Tissue levels of polyunsaturated fatty acids during early human development

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Long-chain fatty acids are analyzed in tissues from infants whose cause of death was not neurologically related. Total n-3 and n-6 polyunsaturated and n-9 monounsaturated fatty acid amounts increased in the whole forebrain during the prenatal and postnatal periods up to at least 2 years of age. The most abundant brain polyunsaturated fatty acids were docosahexaenoic acid (DHA) (22:6n-3), arachidonic acid (AA) (20:4n-6), and adrenic acid (22:4n-6). In neonates receiving total parenteral nutrition for several days, the DHA/AA ratio was outside the normal range in the liver but within the normal range in the brain. Two other children received total parenteral nutrition for many months, but only the one born at 29 weeks of gestation had a low brain DHA/AA ratio. Another infant, born at 25 weeks of gestation, had been fed milk formulas containing high linoleate/α-linolenate ratios for 4 months. This infant had less DHA and a lower DHA/AA ratio in both the brain and the retina than had term infants. These data suggest that preterm infants are especially at risk for the effects of dietary fatty acid imbalances. (J PEDIATR 1992;120:S129-38.)

As important structural components of the brain and retina, long-chain polyunsaturated fatty acids are localized mainly in cell membrane phospholipids where they seem to play an important role in membrane physical properties and function.[1] The two major brain polyunsaturated fatty acids are docosahexaenoic acid (22:6n-3) and arachidonic acid (20:4n-6); adrenic acid (22:4n-6) is the third most abundant brain polyunsaturated fatty acid, particularly in myelin.[2]

The biochemical sequence resulting in the elongation and desaturation of linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3) to form the long-chain polyunsaturated fatty acids such as AA and DHA has been known for some time. However, in the developing animal it is not clear how efficiently the enzymes, particularly those involved in the final desaturation steps, convert the parent 18 carbon fatty acids to their longer-chain products. Observations in humans and animals suggest that there is a proportional increase in fatty acid length and degree of unsaturation from maternal liver to placenta, fetal liver, and fetal brain.[3] To what extent the developing brain incorporates preformed long-chain polyunsaturated fatty acids[4] or is capable of elongating and desaturating fatty acids in situ[5, 6] remains to be determined. Whatever the exact mechanism for the assimilation of these fatty acids during prenatal life, it is very effective. When born at term, the human infant is well provided with long-chain polyunsaturated fatty acids in the liver, as well as the brain.[7] The tissues of infants born early in the third trimester, on the other hand, contain much lower total amounts and concentrations of these long-chain fatty acids.[8] Some investigators have suggested the desaturation enzymes may be not fully mature[6, 9]; thus these infants may be particularly vulnerable to fatty acid deficiency and nutritional imbalance or both.

AA	Arachidonic acid (20:4n-6)
DHA	Docosahexaenoic acid (22:6n-3)

Studies of the fatty acid composition of a series of infant tissues obtained under similar conditions can provide a picture of the biochemical changes that occur during normal development. These data can be used to estimate tissue fatty acid needs and provide a standard by which to assess alterations in fatty acid composition caused by disease or dietary imbalances. This article presents quantitative fatty acid data from the analysis of tissues from human infants at different stages of development. We determined prenatal fatty

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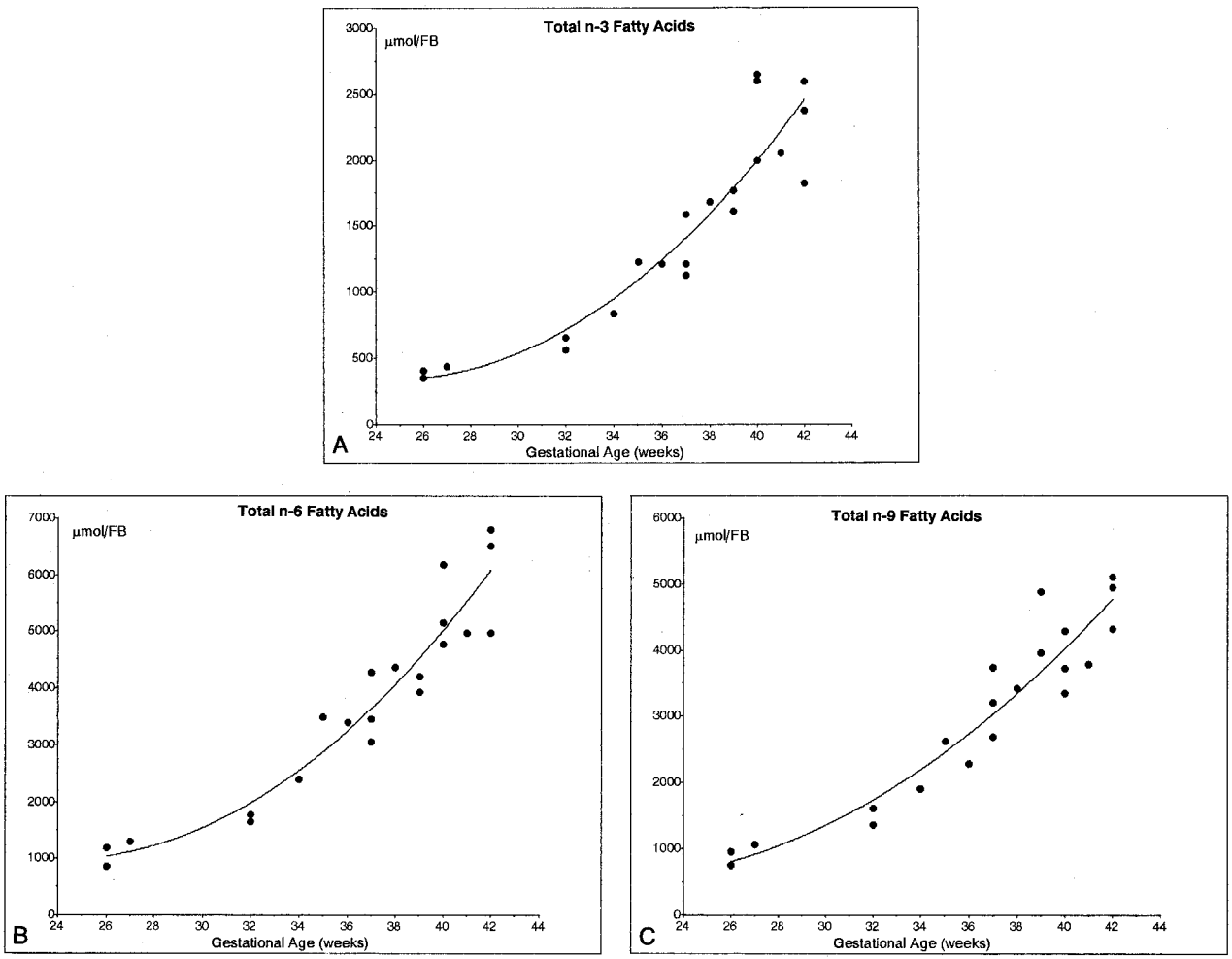

