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Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation

(polyunsaturated fatty acids/mean melting point/fatty acid profile/ω3 fatty acids/linoleic acid)

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ABSTRACT **In a group of 19 normal pregnant women, plasma lipids were extracted, phospholipids were isolated, and the fatty acid (FA) compositions were measured by capillary gas chromatography. Blood samples were taken at 36 wk, at labor, and at 6 wk postpartum. The FA profiles showed deficiencies of ω6 and ω3 FA (ω indicating the length of the terminal saturated chain), the latter more severe, at all three times. Mean melting point (MMP) was calculated for each sample as an index of "fluidity" based upon all FA present. MMP varied linearly with total polyunsaturated FA and with double bond index, current measures of "fluidity" and essential FA status. MMP was elevated 9–11°C in plasma phospholipids of women during pregnancy and labor and postpartum. Lactating mothers showed less recovery from the deficiencies than did the nonlactating mothers, but neither approached normal at 6 wk. The changes seen in phospholipid profiles suggest a significant transfer of ω3 and ω6 polyunsaturated FA from the mother to the fetus. These FA are essential for normal fetal growth and development; their relative deficiency in maternal circulation suggests that dietary supplementation may be indicated.**

Abnormalities of pattern of fatty acids (FA) within plasma and tissue phospholipids (PL) occur in nutritional deficiency of essential fatty acids (EFA) in animals (1–4) and humans (5–8). In Sjogren–Larsson syndrome (9), Reye syndrome (10), cirrhosis and alcoholism (11), multiple sclerosis (12), and other diseases of humans (13–16), significant disturbances of pattern of polyunsaturated fatty acids (PUFA) also occur. Nutritional deficiencies of both ω6 and ω3 PUFA§ occur in humans (5, 16). Genetic diseases may be associated with deficiencies of PUFA as the result of faulty PUFA metabolism. Growth, stress, or excessive loss and replacement of tissue all increase the requirement for PUFA, and unless intake is equal to increased need, deficiency occurs. In pregnancy, growth of new tissue raises the requirement for EFA. The purpose of this study was to assess the EFA status of women whose pregnancies were normal, at 36 wk of pregnancy, at the time of labor, and at 6 wk postpartum for both lactating and nonlactating women.

SUBJECTS AND METHODS

Normal Pregnancies. All subjects chosen for study were normotensive Caucasians with normal singleton pregnancies seen at the Mayo Clinic. Written consent was obtained from the subjects before enrollment. Patients were excluded from study if they had any major underlying medical disease, hypertension, or previous history of complicated pregnancy. All were nonsmokers. Prior to having blood samples drawn, patients abstained from aspirin-containing drugs for 7 days and from other nonsteroidal antiinflammatory agents for the previous 48 hr. The mean age (±SD) was 29.2 ± 4.3 yr, with a range of 24–36 yr. This study was approved by the Committee on the Use of Human Subjects of the University of Minnesota and by the Institutional Review Board at the Mayo Clinic. At 36 wk, venous blood was drawn from the left arm. Pregnant patients had venous blood drawn at 36 wk of gestation, during active labor, and at 6 wk postpartum. The numbers of subjects studied were 12 at 36 wk, 17 at labor, and 19 at 6 wk postpartum. Of the latter, 6 were nonbreastfeeding and 13 were breastfeeding.

Control Subjects. In another study (17), 100 omnivores were recruited as normal controls from the staff and student body of the University of Minnesota. Each completed a health and diet history. From this group, 59 women of child-bearing age were segregated as controls for this study. Mean age was 28.8 ± 5.6 yr, with a range of 19–48 yr.

Methods of Analysis. Plasmas were prepared from blood samples and kept frozen until analyzed at the Hormel Institute. Lipids from 2-ml samples were extracted with 6 ml of chloroform/methanol (2:2, vol/vol) and centrifuged. The aqueous layer was drawn off, and the extract was filtered, dried under N_2, and redissolved in 100 μl of chloroform. PL were separated by thin-layer chromatography and FA composition was measured by capillary gas chromatography as described previously (12).

