Experiments dating back to the early 1970s showed that dietary deprivation of both total fat and n-3 PUFA was associated with changes in the amplitude of electroretinographic waves (26). Deficiency of n-3 PUFA before full retinal maturity also had marked effects on retinal DHA content and function (27). Decreased levels of DHA in the brain tissue of animals fed α-linolenic acid–poor diets have been associated with altered learning patterns, whereas dietary supplementation with preformed DHA increased DHA levels in animal brains and improved their learning skills (28).

The hypothesis that LCPUFAs have a physiologic role in sustaining the developmental achievement of infants is thus plausible owing to their effects on membranes (ranging from nerve cell differentiation to activation of visual pigments and enzymatic activities) and on the metabolism of neurotransmitters.

LONG-CHAIN POLYUNSATURATED FATTY ACIDS AND DEVELOPMENTAL ADVANTAGE: EVIDENCE IN HUMAN INFANTS

Fetal and infant brain DHA content is more affected than is arachidonic acid content by the diet (8,9). It has been calculated that on average, the fetus accumulates ~40–60 mg of n-3 LCPUFA/kg body weight daily (29,30). Compared with term infants, preterm infants are at greater risk of inadequate LCPUFA accumulation owing to interruption of the placental supply (31). Preterm infants should thus theoretically be more exposed to either the negative effects (if deprived) or the positive effects (if fed enriched products) of LCPUFAs.

There is a broad consensus of opinion today that visual development in preterm infants—either breast-fed or fed an enriched formula—is superior to that of infants fed formulas containing no LCPUFAs, irrespective of whether the outcome is assessed by electroretinography, visual evoked potentials, or preferential looking (32). As far as term infants are concerned, earlier observations also showed an advantage of breast feeding over standard formula feeding for visual performance, in association with higher DHA levels (33). In two intervention studies, visual development in breast-fed infants and infants fed DHA-supplemented formula was superior to that of infants fed unsupplemented formula at ages 2 months (34) and 30 weeks (35). In a third study, the visual-developmental advantage was found in the second semester of life, after the end of the supplementation period (36). Others have shown a similar trend but without reaching statistical significance, perhaps because of the small numbers of infants included in the feeding groups (type II error) (37), whereas two studies showed no effect at all (38,39); these latter results perhaps reflected the efficiency of DHA turnover within the ocular tissues (40). Heird et al. proposed that the visual effects of dietary supplementation were seen only in studies in which the placebo diet contained <2% fatty acids as α-linolenic acid (41), but this hypothesis is not consistent with the current evidence (39).

With the limited amount of information presently available, it is thus still controversial whether term infants can accumulate DHA levels adequate for retinal
function when they are given LCPUFA-unsupplemented formulas, and conversely whether there is any favorable effect of a better DHA status on visual function (42).

Although the interpretation of these visual studies is open to speculation, there is no firm evidence about their meaning in terms of mental development. Histologic evidence suggests that DHA in the cerebral cortex depends more on exogenous supply than on the retinal lipid pool (9). To clarify the relations between LCPUFA intake and cognitive achievement, neurodevelopmental performance has been investigated in several studies using standardized tests of child development. As with all global development tests designed for administration in infancy, their primary use is to assess current ability rather than to predict long-term outcome, which is subject to many intervening variables (43).

Studies on preterm infants have reported a functional correlation between early DHA intake and an improved short-term neurodevelopmental performance with Bayley’s developmental test (44). Several trials have been conducted in term infants, with controversial results. In some studies, no beneficial effects of LCPUFA supplementation have been reported with conventional developmental assessment (39,45,46). Conversely, in another study, artificially fed infants examined using an ad hoc problem-solving test at age 10 months were found to have higher developmental scores when compared with counterparts randomized to a nonenriched formula in the 0- to 4-month period (47).

We have reported a scoring advantage on developmental quotient (DQ) testing (assessed by the Brunet-Lezine graded psychomotor scale) in a population of term 4-month-old infants whose diet had included arachidonic acid and DHA, when compared with matching formula-fed groups (48). Whereas DHA was the only PUFA in erythrocytes that we found to be significantly linked to DQ scores at 4 months (49), arachidonic acid concentrations in plasma phospholipids also were correlated with performance \( r = 0.40; \ p = 0.002 \) in a sample of 57 term infants. Among the four developmental areas covered by the Brunet-Lézine test, infants supplied with LCPUFAs scored significantly better in the eye/hand coordination area (50). At a 24-month follow-up examination, the DQ score was no longer different among the three original feeding groups, but a correlation still existed between the LCPUFA composition of erythrocyte phosphatidylcholine and the DQ scores, irrespective of the early division into matching dietary subsets; the arachidonic acid–to–linoleic acid ratio showed the strongest association with neurodevelopmental performance (51). A possible role on membranes of circulating arachidonic acid as distinct from DHA may thus be hypothesized.

