Essential Fatty Acid Deficiency During Total Parenteral Nutrition

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Essential fatty acid (EFA) deficiency has become a clinical problem since the advent of fat-free total parenteral nutrition (TPN). The following study was done to determine the minimum fat requirements for patients receiving continuous TPN solution. Seventy-seven patients who had 97 courses of TPN of at least 14 days duration were prospectively studied. The following fat supplementation was given: a) none, b) 10% soybean oil emulsion intravenously at fixed dosage, c) fat from an oral diet, or d) intravenous and oral fat. No patient was EFA deficient before the onset of TPN. EFA deficiency was prevented when at least 3.2% of total calories were given as intravenous fat or at least 15% as oral fat. Lesser amounts of fat decreased the rate of EFA deficiency development but did not prevent it from occurring. The 7.7 g/day of linoleic acid provided in 1000 ml per week of 10% soybean oil emulsion provides adequate fat to prevent EFA deficiency.

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CLINICALLY SIGNIFICANT ESSENTIAL fatty acid (EFA) deficiency has become a problem since the advent of fat-free total parenteral nutrition (TPN).[1] Before the availability of intravenous fat emulsions, patients maintained on fat-free TPN developed biochemical evidence of EFA deficiency, which in many cases progressed to clinical symptoms including skin rash and alopecia.[2–5] Tashiro,[6] however, was able to prevent EFA deficiency in four pediatric patients on TPN, when they were administered at least 2% of their total calories as linoleic acid. Parenteral fat has also been shown to reverse the abnormal fatty acid patterns in adults maintained on fat-free diets, and resolve the EFA deficiency-related skin lesions.[7–9]

The observation that dietary fats are essential for normal animal growth and development was made by Burr and Burr in 1929.[10] Further studies demonstrated that the deficiency syndrome responded to linoleic acid, a polyunsaturated fat which humans cannot synthesize. When present in adequate amounts, linoleic acid (18:2w6) is desaturated and elongated into arachidonic acid (20:4w6), a tetraene. If there is a deficiency of linoleic acid the same pathway converts oleic acid (18:1w9) into 5, 8, 11-eicosatrienoic acid (20:3w9), a triene. Holman found that the ratio of trienoic to tetraenoic acids (20:3/20:4) could be used as an expression of EFA status, a value of 0.4 or greater defining EFA deficiency.[11]

The present study attempts to define the minimal fat requirements for patients who are receiving continuous, otherwise fat-free, TPN.

Methods

We began a prospective study, in 1975, of the requirements for intravenous fat of patients receiving TPN. Only patients at the Clinical Center of the National Institutes of Health, who received TPN solution for at least 14 days and had at least one triene:tetraene ratio determination at or following 14 days of TPN, were included in the present analysis. Careful follow-up data included accurate calorie counts for intravenous and/or oral fat intake. Seventy-seven patients had 97 courses of TPN, which could be included for prospective evaluation. The patients ranged in age from eight to 68 years and all but eight patients were receiving treatment for malignant disease. Another group of nine patients, all with malignancies but not receiving TPN, were also evaluated.

The TPN solution consisted of 20% dextrose, 4.25% Freamine-II®, supplemental electrolytes, trace metals and vitamins administered through a catheter placed percutaneously into the superior vena cava. Over a 48 hour period, the infusion rate was brought up to at least 2000 cc per day of TPN solution. Patients received the following fat supplementation: a) none, b) 10% soybean oil emulsion intravenously at a fixed dosage schedule, c) fat from an oral diet, or d) intra-

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venous and oral fat. The intravenous 10% soybean oil emulsion contains 54% linoleic acid.[12] The oral diet is assumed to contain approximately 7.5% of fat calories as linoleic acid based on a range of 5–10% linoleic acid content available in the food of a regular American diet.[13]

Fatty acid determinations were performed on blood plasma frozen under nitrogen until analysis. Plasma lipids were extracted by chloroform-methanol[14] and the various lipid fractions separated by thin layer chromatography. The eluted phospholipid band was injected into the gas liquid chromatograph for individual fatty acid separation.[15,16] A ratio of 5, 8, 11-eicosatrienoic acid to arachidonic acid (triene:tetraene) of 0.4 or greater defined biochemical EFA deficiency.