Presentation of Data. Values are expressed as relative percentage of total FA of the lipids, because lipids occur in vesicles and membrane-bounded surfaces, and the kinetics of their metabolism are governed by their concentrations at two-dimensional surfaces rather than by three-dimensional concentrations in the surrounding aqueous medium, in which they are not soluble. The percentage of FA within a lipid class better expresses the concentration of substrate accessible to an interfacial enzyme than does the concentration in the aqueous space. The ratio of experimental to control values (normalcy ratio, NR) indicates relative concentration change of a substrate *in the lipids*. Significances of the differences between the groups were calculated by using Student's *t* test, and NR was calculated from the means of the experimental and control groups.

All measurable FA are displayed in profiles of PUFA and of nonessential endogenously synthesized FA. Several calculated group values assist in comparisons of physical prop-

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Abbreviations: PL, phospholipids; FA, fatty acids; PUFA, polyunsaturated fatty acids; EFA, essential fatty acids; NR, normalcy ratio; MCL, mean chain length; MMP, mean melting point; DBI, double bond index; Tri/Tet, triene-to-tetraene; DP, desaturation products; EP, elongation products; P, products.

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§Abbreviated nomenclature for PUFA indicates chain length, number of methylene-interrupted double bonds, and length of the terminal (ω) saturated chain (which is unaltered by desaturation or elongation).

erties, of families of PUFA, and groupings of products at each step in the metabolic pathway through which essential and nonessential unsaturated FA are converted to more highly unsaturated FA of longer chain length. The profile has been expanded to display differences between groups for calculated mean chain length (MCL) and estimated mean melting point (MMP). Both are expressions of physical change in the lipids related to "fluidity" (12). Compositional values in plasma PL reflect composition of tissue PL (5). Values given in the figure for these two parameters are differences between experimental values and control values. Control values (±SD) for nonpregnant women were MCL = 17.49 ± 0.03 carbon atoms and MMP = 15.3 ± 2.2°C.

In graphic profiles, the vertical axis is an NR of 1 (control value); open bars indicate no significance; bars with wide striations indicate $P < 0.05$; bars with close striations indicate $P < 0.01$; and black bars indicate $P < 0.001$. Triene-to-tetraene (Tri/Tet) ratio is 20:3ω9/20:4ω6, the first proposed index of EFA deficiency (18). Double bond index (DBI) is the number of double bonds per acyl group. DP indicates desaturation products, EP is elongation products, and P is products of linoleic acid (18:2ω6), linolenic acid (18:3ω3), or oleic acid (18:1ω9).[§]

RESULTS AND DISCUSSION

FA Profile of Plasma PL in Nonpregnant Women. The PUFA profile of 59 normal women of child-bearing age used as normal controls in this study is given as mean mol % ± SEM as follows: 18:2ω6, 24.1 ± 0.39; 18:3ω6, 0.10 ± 0.01; 20:2ω6, 0.49 ± 0.02; 20:3ω6, 3.26 ± 0.09; 20:4ω6, 12.5 ± 0.24; 22:4ω6, 0.73 ± 0.04; 22:5ω6, 0.60 ± 0.02; total ω6, 41.8 ± 0.29; 18:3ω3, 0.22 ± 0.01; 20:5ω3, 0.53 ± 0.03; 22:5ω3, 1.04 ± 0.04; 22:6ω3, 3.71 ± 0.14; total ω3, 5.50 ± 0.16; 20:3ω9, 0.12 ± 0.01; and total PUFA, 47.4 ± 0.34. The non-EFA profile was as follows: 14:0, 0.21 ± 0.01; 16:0, 21.4 ± 0.25; 18:0, 12.4 ± 0.22; 20:0, 0.37 ± 0.02; 22:0, 0.10 ± 0.04; 24:0, 0.85 ± 0.08; total saturated FA, 36.5 ± 0.28; 16:1ω7, 0.72 ± 0.03; 18:1ω9, 8.95 ± 0.22; 20:1ω9, 0.24 ± 0.03; 22:1, 0.01 ± 0.01; 24:1, 1.19 ± 0.04; total monoenoic FA, 14.0 ± 0.21; branched FA, 1.01 ± 0.05; and odd-chain FA, 0.19 ± 0.01. Calculated parameters were DBI, 1.54 ± 0.01 double bonds per FA; Tri/Tet ratio, 0.01; Δ^6 DP, 0.10 ± 0.01; Δ^5 DP, 13.1 ± 0.24; Δ^4 DP, 4.32 ± 0.15; Δ^9 DP, 9.67 ± 0.22; C_{20} EP, 4.00 ± 0.1; C_{22} EP, 1.77 ± 0.05; ω6 P, 17.6 ± 0.29; ω3 P, 5.28 ± 0.16; ω9 P, 0.38 ± 0.03; and total ω9 FA, 9.33 ± 0.22. Using these values and the NR values given in the figures and in text, values for the FA and calculated parameters for pregnancy, at labor, and at 6 wk postpartum may be estimated.

