Are deficits of arachidonic and docosahexaenoic acids responsible for the neural and vascular complications of preterm babies?1–3

Michael A Crawford, Kate Costeloe, Kebreab Ghebremeskel, Andreas Phylactos, Louise Skirvin, and Fiona Stacey

ABSTRACT We review evidence suggesting that pre- or postnatal deficits of arachidonic acid (AA) and docosahexaenoic acid (DHA) together with underdeveloped antioxidant protection contribute to neurovisual developmental disorders and other complications of premature birth. These two synergistic deficits occur at a time when 70% of energy is focused on brain development and when the brain and blood vessels are growing at high speed. The types of essential fatty acids fed to preterm babies bear no relation to what the infant would have received had it remained a fetus. This failure to meet essential fatty acid requirements exacerbates the AA and DHA deficits seen at birth; furthermore, the immature superoxide defenses remain depressed until the expected date of delivery. Deficits of these systems, which are required for cell membranes, the endothelium, and neural tissue, could provide the biochemical prerequisite for the membrane disorders to which these babies are at high risk: intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and bronchopulmonary dysplasia. Although poor vascular development during fetal and neonatal life may be repaired, the structural and antioxidant deficits identified in preterm babies may impair blood vessel development with long-term consequences. The conclusion drawn from this review is that present parenteral and enteral lipid nutrition for preterm babies is flawed and could be pathogenic. Full-term milk composition is the basis for the design of preterm infant foods, but full-term milk is different from the placental product that is rich in AA and DHA. Preterm lipid nutrition should be revised to be more in line with placental lipid transfer to the fetus.

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The composition of the lipid bilayer provides the physical conditions within which membrane-bound enzymes, transport proteins, glycosaminoglycans, and receptors operate. The interaction between the lipid bilayer and proteins also provides the structural organization for subcellular organelles such as peroxisomal, reticular endothelial, and mitochondrial function and is quite possibly responsible for maintaining the physical environment of the nucleus both in rest and during cell division.

Essential fatty acids (EFAs) are required as constituents of the lipid bilayer phosphoglycerides in a way similar to which the essential amino acids are required for the biosynthesis of proteins. The physical and biological properties of cell membranes are dependent on fatty acid and cholesterol composition. The membranes with the more saturated fatty acids are involved in the more rigid structures such as those of the myelin sheath. The most unsaturated bilayer membranes are at sites of high signaling activity.

Linoleic acid (LA) is the parent fatty acid of the n–6 family of EFAs. It has 18 carbons in a straight chain and two methylene-interrupted double bonds, with their sequence commencing at the sixth carbon from the methyl end (n–6) of the molecule (Figure 1). LA is converted by desaturation and chain elongation to arachidonic acid (AA; 20:4n–6), which has 20 carbons and 4 double bonds.

α-Linolenic acid (ALA; 18:3n–3) has 18 carbons and 3 double bonds with the sequence starting 3 carbons from the omega end of the molecule (Figure 2). ALA is desaturated and chain elongated to docosahexaenoic acid (DHA), which has 22 carbons and 6 double bonds (22:6n–3). However, the conversion process is limited and slow. Only a small proportion of parent acid is converted to its long-chain derivative. Providing AA and DHA preformed as opposed to synthesis from LA and

1 From the Academic Department of Paediatrics of St Bartholomews Hospital Medical School; the Neonatal Unit, The Homerton Hospital, London; and the Institute of Brain Chemistry and Human Nutrition, University of North London.
2 Supported by the Christopher HR Reeves Charitable Trust and the Mother and Child Foundation.
3 Address reprint requests to MA Crawford, University of North London, 166-222 Holloway Road, London N7 8DB, United Kingdom. E-mail: michael@macrawf.demon.co.uk.
ANIMALS CAN INSERT DOUBLE BONDS

\[ \text{CH}_3 - \text{CH} = \text{CH} - \text{CH} = \text{CH} - \text{CH}_2 - \text{COOH} \]

FIGURE 1. 9,12-Octadecadienoic acid (linoleic acid, 18:2n–6). The n–6 nomenclature defines the start of the methylene-interrupted double bond sequence that remains fixed during chain elongation at the carboxyl end.