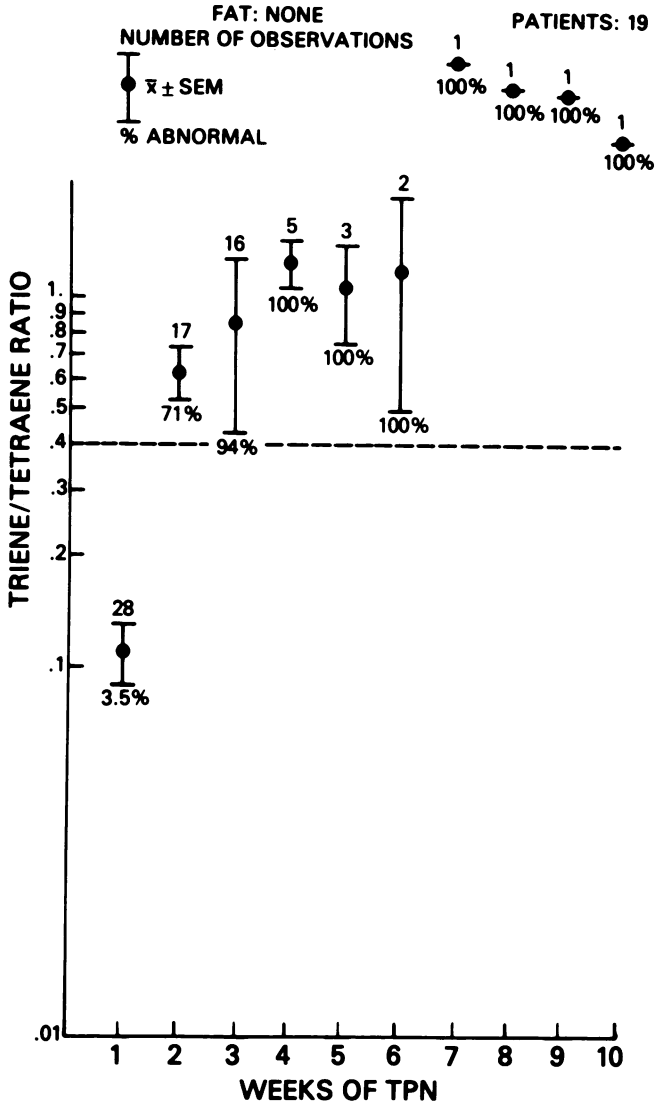

FIG. 1. Triene:tetraene ratios during TPN in 19 patients who received no supplemental fat. The majority of observations were abnormal by the end of two weeks.

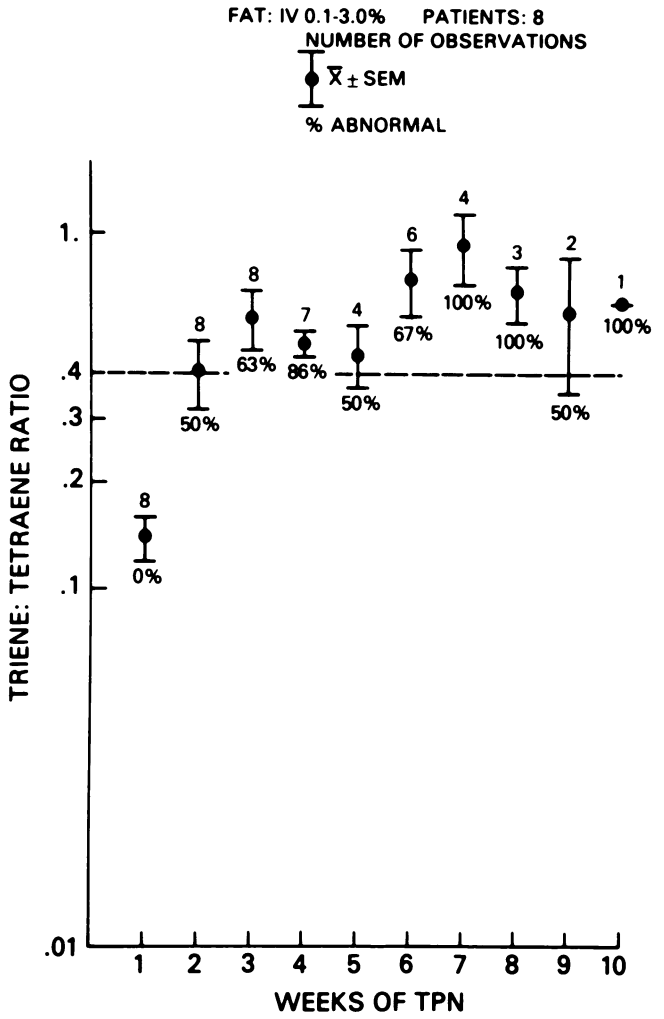

FIG. 2. Triene:tetraene ratios during TPN in eight patients who received up to 3% of their calories as intravenous fat. The rate of development of EFA deficiency is delayed compared with Figure 1.

