The role of essential fatty acids in neural development: implications for perinatal nutrition

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ABSTRACT The brain is 60% structural lipid, which universally uses arachidonic acid (AA; 20:4n-6) and docosahexaenoic acid (DHA; 22:6n-3) for growth, function, and integrity. Both acids are consistent components of human milk. Experimental evidence in animals has demonstrated that the effect of essential fatty acid deficiency during early brain development is deleterious and permanent. The risk of neurodevelopmental disorder is highest in the very-low-birth-weight babies. Babies born of low birth weight or prematurely are most likely to have been born to mothers who were inadequately nourished, and the babies tend to be born with AA and DHA deficits. Because disorders of brain development can be permanent, proper provision should be made to protect the AA and DHA status of both term and preterm infants to ensure optimum conditions for the development of membrane-rich systems such as the brain, nervous, and vascular systems. The origin of the brain and n-3 fatty acids

The origin of the aerobic life

It is interesting to speculate that this adhesion to the consistent fatty acid profile found in neural tissue might well date back to its very origin. The planet is some 4.6 billion years old and life has existed on it for probably 3 billion years. However, until 600 million years ago, the dominant life form seems to have been blue-green algae and bacteria. The algae carried out photosynthesis and in so doing, excreted oxygen into the environment. About 600 million years ago, the oxygen tension rose above the Pasteur point, at which aerobic metabolism becomes thermodynamically feasible. Animal life then appeared on the scene and, with remarkable rapidity, all 30 or so phyla were established.

The origin of the brain and n-3 fatty acids

From what we know about the chemistry of the algae, the photosynthetic process synthesized a wide range of molecules, some used as energy traps, others for biosynthetic processes and for structural purposes. Of particular interest is the synthesis of β-carotene, α-linolenic acid (ALNA; 18:3n-3) and other n-3 fatty acids, tocopherols, and ascorbic acid. It is not surprising that these oxygen-sensitive molecules are synthesized together because the planet originated in a fireball, in which oxygen, a highly reactive element present in great abundance, combined with every other feasible element. So, when life emerged, it was operating anaerobically. Consistent with the third law of thermodynamics, the system was liberating oxygen and hence

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Introduction

Present-day concepts of nutrition requirements or reference values tend to be concerned with growth and evidence of disease. However, the feature that distinguishes Homo sapiens from other species is not growth but the remarkable extent to which the brain is developed. Indeed, the comparative evidence states that those species that developed rapid growth to a large size sacrificed relative brain capacity as they did so (1). The question raised by such evidence is that it could be more appropriate to address recommendations from the positive standpoint of optimum needs and brain development.

It is generally accepted that protein is relevant to body growth and minerals, to skeletal growth. However, the main structural material of the brain is lipid, which has a unique profile of long-chain, polyunsaturated fatty acids (LCPUFAs), which are essential fatty acids (EFAs). This profile is maintained in all species so far studied and it is relative size that appears to be sacrificed rather than composition (2). This observation led us to the interpretation that the availability of these fatty acids was a limiting factor in brain development and evolution (1, 3).
molecular products would tend to be reduced. This means that in today’s terminology, they would be susceptible to peroxidation.

Perhaps the most important evolutionary event that eventually led to our own type of life form was the origin of the animal photoreceptor. The cluster of molecules involved is of the same family as those made by the plant photoreceptor (i.e. retinol, docosahexaenoic acid (DHA), α-tocopherol, and ascorbic acid). The difference between these molecule clusters is that the photoreception by the blue-green algae had resulted in converting the sun’s energy into chemical energy, whereas the animal photoreceptor converted it into electrical energy. The symbiotic relationship between the photoreception and electron-transfer processes, which in an aerobic environment, could now operate with far greater efficiency, could have on its own or in collaboration with attendant proteins susceptible to electrical energy resulted in movement. That movement would have been toward light. If the system faced away from light, the energy would fade, if it faced the light, it would strengthen. This meant that the primitive photoreception-based systems would move towards light and hence toward the source of photosynthesis, which means toward food. In that sense, the subject of nutrition was born and the seed for our contemporary brain was sown.