ALA in the same animals was found to be ~10 times more efficient for brain cell membrane incorporation during growth.

There are many examples in the literature of the fatty acid composition of the lipid bilayers exhibiting a high degree of organ, organelle, and species specificity. Although most organs use different mixtures of fatty acids including LA and ALA, the brain is unique: it uses only AA, its 22-carbon elongation product, and DHA (Figure 3).

The structural material of the brain is 60% lipid. AA and DHA are selectively acquired by developing neural cells. Although brain tissue homogenates and microsomes can convert LA to AA, in practice there appears to be a barrier to LA entering the brain in substantial amounts or gaining access to the microsomal system. AA and DHA are preferentially incorporated. AA and DHA constitute a high proportion of the fatty acids used for the construction and function of the brain and its blood vessels. AA has a special significance in the structure and function of endothelial cells. It serves also as the precursor for endoperoxides called eicosanoids. These are local cell regulators. One group participates in maintaining homeostasis while another is part of the defenses against injury.

It is in general difficult to make cell membranes deficient in AA and DHA. Deficiency of AA and DHA in the membrane alters the physical properties of the lipid bilayer, in many instances changing the activity of membrane-bound enzymes and receptors, reducing the flexibility of the endothelium, and inducing leakage. Western diets, which are rich in saturated fatty acids, are correspondingly low in EFAs. They are also low in antioxidant content because antioxidants such as vitamins A and E and β-carotene occur with EFAs in nature. Because EFAs are polyunsaturated, they are susceptible to peroxidation. Hence, deficits of EFAs and antioxidants are expected to result in loss of membrane integrity and membrane lipid peroxidation. This in turn leads to lysosomal enzyme release, liberation of free AA, and its peroxidation to eicosanoids. Peroxidation can result in an exaggerated response to injury, namely, cell membrane rupture, platelet stimulation, adhesion, and vasoconstriction with a risk of local damage.

The hypothesis presented here is that consistent with the above physiology, insufficient amounts of AA, DHA, and antioxidants before and after birth may predispose to intraventricular hemorrhage (IVH), the ischemic lesion of periventricular leukomalacia, retinopathy of prematurity, and bronchopulmonary dysplasia (BPD).

LIPID REQUIREMENTS FOR BRAIN GROWTH

Brain structure and essential fatty acids

The brain is developed to the highest degree in the human species. Many of the most serious complications associated with low birth weight affect the brain. The adult brain is ~2% of body mass by weight and uses 20% of the body’s energy. The fetal brain can be ≥16% of body mass and utilizes ≥70% of energy for growth. Hence, nutritional deficits during fetal and early postnatal development affect the brain especially. In babies born preterm, severe developmental damage to the brain “is one of the most feared complications of intensive care” (1).

The structural requirements of the brain, being 60% lipid, are different from the rest of the body. The lipid needed is predominantly membrane lipid for which AA and DHA are required (Figure 3 and Figure 4) (2). To meet the demand for energy, EFAs, and other nutrients, coordinated growth of the heart and blood vessels is needed. The involvement of DHA in signal transduction is particularly evident in synaptic membranes and especially in the photoreceptor, where DHA accounts for 60% of the membrane lipid fatty acids in the discs. These discs accommodate rhodopsin (3) and provide the physical medium for its photoexcited form to initiate the cascade that amplifies the signal 1000 times to fire the synapse and send the signal to the brain.

An inadequate supply of EFAs or energy to the growing brain results in an inability of the neural cell membranes to acquire their correct components, with consequent loss of natural cellular organization and connectivity between cells (4), leakage, risk of hemorrhage (5), microthrombi, local ischemia, and cell death (6).

The conversion of LA to AA and especially of ALA to DHA is rate limited by Δ6 desaturation; two such desaturations are involved in the synthesis of DHA (7). Double-labeled radioisotope experiments show the implication of the slow rate of conversion of LA to AA and ALA to DHA. The incorporation of preformed AA and DHA into the developing brain is selective and more than 10 times faster than incorporation via the biosynthetic routes from LA and ALA (8). To meet the high demand for AA and DHA for fetal brain growth, the placenta appears to extract AA and DHA to pass on to the fetus while returning their precursors to the maternal circulation (Figure 5) (10, 11). Postnatally, human milk continues to provide AA and DHA preformed although at much reduced proportions (11). In rats, accumulation of AA and DHA can be observed by brain analysis well ahead of myelination when nervonic (24:1n–9) and lignoceric (24:0) acids accumulate (8).