Results

The triene:tetraene ratio at the end of each course of TPN reflected the essential fatty acid status of each patient. No patient was EFA deficient at the onset of this study. Of those patients receiving no fat during TPN, one had an abnormal triene:tetraene ratio by day 5 and the majority (71%) of the 19 patients in this group developed biochemical EFA deficiency by the end of two weeks. Virtually all were EFA-deficient by the end of three weeks TPN (Fig. 1). Up to 3% of nonprotein calories, given as intravenous fat, delayed the onset of EFA deficiency for up to six weeks (Fig. 2), but when greater than 3% of calories were administered as fat biochemical EFA deficiency was prevented in all but one observation, which was noted in one patient during the third week of TPN (Fig. 3).

A highly significant correlation ($p < 0.001$) was

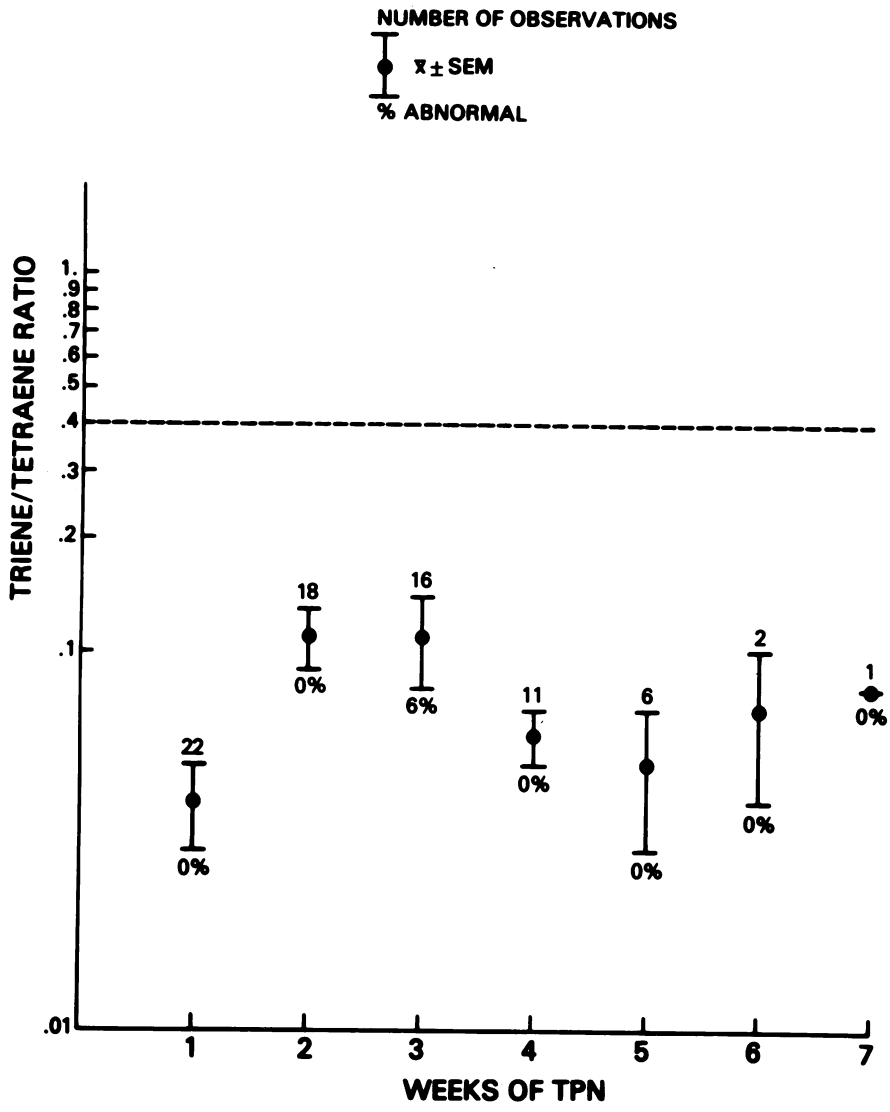

FIG. 3. Triene:tetraene ratios during TPN in 17 patients who received greater than 3% of total calories as intravenous fat. One patient who received 3.1% of calories as fat developed biochemical EFA deficiency at day 15. No other abnormal values were noted.