Fig. 1. Total n-3 (**A**), n-6 (**B**), and n-9 (**C**) fatty acids measured in the cerebrum of 21 infants who died soon after birth. *FB*, Total forebrain. **A,** Curve is represented by the equation: $\mu mol/FB = y = 4632.02 - 347.72x + 7.05x^2$; x = gestational age in weeks ($r = 0.93$; $p < 0.001$). **B,** Curve is represented by the equation: $\mu mol/FB = y = 10{,}038.45 - 755.32x + 15.74x^2$; x = gestational age in weeks ($r = 0.95$; $p < 0.001$). **C,** Curve is represented by the equation: $\mu mol/FB = y = 4410.86 - 377.92x + 9.21x^2$; x = gestational age in weeks ($r = 0.94$; $p < 0.001$).

acid accretion by analyzing the tissues of infants who were born at different gestational ages and died soon after birth. These infants had not been fed and their mothers belonged to a well-nourished population, so we believe that the fatty acid patterns measured represent normal developmental patterns. Tissues for assessment of postnatal fatty acid accretion were obtained from well-nourished infants who died of acute causes that were not related to the central nervous system. The details of the selection criteria, the handling of tissue samples, and the methods of analysis have been described previously.[10, 11]

This article also discusses the effects of parenteral nutrition on brain and liver fatty acid composition, and these observations are compared with the more striking alterations found in a preterm infant nourished by diets with unbalanced n-6/n-3 fatty acid ratios. From these data, we can speculate about the effects of nutrition on the long-chain polyunsaturated fatty acid composition of the developing nervous system.

PRENATAL DEVELOPMENT

Fig. 1 illustrates the accretion curves for the n-3, n-6, and n-9 fatty acid families in the forebrain during the second half of gestation. The shape of the curves and the corresponding equations show that fatty acid accretion increases as gestation progresses, reaching a maximum rate of accretion toward the end of gestation. A similar pattern is observed for all three families of fatty acids, although the accretion of the n-9 fatty acid series is more nearly linear than that of the n-6 and n-3 series.

Although the absolute amount of most fatty acids increases in whole cerebrum with development, calculation