These results strongly suggest that the relation between LCPUFAs and DQ belongs to that area of infant development directly dependent on visual function, so linking the results of the visual and the developmental studies. Nevertheless the lack of any association between the 4-month LCPUFA pattern and later developmental performance raises doubts about the long-term effects of early differences associated with the LCPUFA supplementation. Alternatively, the available conventional tests may not be optimal for detecting differences in the neural domain influenced by early LCPUFA status.
It is quite difficult to compare the results of developmental studies in term infants. Various LCPUFA mixtures, amounts, and sources (triglycerides of marine and single-cell oils, phospholipids from egg yolk, and so on) have been used for dietary enrichment. Different outcome measures (neurodevelopmental, visual function) and different methods of assessment (Bayley, Brunet-Lézine, MacArthur, and problemsolving tests for neurodevelopment; electroretinograms, visual evoked potentials, preferential looking, and other vision tests for visual function) make comparisons difficult. Moreover, most studies have concentrated on short-term outcome, whereas few have assessed medium-term outcome, and none, long term; in addition, study design and sample size varied. Thus the possible independent effects of dietary LCPUFA enrichment in healthy, artificially fed, term babies are still far from being defined, and scientific agreement on methods (particularly for assessing development) and on the appropriate LCPUFA composition for dietary enrichment is needed before wide scientific consensus can be achieved.

The ability to show that better maternal DHA status (as reflected by breast-milk DHA levels) may be an advantage for breast-fed infants would help to define the value of greater DHA bioavailability for infant development. There is only one published trial examining the effects of maternal dietary DHA enrichment on infant development. This showed a minor advantage at 1 year but not at 2 years (52). A cause-effect relation between the LCPUFA content of human milk and developmental achievement has still not been established. Future studies should focus on the role of LCPUFAs in pregnancy, and their possible effects on fetal growth and development.

Maternal LCPUFA status affects the LCPUFA status of the newborn infant (53). In trials conducted so far on the effects of the dietary enrichment with n-3 LCPUFAs in pregnancy, only gestational length and infant birth weight were identified as outcome measures, with contrasting results (54-56). If we accept a functional role for LCPUFAs, the changes resulting from alterations in DHA status at birth could extend their influence to postnatal development and represent a major factor in analyses of the functional effects of LCPUFAs supplied during the postnatal period. In a recent study, dietary DHA intake accounted for only 32% of the variability in the apparent DHA status of term infants at age 6 weeks, whereas DHA concentrations in plasma phospholipids at birth accounted for >50% of the variability (57).

**DIETARY LONG-CHAIN POLYUNSATURATED FATTY ACIDS: OTHER ROLES**

In spite of the many trials on the role of LCPUFAs in the neural domain, few studies are available in which their effects on other tissues and regulatory systems have been investigated.

It has been shown that low levels of DHA and LCPUFAs in skeletal muscle membrane phospholipids are associated with insulin resistance and obesity in adults (58). The interrelations between the type of early infant feeding, skeletal muscle phospholipid fatty acid composition, and glucose regulation have been investigated in a group
of young children undergoing elective surgery (10). Skeletal muscle biopsies and fasting blood samples were obtained from 56 normally nourished young children younger than 2 years. Subgroups of breast-fed and formula-fed infants were compared. Breast-fed infants had a significantly higher percentage of DHA and total LCPUFAs in muscle phospholipids than those in the formula-fed group, with lower plasma glucose levels. In a further analysis on a third group of children, significant inverse correlations between fasting plasma glucose and the percentage of both DHA and total LCPUFAs in membranes were found, in agreement with data on adults (59). The authors speculated that early changes in skeletal muscle membrane phospholipid fatty acid saturation might play a role in the subsequent development of diseases associated with insulin resistance. Indeed, the relations between the LCPUFAs synthesis rate and insulin levels seem quite complex, as shown by the increased levels of n-6 LCPUFAs in plasma lipids of obese children with increased insulin levels (60). Moreover, desaturases show different responses to obesity states (61), as confirmed by negative correlations between indices of Δ-6 desaturase activity and blood insulin levels found in a group of obese preadolescents (62). These data suggest that the insulin-associated stimulatory effects on LCPUFA synthesis shown in earlier experiments (63) could depend on the degree of insulin sensitivity. Studies of the effects of dietary PUFAs on the expression of the genetic message may highlight the complex interactions between dietary fats, membrane composition, and insulin action (64).

The interaction between dietary supplementation with LCPUFAs and eicosanoid synthesis and function is another area poorly investigated in infancy. Dietary enrichment with LCPUFAs did not affect the urinary excretion of arachidonic acid–related end products (65), but no data on intermediate reactions and functional indices are available.