found between the logarithm of the final triene:tetraene ratio and the daily percentage of nonprotein calories given as intravenous fat (Fig. 4). A triene:tetraene ratio of 0.4 corresponded to 1.9% of the calories given as IV fat. No abnormal values were noted, however, when intravenous fat constituted at least 3.2% of the total calories. This data is expressed as a function of bottles or units per week of fat emulsion in Table 1. Of the 19 patients who received no fat there was only one normal triene:tetraene ratio from a patient who received TPN for only 15 days. Three other patients who had normal ratios up to 15 days of TPN all developed biochemical EFA deficiency by 21 days. Seventy per cent of the patients, who were given one unit (500 ml) or less of intravenous fat per week, became EFA-deficient. The 15 patients, who were given more than one unit of fat per week, received a significant percentage of their nonprotein calories as fat (at least 5.6%). No patient in this group developed EFA deficiency.

There were 23 patients who had 32 courses of TPN during which their source of fat was given by mouth alone. These patients received TPN solution in quantities similar to the other groups, but were able to tolerate an oral diet from which they received varying amounts of fat. The time course for developing EFA deficiency during TPN, when up to 15% of nonprotein calories are given as fat by mouth, is shown in Figure 5. By three weeks, 75% of the triene:tetraene ratios were abnormal as compared with none in the group of ten patients who received greater than 15% of their calories as fat by mouth (Fig. 6).

A significant correlation ($p < 0.001$) of the logarithm of the triene:tetraene ratios at the end of TPN with the per cent calories given as oral fat is seen in Figure 7. A 0.4 triene:tetraene ratio corresponded to a 9.3%

PO fat intake, with no abnormal values, when at least 13.5% of the nonprotein calories were given as oral fat. Table 2 summarizes these findings and illustrates the differences in fat requirements according to the means of administration. Nine patients were also evaluated who were not receiving TPN solution but were taking fat by mouth in varying amounts. There were no abnormal triene:tetraene ratios in this group even when as little as 8.6% of calories were given as fat.

The route of fat administration is considered further in Table 3. Twenty-one patients on TPN received fat by both oral and intravenous routes. All patients receiving a total of 5.1–10% or greater than 15% of nonprotein calories as fat were receiving at least 1.9% from the intravenous route which, from Figure 4, would alone be expected to provide adequate fat to prevent EFA deficiency in the majority of cases. Three