FA Profile of Plasma PL in Pregnancy. PL are the major structural lipid components of membranes, the major locus of PUFA in tissues. PL of plasma respond to change in EFA status as do PL of vital organs (5), with which they are in equilibrium. The NR profile for pregnant women compared with nonpregnant women is shown in Fig. 1*A*. The PUFA profile reveals that all individual PUFA were less than normal except 22:5ω6, which was significantly elevated. The ω6 and ω3 groups of PUFA were 83% and 57% of normal, respectively, both significant at $P < 0.001$. Levels of arachidonic acid (20:4ω6) and eicosapentaenoic acid (20:5ω3) were 65% and 42% of normal values, respectively. These are 5-desaturase products in the ω6 and ω3 metabolic cascades, respectively, and precursors of many important autacoids. The most suppressed PUFA was 22:5ω3, which was present at 35% of normal value. Despite this abundant evidence of deficient PUFA, Mead's acid (20:3ω9) was not increased as it is in simple nutritional ω6 EFA deficiency (5, 18). The 20:4ω6, 20:5ω3, and 20:3ω9 are all products of 5-desaturation. Each was found at subnormal level, and total 5-desaturase products were suppressed to 64% of normal value. The profile of non-EFA revealed skewing of saturated and monounsaturated FA toward shorter chain length. The saturated FA 14:0 and 16:0 were elevated significantly ($P < 0.001$), whereas 18:0, 20:0, and 22:0 were progressively suppressed. Branched acids were subnormal, whereas 15:0 was elevated. Total saturated FA were elevated to 132% of normal, but total monoenoic FA were not significantly different from normal. Chain shortening partially compensated for the loss of long-chain PUFA. MCL was 17.21 ± 0.02 carbon atoms for pregnant women vs. 17.49 ± 0.03 for nonpregnant women ($P < 0.001$). The DBI was 1.15 ± 0.02 double bonds per FA for pregnant women and 1.54 ± 0.01 for normal nonpregnant women ($P < 0.001$). Total PUFA were 37.8 ± 0.48% of total FA in pregnancy and 47.4 ± 0.34% in normal nonpregnant women ($P < 0.001$).

FA Profile of Plasma PL During Labor. Fig. 1*B* shows that the FA profile during labor was very similar to that at 36 wk of pregnancy, except that the subnormal 18:2ω6 and 18:3ω3 values became significant at $P < 0.01$ and $P < 0.05$, respectively, and the elevated 22:5ω6 became significant at $P < 0.001$. Total PUFA fell from 80% of normal in pregnancy to 78% at parturition, and DBI fell from 75% to 73% of normal. The MCL was found to be 17.20 ± 0.03 carbon atoms, and the MMP was 26.09 ± 1.18°C. DBI was 1.12 ± 0.01 double bonds per FA, and total PUFA was 37.1 ± 0.40% of all FA. Abnormalities found at 36 wk of pregnancy had increased slightly but not significantly at parturition.

Plasma PL Profile in Lactating Women 6 wk Postpartum. This profile is shown in Fig. 1*C*. The profile was very similar to that during pregnancy and at parturition. Minor changes since parturition included elevation of 18:3ω6 (no significance), lowered 20:2ω6 and 20:3ω6, improved 20:4ω6, suppressed 22:5ω6, diminished 18:3ω3, and 20:5ω3 and 22:5ω3 increased toward normal. Proportions of desaturase and elongation products remained subnormal. MCL increased slightly to 17.29 ± 0.03 carbon atoms and MMP decreased to 25.1 ± 0.62°C. The DBI was 1.16 ± 0.01 double bonds per FA (normal controls = 1.54 ± 0.01), and the total PUFA was 38.3 ± 0.35% (normal controls = 47.4 ± 0.34%). Thus, some indicators showed minor improvement toward normal. Clearly, full recovery from the stress of pregnancy had not been achieved.