In terms of fatty acids, the first animal life forms with photoreception evolved in a sea rich in n-3 fatty acids and their attendant, protective molecules. It is most interesting to note that this cluster has apparently not changed with time.

**The origin of n-6 fatty acids and mammals**

The second aspect of evolution that has a bearing on the fatty acids is the collapse of the giant dinosaurs, ginkos, ferns, and their allies with their replacement by the more gentle flowering plants, which reproduced with protected seeds. This started to happen about 100 million years ago. We do not have evidence on the nutrient requirements of the land-based animals of that time, but the fish had dominated the oceans and we can assume from today’s fish that they required n-3 fatty acids for their reproduction (4). As the land-based plants produced a wealth of green leaves, this too would have been an n-3-rich food chain. However, the new plants with protected seeds introduced oil rich “packages” into the food chain, and the oil was rich in linoleic acid, the parent of the n-6 family of EFAs. It is likely to be no coincidence that the mammals which evolved at the same time used n-6 fatty acids for their reproduction.

One key to this response may well be the dependence of the vascular system membranes on the n-6 fatty acids. The vascular system is not only a key component responsible for delivering energy and nutrients to the brain, but it also featured to a remarkable degree in the evolution of the placenta. The placenta is basically a rapidly growing vascular system with a high concentration of n-6 fatty acids, especially arachidonic acid (AA), in its membrane lipids. Of added interest is the fact that the brain in all species so far studied uses a balance close to 1:1 as n-6:n-3 fatty acids in the inner cell-membrane lipids (2).

Hence, the probability is high that the principles of the food chain in relation to these EFAs and their attendant nutrients were fundamental to the evolution of the human brain and that the same cluster of nutrients may be relevant to brain and vascular system disorders.

**Neurodevelopmental disorder**

Each year some 1.4 million babies are born with or develop severe neurodevelopmental disorders with lifelong consequences. Ever since the discovery of the link between iodine deficiency and cretinism, it has been known that inadequate nutrition can lead to neurodevelopmental disorders that can be eradicated with appropriate nutritional intervention. Handicaps associated with neurodevelopmental disorders are, however, still serious problems with a disproportionately high cost to society because of their lifelong impacts. The cost could be in excess of £2 billion (~$3.2 billion) a year in the United Kingdom alone. This cost excludes the very much larger number of those with mild disabilities, which means that they have lost the opportunity of reaching their full genetic potential.

The causes of such handicaps are largely unknown. However, there is an important clue to the prevention of such disorders because there is a close relationship between low birth weight and handicap that includes poor cognitive ability, mental retardation, poor vision, hearing, cerebral palsy, retinopathy, blindness, and autism. The incidence of such handicaps at its lowest is 6–8/1000 live births in the birth-weight range from 3.5 to 4.5 kg. In the very-low-birth-weight range (< 1.5 kg), the incidence rises to > 200/1000.

Although there has been a rapid reduction in the number of babies dying at birth, there has been no corresponding decrease in the number of handicapped babies or those who develop mental or visual defects after birth. Reports from Sweden (5) and the United Kingdom (6) indicate that since 1967, there has been a nearly threefold increase in the incidence of cerebral palsy among low-birth-weight babies.

Excess oxygen and a vitamin E deficit used to be considered the cause for the retinopathy of prematurity. By contrast, lack of oxygen during birth (asphyxia) was considered the principal reason why babies developed mental handicaps such as cerebral palsy. Both assumptions are now being questioned. Quite often there may be a sudden lack of oxygen during birth but in a healthy baby, this does not seem to cause much harm. In others, damage follows and it is still difficult to predict which baby will eventually become spastic or have a mental, visual, hearing or physical handicap. The common denominator in the apparently different defects associated with low birth weight is that they occur when the brain is developing.

**Brain growth and the mother**

The individual responsibility for the development of the brain rests with the mother. Some 70% of the total number of brain cells to last an individual’s lifetime have divided before birth. Indeed, the most active period of brain cell division is in the first few weeks of embryonic development, almost before a woman knows she is pregnant. At this stage the nutrition of the embryo is solely dependent on its mother’s health, nutrition, and metabolism because the placenta has not yet formed.