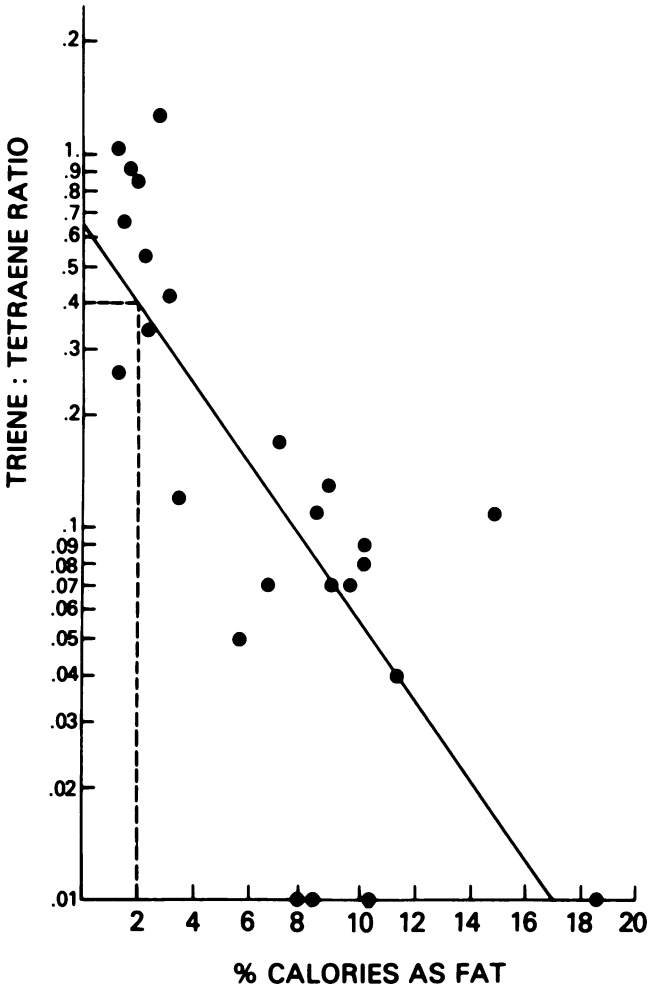

FIG. 4. Correlation of the per cent of total nonprotein calories given as intravenous fat with the triene:tetraene ratio at the end of each TPN course. A ratio of ≥0.4 defines biochemical EFA deficiency. No abnormal ratios noted when at least 3.2% calories are given as intravenous fat. N = 25. r = ⁻.7514. $p < 0.001$.

TABLE 1. *Triene:Tetraene Ratio at End of TPN**

IV Fat Units/Wk†	N	T:T Ratio (Mean ± SEM)	Per Cent Abnormal‡	Per Cent Calories as Fat§
0	19	1.17 ± .21	95	0
0.1–1.0	10	.64 ± .12	70	2.1 ± 0.2
1.1–2.0	3	.10 ± .04	0	6.4 ± 0.4
>2.0	12	.06 ± .01	0	10.0 ± 1.1
Controls‖	10	.08 ± .01		

* TPN given at least 14 days.
† One unit of fat = 500 ml 10% soybean oil emulsion.
‡ Biochemical EFAD; triene: tetraene ≥ 0.4.
§ Per cent of total nonprotein calories given as fat, mean ± SEM.
‖ Normal volunteers on regular diets.

of the four patients receiving only 2–5% of calories as fat had abnormal triene:tetraene ratios at the end of TPN. The one patient in this group, who remained normal, received 2.2% of the fat intravenously, the other three patients received 1% or less fat via this route, and only up to 3.3% via the oral route. Figure 8 shows the triene:tetraene ratios of the five patients who received 10.1–15% of total nonprotein calories as fat orally and intravenously. The two patients who developed EFA deficiency had insufficient fat from either source, as compared with the three other patients, who remained normal throughout their course of TPN.

Discussion

George and Mildred Burr first identified a clinical syndrome associated with an absence of any fat in the diet given to rats.[10] Clinical signs developed in a few weeks and included a scaly condition of the skin, necrosis of the tail and renal degeneration with hematuria. They further defined the deficiency and identified linoleic and arachidonic acids as being effective in resolving the syndrome.[17] A later attempt to simulate the findings in a human adult were unsuccessful though all rats given the same diet developed the EFA deficiency syndrome.[18] An extensive study in newborns, however, was able to document the importance of linoleic acid in the diet.[19] Of 428 infants fed milk mixtures varying in kind and amount of fat, those who received 1% or more of their total calories as linoleic acid did not develop biochemical or clinical signs of EFA deficiency.

In 1971, Collins et al.[7] reported a case of biochemical and clinical EFA deficiency in an adult patient maintained on fat-free IV therapy following extensive small bowel resections. After giving IV fat emulsion the elevated level of 5, 8, 11-eicosatrienoic acid returned towards normal and the dry scaly skin rash disappeared. These authors concluded that at least