This switch from long-chain, highly unsaturated fatty acids to the more saturated types is consistent with the change at full-term birth from cell division to myelination. The formation of myelin has a higher requirement for long-chain saturated and monounsaturated fatty acids (12) and a lower demand for AA and DHA than is needed for neural cells and synaptic junctions. Normal, full-term birth is associated with a substantial switch in physiologic emphasis in neural development from cell division to myelination and a switch in lipid nutrient requirements.
AA and endothelial integrity

The role of AA is particularly important in the endothelial cells lining the blood vessels. The eicosanoids derived from AA and other long-chain polyunsaturated fatty acids are, however, active in cell regulation at nanomolar concentrations (13–15). Under conditions of normal blood flow and vascular control, eicosanoid (prostaglandin E₁ and prostacyclin) activity suppresses platelet aggregation and adhesion to the blood vessel walls and acts to maintain vascular tone to favor good blood flow. Under these conditions, the eicosanoids have been described as local, homeostatic hormones.

Cell stimulation, cell death, and membrane rupture are associated with lysosomal phospholipase activation, which releases substantial amounts of free AA from the membrane lipids. The products of AA, particularly thromboxane, result in platelet activation, adhesion and aggregation, formation of thrombi, and vasoconstriction. The phosphoglyceride breakdown products, locally synthesized eicosanoids from AA and free AA itself, also result in protein kinase C activation, cytokine production leading to macrophage activity, and recruitment to and around the damaged or infected zone. In this context, AA and eicosanoid function move into the frame of local defense hormones. Chronic stimulation or overproduction results in yet another frame of disorder arising from severe vasoconstriction, thrombus formation, and opening of endothelial cell junctions. Hence,

![Figure 3](https://academic.oup.com/ajcn/article-abstract/66/4/1032S/4656017)

**FIGURE 3.** Brain ethanolamine phosphoglyceride composition. The ethanolamine phosphoglycerides are inner cell membrane lipids and the most unsaturated. Linoleic and α-linolenic acids are not represented to any significant degree. Between different species, there is a remarkable constancy of fatty acid composition; the main difference is in the extent of brain development, not the fatty acid composition. x̄; n = 16 human motor cortex samples.

![Figure 4](https://academic.oup.com/ajcn/article-abstract/66/4/1032S/4656017)

**FIGURE 4.** Arterial endothelium ethanolamine phosphoglyceride composition. Arachidonic acid is a major component of the inner membranes of the endothelial cell. The endothelium will grow to become the largest organ. x̄; n = 14 samples from humans aged 25–45 y.
the function of free AA and its eicosanoids is a balancing act.

Indeed, the balancing act extends to the relation between the n-6 and n-3 fatty acids. DHA and its precursor eicosapentaenoic acid (EPA) down-regulate the AA-eicosanoid response. Endothelial destruction also results in reduced nitric oxide synthesis that might otherwise contribute to vasodilation. Hence, under physiologic conditions, the result is good blood flow. With mild stimuli or cell damage the result is repair. If the conditions are severe, the result is thrombus formation, occlusion, and edema. Localized ischemia can follow, leading to cell death.

Such events in the brain are further complicated by the fixed space of the brain case, limiting tolerance to edema, although there is likely to be more leeway in preterm babies than in adults. The high demand for energy and unique sensitivity to oxygen deprivation means that ischemia results in massive release of free AA, exacerbation of the ischemia, and localized cell death. In the brain there is little or no repair mechanism.

**Prenatal nutrition**

At full term, a baby's brain is growing at the rate of 1 mg/min. In the last trimester the fetal brain and its blood vessels are in a rapid and active period of growth and development with a high requirement for AA and DHA, which are put in place under conditions of the low intraterine oxygen tension. Low oxygen tension is important because AA and DHA are polyunsaturated and especially susceptible to peroxidation. If a baby is born ≥ 10 wk preterm, it has to breathe atmospheric air or oxygen at a time when it is physiologically unprepared for a change from low to high oxygen tension.