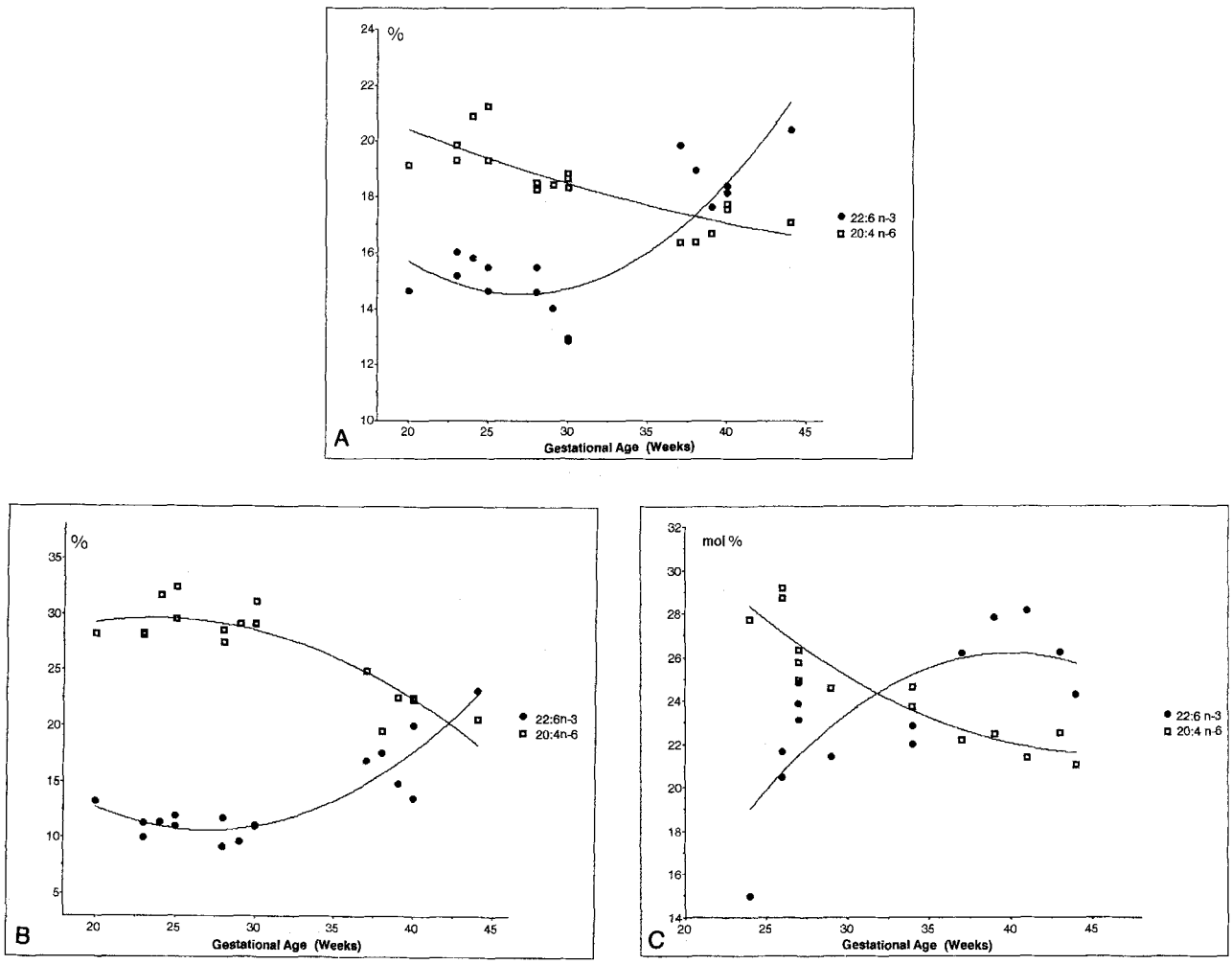

Fig. 2. DHA (22:6n-3) and AA (20:4n-6) as a percent of total fatty acids in forebrain (**A**), liver (**B**), and retina (**C**) ethanolamine phosphoglycerides from 18 infants who died soon after birth. **A,** Curves are represented by the equations: y = percent AA = $25.892 - 0.326x + 0.003x^2$ ($r = 0.819$; $p = 0.002$); y = percent DHA = $32.097 - 1.3x + 0.024x^2$ ($r = 0.841$; $p = 0.001$). **B,** Curves are represented by the equations: y = percent AA = $14.194 + 1.303x - 0.027x^2$ ($r = 0.89$; $p = 0.001$); y = percent DHA = $41.547 - 2.283x + 0.042x^2$ ($r = 0.913$; $p = 0.001$). **C,** Curves are represented by the equations: y = percent (molar) AA = $51.285 - 1.295x + 0.014x^2$ ($r = 0.918$; $p = 0.001$); y = percent (molar) DHA = $-18.898 + 2.258x - 0.028x^2$ ($r = 0.757$; $p < 0.01$).

of the percent of total fatty acids of a given lipid fraction indicates that there are differences in the rates of assimilation of different n-6 and n-3 fatty acids. In ethanolamine phosphoglycerides, which are the most unsaturated brain phospholipids, DHA as a percentage of total fatty acids increases, whereas AA decreases in both the cerebrum (Fig. 2, *A*) and the liver (Fig. 2, *B*) during the last trimester of intrauterine life. This relative enrichment of brain DHA is consistent with the rapid formation of synapses and dendritic spines taking place during this period.[10, 12] The percentages of AA and DHA in brain ethanolamine phosphoglyceride are closely and linearly correlated with those in liver ethanolamine phosphoglyceride.

In addition, DHA increases and AA decreases in a curvilinear manner during the prenatal period in the ethanolamine phosphoglyceride fraction of the retina (Fig. 2, *C*). An increase in the percentage of DHA can be explained by the rapid development of the photoreceptor cells during the last half of gestation.

POSTNATAL DEVELOPMENT

A single regression equation relating amounts of brain n-3 fatty acid to time from the prenatal period to the second postnatal year provides an overall view of accretion during the major developmental period of rapid brain growth (Fig. 3A). This data analysis includes two popula-

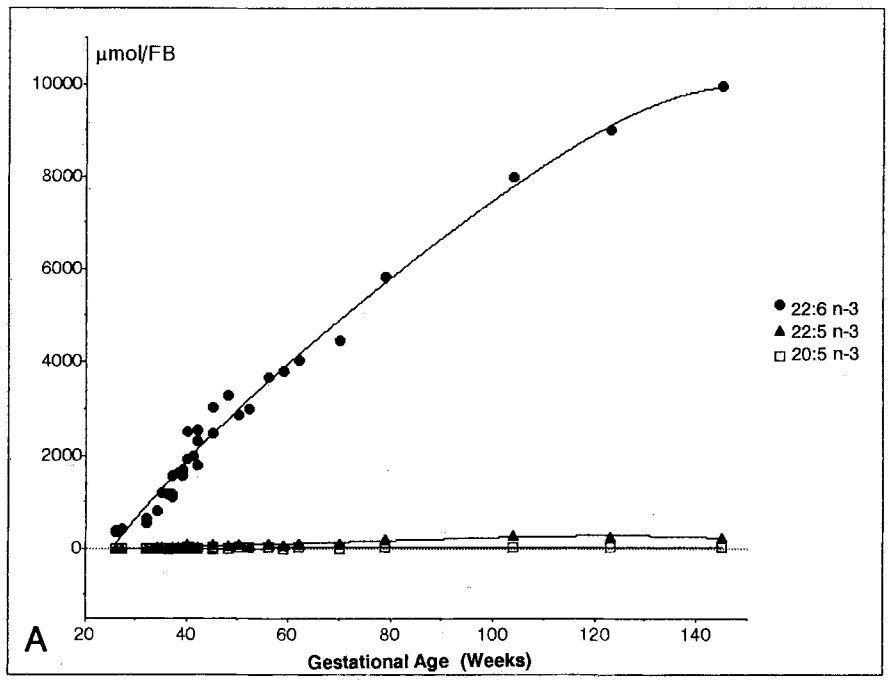

Fig. 3A. The three major n-3 brain fatty acids, DHA (22:6n-3), docosapentaenoic acid (22:5n-3), and eicosapentaenoic acid (20:5n-3), in the forebrains *(FB)* of 34 infants, including both preterm and postnatal normally fed infants up to 2 years of age. Curves are represented by the equations: y = µmol/FB DHA = $-4519.446 + 226.459x - 2.245x^2 + 0.017x^3 - 5.244E - 5x^4$ ($r = 0.992$); y = µmol/FB 22:5n-3 = $-106.538 + 5.484x - 0.074x^2 + 0.001x^3 - 4.008E - 6x^4$ ($r = 0.949$); y = µmol/FB 20:5n-3 = $-59.29 + 3.489x - 0.062x^2 + 0.001x^3 - 1.671E - 6x^4$ ($r = 0.736$). For all equations, x = postconceptional age in weeks and $p = 0.0001$.