Plasma PL Profile in Nonlactating Women 6 wk Postpartum. The PL profile of nonlactating women (Fig. 1*D*) was very similar to that of lactating women, but abnormalities of profile were somewhat less severe or of lower significance. MCL was 17.30 ± 0.04 carbon atoms and the MMP was 24.7 ± 0.75°C. The DBI was 1.18 ± 0.02 double bonds per FA, and the total PUFA was 38.5 ± 0.78% of total FA. These values, closer to normal than in lactating women, still differed grossly from values in control nonpregnant women. Clearly, the stress of pregnancy upon PUFA metabolism was not corrected by 6 wk postpartum, even without the stress of lactation. A longer longitudinal study is needed to determine when deficiencies appear and how long is required for PUFA metabolism to return to normal after pregnancy.

Deficiencies of ω6 and ω3 PUFA in PL during pregnancy were not accompanied by increased 20:3ω9, suggesting that they were not a simple nutritional deficiency of EFA. Neither were they accompanied by a decrease in 20:3ω9, indicating that they were not due to inhibited 5-desaturation. Pregnancy probably affects equilibria governing release, transfer, or exchange of PUFA between maternal and fetal lipids.

Membrane Fluidity. All shifts in FA composition induced by pregnancy affect physical properties of the PL. Formerly, the best measures of "fluidity," measurable in living subjects from the composition of the FA of PL and without artificial probes, were the DBI and total PUFA. However, these do not take into consideration differences in chain length or of branching, known to occur in disease or malnutrition. DBI