The possibility that intrauterine nutrition may play a part in the etiology of developmental central nervous system and visual disorders as well as the relevance of intrauterine nutrition to chronic ill health has been discussed frequently. However, the lipid construction of the brain and its blood vessels has not been focused on. At the beginning of pregnancy there appears to be a mobilization of DHA from tissue stores. However, circulating plasma concentrations diminish in the last trimester (16, 17).

Although the focus of this discussion is on AA and DHA, other nutrients also are linked to developmental disorders. Poor maternal diets especially around the time of conception are related to low birth weight in connection with deficiencies of a wide range of nutrients, particularly the B vitamins and magnesium (18–22). There is also biochemical evidence at birth that preterm and low-birth-weight babies had been exposed to intraterine deficits of nutrients. However, the B vitamins and trace elements are not important just for protein synthesis, but are also required for lipid metabolism, desaturation and chain elongation, EFA incorporation into membrane phosphoglycerides, and membrane synthesis. Antioxidant vitamins, however, occur in the food chain together with EFAs, so deficiency of one is likely to be associated with a deficiency of the other.

Biochemical signs of EFA deficiency have been reported in the endothelium of the umbilical arteries of low-birth-weight babies with reduced prostacyclin synthesis by the umbilical endothelium (23). Reduced AA and DHA concentrations in maternal and cord blood have been observed in relation to low head circumference, low birth weight, and low placental weight. In low-birth-weight babies, significant correlations were found between birth weight and head circumference at
birth and biochemical signs of AA and DHA deficiency (24, 25).

Similarly, plasma choline phosphoglyceride concentrations of AA and DHA at birth have been found to correlate with birth weight (for plasma AA) and gestational age (for DHA). Both AA and DHA independently and together correlated with head circumference at birth (26, 27).

The independent association of DHA with gestational age is likely to be a function of maturation of the placenta (17). The association of AA with birth weight when controlled for gestational age implies a relation specifically between the genetic expression of growth and intrauterine AA status. The signs of EFA deficiency in the umbilical artery in the inner membrane lipid indicate a deficiency that is prenatal in origin. It is likely that both maturation and reduced intrauterine nutrition contribute to reduced blood concentrations at birth in preterm and small-for-date babies compared with normal-weight, full-term babies.

Placental function

Intrauterine malnutrition can result from maternal malnutrition, placental malfunction, or both. At the time of cell commitment to form the placenta and during its development, placental cell division could be jeopardized by inadequate nutrition, which could conceivably be linked to confined placental mosaicism. Placental insufficiency resulting from nutritional inadequacy early in the pregnancy could influence fetal growth even though the mother appears to be well nourished in the latter part of pregnancy.

A period of relative maternal malnourishment, whether primary or secondary to illness or stress, affecting the supply and utilization of AA and DHA could also influence vascular development. Diets rich in saturated fats or inadequate in AA and DHA could jeopardize placental development because the placenta is essentially a rapidly growing vascular network. Placentas from intrauterine-growth-restricted babies are usually small and often have multiple infarcts.

Fat store at birth

There is a fundamental requirement for an adequate adipose tissue store before conception will take place. However, if adipose tissue and nutrient stores in the mother are marginal, a period of stress or sickness may reduce maternal nutrient status below the critical level, thus exposing the embryo, placenta, or fetus to risk. By contrast, a full-term baby from a well-nourished mother has fat stores of ≈300–500 g. Because of the placental enrichment of AA and DHA, that fat store will contain 8–10% (≈30 g) AA and DHA. With such stores of energy, AA, DHA, and other nutrients, the baby can tolerate brief periods of illness or food shortage. However, a baby born prematurely will have little fat reserves on which to call.

Evidence for AA and DHA requirements postnatally

Feeding preterm or full-term infants with formula that does not contain AA or DHA compared with breast milk, which does, leads to lower plasma triacylglycerol and phosphoglyceride AA and DHA concentrations (8, 28, 29), loss of brain cortex DHA (30), and lower cognitive and visual developmental scores (31–33). An eight-point intelligence quotient deficit was observed at 8 y of age in children who as preterm babies had previously been fed formula compared with children who consumed human milk. A significantly higher incidence of mild neurologic disabilities was found in 9-y-old children who as full-term babies had been fed formula compared with those who had their mother’s milk (34, 35).

