Essential Fatty Acids and the Major Urinary Metabolites of the E Prostaglandins in Thriving Neonates and in Infants Receiving Parenteral Fat Emulsions.

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Summary

The administration of parenteral fat emulsion—Intralipid, a preparation rich in the essential fatty acid (EFA), linoleic acid, is widely used as an integral part of therapy for sick infants along with total parenteral nutrition (TPN). EFAs serve as precursors for prostaglandin (PGs). We measured tissue lipid composition and the excretion of the major urinary metabolite of prostaglandins E_1 and E_2 , 7 α -hydroxy-5, 11 diketotetranor-prostane-1,16 dioic acid (PGE-M) in three infants who received TPN with Intralipid for prolonged periods and compared these values with control infants. Linoleic acid is incorporated into the major lipid classes of the plasma, RBC, and tissues in the infants receiving Intralipid. Concomitantly with the increase in the relative concentration of linoleate, a decrease in the higher polyunsaturated fatty acid homologue, arachidonate is apparent. However, the sum of the two EFAs, linoleate and arachidonate, is similar in red blood cells (RBC) and tissue phospholipids of control infants and in infants who received Intralipid. A significant difference between the PGE-M excretion in the group of infants before and after the administration of Intralipid also is apparent ($P < 0.05$). Differences in the urinary excretion of PGE-M are seen between the control group and the infants receiving Intralipid ($P < 0.05$). PGE-M excretion after the administration of Intralipid is similar to that obtained from infants with EFA-deficiency.

Speculation

The increase in the relative concentration of linoleic acid in plasma, RBC, and major tissue lipid classes and a concomitant decrease in the level of the higher EFA homologue arachidonate after the administration of Intralipid may indicate a competition between these EFAs for esterification and storage in tissue lipids, a balanced content of the intake of the linoleic and linolenic acids, a rapid turnover of the long chain polyunsaturated fatty acids or a combination of these factors. The decrease in PGE-M excretion in patients receiving high content of linoleic acid is most likely related to a decrease in the precursor EFA, arachidonate, although an inhibiting effect of linoleic acid on prostaglandin synthesis is possible. Further investigation is needed into the pathophysiologic consequences of increased linoleic acid consumption as well as decreased PG biosynthesis and turnover in sick infants.

Since Burr and Burr (2) demonstrated the importance of certain fats necessary for normal growth, research on EFAs has been mainly concerned with the symptoms of EFA-deficiency and the determination of the minimal EFA requirement to prevent or treat the deficiency state. EFA-deficiency has been described in infants and children who were maintained on fat-free diets (12), and rapid

onset of EFA-deficiency was found in low birthweight infants receiving fat-free iv alimentation (7).

The provision of optimal nutrition for low birthweight infants, infants with congenital anomalies of the gastrointestinal tract and those with inflammatory bowel disease remains a significant problem. The administration of parenteral fat emulsion—Intralipid (Vitrum Co., A. B., Stockholm, Sweden), a preparation rich in the EFA, linoleic acid, is widely used as an integral part of therapy for these conditions along with TPN (8).

The effect of long-term administration of linoleic acid on the fatty acid composition of the various lipid classes of tissues and on prostaglandin E biosynthesis and turnover never have been studied adequately in man. We have measured tissue lipid composition and the excretion of the major urinary metabolite of prostaglandins E_1 and E_2 , PGE-M in three infants who received TPN with Intralipid for prolonged periods and compared these values with three control infants fed adequate calories with human milk or artificial infant's formula.