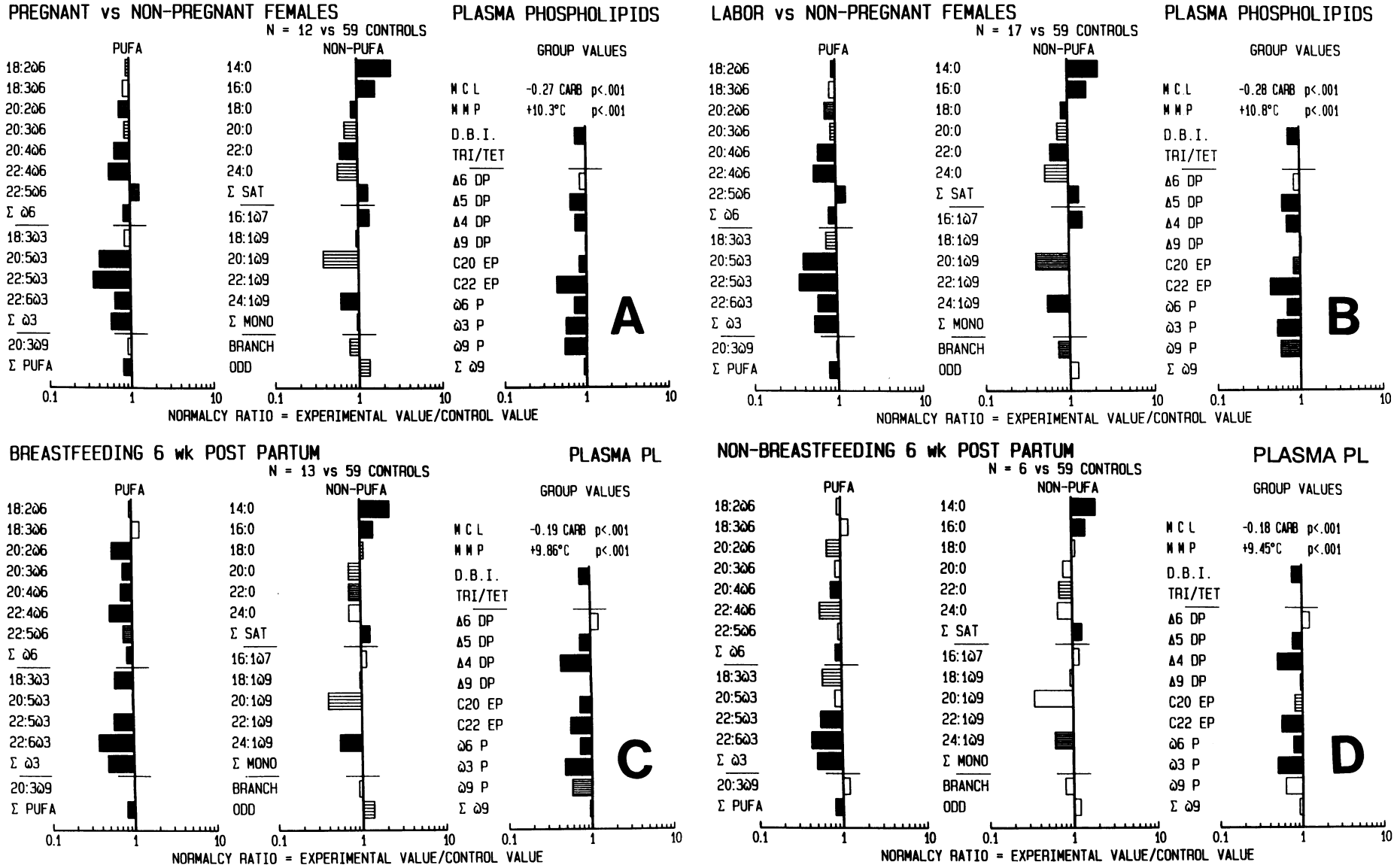

FIG. 1. FA profiles of plasma PL of study groups compared with those of 59 control nonpregnant women of child-bearing age. See *Presentation of Data* for details. (*A*) At 36 wk of pregnancy. (*B*) At parturition. (*C*) At 6 wk postpartum, lactating. (*D*) At 6 wk postpartum, nonlactating.

considers only the degree of unsaturation. Total PUFA does not consider contributions by monounsaturated FA, and it gives equal weight to all individual PUFA, although they must contribute very differently to "fluidity" of PL. MMP is calculated from all FA present; it considers chain length, branching, and unsaturation; and it is based upon the transition temperature from solid to liquid state, from rigidity to fluidity (12). It is calculated by summing the products of mole fraction times melting point for each FA in the mixture, assuming additivity of melting points of FA in mixtures and assuming that "fluidity" of PL is related to the association of all the acyl chains in the PL. The MMP of plasma PL FA was calculated to be 25.61 ± 1.29°C for pregnant women and 15.25 ± 2.24°C for nonpregnant women, an elevation of 10.3°C, $P < 0.001$.

MMP involves contributions of all FA present in the PL and thus offers the advantage of an index not based on selected data, such as is the case with total PUFA, selected as principal contributors of "fluidity" to the total FA of PL. MMP is inversely related to "fluidity" membrane characteristics. High MMP implies inherent decreased fluidity, a diminished temperature range below body temperature at which membranes remain fluid. MMP is useful for comparison of nutritional and disease states. Table 1 shows the MMP values for human plasma PL in 40 nutritional, physiological, ethnic, and disease states studied in this laboratory in the last decade, including the stresses of pregnancy and lactation. Only data from this laboratory are included to ensure that the method of analysis is uniform. Pregnancy induces changes in EFA that significantly elevate the MMP of structural lipids. On the scale of conditions and diseases thus far studied, MMP of PL during pregnancy and lactation is relatively high, indicating a relatively low "fluidity." Correlation of MMP with DBI was $R^2 = 0.84$, and correlation of MMP with PUFA was $R^2 = 0.75$. Similar correlations were calculated for the population of 59 normal females of child-bearing age, used as controls in this study, and the corresponding values for R^2 were 0.85 and 0.66, suggesting that DBI may be a better measure of the fluidity phenomenon than is PUFA. This agrees with theoretical considerations, for MMP is calculated from *all FA present in the sample*, whereas DBI is calculated from only the unsaturated FA, and PUFA excludes monosaturated FA, which compensate partially for losses of PUFA.