EFAs and antioxidant deficits

Deficits in dietary EFAs affect membrane composition, the activities of membrane-bound enzymes and receptors, and metabolic reactions such as superoxide dismutase activity and nitric oxide synthesis, and contribute to vasoconstriction and endothelial membrane instability and brain damage (5, 36, 37). Studies in several species have shown that inadequate provision or an inappropriate balance of AA and DHA during brain development affects visual development (38) and results in hemorrhage similar to IVH with inflammation, ischemia, and tissue destruction (4, 5, 39, 40). The ischemic lesion periventricular leukomalacia, an antecedent of cerebral palsy, results in large-scale release of free AA with exacerbating vasoconstrictive consequences.

The pathogenesis of acute lung disease (41) and IVH in preterm babies (42, 43) is thought to involve antioxidant insufficiency and may also involve EFA insufficiency. BPD is preceded by leaky endothelial membranes through which fibrin passes and forms a hyaline membrane, restricting oxygen transport. BPD and its consequences are complex processes. BPD involves peroxidation of AA, leading to inflammation and edema. The cause of the leakiness is considered to be a deficiency of surfactant, which is a dipalmitoyl membrane phosphoglyceride. In fact, these babies are treated with surfactant. Hence, cell membrane integrity is already considered to be a component of this disorder.

Deficits of n−3 fatty acids in membrane lipids along with deficits in vitamin E induce hemorrhage in the chick brain. A reduced EFA content of the membrane results in low binding of vitamin E by the membrane. That is, deficiency of both structural and protective elements are required for damage to occur in this model of IVH. It is pertinent to this discussion that the condition involves hemorrhage, microthrombi, and edema. It is possible to stop a colony of chicks from dying from this disease by supplementing their diets with ALA (5).

Protection against peroxidative damage

Depending on their lipid- or water-solvent properties, antioxidants are present in the membrane, the cytosol, or in extracellular fluids. Normally, protection against oxidative or free radical attack is provided by endogenous antioxidant enzymes within the cytosol in the cell membranes. Further protection is afforded by the exogenous antioxidant vitamins E, A, C, and β-carotene as well as other naturally occurring antioxidants in the diet such as the flavones (plant coloring matter).

At birth, antioxidant enzyme activity of red cell membrane copper-zinc superoxide dismutase in preterm babies is <50% of that of full-term babies; activity at expected date of delivery in preterm babies is still about two-thirds of that of full-term babies at birth (42) (Figure 6). Low-birth-weight infants also have lower than expected blood concentrations of vitamins E and A. This combined, reduced antioxidant status may contribute to susceptibility to damage in the lungs, vascular systems, and brain (43, 45–47).
There is some evidence that repair to damage can occur during brain development (48). That is, the door is open for nutritional intervention trials postnatally, both for prevention and treatment. If successful, such trials would lay the foundations for nutritional pharmacology.

Although peroxidative damage is considered to play a role in the pathogenesis of IVH (42–44, 49), retinopathy of prematurity (50, 51), and BPD (45, 52), vitamin E supplementation and more careful use of oxygen have not resolved these problems (42, 53). From the discussion above on membrane composition and lipid peroxidation, it should be evident that considering a single nutrient alone deals only with a small part of an integrated biological system involving structural integrity and intracellular and extracellular protection. Hence, negative results of trials with a single component such as vitamin E need to be interpreted with caution. It is likely that deficits of EFAs are linked with the exogenous and endogenous antioxidant systems in the pathogenesis of these disorders.

The inadequacy of current EFA nourishment for preterm babies

The placental selection and enrichment of AA and DHA for the fetus is denied to babies born prematurely. Full postnatal nutrition is often deferred for several days. When feeding is initiated, neither breast milk, parenteral nutrition, nor supplemented formulas match placental provision of AA and DHA. As a result, the proportions of plasma AA and DHA fall within 2 wk to one-third of what the placenta would have provided (Figure 7 and Figure 8) (26). This serious postnatal deficit of AA and DHA coincides with the period of most rapid development of the neurovascular and vascular systems. The AA deficit occurs despite an abundance of its precursor LA, the proportions of which triple in the infant’s plasma.