Finally, we should mention the potential role of dietary LCPUFAs as coadjuvant treatment in inborn errors of metabolism, even in older children. Although a beneficial effect has been shown in neurodegenerative disorders (66), other inherited diseases that may affect the development of the brain and visual function might also benefit from dietary supplementation with LCPUFAs. We have recently investigated the effects of a 12-month period of supplementation with LCPUFAs in a double-blind, placebo-controlled trial in children treated for phenylalanine hydroxylase deficiency (type I hyperphenylalaninemia) (67). These patients require a low-phenylalanine diet, severely restricted in animal foods and LCPUFAs. Consequently they have poor LCPUFA status, particularly for DHA. Twenty children with well-controlled hyperphenylalaninemia were randomly allocated to receive either a fat supplement (supplying 26% of fatty acids as LCPUFAs, including 8% as DHA) or placebo. The fatty acid composition of plasma and erythrocyte lipids and the visual evoked potentials were measured at baseline and after 12 months of supplementation. At baseline, the children with hyperphenylalaninemia had a worse DHA status and prolonged P100-wave latencies compared with controls. At the end of the trial, the LCPUFA group showed a significant increase in DHA levels in both plasma and erythrocyte lipids, whereas the P100-wave latency decreased. Changes in P100-wave latency were negatively associated with the DHA changes. Thus we may conclude that
balanced dietary supplementation with LCPUFAs in children with hyperphenylalaninemia is associated with an increase in the DHA pool and improved visual function.

CONCLUSIONS

It is difficult to establish that the developmental advantage derived from breast feeding somehow depends on human milk fatty acid composition. Trials comparing breast-fed with formula-fed infants have proved difficult to interpret because there are so many nutritional differences between breast milk and infant formulas, apart from their respective LCPUFA contents. Developmental outcomes are multifactorial processes that encompass demographic, social, cultural, economic, and family variables, all of which may influence the early developmental advantage recognized for breast-fed infants. Conversely, whether LCPUFAs are supplied in the diet or are derived from endogenous synthesis, LCPUFA status has been linked with aspects of early development in several studies.

We still must differentiate between the role of DHA status at birth (which depends on the maternal dietary supply in pregnancy and on placental transfer) and that of postnatal dietary supply. The fatty acid composition of cell membranes and circulating lipids is a dynamic system; thus functional effects also may be transient unless they involve complex mechanisms such as memory and associative processes. In any event, we stress that feeding human milk and breast-feeding practice are two clearly distinct issues, so LCPUFAs might have positive "pharmacologic" effects only in formula-fed babies, whereas many other factors could account for the developmental advantage observed in breast-fed babies.

Studies dealing with the functional effects of LCPUFAs should clearly differentiate between outcome measures observed in the short term (when infants are still receiving the study diets), in the medium term (from weaning up to age ~2 years), and in the longer term (adolescence and adulthood). Researchers should separate the effects of breast-feeding practice from those of human milk as a nutrient source, and clearly identify the roles of LCPUFAs in human milk and infant formulas. An ideal study design should compare outcome measures in babies fed human milk at two different LCPUFA levels (low vs. high), a formula enriched with LCPUFAs extracted from human milk, a formula enriched with LCPUFAs from different sources, and a standard formula. Whereas it is possible to extract and prepare fats from human milk, including them in a formula may present technical problems. After adjusting for the infants' fatty acid status at birth, a similar design could allow one to explore the effects of human milk LCPUFAs while overcoming the bias introduced by the fact that breast-fed babies are a self-selected, nonrandomized group.

LCPUFAs also may play different roles in immune function, membrane-related activities, and hormone–receptor interrelations. These are poorly explored, but should be studied for their potential applications in the fields of preventive and developmental medicine and clinical nutrition.
REFERENCES


DISCUSSION

Dr. Räihä: One of the first slides you showed was concerned with the placental transport of LCPUFAs, and if I am not completely wrong, it seems that the amount of LCPUFAs transported through the placenta—say during the last trimester—is substantially more per kilogram body weight than is provided by breast milk after birth. How do we know that we should not be supplementing breast milk with LCPUFAs? We know, for instance, that we need to supplement formulas for preterm infants, and maybe even for term infants, with LCPUFAs. Why not provide supplements for breast milk?