MATERIALS AND METHODS

PATIENTS (30)

Case 1. A female was born to an 18-yr-old gravida 2 para 0 caucasian woman after an uneventful pregnancy and spontaneous vaginal delivery. Estimated gestational age was 30 wk and birthweight was 1280 g. The clinical course was complicated by hyaline membrane disease requiring endotracheal intubation and intermittent ventilatory assistance, chronic bronchopulmonary dysplasia, bilateral pseudomonas pneumonia, patent ductus arteriosus that required surgical ligation, intracranial hemorrhage, and necrotizing enterocolitis. Fluid and calories were supplied solely by the iv route for 70 days. The iv solutions included dextrose, electrolytes, and a parenteral mixture containing Freamine II (31) Parenteral fat emulsions—10% Intralipid was started on day 10. The iv solutions included the daily supplementation of 0.9 mEq magnesium and 1.1 mg zinc and the following vitamins: A, 1000 IU; B₁, 5.0 mg; B₂, 1.0 mg; B₆, 1.5 mg; C, 50 mg; D, 100 IU; E, 5 IU; niacin, 10 mg; K₁, 20 μ g; B₁₂, 0.4 μ g; folic acid, 66 μ g; and pantothenic acid, 2.5 mg. Fluid intake varied from 120–200 ml/kg/24 hr and calories from 60–125 cal/kg/24 hr. Intralipid infusion ranged from 0.5–4.0 g/kg/24 hr, depending on the ability of the infant to clear the infused triglycerides that was assessed by visual inspection of the plasma. She received a total of 142 g of Intralipid. The infant expired on the 70th day. Necropsy revealed chronic bronchopulmonary dysplasia, acute focal bronchopneumonia, infarcts of the basal ganglia, and the paraventricular regions, acute multifocal myocardial necrosis, peritoneal adhesions, intrahepatic cholestasis, old subarachnoid hemorrhage, and hemosiderosis of the spleen.

Case 2. A female, the second of twins, was born to an 18-yr-old gravida 1 caucasian woman. Estimated gestational age was 31 wk and the birthweight was 1200 g. The infant had multiple congenital anomalies including tracheoesophageal fistula with a blind upper pouch, imperforate anus, thoracic hemivertebra and scoliosis, rib anomalies, single ectopic pelvic kidney, and absence of uterus and vagina. Karyotype revealed 46 chromosomes XX. She was maintained solely on peripheral TPN for 83 days. The iv solutions were similar to those described in Case 1. Fluid intake varied from 120–180 ml/kg/24 hr, and calories from 60–105 cal/kg/24 hr. Intralipid infusion, started on day 7, ranged from 0.5–4.0 g/kg/24 hr and she received a total of 185 g. The clinical course was complicated by cholestatic jaundice, repeated episodes of pneumonia, septicemia, and disseminated intravascular coagulation. She expired on the 83rd day. Necropsy revealed in addition to the congenital anomalies, disseminated fungal microabscesses, cholestasis, diffuse gastrointestinal and subendocardial hemorrhage.

Case 3. A male was born to a 22-yr-old gravida 1 caucasian female after uneventful pregnancy. Estimated gestational age was 30 wk and the birthweight 1240 g. The clinical course was complicated by hyaline membrane disease requiring endotracheal intubation and intermittent ventilatory assistance, chronic bronchopulmonary dysplasia, patent ductus arteriosus, intracranial hemorrhage, and repeated episodes of necrotizing enterocolitis. The infant was maintained solely on peripheral TPN for 53 days. The iv solutions were similar to those described in Case 1. Fluid intake varied from 120–200 ml/kg/24 hr and calories from 60–105 cal/kg/24 hr. Intralipid infusion, started on day 7, ranged from 0.5–4.0 g/kg/24 hr and he received a total of 131 g. The infant expired on the 54th day. Necropsy revealed disseminated microabscesses, gastrointestinal and pulmonary hemorrhage, organized intraventricular hemorrhage, and bronchopulmonary dysplasia.

CONTROLS

Twelve thriving, low birthweight infants were selected from the Newborn Care Unit as controls for the excretion of PGE-M. There were five males and seven females whose clinical data are shown in Table 1. Three infants served as controls for tissue lipid analysis and their clinical data are shown in Table 1. The control infants were fed Similac (Similac, Ross Laboratories, Columbus, OH), SMA (SMA 20, Wyeth Laboratories, Philadelphia, PA.) or breast milk with a linoleic acid content of 8.0–23.0% composition of the fat. The cause of death in infant W. E. was cyanotic congenital heart disease, in infant B. J., sudden infant death syndrome, and in infant R. B., multiple congenital anomalies. Neither mothers or infants had received any drugs known to inhibit prostaglandin synthetase.