Present formulas for feeding preterm infants are based on full-term milk fatty acid composition, that is, they are rich in LA. Recently, small quantities of ALA, AA, and DHA have been added. Some formulas have no AA or DHA although there was sufficient evidence in 1978 for the FAO/WHO Expert Consultation on the Role of Dietary Fats and Oils in Human Nutrition (54) to state that formula for preterm and full-term infants should follow human milk in this respect. This view was reaffirmed in the 1995 FAO/WHO report (55).

Being born ≥ 10 wk too early imposes special nutritional demands. It is now recognized that provision of protein, energy, and minerals needs to be modeled on the placental supply. The difference between full-term breast milk and the placental supply for EFAs is illustrated in Figure 8. No postnatal feeding system mimics the placental product for fatty acids. The difference between the composition of preterm formulas and placental provision is so large and the postnatal loss in the proportions of AA and DHA so rapid (26, 27) that serious questions need to be asked about the appropriateness of any of the present formulations of foods for preterm infants. It is our view that, as is now the practice for other macronutrients, formulas for preterm infants be redesigned to more closely match the placental provision with respect to dosage and proportions of EFAs.

CARDIO- AND CEREBROVASCULAR DISEASE AND EARLY DEVELOPMENT

Despite 40 y of clinical trials aimed at reducing cardiovascular risk by diet, success has been limited. The relatively poor success has raised the question that nutritional intervention in midlife may have little chance of success if the disease process in an individual has been in progress for one-half a century. Because of the common EFA biochemistry in the neural and vascular systems, there may indeed be a common denominator between the neurovascular disorders of low-birth-weight babies and vascular diseases of adulthood.
The first evidence for a common denominator is that mortality from cardiovascular and cerebrovascular diseases follows the pattern of low birth weight within Western societies, with the highest prevalence in the lower socioeconomic groups (56, 57). Hence, the same population group has been known for some time to be at risk to both low birth weight, coronary artery disease, and high blood pressure. Recent epidemiologic evidence suggests that the connection is even tighter. The same people with low birth weights seem to be those at greatest risk in adult life for cardio- and cerebrovascular diseases, which leads to the suggestion that these diseases have their origin in poor maternal, fetal, and neonatal nutrition (58).

The second common denominator is derived from developmental biology. The developing brain has an astonishingly high energy demand. This demand can be served only by simultaneous development of the vascular system to pump the blood from the umbilical cord to the brain. This means that the cardiovascular system is developing at a rapid rate simultaneously with the cerebrovascular system. The cerebrovascular system is a major target for both hemorrhage and ischemia in preterm neonates and stroke in adults. The most sensitive period to nutritionally induced disturbance is during growth and AA is particularly prominent in the endothelial cell membrane.

The possibility that the fetus could be threatened nutritionally is indicated by two principles:

1) Nutrient intakes in relation to low birth weight have been reported to be dose responsive up to 3270 g (21), which suggests that the problem of inadequate, prenatal nutrition may be more widespread than previously thought.

2) Women in a community with a high risk of coronary artery disease are exposed to nutritional and environmental backgrounds associated with atherosclerosis and heart disease more common in men in midlife. A baby born in these circumstances will have a high risk of being similarly exposed both pre- and postnatally.

Of the environmental factors relating to heart disease, nutrition is in fact the one that has been tested most rigorously over the past half century and that carries the strongest evidence in the laboratory species studied so far. Although emphasis was originally placed on saturated fatty acids, it was subsequently recognized that LA was protective (59, 60). Oleic acid (61) and especially the n-3 fatty acids also seem to play a protective role (62–64). The classic atherogenic diet is one rich in saturated fats. In practice, however, such a diet is also low in EFAs and antioxidants. The vascular endothelium in the human body is an especially large organ. The endothelial cell also has the highest membrane-to-cytoplasm ratio. It follows that it will have a specialized requirement for the essential fatty acids AA and DHA for its growth and integrity (65, 66).