tions of infants: those nourished in utero and those nourished after birth. Although it is more appropriate to analyze these populations separately, a combined analysis produces a highly significant curve.

From a quantitative point of view, DHA (22:6n-3) is the only n-3 fatty acid present in significant amounts in the brain. According to this analysis, it seems clear that the n-3 fatty acids do not stop increasing after birth, as has been postulated by some investigators.[13] The very rapid prenatal increase becomes more moderate but is still very significant until at least 2 years of age.

In contrast to the n-3 fatty acids, two n-6 fatty acids are quantitatively important in brain development (Fig. 3B). During the prenatal period, the most abundant n-6 fatty acid is AA (20:4n-6), and its accretion is most rapid. After birth, 22:4n-6 increases as rapidly as AA. This may be explained by a spurt in the myelination process and the major contribution of myelin lipid deposition to brain fatty acid accretion during this period.[14, 15] In contrast to DHA, the other product of delta-4 desaturation, 22:5n-6, increases only before birth and then changes very little, remaining a minor constituent throughout brain development. The n-6 precursor fatty acid, linoleic acid, is also a minor constituent of nervous tissue.

Although scientists studying fatty acids and infant nutrition are concerned mainly with the adequacy of the n-6 and n-3 fatty acid series, attention should also be given to the n-9 fatty acid series. These fatty acids are not essential in the diet, but brain accumulation is very high during the early postnatal period, when myelin is being formed most rapidly. Oleic acid (18:1n-9) is a ubiquitous component of tissue glycerolipids and is especially enriched in the myelin sheath. It is elongated to nervonic acid (24:1n-9), which is the most characteristic monoene in myelin, and to longer monoenoic fatty acids (25:1n-9 and 26:1n-9), which are characteristic of myelin sphingolipids.

Although present in very different amounts, the three monoenes, 18:1n-9, 24:1n-9, and 26:1n-9, increase significantly during the postnatal period (Fig. 3C). The parent fatty acid in this series, oleic acid, increases very rapidly during the prenatal, as well as the postnatal, period, whereas the accretion of 24:1n-9 and 26:1n-9, which are more specifically in myelin, starts at term. Although 26:1n-9 is a minor constituent, it does increase markedly.

Fig. 4 illustrates the distribution of the mean values of the different fatty acid series (saturated, n-3, n-6, and n-9) at birth and during the postnatal period. Apart from the overall increase in total fatty acids, a general trend toward an

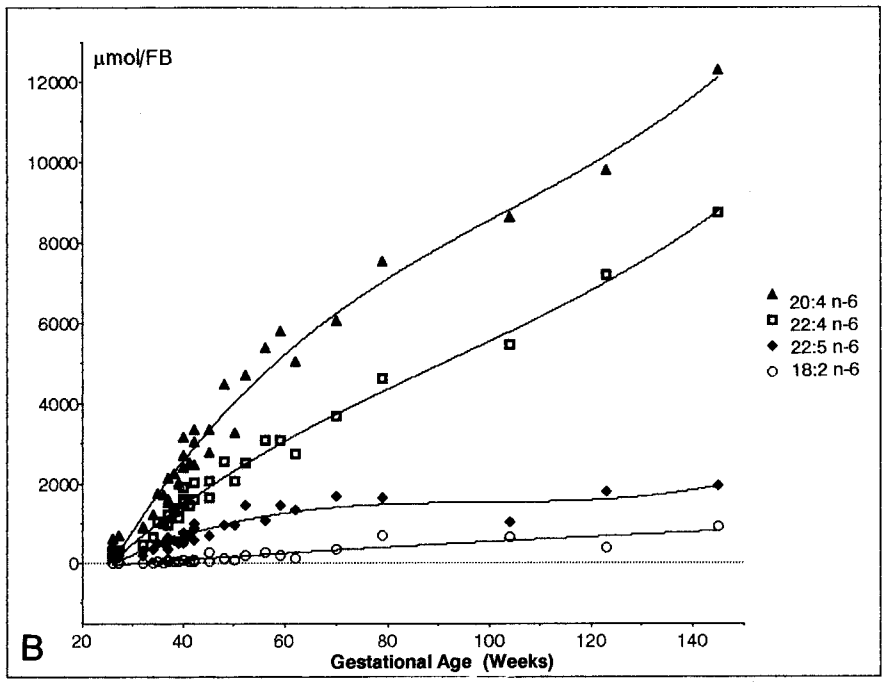

Fig. 3B. The n-6 fatty acids, AA (20:4n-6), adrenic acid (22:4n-6), 22:5n-6, and linoleic acid (18:2n-6), in the forebrains *(FB)* of 34 infants, including both preterm and postnatal normally fed infants up to 2 years of age. Curves are represented by the equations: $y = \mu mol/FB$ AA $= -6536.123 + 308.597x - 2.323x^2 + 0.007x^3$ ($r = 0.988$); $y = \mu mol/FB$ 22:4 n-6 $= -3345.163 + 156.799x - 1.066x^2 + 0.004x^3$ ($r = 0.993$); $y = \mu mol/FB$ 22:5 n-6 $= -2222.266 + 111.719x - 1.12x^2 + 0.004x^3$ ($r = 0.934$); $y = \mu mol/FB$ 18:2 n-6 $= -305.219 + 11.078x - 0.031x^2 + 5.592E - 5x^3$ ($r = 0.908$). For all equations, x = postconceptional age in weeks and $p = 0.0001$.

increase in n-9 fatty acids at the expense of saturated fatty acids is clearly discernible. Less apparent in Fig. 4, although real, is the increase in the proportion of n-3 fatty acids, accompanied by a much smaller decrease in n-6 fatty acids.