At the end of the first two months, the head makes up almost half of the embryo and directs the first movements of the tiny hands and feet. This illustrates the overriding priority that human physiology devotes to brain development. Then the placenta takes over and literally pumps selected nutrients into the growing fetus. At this stage, the fetal brain is consuming 70% of the dietary energy fed to it by the mother to meet the demands for its pro-
digous rate of growth. When the baby is born, it will still use up to 60% of the energy from its mother’s milk for growth, but now the rate of cell division has slackened and in response to light and to the need to breathe and make deliberate movements, synaptic connections are made at a furious rate between the cells, possibly resulting in a cell making as many as 6000 to 10,000 connections with other cells. The surface area of the membranes constructed to serve these purposes is phenomenal and makes use of both AA and DHA as basic building blocks.

**Essential fatty acids**

The first evidence that the EFA component of the neural membranes was limiting for neural integrity was derived from studies on allergic encephalomyelitis when Clausen and Møller (7) reported in 1967 that the rat brain could be made susceptible to an induced autoimmune attack by depleting its membranes through dietary deficiency of EFAs. There is now much evidence (3, 8–14) that both neural integrity and function can be permanently disturbed by deficits of n−6 and n−3 EFAs exercised through the mother on fetal and neonatal development.

**AA and DHA**

Fats are used for two purposes in the body: storage (energy reserves) and structural. The structural fat is built from nonessential and essential fatty acids in a manner similar to the way in which protein is built from nonessential and essential amino acids.

The EFAs occur in plants as linoleic acid (LA; parent n−6) and ALNA (parent n−3), which are chain elongated and desaturated from 18-carbon-chain lengths with two and three double bonds to 20 and 22 carbon-chain lengths and much higher degrees of unsaturation with four and six double bonds.

The biosynthetic process responsible is slow, alters with age, and in some species, is almost nonexistent. The preformed long-chain fatty acids are incorporated into the developing rat brain with a >10-fold efficiency when compared to the parent EFAs (8). The importance of this point is that the brain uses only the preformed long-chain EFAs and not the parent EFAs.

**Dynamics of EFA metabolism**

If radioactively labeled fatty acid is administered to a rat by stomach tube as a pulse dose, the extent to which it is oxidized, compartmentalized into different lipid pools, desaturated, and chain elongated to AA can be followed. The desaturation of LA is slow (15) but its distribution within the different individual lipid pools is rapid. Consequently, the LA is removed from the free fatty acid pool, leaving only a small amount available for desaturation. Much of it enters triglyceride, phosphoglyceride, or sterol ester pools, leading to oxidation, sequestering into membranes, or biliary excretion. In such experiments, between 50% and 60% of the LA was found in the triglycerides, with the remainder found in the phosphoglycerides (40–50%), cholesterol ester (2%), and free fatty acid (0.6%) compartments. ALNA was oxidized at a marginally higher rate but only 12–15% of AA and DHA was oxidized over a 24-h period (16). The reason for the difference is that AA and DHA are preferentially incorporated into cell membranes, and because they then become part of the cytoskeleton, they are less available for oxidation.

In rats, where most of the studies have been done, the rate of conversion in the intact animal is slow and preformed AA and DHA are used nearly 30 times more efficiently for incorporation during brain development (8). In species more similar to humans, the rate appears to be much slower and is barely detectable in carnivores (17). In the larger, land-based mammalian species, which, other than *Homo sapiens*, have small brain capacities, there is ample LA and ALNA in their liver lipids and other tissue stores, but the LCPUFAs are present in only small amounts (2). In multigeneration experiments on low EFA intakes, loss of LCPUFAs was found to be associated with a reduction in brain-cell DNA at birth (18). This reduction occurred in the absence of any significant difference in birth weight.