LIPID ANALYSIS

Whole blood, anticoagulated with EDTA, was obtained via a central line or a peripheral venipuncture and centrifuged at 4°C. The RBC were washed thrice with saline. The plasma and red

cells were frozen and stored at –20°C in 100% nitrogen until lipid extraction was begun. Tissue samples were obtained within 4 hr of death (Fig. 1, Tables 2–5), weighed immediately, and then frozen similarly before analysis. The tissues were homogenized and the various lipid fractions—cholesterol esters, triglycerides, free fatty acids, and phospholipids were separated by thin-layer chromatography according to the methods described previously (5). The fatty acid composition of each lipid fraction was then determined by gas-liquid chromatography (5, 6).

PGE-M

Urine from each subject was collected in plastic bags for 16–24 hr. The urine was aspirated, stored in glass containers with toluene, and kept frozen at –40°C until analysis. The urine was analyzed for PGE-M according to the methods described previously (11, 24). Urine creatinine was determined by the Jaffe method on an auto-analyzer (Technicon SMA 12–60). Urine from the three patients was obtained during the period preceding the administration of Intralipid and during its administration. Urinary excretion of PGE-M is expressed as ng/mg creatinine, thus relating PGE-M excretion to an index of lean body mass.

STATISTICAL METHOD

Student's *t* test for paired and unpaired data was used for statistical analysis.

RESULTS

ADMINISTRATION OF INTRALIPID

The fatty acid composition of plasma and tissue phospholipids, triglycerides, cholesterol esters, and free fatty acids is shown in

Fig. 1. Fatty acid composition of phospholipids of infants receiving Intralipid, (N 3) and in controls (N 3).

Table 1. Clinical Data¹

Number	Sex		Gestational age (wk)	Postconceptual age at the time of study (wk)		Birth weight (g)	Weight at the time of study (g)	
	M	F		Before Intralipid	After Intralipid		Before Intralipid	After Intralipid
Patient 3	1	2	30.3 ± 0.3	30.8 ± 0.3	38.8 ± 0.9	1220 ± 16.3	1186 ± 29.0	1960 ± 125
Controls 12 for PGE-M excretion	5		30.2 ± 1.2		34.4 ± 1.6	1260 ± 64.2		2060 ± 140
		7	29.6 ± 0.6		35.2 ± 2.1	1180 ± 86.4		2240 ± 180
Controls for tissue lipid analysis								
W. E.		1	40		66	3400		4400
B. J.		1	40		48	3550		4760
R. B.	1		39		48	2650		3350
			39.7 ± 0.3		54.0 ± 6.0	3200 ± 278.4		4170 ± 423

¹ Mean ± SEM.

Table 2. Fatty acids (FA) composition of tissue RBC and plasma phospholipids of infants receiving intralipid (IL) and control infants (C)¹