The Tri/Tet Ratio. This ratio (20:3ω9/20:4ω6), originally proposed as an index of EFA status and deficiency of linoleic acid (18), was useful as a measure of simple nutritional ω6 EFA deficiency. Assessment of EFA status is complicated by competitive interactions between ω3, ω6, and ω9 FA (26, 27). Study of interactions between ω6 and ω3 families of PUFA revealed that 18:3ω3 suppressed metabolism of 18:2ω6 to 20:4ω6 and greatly suppressed the metabolism of 18:1ω9 to 20:3ω9, strongly affecting the Tri/Tet ratio, yet ω3 FA were not a factor in its calculation. Other phenomena induce diminished proportions of EFA but do not always change the Tri/Tet ratio. For example, conditions affecting 5-desaturation may affect the 5-desaturation of 20:2ω9 to 20:3ω9 and 20:3ω6 to 20:4ω6 equally, leaving the Tri/Tet ratio unchanged. Many conditions listed in Table 1 involve diminished PUFA in structural lipids without changing the Tri/Tet ratio. For these reasons, we now recommend caution in applying the Tri/Tet ratio as sole index of EFA status. We consider that MMP is the best current single measure of PUFA status, but we prefer to use the entire set of FA profiles, because without them, changes in minor FA would be missed. For example, without the entire profile, changes in odd-chain acids in biotin deficiency would not be noticed (23).

FA and Pregnancy. Pregnancy is a programmed stress necessary for the preservation of the species. It involves mobilization of PUFA from maternal tissue stores to the fetus, and the deficit experienced by the mother must be minimized by elevated intake of EFA prior to, during, and following pregnancy, to ensure adequate supplies for the special needs of the fetus and child for PUFA for brain and vital organ development (28).

Table 1. MMP of FA of plasma PL calculated for human nutritional and disease states, listed in increasing order

Condition or group	MMP, °C	*n*	Ref.
Hepato-pancreato-renal synd.	12.8	1	19
American normal omnivores	14.8 ± 2.5	100	17
American nonpregnant females	**15.3 ± 2.2**	**59**	
Coronary artery disease	15.4 ± 2.8	28	
Reye synd.	16.0 ± 3.9	12	10
American normal vegans	16.0 ± 2.1	23	17
Normal Swedes	17.8 ± 2.4	18	
Normal Nigerians	17.9 ± 4.7	38	
Sepsis	18.0 ± 9.4	8	20
Sjogren–Larsson synd.	18.2 ± 3.1	13	9
AIDS	18.6	1	
Huntington disease	18.9 ± 1.3	3	
Diabetes, insulin-dependent	18.9 ± 3.0	31	
Diabetes, non-insulin-dependent	19.1 ± 2.7	79	
Rheumatoid arthritis	19.3 ± 3.0	13	
Preeclampsia	19.3 ± 3.3	11	21
IgA nephropathy	20.0 ± 3.6	4	
Renal transplant cyclosporin	20.3 ± 4.0	6	
Coronary occlusion	20.3 ± 3.3	4	
Multisystem neuronal degen.	20.5 ± 1.1	4	22
Cystic fibrosis	20.5 ± 4.3	42	
Normal Bulgarians	20.7 ± 2.2	46	
Infant hepatitis	21.0 ± 1.7	6	
Multiple sclerosis	21.3 ± 2.3	14	12
Alcoholism	21.7 ± 2.4	20	11
Biotin deficiency	21.7 ± 2.1	3	23
ω3 deficiency	21.8	1	16
Cirrhosis	22.2 ± 2.3	10	11
Anorexia nervosa	22.3 ± 1.2	8	
Closed head injury	22.6 ± 3.3	4	24
Chronic malnutrition	23.5 ± 7.4	40	7
Crohn disease	23.5 ± 2.3	22	25
Postpartum 6 wk, nonlactating	**24.7 ± 0.7**	**6**	
Postpartum 6 wk, lactating	**25.1 ± 0.6**	**13**	
Pregnancy, 36 wk	**25.6 ± 1.3**	**12**	
Pregnancy, parturition	**26.1 ± 1.1**	**17**	
Abetalipoproteinemia	26.1 ± 1.6	3	
Tocopherol deficiency	31.5	1	
Wiscott–Aldrich synd.	31.5 ± 2.6	6	
EFA deficiency	32.4	1	5

Results are mean ± SD. synd., Syndrome; degen, degeneration.