**The vascular system**

Another membrane-rich system is the endothelial cell system, which lines the arteries. Endothelial cells are flat and thin, so a large part of it is outer membrane. It uses EFAs for its structural integrity and also as precursors for the synthesis of prostacyclin, a hormone-like substance that prevents accidental thrombus adhesion during physical contact under high pressure between the platelet and the arterial wall (19). Again, the balance of n−3 and n−6 fatty acids is relevant to the control of vasoconstrictive and thrombogenic activities via the cyclooxygenase products, the prostaglandins, derived from the long-chain EFAs (20, 21).

Additionally, lipoxygenase products are involved in vascular constriction and dilation and in interactions between the white-cell population and the endothelium. In the immune response: the products have activities some 1000 times more powerful than histamine. The synthesis of these physiologically active derivatives of EFAs is in turn dependent on the balance of EFAs in the diet (21).

It has been known for some time that specific n−3 deficits may lead to deficits in learning ability (22). More recently, the extensive use made by the photoreceptor of DHA has led to research that may be relevant to retinopathy of prematurity.

**Preconceptional maternal nutrition and pregnancy outcome**

In view of the association between low birth weight and neurodevelopmental disorder, we attempted to test the experimental data in humans by studying 513 pregnancies in a population in Hackney, in the East end of London, where the incidence of low birth weight is high (23). We tracked 44 nutrients by use of a computerized nutrition database that provides a wide range of information on the nutritional quality of the individual intakes. In general, we entered data from 7-d weighed-food-intake diaries. If data on a food item was not in the database, the item was analyzed in the laboratory and the food-composition data were then added to the database.

We found significantly reduced intakes of several vitamins, minerals, and fatty acids by mothers who produced low-birth-weight babies compared with those whose babies were in the 3.5–4.5-kg reference range, in which neurodevelopmental disorder is at its lowest. Of the 44 nutrients measured, in the diets of the mothers who produced low-birth-weight babies, 43 were below those of the intakes of the mothers who produced babies in the optimum, reference range. Additionally, nutrient data
to influence the outcome of pregnancy, our studies on diet that
had relatively low disposable incomes, which would have reduced
their ability to so indulge. Smoking correlated negatively with
this evidence implies that any intervention to reduce the inci-
duction of low birth weight and the associated neurodevelop-
mental disorders must be initiated before the mother conceives,
a principle consistent with the fact that so much brain-cell di-
vision takes place in the embryo even before the mother knows
she is pregnant. While smoking and alcohol abuse are known
to influence the outcome of pregnancy, our studies on diet that
controlled for these factors indicate that maternal nutrient intake
and the habitual diet independently related to birth weight and
head circumference. In our study population, the participants
had relatively low disposable incomes, which would have reduced
their ability to so indulge. Smoking correlated negatively with
nutrient intakes in the population (0–15 cigarettes/d).

The conclusion that maternal nutrition in preparation for
conception is the most critical is supported by retrospective data
of the Dutch, German, and Norwegian food shortages, which
occurred during and after the World War II (24), and our own
prospective study. It is also supported by the basic biological
principle that the most active period of cell division is within
the first few weeks after conception. Indeed, it can be said that
the period before a mother knows she is pregnant, sees a health
professional and has pregnancy confirmed, is the period of the
greatest rate of cell division. That means that this sensitive period
occurs under conditions that applied before conception and
without the protection of the placenta, which is yet to form.

From the behavior of other animal systems, it is evident that
“nature prepares in advance of conception.” The bird’s egg is
laid with 100% of all nutrients required to convert the fertilized
cell into a chick. Similar advance preparations can be seen in
the insect world, and the farming community has learnt the
same principle empirically. The same principle can, in fact, be
seen in human pregnancy, with egg secretion being canceled
when the proportion of body fat drops below a certain level, as
in anorexia. Again, fat deposition and placental growth proceed
rapidly in the first half of pregnancy whereas fetal growth is in
the last half. That is, the mechanism for fetal nourishment is
built ahead of the need. Furthermore, the parturition at term in
the well-nourished mother leaves her with a fat store that provides
for one-third of the energy requirements for the first 100 d of
lactation (25).