FA ²	Lung		Liver		Skeletal muscle		Brain		Renal medulla	
	C	IL	C	IL	C	IL	C	IL	C	IL
c16:0	33.4 ± 2.4	30.2 ± 0.3	21.8 ± 0.3	22.4 ± 0.4	13.7 ± 0.3	14.3 ± 0.3	19.2 ± 0.8	20.2 ± 0.4	23.8 ± 0.6	25.1 ± 0.3
c18:0	14.2 ± 0.8	12.1 ± 1.3	18.4 ± 0.3	16.9 ± 0.2	17.5 ± 0.2	18.4 ± 0.4	20.8 ± 0.3	19.4 ± 0.4	15.4 ± 0.3	16.1 ± 0.5
c18:1ω9	23.6 ± 1.9	17.6 ± 2.2	14.5 ± 0.2	14.2 ± 0.3	11.5 ± 0.3	11.2 ± 0.2	18.6 ± 0.7	17.8 ± 0.8	23.4 ± 1.1	21.0 ± 0.4
c18:2ω6	9.8 ± 2.2	22.4 ± 3.2 ³	16.8 ± 0.5	23.6 ± 0.8 ³	22.4 ± 0.6	29.5 ± 1.2 ⁴	0.9 ± 0.1	2.4 ± 0.1 ⁴	12.6 ± 0.4	22.7 ± 0.7 ³
c20:4ω6	18.6 ± 0.8	7.4 ± 0.2 ³	15.8 ± 0.7	8.6 ± 0.2 ³	18.2 ± 1.1	10.8 ± 0.3 ³	12.1 ± 0.2	9.8 ± 0.2 ⁴	19.7 ± 0.8	9.2 ± 0.3 ³
>c20:4	1.1 ± 0.2	1.5 ± 0.3	4.2 ± 0.2	3.3 ± 0.2 ³	0.3 ± 0.1	0.3 ± 0.1	7.8 ± 0.2	7.6 ± 0.2	⁵	⁵
FA ²	Renal cortex		Adipose tissue		Red blood cell		Plasma			
	C	IL	C	IL	C	IL	C	IL		
c16:0	19.5 ± 0.4	18.6 ± 0.6	21.0 ± 0.2	22.5 ± 0.3	26.8 ± 1.2	28.2 ± 0.6	28.4 ± 0.8	31.8 ± 0.2		
c18:0	16.2 ± 0.3	15.5 ± 0.3	13.9 ± 0.3	14.9 ± 0.2	11.4 ± 0.3	12.3 ± 0.2	12.8 ± 0.4	13.8 ± 0.3		
c18:1ω9	17.7 ± 0.5	18.4 ± 0.4	18.8 ± 0.4	16.8 ± 0.3	15.2 ± 0.4	16.7 ± 0.3	19.6 ± 0.3	20.2 ± 1.2		
c18:2ω6	15.7 ± 0.4	22.9 ± 1.1 ³	15.9 ± 0.8	34.6 ± 1.5 ³	13.3 ± 0.3	21.8 ± 0.3 ³	16.9 ± 0.4	25.6 ± 0.7 ⁴		
c20:4ω6	21.6 ± 0.9	13.8 ± 0.3 ³	14.7 ± 0.3	6.0 ± 0.4 ³	18.3 ± 0.3	9.8 ± 0.3 ³	9.4 ± 0.3	4.5 ± 0.3 ³		
>c20:4	0.8 ± 0.1	1.1 ± 0.1	⁵	⁵	4.3 ± 0.2	2.4 ± 0.1	3.2 ± 0.1	2.6 ± 0.2		

¹ Data reported as mean percent ± SEM of total fatty acid methyl esters.² c16:0 (palmitic), c18:0 (stearic), c18:1ω9 (oleic), c18:2ω6 (linoleic), c20:4ω6 (arachidonic).³ $P < 0.05$.⁴ $P < 0.10$.⁵ Data omitted less than 0.5% of total.Table 3. Fatty acid (FA) composition of tissue and plasma triacylglycerols of infants receiving intralipid (IL) and control infants (C)¹