EFFECTS OF NUTRITION ON POLYUNSATURATED FATTY ACIDS

The percentage of DHA increases and the percentage of AA decreases in both brain and liver ethanolamine phosphoglyceride during prenatal development; the ratio of DHA/AA is therefore very useful for the evaluation of DHA enrichment of brain and retina membrane phospholipids during the spurt of synaptogenesis and photoreceptor cell development. Until about 30 weeks of gestation, the liver DHA/AA ratio is lower than the brain DHA/AA ratio (Fig. 5). However, toward the end of gestation, the liver DHA/AA ratio increases rapidly, suggesting that the fetal liver is capable of providing the DHA/AA ratio needed by rapidly developing brain membranes. Compared with the normal fetus, five preterm infants who received total parenteral nutrition with Intralipid (10% safflower oil emulsion) for a short period had significantly decreased DHA/AA ratios in their livers but no alteration in the ratios in their brains.[7]

Because both DHA and AA increase markedly in brain total fatty acids, changes in the total fatty acid DHA/AA ratio are not significant, in contrast to the ethanolamine phosphoglyceride fraction (Fig. 6). However, an increase in this ratio can still be detected in brain total fatty acids during prenatal development. After birth, individual variation predominates, possibly because of differences in postnatal nutrition, and this variation masks any trends. Even so, during the period of rapid brain development, an imbalance in the dietary ratio of linoleic acid/α-linolenic acid can result in a DHA/AA ratio outside of the normal range. This is illustrated by the marked decrease in the DHA/AA ratio found in a preterm infant (born at 25 weeks of gestation) fed milk formulas with a high linoleic acid/α-linolenic acid ratio for 4 months (Fig. 6). The formula fed most had a linoleic acid/α-linolenic acid ratio of 66:1 and 0.38% α-linolenic acid. There were some intervals when the infant received a formula with an 18:2n-6/18:3n-3 ratio of 18:1 and 0.41% α-linolenic acid. The decreased DHA/AA ratio was also detected in this child's retina,[16] a tissue in which the fatty acids are usually not affected by nutritional fatty acid deprivation or imbalance[17] (Fig. 7).

The DHA/AA ratios in the brain total fatty acids of two children who received total parenteral nutrition are also il-

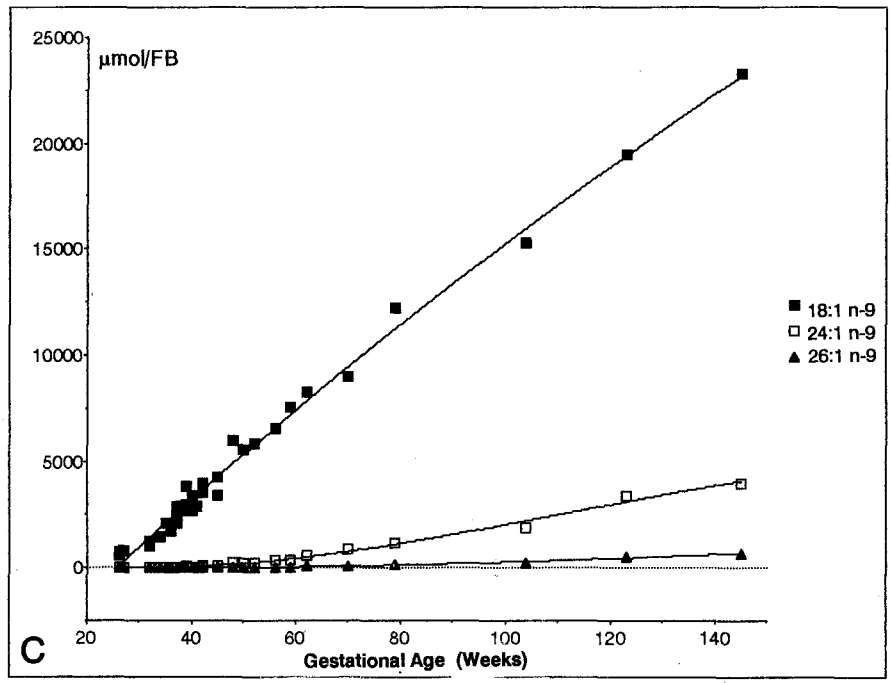

Fig. 3C. The n-9 fatty acids, 18:1n-9, 24:1n-9, and 26:1n-9, in the forebrains *(FB)* of 34 infants, including both preterm and postnatal normally fed infants up to 2 years of age. Curves are represented by the equations: $y = \mu mol/FB\ 18{:}1n{-}9 = -5903.622 + 239.336x - 0.288x^2 + 1.331E-4x^3$ ($r = 0.996$); $y = \mu mol/FB\ 24{:}1n{-}9 = 600.333 - 42.375x + 0.812x^2 - 0.002x^3$ ($r = 0.996$); $y = \mu mol/FB\ 26{:}1n{-}9 = 68.21 - 4.562x + 0.0772x^2 - 1.084E-4x^3$ ($r = 0.995$). For all equations, x = postconceptional age in weeks and $p = 0.0001$.

lustrated in Fig. 6. One infant was born at 29 weeks of gestation and received total parenteral nutrition from birth to 75 days of life (equivalent to most of the last trimester of gestation) and died at 7 months of age, or 4 months of adjusted postnatal age. This child had a low DHA/AA ratio. However, another infant who was born at term and died at 14 months of age, after having received total parenteral nutrition all his life, had normal brain and liver n-6 and n-3 fatty acid composition and a normal DHA/AA ratio. This child had Hirschsprung disease and underwent several operations. He was maintained in good nutritional status with total parenteral nutrition until he died of a complication.