Involvement of EFA in reproduction was found in the initial studies by Burr and Burr (29), who observed that conception occurring in female rats fed a fat-free diet was followed by resorption of the fetuses or by perinatal death. The diet used to demonstrate this effect was extreme and unlike the modern diet of Western humans. On the other hand, our food supply now emphasizes ω6 PUFA at the expense of the ω3 PUFA, which are also essential for tissue and function (16). Pregnancy and lactation are times of special mobilization of PUFA for the synthesis of fetal and infant tissue, of which the brain, rich in ω3 PUFA, is a large part (30). The basal requirement of EFA has been estimated at 3% of total calories (31), and the requirement may rise to 4.5% during pregnancy and 5–7% during lactation (32). Of these requirements, an appreciable proportion must be ω3 acids needed for development of brain and nervous system (33). Low birth weight has been found to correlate with the low intake of linoleic, arachidonic, and long-chain ω3 FA. Because EFA decrease in the maternal circulation during pregnancy and remain low at least 6 wk beyond the preg-

nancy, it may be reasonable to increase the ω3 PUFA in the diet before, during, and after pregnancy.

The decrease in PUFA during pregnancy appears among both ω6 and ω3 FA, the latter being the greater, due to high requirement by the fetus, increased drain of ω3 acids from the mother, or marginal supplies of dietary ω3 acids. The latter cause is suggested by the observation that the ω3 PUFA in our control population (Minnesota) is lower than in normals from Nigeria and Sweden (Table 1). It may be advisable, therefore, to enrich the diet of pregnant women with eggs and organ meats rich in arachidonate and other long-chain ω6 acids, with fish rich in long-chain ω3 PUFA, and with a source of linolenic acid. Unhydrogenated soybean oil and low-erucic acid rapeseed oil are rich in linolenic acid and are thus extremely valuable foods for maintaining a balance of ω3 and ω6 fatty acids in the diet. Oils containing linolenic acid, now known to be required by humans (16), have heretofore been routinely hydrogenated to remove it and to avoid off-flavors related to its oxidation, thus increasing stability and shelf life of those oils. Now that ways are known to preserve and market these natural rich sources of linolenic acid, hydrogenation of our best sources of ω3 FA should no longer be needed.

General Considerations. During the past 30 yr, the control of plasma cholesterol levels by PUFA and the consequent decrease in the incidence of circulatory problems have been amply demonstrated, and the food industry has responded by developing oils that are rich in PUFA. Unfortunately, the focus has been upon suppressing cholesterol rather than providing balanced essential PUFA, and linoleic acid-rich oils dominate the market because they are easier to store than are oils containing linolenic acid. We now have corn oil, cottonseed oil, peanut oil, safflower oil, and sunflower oil as common food oils, and all are rich in linoleic acid but poor in linolenic acid. This has occurred despite knowledge that linoleic and linolenic acids are competitive substrates in the metabolic cascade by which 18-carbon PUFA yield 20- and 22-carbon more highly unsaturated PUFA (34). High 18:2ω6 suppresses the conversion of 18:3ω3 to 20:5ω3, 22:5ω3, and 22:6ω3. Such a suppression occurred when an intravenous lipid emulsion having an 18:2ω6/18:3ω3 ratio of 115:1 induced the first recognized deficiency of ω3 PUFA with neuropathy in a 6-yr-old girl (16). Current availability of many oils rich in 18:2ω6 but poor in 18:3ω3 may be raising the proportion of 18:2ω6 in our diet so high that it suppresses the utilization of the small proportion of linolenic acid present. This possibility should be considered in recommendations for increasing dietary PUFA. The appropriate proportion of the essential nutrients linoleic and linolenic acids for best utilization of both should be the subject of active research. Until that happens, extremes in ratio of these acids should be avoided. Our best wisdom suggests that linolenic acid not be hydrogenated away, converting it to saturated and isomeric monoenoic acids that inhibit PUFA metabolism and form unusual isomers of PUFA (35), but rather that native oil be used as much as possible, providing ω3 acid for our diet.

It seems reasonable to suggest that 18:3ω3 intake be increased during pregnancy, lactation, and infancy, when the requirements for ω3 PUFA are highest, during the development of the nervous system, which is rich in lipids containing high proportions of ω3 PUFA. The mental apparatus of the coming generation is developed *in utero*, and the time to begin supplementation is before conception. A normal brain cannot be made without an adequate supply of ω3 PUFA, and there may be no later opportunity to repair the effects of an ω3 fatty acid deficiency once the nervous system is formed.

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