FA ²	Lung		Liver		Skeletal muscle		Adrenal	
	C	IL	C	IL	C	IL	C	IL
c16:0	20.8 ± 0.9	19.8 ± 0.5	25.2 ± 1.1	23.8 ± 1.4	27.8 ± 2.4	26.8 ± 1.8	24.4 ± 0.8	25.6 ± 1.1
c18:0	5.6 ± 0.3	6.4 ± 0.2	5.9 ± 0.2	5.6 ± 0.4	5.2 ± 0.3	5.6 ± 0.2	6.2 ± 0.3	6.0 ± 0.2
c18:1ω9	36.4 ± 2.1	34.4 ± 1.7	26.8 ± 1.4	27.6 ± 1.1	34.3 ± 2.2	36.3 ± 1.6	24.6 ± 0.8	23.6 ± 0.6
c18:2ω6	22.8 ± 1.1	30.5 ± 1.8 ³	22.4 ± 0.8	30.2 ± 1.2 ³	8.3 ± 0.6	14.6 ± 0.4 ³	13.4 ± 1.2	22.7 ± 1.8 ³
c20:4ω6	9.0 ± 0.4	2.6 ± 0.2 ⁵	5.8 ± 0.3	0.5 ± 0.1 ⁶	5.8 ± 0.3	1.4 ± 0.1 ⁶	14.8 ± 0.9	8.4 ± 0.6 ⁴
FA ²	Renal medulla		Renal cortex		Adipose tissue		Plasma	
	C	IL	C	IL	C	IL	C	IL
c16:0	29.8 ± 2.8	27.8 ± 1.4	28.3 ± 1.2	26.8 ± 1.7	26.4 ± 2.4	28.6 ± 3.2	28.2 ± 1.2	25.2 ± 2.4
c18:0	10.8 ± 0.8	9.6 ± 0.8	11.8 ± 0.4	10.3 ± 0.4	6.4 ± 0.3	5.5 ± 0.4	4.6 ± 0.3	6.8 ± 1.1
c18:1ω9	25.6 ± 1.6	24.8 ± 1.1	30.4 ± 1.8	28.6 ± 0.2	36.2 ± 1.8	34.6 ± 2.8	24.8 ± 2.1	26.6 ± 1.8
c18:2ω6	16.4 ± 1.2	22.5 ± 2.4 ³	20.8 ± 1.4	27.5 ± 2.4 ³	17.8 ± 1.8	23.3 ± 1.6 ³	8.4 ± 0.4	42.2 ± 3.4 ⁴
c20:4ω6	4.2 ± 0.4	1.1 ± 0.3 ⁴	2.6 ± 0.2	^{4, 7}	2.0 ± 0.1	^{3, 7}	1.4 ± 0.1	^{3, 7}

¹ Data reported as mean percentage ± SEM of total fatty acid methyl esters.² c16:0 (palmitic), c18:0 (stearic), c18:1ω9 (oleic), c18:2ω6 (linoleic), c20:4ω6 (arachidonic).³ $P < 0.10$.⁴ $P < 0.05$.⁵ $P < 0.01$.⁶ $P < 0.005$.⁷ Data omitted less than 0.5% of total.Table 4. Fatty acid (FA) composition of tissue and plasma cholesteryl esters of infants receiving intralipid (IL) and control infants (C)¹

FA ²	Lung		Liver		Renal medulla		Plasma	
	C	IL	C	IL	C	IL	C	IL
c16:0	23.6 ± 0.9	26.2 ± 1.8	20.1 ± 0.8	22.6 ± 0.6	23.8 ± 1.8	25.2 ± 0.8	7.7 ± 0.3	8.5 ± 1.1
c18:0	4.8 ± 0.3	5.6 ± 0.4	4.9 ± 0.3	5.4 ± 0.2	5.8 ± 0.6	5.4 ± 0.4	1.3 ± 0.2	0.8 ± 0.1
c18:1ω9	33.7 ± 2.6	31.4 ± 1.6	34.6 ± 3.2	32.8 ± 1.8	38.3 ± 3.4	36.4 ± 2.8	17.2 ± 0.9	18.8 ± 1.6
c18:2ω6	13.4 ± 0.8	16.8 ± 1.8 ³	19.9 ± 1.1	25.7 ± 2.4 ³	10.6 ± 0.4	13.2 ± 0.6 ³	18.6 ± 1.2	45.0 ± 6.2 ⁴
c20:4ω6	4.5 ± 0.2	2.1 ± 0.1 ⁵	3.3 ± 0.1	1.0 ± 0.2 ⁵	3.7 ± 0.2	^{4, 6}	4.3 ± 0.4	^{5, 6}

¹ Data reported as mean percent ± SEM of total fatty acid methyl esters.² c16:0 (palmitic), c18:0 (stearic), c18:1ω9 (oleic), c18:2ω6 (linoleic), c20:4ω6 (arachidonic).³ $P < 0.1$.⁴ $P < 0.05$.⁵ $P < 0.01$.⁶ Data omitted less than 0.5% of total.