The ratio of 22:5n-6/22:4n-6 is an index of delta-4 desaturation for the n-6 series. The child fed very high linoleic acid/α-linolenic acid ratio formulas had a high value of this index in the brain, indicating n-3 fatty acid deficiency (Fig. 8). However, the 22:5n-6/22:4n-6 ratios in the brains of the two children who received total parenteral nutrition were either normal or low.

CONCLUSIONS

These data indicate how rapidly long-chain fatty acids accumulate in the human brain during the brain's growth spurt. The active formation of synaptic structures and dendritic arborizations, with rapidly multiplying dendritic spines, increases significantly between 31 weeks of gestation and term. This change is detectable both morphologically[12] and biochemically[10] and explains the sudden increase in polyunsaturated fatty acids, particularly DHA.

Although synaptogenesis continues during the postnatal period, myelination of the human cerebrum starts just before term.[15] Therefore it is logical to assume that long-chain fatty acid accretion continues after birth, particularly in the developing synapses, as these data corroborate. Our results do not support a view that AA (20:4n-6), 22:4n-6, and DHA (22:6n-3) fatty acid accretion ceases or diminishes during the first weeks of postnatal life.[13]

Although birth results in a great change in the type of fatty acids supplied to the human infant, long-chain fatty acids continue to accumulate in the brain unless a serious imbalance in the supply of linoleic acid and α-linolenic acid occurs. This may be especially deleterious for the preterm infant, who undergoes a change from an optimal intrauterine supply to an unbalanced diet just at the time of maximum brain development. Unfortunately, many current milk formulas are more or less imbalanced in n-6 and n-3 fatty acid precursors and practically devoid of longer-chain polyunsaturated fatty acids. The range of linoleic acid/α-linolenic acid ratios provided to the preterm infant born at 25 weeks of gestation described in this article is quite common in milk formulas.

Current intravenous lipid formulas based on soybean oil,

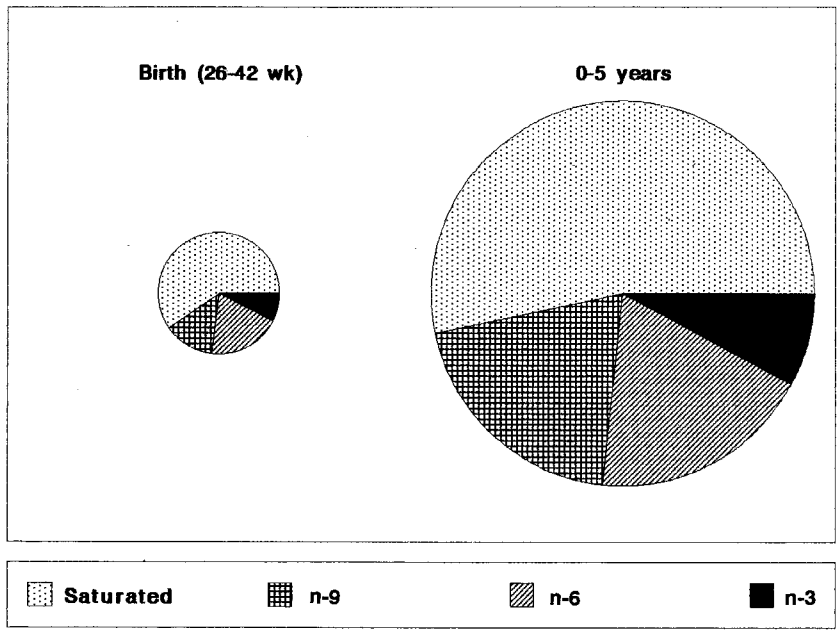

Fig. 4. Mean distribution of total brain fatty acid families, saturated, n-3, n-6, and n-9 fatty acids, at birth (n = 21) and during the first 5 years of life (n = 15). Size of the graph is proportional to the total fatty acids present.

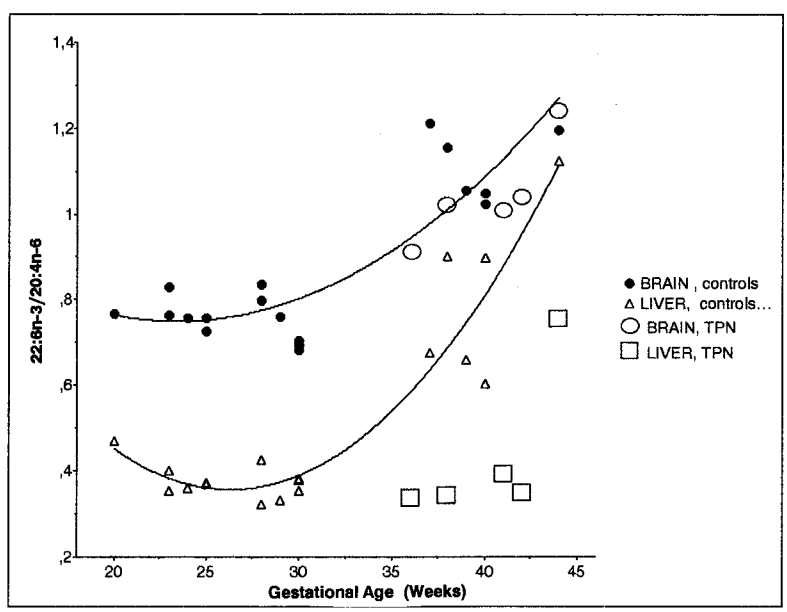

Fig. 5. Brain and liver ethanolamine phosphoglyceride DHA/AA ratios measured in 18 infants who died shortly after birth and 5 infants who received total parenteral nutrition *(TPN)* (Intralipid) for a few days. Curves for infants who had not been fed are represented by the equations: y = DHA/AA ratio in cerebrum = $1.427 - 0.058x + 0.001x^2$ (r = 0.874; p = 0.001); y = DHA/AA ratio in liver = $2.027 - 0.127x + 0.002x^2$ (r = 0.938; p = 0.001). (Data from Martinez M, Ballabriga A. Lipids 1987;22:133-8.)