The conclusion that nature prepares in advance has important
implications for our understanding of 1) the influence of ma-
ternal nutrition on fetal growth and 2) of our interpretation of
events that occur in the immediate neonatal period.

Essential fatty acid indexes of fetal undernutrition

In an attempt to obtain further objective evidence, we studied
the EFA content of maternal and cord-blood phosphoglycerides
(26). Reduced concentrations of arachidonic acid were associated
with low birth weight, head circumference, and placental weight.
More recent studies suggest that arachidonylphosphoglyceryl
choline is a better index of birth weight than is docosahexaenyl
glyceride, which correlates more closely with degree of prema-
turity (27).

Ongari et al (28) found that the reduction in prostacyclin
synthesis by the endothelium of the umbilical artery was cor-
related with low birth weight associated with lower maternal
concentrations of arachidonic acid (see also refs 26 and 29).

A differential relationship related separately to intrauterine
growth retardation and degree of prematurity would not only
provide further confirmation of the contrasting roles of AA and
DHA, but also would indicate that premature babies, even if
appropriately grown, may nonetheless be born with nutritional
deficits. This possibility needs logically to be extended to term
babies, where it now becomes necessary to ask the same question.
Growth per se is by no means the sole criterion of nutritional
provision to meet the specialist demands of Homo sapiens. It is
therefore possible that a small number of term babies born at
appropriate birth weights may not have been appropriately
nourished in the interests of the nervous and vascular systems.

Periventricular hemorrhage and cerebral palsy

Hemorrhage appears to occur to a varying extent in a large
proportion of preterm infants (30). In certain circumstances it
may repair while in others, it may result in spasticity and cerebral
palsy. The chicken provides a model. Hemorrhage can be in-
duced in the cerebellum between 10 and 28 d after hatching.
The cerebrum appears unaffected. The reason for this difference
could be that the cerebrum is mainly formed before hatching,
whereas the cerebellum is growing rapidly and acquiring its
LCPUFA profile after hatching and, indeed, in exactly the period
during which it is susceptible to hemorrhage.

Provision of vitamin E, or ALNA without vitamin E, to a
chick colony suffering from encephalomalacia arrests the disease
(14). Brain can be effected differentially, with regional growth
being a major determinant of risk. Deficits of both the protective
antioxidant and the n–3 fatty acids are needed to cause hemor-
rhage (14).

Hence we need to ask whether, in the human preterm infant,
a reduced supply of the precursors for membrane growth and
protection would contribute to the fragility of the peri- and in-
traventricular vascular system and to hemolysis. The vascular
network serving the developing brain must necessarily develop
at a rapid rate to accommodate the brain growth thrust occurring
at that time (14).

There is now evidence from several laboratories and our own
that the premature infant is denied the substantial supply of AA
and DHA that it otherwise would have received if it had remained
as a fetus fed by the placenta. Within 3–6 d of birth, their con-
centrations may fall to less than one-fifth of those found in the
placental-fetal supply (27, 31).

Both these fatty acids are key components of neural and vas-
cular membranes. AA and other 20-carbon PUFAs are also pre-
cursors for eicosanoids, which regulate blood flow and coagu-
lation. The deficits of these fatty acids, induced by prematurity,
would be expected to lead to loss of the membrane integrity
manifested by hemolysis and hemorrhage. The answers to these
questions would suggest a route for prevention.

To meet the outstanding demands for brain growth, the neo-
natal cerebrovascular system has to be efficient. During the last
trimester, the brain enjoys its major growth spurt, which carries
with it a growth spurt of the cerebrovascular system. An inade-
quate nutrient flow during a period of critical development can
induce "susceptibility." Hence a question arises: is the periventricular hemorrhage due to inadequate nutrient supply to the fetus in the last trimester when the cerebrovascular system is undergoing rapid development?

Winick (32) pointed out that fetal-growth-retarded babies are born from small placetas with multiple and often massive infarctions (33). He therefore argued on the basis of the pathology that poor placental development was responsible for fetal growth retardation. This implies that the nutritional and biochemical conditions induce inadequate vascular growth and risk to membrane rupture and coagulation. The low intake of EFAs that we found associated with low birth weight would be expected to compromise endothelial growth and function. Indeed, reduced synthesis of prostacyclin has been reported in the umbilical arteries and placentas from low-birth-weight babies in association with increased mead acid (28).