Table 5. Free fatty acid percent composition of tissue and plasma of infants receiving intralipid (IL) and control infants (C)¹

FA ²	Adipose tissue		Plasma	
	C	IL	C	IL
c16:0	24.6 ± 1.8	27.5 ± 2.4	18.1 ± 1.2	18.7 ± 1.8
c18:0	7.6 ± 0.8	8.6 ± 1.4	7.8 ± 0.4	8.1 ± 1.6
c18:1ω9	23.4 ± 2.4	21.8 ± 3.2	18.9 ± 1.4	17.6 ± 0.9
c18:2ω6	14.8 ± 1.4	24.5 ± 2.4 ³	15.2 ± 2.3	23.4 ± 2.1 ³
c20:4ω6	2.2 ± 0.3	1.1 ± 0.2 ³	2.6 ± 0.3	1.2 ± 0.3 ³

¹ Data reported as mean ± SEM of total fatty acid methyl esters.

² c16:0 (palmitic), c18:0 (stearic), c18:1ω9 (oleic), c18:2ω6 (linoleic), c20:4ω6 (arachidonic).

³ $P < 0.1$.

Tables 2–5. Linoleic acid was incorporated into these major classes of the plasma and tissues that were investigated. The differences in the relative concentration of linoleic acid in plasma and tissues between the controls and the infants who received Intralipid is apparent, but less obvious in the brain, which normally contains relatively only a small amount of this fatty acid (3). Concomitantly with the increase in the plasma and the tissue relative percent of linoleate, there was a dramatic decrease in the higher polyunsaturated fatty acid homologue, arachidonate. However, the sum of the two essential fatty acids, linoleate and arachidonate in the phospholipid fraction, was similar in RBC and tissues of control infants and in infants who received Intralipid, except in adipose tissue (Fig. 1).

PGE-M

The urinary excretion of PGE-M is seen in Figure 2. The difference between the PGE-M excretion in the group of infants before and after the administration of Intralipid is apparent ($P < 0.05$). Differences in the urinary excretion of PGE-M are seen between the control group and the infants receiving Intralipid ($P < 0.05$). PGE-M excretion after the administration of Intralipid is similar to the levels obtained from infants with essential fatty acid deficiency (9).

DISCUSSION

It can be concluded from these studies that the relative concentration of linoleic acid of plasma, RBC, and tissue lipids can be increased substantially when infants receive TPN with fat emulsion, e.g., Intralipid. Intralipid, like most vegetable oils, is rich in the essential fatty acid, linoleate, which accounts for 54% of the fatty acid content. Enrichment with linoleic acid was observed in all three major lipid classes as well as in the fatty acid fraction. It is probable that the tissue free fatty acids which are released largely during handling and homogenization of tissue do not reflect the actual content *in vivo*, but rather the potential of the tissue to release free fatty acids of a given composition when the appropriate acyl hydrolases are activated (5). It is of interest that concomitantly with the increase in the relative concentrations of linoleic acid content in plasma, RBC, and tissues, the level of its higher homologue, arachidonic acid, decreased. The sum of the relative concentrations of the essential fatty acids linoleic and arachidonic acids was similar in RBC and most tissue phospholipids when levels from control infants were compared with infants receiving Intralipid. This phenomenon may indicate competition between linoleic and arachidonic acids for esterification and storage in tissue lipids. Further support for the latter can be derived from studies where the complete diet of animals and man was supplemented with polyunsaturated fatty acids other than linoleic acid, i.e., dihomo-γ-linolenate and arachidonate, which resulted in increasing their relative percent in plasma and tissue lipids, whereas linoleic acid content decreased (5, 18, 23).

Increased consumption of linoleic acid does not always result in raised tissue arachidonate as has been demonstrated in rats upon

Fig. 2. Comparison of the urinary excretion of PGE-M expressed as nanograms/mg urinary creatinine between three groups of infants: 1) infants pre- and posttreatment with Intralipid; 2) thriving neonates (controls); and 3) infants with EFA deficiency and upon recovery.

dietary intake in excess of 13cal% (20). Moreover, increased intake of linoleic acid resulted in the increased level of the linoleic acid content in platelet and RBC phospholipids, whereas no increase in arachidonate level was noted, and the elongation of the linoleic acid was inversely proportional to its availability in the diet (1, 15, 17). *In vitro* cultures of skin fibroblasts suspended with Intralipid resulted in the increased incorporation of linoleic acid with a concomitant decrease in the level of arachidonic acid in the triglyceride and the phospholipid fractions (22). Competitive substitution exists between linoleic and linolenic acids, and the equilibrium can be displaced in either direction, the substituer acid which is favored being dependent upon the relative dietary levels of these acids (16, 20). Thus, it is conceivable that the increased tissue relative concentration of linoleic acid with no change in arachidonate could be due to the balanced content of linoleic and linolenic acids in the diet (15, 17, 25), although rapid turnover of the long chain polyunsaturated fatty acids is possible.