with about 45% to 55% linoleic acid and 6% to 8% α-linolenic acid, have a 18:2n-6/18:3n-3 ratio between 7:1 and 8:1. This may partly explain why the infant receiving total parenteral nutrition for 14 months had appropriate levels of DHA in his liver and brain; this infant had been born at term, with an excellent body weight, and his desaturase systems were probably mature enough to convert linoleic and α-linolenic precursors into their highly unsaturated, long-chain products. However, the other infant born prematurely received total parenteral nutrition instead of pre-

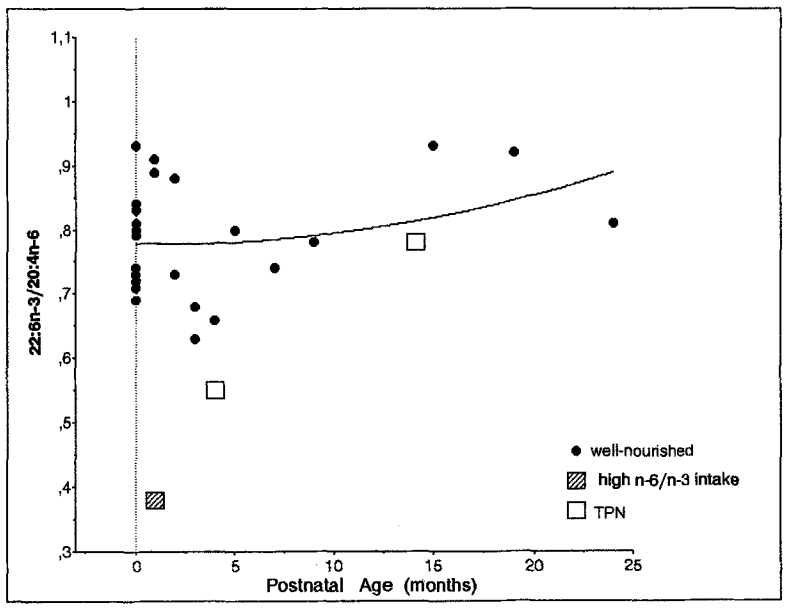

Fig. 6. Total brain fatty acid DHA/AA ratios of term neonates and well-nourished infants who died at various postnatal ages compared with those of an infant born at 25 weeks of gestation fed formulas with high linoleic/α-linolenic acid ratios for 4 months and two infants who received total parenteral nutrition *(TPN)*, one for 75 days after birth at 29 weeks of gestation and one for 14 months after a term birth. Curve is not statistically significant.

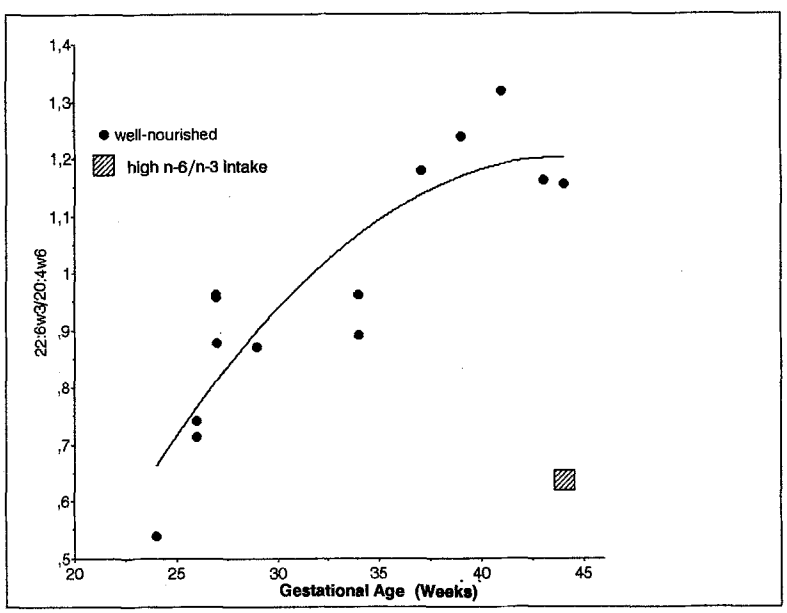

Fig. 7. Retinal ethanolamine phosphoglyceride DHA/AA ratio in 13 well-nourished infants and 1 infant born at 25 weeks of gestation fed formulas with high linoleic/α-linolenic acid ratios for 4 months (not fed, n = 11; postnatally nourished, n = 3). Curve for well-nourished infants is represented by the equation: $y = \text{DHA/AA} = -1.41 + 0.119x - 0.001x^2$ ($r = 0.887$; $p = 0.002$).

natal maternal nutrition. This child had a significantly decreased brain DHA/AA ratio, but his brain 22:5n-6/22:4n-6 index was within normal limits.