The placenta is largely a new and rapidly growing vascular system, which develops in the first part of pregnancy to serve the fetal growth thrust of the last trimester. In association with low birth weight there is evidence of much placental vascular pathology. One must therefore ask whether or not the conditions that resulted in a poorly developed and infarcted placenta have adversely influenced fetal vascular development. The placental evidence indicates that the conditions, not favorable to a rapidly developing vascular system, may result in serious vascular disorder in the placenta. It may be that the vascular system serving the brain may also succumb to a similar stress.

Although the above findings point the way to better pregnancies, no matter how good we are at developing methods to prevent low birth weight, we will not prevent all of it nor will we prevent all neurodevelopmental disorder. So the question arises, what do we do with the baby born premature or small and hence at high risk of developing some form of disorder after birth?

Again, much experimental evidence implies that certain nutrients, especially AA and DHA, might be beneficial in protecting the premature baby’s brain from the bleeding into the brain that can cause inflammation and damage leading to spasticity and cerebral palsy. A similar approach to providing nutritional support for the EFAs could be important in preventing retinopathy and blindness and encouraging full cognitive development. One recent report claimed that premature babies fed breast milk were more intelligent than those fed formula (34). Unfortunately, no fatty acid data were collected on those babies. However, it had been shown previously that the plasma LCPUFA status of formula-fed babies dropped below that of the breast-fed babies (35, 36).

The AA and DHA content of human milk

Producers of the formulas for term and preterm infants take into account current information about fetal protein, mineral, and vitamin requirements. However, the one feature they have wrong is the essential fatty acid component. They do not provide the long-chain EFAs. Because AA and DHA were always found in significant amounts in mothers’ milk from across the world (35), because deficits of both appeared in the plasma of babies fed formula compared with human milk, and because of other evidence available in 1977, AG Hassam and I argued the case that long-chain EFAs should be included in formulas (25). The committee accepted the principle and its report included the recommendation that milk formula should use human milk as its guide with regard to the composition of these long-chain EFAs. Since then, further clinical and experimental evidence has suggested more specific roles for DHA (36–38).

In the mid-1970s, in collaboration with B Laurance, we tested a formula made to include AA from egg lecithin and DHA from cod-liver oil in > 60 babies. We found that the performance of human milk could be closely matched by the formula as measured by plasma phosphoglyceride concentrations (unpublished observations). The formula was also tested in New Zealand. As expected, the AA and DHA contents of the plasma phosphoglycerides was superior in the breast-fed babies compared with those fed formula and followed for 18 wk. The formula was well tolerated and the nursing staff commented that stool texture and characteristics were much more like those produced by babies fed human milk rather than formula. Although the project was dropped by the sponsor because of expense, the feasibility of such a product was demonstrated.

Milk formulas are still not supplemented with AA and DHA, and the so-called “humanized” milks may not even contain significant amounts of n−3 fatty acids, as ALNA, because they are formulated with vegetable oils that are LA rich.

Human milk fat is an animal fat, yet there was a curious insistence on replacing the animal lipid by a vegetable oil with only linoleic acid in it. The inadequacy of this approach was clear at an early stage (25) and could readily have been derived from the knowledge that both LA and AA occurred in choline phosphoglycerides in most tissues other than nervous tissue and that there is more LA than AA. If the conversion process was as effective as supposed, it should have been the other way around.

The comparative data also showed that LA and ALNA were present in substantial amounts in the tissues of herbivorous species, where they are almost inversely related to the amounts of AA and DHA. Evidence of an abundance of the two parent acids in the presence of a dirth of LCPUFAs does not argue for an effective conversion process. Studies on adult vegetarians were sometimes quoted as a defense. However, neither the human fetus nor the neonate is a vegetarian, and this early period is involved in rapid growth, where the requirements are quite different from those of adults. During growth that focuses on the brain, optimum conditions should prevail to support that growth.