Arachidonic acid is an essential fatty acid which serves as the precursor of the dienoic prostaglandins. In tissue and plasma, arachidonic acid is found in ester linkage usually to position -2 of glycerol in the phospholipids, and in cholesteryl esters and triglycerides. In order for the arachidonic acid to become available for enzymatic conversion by prostaglandin synthetase, it must be released by the appropriate acyl hydrolases (4, 13, 14, 28). This reaction is the rate limiting step in prostaglandin production (13, 14, 28). The biosynthesis of prostaglandins is reduced in essential fatty acid-deficient animals (27) and newborn infants (9), but the enrichment of the diet with prostaglandin precursors, ethyl dihomo-γ-linolenate, and ethyl arachidonate, resulted in the increase excretion of PGE-M (18, 23). However, inverse correlation was found between the amount of linoleic acid supplement in the diet and prostaglandin E synthesis by the rat renal medulla (26).

The reduced relative concentration of arachidonic acid in plasma, RBC, and tissue lipid fractions in the three infants receiving Intralipid was correlated with the reduced excretion of PGE-M. This finding, thus, provides evidence that total body biosynthesis of prostaglandin E is reduced, perhaps as a consequence of the reduced precursor pool. The level of PGE-M excretion after linoleic acid (Intralipid) administration was similar to the level found in infants with EFA-deficiency and, in both circumstances, the PGE-M level was directly correlated with tissue levels of arachidonic acid. Because PGE-M is a terminal product arising

from sequential 15-dehydrogenation, Δ 13 reduction and both β and ω oxidation of prostaglandins E_1 and E_2 , any decrease, in its excretion, reflects decreased prostaglandin synthesis and turnover in the body (11). Because endogenous prostaglandins are not stored (21) and are rapidly synthesized and metabolized, PGE-M accurately reflects precursor availability and cyclooxygenase activity. Because no significant differences in PGE-M excretion were found between the sexes during the neonatal period (9), as is the case among prepubertal boys and girls (24), the differences in postconceptional ages cannot explain the differences in PGE-M excretion between the infants receiving Intralipid and controls.

Inhibition of the conversion of arachidonic acid to PGE₂ was demonstrated *in vitro* in the presence of a number of fatty acids including linoleic acid (19). Preincubation with linoleic acid before the addition of arachidonic acid greatly increased the effectiveness of inhibition at lower inhibitor concentration. It appears that linoleic acid competes with arachidonic acid for the prostaglandin synthetase and reacts irreversibly. Moreover, linoleic acid was found to inhibit platelet labile aggregation stimulating substance (10) and the formation of PGE₂ from arachidonic acid by the microsomal fraction from human skin (29). Thus, the incorporation of the linoleic acid into tissue lipids in the infants who received Intralipid resulted in the release of polyunsaturated fatty acids other than arachidonate upon the action of the various acyl hydrolases, and these fatty acids could exert an inhibiting effect on prostaglandin biosynthesis.

In conclusion, the content of prostaglandin precursors in tissue lipids can be altered qualitatively by the administration of linoleic acid and the increased consumption of linoleic acid does not necessarily result in raised tissue arachidonate. Furthermore, the excessive administration of linoleic acid resulted in a relative decrease in tissue arachidonate to a level similar to that found in EFA-deficiency which was associated with diminished prostaglandin E biosynthesis. Thus, supplementation of linoleic acid must be carefully monitored. Physiologic or pathologic response mediated by endoperoxides may occur and their respective prostaglandins might also be modified.

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