Considering these data, we can speculate on the different factors that may influence fatty acid accretion in developing tissues and that should be taken into account when designing infant formula fat blends. Apart from the possible problems of enzyme immaturity, which cannot be measured

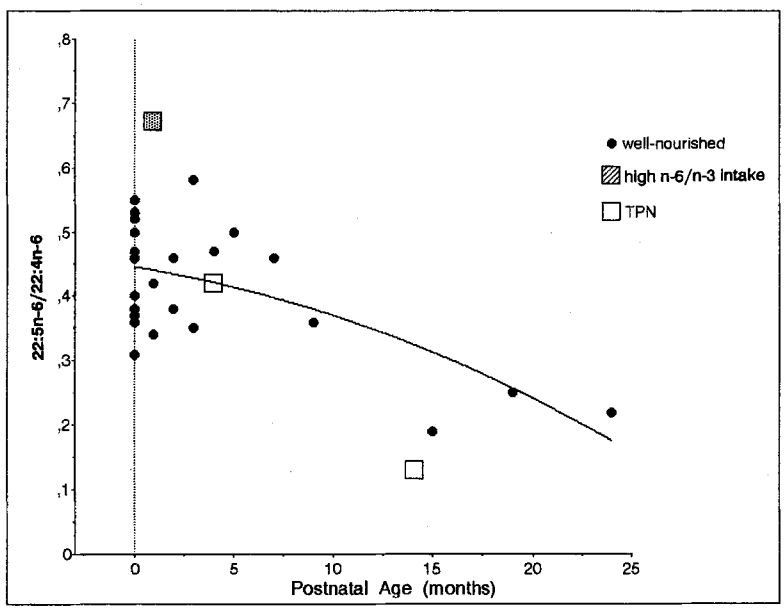

Fig. 8. Brain 22:5n-6/22:4n-6 ratio, an index of delta-4 desaturation, of 11 term neonates and 13 well-nourished infants who died at various postnatal ages compared with those of an infant born at 25 weeks of gestation fed formulas with high linoleic/α-linolenic acid ratios for 4 months and 2 infants who received total parenteral nutrition *(TPN)*, 1 for 75 days after birth at 29 weeks of gestation and 1 for 14 months after a term birth. Curve for the 13 postnatal infants is represented by the equation: y = 22:5n-6/22:4n-6 = $0.447 - 0.006x - 2.204E - 4x^2$ ($r = 0.842$; $p < 0.01$).

directly, these data suggest that the linoleic/α-linolenic acid ratio in milk formulas is important, especially when provided to preterm infants.

A second issue is whether it is important that preterm formulas for oral or parenteral nutrition contain 20 and 22 carbon polyunsaturated fatty acids. These data suggest that at least DHA should be added to formulas, and a tissue deficiency of AA is probably very difficult to produce with the high linoleic acid/α-linolenic acid ratios provided in milk formulas. Although delta-6 and delta-5 desaturases may be immature in the human infant,[9] the amount of linoleic acid provided in all formulas is so high that enough AA is formed, at least in quantitative terms.

Formation of DHA also depends on an efficient delta-4 desaturation system. It has been suggested that this last step of desaturation may be affected by feeding imbalanced ratios of linoleic acid/α-linolenic acid in formulas to preterm infants.[9] According to recent evidence, delta-4 desaturation may be deficient in peroxisomal disorders; these patients have extremely reduced tissue levels of DHA.[11, 18] However, most n-6 fatty acids such as linoleic acid, 20:2n-6, 20:3n-6, 20:4n-6, and 22:4n-6 are normal or high in most patients with peroxisomal disorders. The exception is 22:5n-6, which is reduced in Zellweger syndrome. In some cases of neonatal adrenoleukodystrophy, 22:5n-6 also increases, just as it does in n-3 fatty acid deficiency.[19] Thus even in these very abnormal conditions, it seems that the n-6 fatty acids are less likely to be affected than the long-chain n-3 fatty acids. The existence of an enzyme responsible for direct delta-4 desaturation has recently been questioned, and some alternate metabolic routes involving chain elongation, delta-6 desaturation, and retroconversion have been proposed.[20]

Whatever the mechanism and enzymes involved, the formation of DHA is clearly an important reaction. If the reaction or reactions do not function properly, this important fatty acid must be provided in the diet. Human milk does contain DHA; the small amount present has been estimated to be enough to fulfill the infant's requirements for brain growth.[21, 22]

Although not considered to be an essential fatty acid in the diet, the high oleic acid content of human milk[22, 23] is interesting in view of the significant increase in n-9 fatty acids in the developing human brain. This increase suggests the possible importance of the high monoene content of human milk and that the low monoene content of milk formulas should be considered. If the dietary level of 18:1n-9 is too low, a large excess of the polyunsaturated fatty acid precursors (linoleic and α-linolenic acids) would have a competitive advantage for delta-6 desaturation.[24]

In the light of this evidence, it seems highly desirable to enrich parenteral lipids and milk formulas with DHA to provide between 0.5% and 1% of total fatty acids (weight/weight) similar to those in human milk. A total n-6/n-3

fatty acid ratio between 5 and 7 seems appropriate according to our analyses of human milk from mothers consuming complete, balanced Mediterranean diets rich in fish.

There are concerns about the use of fish oils as a source of DHA for formulas. Most marine oils are extremely rich in eicosapentaenoic acid (20:5n-3), a minor constituent of brain membranes. However, it is metabolically active as a precursor of the series 3 prostaglandins. There is the risk that such an excess in eicosapentaenoic acid may compete with AA in the synthesis of series 2 prostaglandins. A good source of DHA without the disadvantages of fish oils is the n-3-rich brain phospholipids, such as phosphatidylethanolamine or phosphatidylserine. Alternatively, the addition of small amounts of DHA ethyl ester could be tested. Whatever the source of DHA, only formulas without any excess in the precursors, linoleic and α-linolenic acids, and with small amounts of DHA should be used in formulas for preterm infants. This conclusion is based partly on our data from neonates receiving Intralipid, which has a good precursor ratio.

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