The arguments consistently used against supplementing formulas with AA and DHA are difficult to understand and are generally countered by two replies.

1) Both AA and DHA are principle structural building blocks for the brain and other neural and vascular tissue. In term babies fed formula, the plasma concentrations of these compounds are below those of breast-fed babies, and such deficits in term babies might be expected to lead to deficits in postnatal neurodevelopment (31, 35, 36). Even if these deficits had only mild effects on hearing, vision, cognitive function, or coordinative abilities, the gravity of the situation is heightened by the animal evidence. That evidence implies that any disability induced at this stage of development would be permanent, a point emphasized by the fact that the differences between human-milk- and formula-fed infants persist to age 8 y. The objective should be to optimize the conditions for infant neural development, not to downgrade them.

For the preterm infant, the situation is more serious, because as the data now show, they may be born with deficits (26–29, 31, 35, 36). Even without those data, it has been known since
the mid 1970s (37) that these infants are being denied the benefits of the placental system that selects LCPUFAs for the developing fetus, whose brain is developing very rapidly.

Furthermore, the clinical evidence on these babies clearly states that the most common disturbances are associated with membranes in which AA and DHA are of critical importance. These include bronchopulmonary dysplasia, retinopathy of prematurity, and hemolytic anemia and intraventricular and periventricular hemorrhage, which, if persistent, potentially leads to spasticity or cerebral palsy. These are situations in which the antioxidants are thought to be preventive. However, antioxidant therapy can only protect against loss of existing resources, it cannot add the new resources needed for growth. The requirement for n-3 fatty acids has recently been a subject of interest in the prevention of cardiovascular disease, but the relevance of n-3 fatty acids to neurodevelopment (38-40) was well established prior to such interest.

2) The case that has to be justified is not the case of putting the LCPUFA into substitutes for human milk. The case that has to be justified is leaving them out. On the evidence, the omission of LCPUFAs cannot be justified.

Finally, the two 8-y follow-up studies of premature babies showing that the functional deficits persist indicate that deficits induced at this vulnerable stage are likely to be permanent (34, 41, 42).

Conclusions

From the evidence so far accumulated, the baby born small for dates should be considered to have been malnourished as a fetus. The premature baby, even if appropriately grown, may still have experienced a degree of malnutrition, although it is likely to be of a different nature from that of the small-for-dates baby.

Fetal malnourishment could be due to several causes including extent of placental development and maternal nutrition. However, it seems that maternal nutrition before conception is more important than nutrition during the later part of pregnancy, when it is too late to affect the most sensitive period of fetal cell division. However, the preterm infant is born at a time when cell-membrane development is unprepared for the different conditions of the extraterine environment and is likely to be further effected by feeding regimes that currently do not replace all placental provisions, especially the EFAs.

Additionally, if nutritional or other constraints in the supply of nutrients do result in fragile membranes in the preterm infant, it would hardly be surprising if the integrity of membrane-rich systems is in jeopardy.

These considerations suggest that the several developmental disorders to which the low-birth-weight infant is at high risk need not be due to obstetric or pediatric mismanagement but are the result of a poor maternal nutrition before and during the first trimester of pregnancy.

References

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Discussion

Frits Muskiet: Could you give us your opinion on the ideal ratio between long-chain (n-6) and (n-3) essential fatty acids [EFAs] in formula for term infants?

Michael A. Crawford: One can answer that from studies on the composition of human milk throughout the world. When comparing the amounts of the long-chain polyenes AA and DHA, we found a ratio between 1:1 to 2:1. If you want to include the parent EFAs also (linoleic acid and α-linolenic acid), the ratio between the (n-6) and (n-3) families will be around 5:1.

Muskiet: I guess what you say now is based on human milk from Western origin?

Crawford: No, it is based on the analyses of milk from Sri Lanka, Thailand, Hungary, Holland, Denmark, Saudi Arabia, Tanzania, Uganda, and the UK.