Dr. Agostoni: Thank you for this stimulating question. I will try to give an objective picture of the long-chain PUFA status. To me it is clear that for preterm infants, we must provide supplementation, at least for those before week 37 of gestation, because even at 35 weeks, 40 to 60 mg of n-3 LCPUFAs per kilogram per day are being supplied through the placenta, which is a great deal. It is clear that in term babies, if there are good stores of LCPs at birth, then during the first few days of physiologic weight loss the LCP levels in blood are maintained by
release from storage. So nature has provided the healthy term infant in the last stages of pregnancy with sufficient stored LCPs to maintain levels at a time that is crucial for new synaptic connections and so on. For preterm infants, it appears from the work of Friedman et al. (1) that the critical period is about weeks 34–37 of gestation. Before that the storage of LCPs is much less. There is now no question that such infants should have LCP supplements. For me, the problem is more the term baby in the first 2 to 4 weeks. Human colostrum is a low-fat food in which the percentages of arachidonic acid and DHA are double those in mature human milk, but in 3 to 4 days of lactation, you have a switch to triglycerides.

Dr. Endres: I am glad that I am able to agree with your very cautious conclusions concerning the administration of LCPUFAs to term infants. However, I know about your participation in a recent consensus conference, the proceedings of which have been submitted for publication (2). This consensus conference gives a strict recommendation that formulas for term infants should be supplemented with LCPUFAs. I think that what we have heard in this Workshop gives quite a different impression, so maybe there is not really a consensus among these experts?

Dr. Agostoni: This is a political question! You know that at that consensus meeting, other people were even less favorable than I am over the use of LCPs—Gibson (3,4), for example, whose data were published in Pediatrics and the American Journal of Clinical Nutrition. For me, the sense of those final conclusions was that preterm infants should definitely receive supplements of LCPs. The problem is at what level. If we supply the levels found in human milk, they do not reach the amounts transported through the placenta. Crawford (6) would supply levels similar to those found in cord blood, but the lesson from many studies is that we should be more cautious, because we do not know the effects on peroxidant and oxidant status of giving such large amounts. For term infants, the message was that there is no evidence that LCPs are in any way dangerous. A consensus view of recent publications on the subject suggested a lack of either positive or negative effects. The advice was, if we want to supplement a formula with LCPs, we need to match the levels found in human milk. I would have preferred to recommend that babies who are formula fed from birth should be supplemented with LCPs. If formula feeding is started only after 1–2 months, then maybe you do not need such supplementation. For me, this is the meaning of the consensus statement.

Dr. Hernell: The original idea was that the preterm infant does not have the capacity for elongation and desaturation. There are now several articles showing that they do have the machinery for it, as you mentioned (3,4). Recently Uauy et al. (7) presented a paper in which they showed that the low-birthweight infant may even have a greater capacity for synthesis. Would you like to comment on that?

Dr. Agostoni: The only comment I can make is that I am not surprised about this increased capacity—the problem is whether such infants can achieve the synthesizing capacity necessary to meet their needs. Another problem is whether, if we give these molecules preformed, we may derange the capacity for endogenous synthesis.

Dr. Haschke: Here is another political question. You mentioned several times that studies have shown that breast-fed infants have a favorable outcome compared with formula-fed infants in terms of neural development. But you probably also know about Lucas’s study (5)—the largest one ever done under controlled conditions, in which children who were exclusively breast-fed according to World Health Organization requirements were compared with formula-fed infants with or without LCPUFAs. In this large group, Bailey tests were done at 9 and 18 months, and there was no difference in the Bailey scores between the breast-fed and formula-fed infants. It was not even necessary to adjust for socioeconomic factors.
Dr. Agostoni: We need statisticians sometimes! We combined many studies in our meta-analysis, and the difference in scores is clear. I am not surprised that in some populations, such differences cannot be found. Many factors can affect developmental tests—for example, whether feeding is given on demand, the type of follow-up, the sample size, the fact that infants selected for trials are a special group, and so on. Infants in any trial may be growing up in particular conditions, so that bias is unavoidable. This is an area in which long-term follow-up is essential.

Dr. Haschke: This is what Lucas is presently doing. He is now following up this cohort at ages 4–5 years. It might be possible that the question on long-term outcome can be solved by performing IQ tests, which are predictive of adult IQ.

Dr. Moro: You spoke about the possible advantages of LCPUFAs regarding visual acuity and neurodevelopmental functions. What about the role of LCPUFAs in immunologic activity? These agents are used regularly to treat some types of disorders such as skin disease caused by atopic disease or allergy. Could this be a good reason to give LCPUFA-enriched formulas to babies with a history of allergy?

Dr. Agostoni: If you look at the literature on the effects of the LCPs in atopic disorders, you find all types of result. Some people improve, and some people worsen, particularly with n-3 and eicosapentaenoic acid. On these grounds, it is still too early to suggest supplementing formulas for atopic individuals with LCPs. I am convinced that some atopic people are particularly sensitive to LCP enrichment. We need a marker to select this population of atopic subjects.

REFERENCES