Since the earliest days of research on heart disease etiology, it has been known that two principle risk factors, blood cholesterol and blood pressure, rise in North American and European children with age (67). Although European children born in countries where coronary artery disease is rare are born with the same blood cholesterol and blood pressure values as native children, there is little rise in blood cholesterol and blood pressure with age in native children such that North American and European children can be separated statistically from the children of the native, low-risk populations by 6 y of age if not earlier (68–70). This means that, even in young children, the process that gives rise to raised blood pressure, raised cholesterol, and atherosclerosis has been in operation for some time, as is suggested by the Bogolusa Heart Study (71).

Babies that were marginally undernourished as a fetus or postnatally, and who escaped severe disorder, could nonetheless have suffered a degree of impaired development of the cerebro- or cardiovascular system without clinical signs. Atherosclerotic lesions have been described in the umbilical arteries of women who smoked (72) and from postmortem studies of coronary arteries in infants (73, 74). In a study of 1500 postmortems, a higher proportion of these vascular changes were found in babies that had been bottle fed (73). Evidence of advanced aortic atherosclerosis in men in their late teens and early twenties came from postmortem studies of American soldiers killed in Korea (75).

Blood lipids and lipoproteins

A low ratio of high-density lipoprotein (HDL) to low-density lipoprotein (LDL) is associated with increased risk of coronary artery disease. Dietary fatty acids influence the clearance of both triacylglycerol and cholesterol-rich lipoproteins from the plasma. Saturated fatty acids reduce the ability to clear an exogenous load (76). Fish oils (rich in DHA and other long-chain n-3 fatty acids) decrease triacylglycerol synthesis and very-low-density-lipoprotein production (77, 78).

Healthy full-term infants fed breast milk compared with conventional formula were found to have higher serum concentrations of cholesterol esters and HDL₂b (79). Feeding γ-
Preterm infants are at high risk for disease processes common in premature infants. These processes include cerebral palsy, retinopathy of prematurity, intraventricular hemorrhage, and death. The incidence of these conditions is predicted to increase during the next decade. Prematurity coincided with increased environmental and genetic factors, suggesting a far greater degree of HDL maturation as seen in full-term infants.

Raised plasma concentrations of lipoprotein(a) is a risk factor for coronary artery disease. In one study of neonates and parents, a relation between raised lipoprotein(a) in neonates coincided with raised concentrations in one of the parents. No significant relation between lipoprotein(a) and diet has so far been observed. Lipoprotein(a) is considered to be a largely genetic risk factor for coronary artery disease. Hence, both environmental and genetic factors seem to be operating at the earliest ages.

Often, children with raised blood pressures or blood cholesterol concentrations also have high concentrations as teenagers, suggesting a tracking of the risk factor with age. Fatty acids are known to influence gene expression. Such tracking might imply that dietary fatty acids could be one of the factors that influence the expression of genetic information at an early stage.

CONCLUSION

We have presented evidence of structural requirements for polyunsaturated fatty acids. We have tried to give a rationale for IVH, periventricular leucomalacia, BPD, and retinopathy of prematurity based on requirements for AA, DHA, and antioxidant protection. The commonly held view that polyunsaturated fatty acids cause peroxidative damage has been challenged. Here and elsewhere, the converse is suggested: polyunsaturated fatty acids protect and repair damaged membranes. The conclusion is that IVH, periventricular leucomalacia, retinopathy of prematurity, and BPD have a vascular pathogenesis in common. Pre- and postnatal deficits of AA, DHA, and antioxidant defenses provide a biochemical rationale for pre-disposition to these complications of prematurity. A similar view based on tissue injury by oxygen radicals was published recently with the suggestion that these "ill-understood conditions. . . . of neonatology are not different diseases but represent different facets of one disease".

We also conclude from the biochemistry that there is a common requirement for the nutritional systems needed for vascular and neural development. Low-birth-weight babies who escape severe disorders may nonetheless have experienced deficits in vascular development or manipulation of gene expression leading to structural defects and the establishment of lipid and blood pressure risk profiles at an early age. Thus, the pathogenesis of coronary or cerebrovascular disease in adult life may have a biochemical and nutritional denominator common to the vascular and neurovisual complications of low-birth-weight babies.

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