Muskiet: That is a very impressive list of human-milk data that you just gave. However, considering the influence of maternal diet and the evolutionary aspects of long-chain ω3 fatty acids that you mentioned in your talk, I am not entirely sure that the composition of human milk shows us what the optimum intake of these fatty acids really is.

Crawford: I don’t think we know. This is a question that applies to any nutrient. I think that the whole nutrient focus on protein is wrong, and daily recommended values are really questionable because they don’t consider the developmental process, which is by far the most important issue. Most nutrient recommendations are based on studies with students or adults, but that is not really what matters. What matters is the health of the next generations, and all the evidence today indicates that because of the various developmental processes, conditions like cardiovascular disease, diabetes, and possibly disorders of the immune system may well have a predisposition at birth. The link between the cardiovascular and the central nervous systems is certainly there, because the systems have to develop at the same time. The developing fetal brain consumes 70% of all energy available to it and this would, of course, be impossible without a well-developed cardiovascular system. So, heart and brain go together. In fact, I think it is wrong to emphasize “recommendations” because it gives the public and industry a distorted view of the perception that science has.

Muskiet: Just one more quick comment. Would you put eicosapentaenoic acid in there?

Crawford: Maybe a small amount, but it should be realized that there is very little EPA in the fetal circulation. That is another interesting point: neither α-linolenic acid nor eicosapentaenoic acid is present to any significant extent. In fact, all the “amplification” of DHA in the fetus takes place purely by DHA selection, not by metabolism. We know that the placenta doesn’t use the metabolic route, it doesn’t desaturate linoleate to get arachidonic acid; it just “steals” arachidonic acid from the mother and it also “steals” DHA. It is a deliberate utilization of these preformed LCPs.

Muskiet: Are there any hazards—with EPA, I mean?

Crawford: There is always a risk in putting things into pills and potions. It depends on the way it is done. I can’t see any hazard of getting EPA from breast milk.

Muskiet: But it is not in there—EPA, I mean—at least not much. Crawford: Human milk contains 60% of its energy as fat. The amounts of EPA and DHA are small in relation to the amount of total fat. But we should not forget that most fat will be burned...
for the production of energy. However, EFAs do not function as fuel; they are building blocks. Let’s take other building blocks: the proteins. Milk contains about 6 to 7 en% protein. The amount of EFAs in milk is also about 6 to 7 en%, throughout the world. Those 6 to 7 en% of protein include both essential and nonessential amino acids. The amounts of the essential fatty acids are in balance with the essential amino acids. So you can’t say EFAs are trivial. They present in highly significant quantities in relation to cell growth and development.

John E Blundell: For more than two decades there has been an epidemic of dieting and slimming in Western Europe and North America, which mainly concerns women. Is there any evidence that women who are dieting prior to conception or possibly during gestation endanger the brains of their infants by limiting the availability of fatty acids?

Crawford: I don’t know about limiting the availability of fatty acids, but the data on the Dutch famine at the end of the Second World War are very clear on this. These mothers who had low calorie [energy] intakes prior to conception had poorly developed babies.

Blundell: Would you care to say how low the caloric [energy] intake can be before fetal brain development is endangered?

Crawford: In our studies the caloric [energy] intake associated with poor pregnancy outcome was about 1600 cal/day [6.70 kJ/d] or less.

Kristian S Bjerve: I would like to comment on the discussion because I think it points to a very important fact: we shouldn’t give data on essential fatty acids as percentage of energy. I think we should do it the same way as for all other essential nutrients—grams or milligrams per day or per kilogram of body weight. I think this is essential when we describe how much essential fatty acids is needed by an infant of, for instance, 1500 grams body weight. To give it as percentages of calories [energy intake] is theoretically wrong and often directly misleading.

Crawford: You are absolutely right. If you look at the nutrient intakes of the mothers in our study who produced low-birth-weight babies, 4.5% of their calorie [energy] intake was as essential fatty acids. The mothers who produced healthy babies consumed 4.6% of their calories [energy] as essential fatty acids. Thus, EFA consumption did not differ in terms of energy %, but in absolute amounts per day. You are absolutely right.