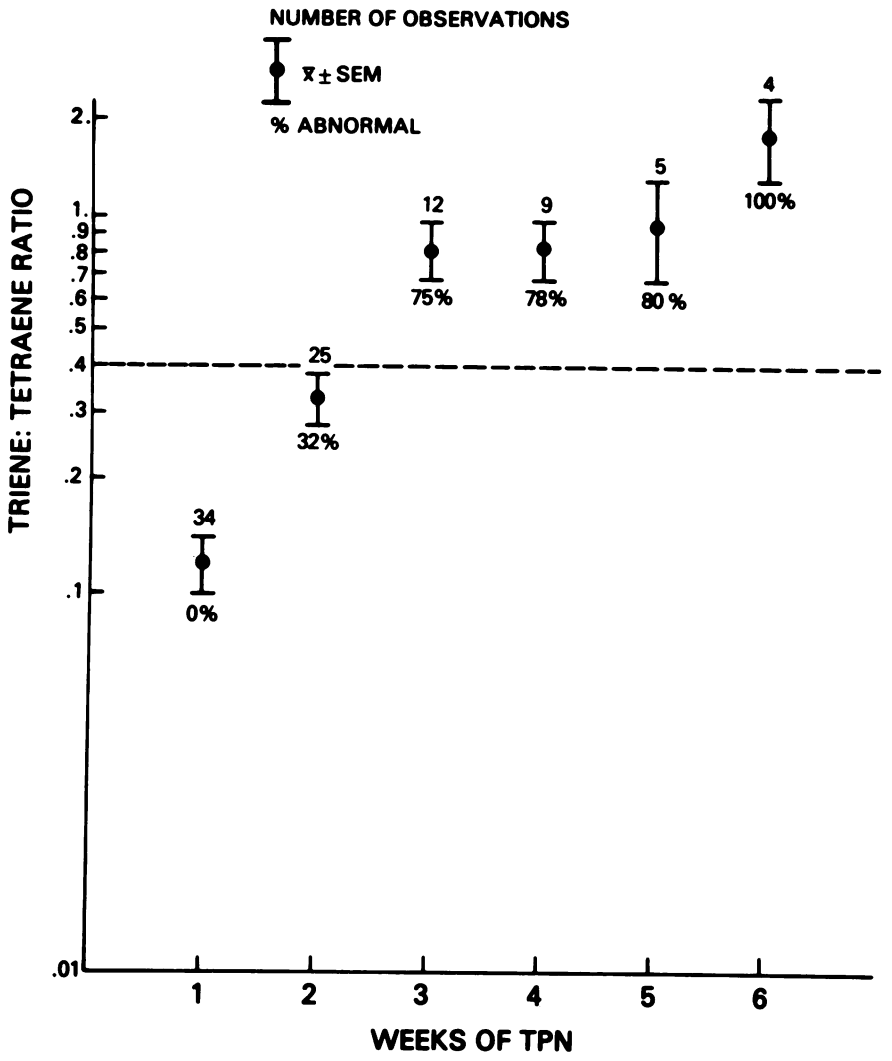

FIG. 5. Triene:tetraene ratios during TPN in 22 patients who received up to 15% of their calories as oral fat. The majority (75%) of observations were abnormal by the end of three weeks.

7.5 g/day of linoleic acid is the minimal requirement for an adult man. In this study, the patients who had the lowest triene:tetraene ratios (mean of 0.06) received at least 1000 ml (2 units) per week of 10% soybean emulsion. The 7.7 g/day of linoleic acid given with this regimen is remarkably similar to that recommended by Collins et al.[7] and Wretlind.[20]

Those patients given at least 3.2% of calories as fat IV received 1.7% of those calories as linoleic acid. Several authors have recommended that 1–2% of calories of patients on TPN be given as linoleic acid.[6,21,22] Tashiro found he could prevent EFA deficiency in growing puppies on TPN, and in two human newborns, if he administered 4% of calories as a 10% soybean oil emulsion.[21] He later found that after one week of fat-free TPN, infants were able to restore the triene:tetraene ratios to normal when administered 4% of daily calories as fat, but not with a 2% calorie fat source.[6]

The minimum requirement for linoleic acid can also be met from an oral source, as demonstrated in the 32 patients in this study (Fig. 7). The ten patients who were administered at least 15% of calories as fat by mouth, and did not become EFA-deficient, received 1.1% of calories as linoleic acid. The two patients who received both intravenous and oral fat and became EFA-deficient each received a total of 1.5% of calories as linoleic acid. It would seem, therefore, that at least 1.7% of calories as linoleic acid is needed to prevent biochemical EFA deficiency from either intravenous or oral sources during TPN.

The mechanism whereby patients on TPN became EFA-deficient is believed to be related to the continuous glucose infusion. The increased insulin during glucose-amino acid infusion decreases the hormone-sensitive lipase activity in adipose tissue, preventing breakdown of triglycerides into free fatty acids.[22,24] Thus, the patient receives neither linoleic acid nor has access to endogenous stores of essential fatty acids, believed to be 8–10% of normal adult adipose tissue.[1]

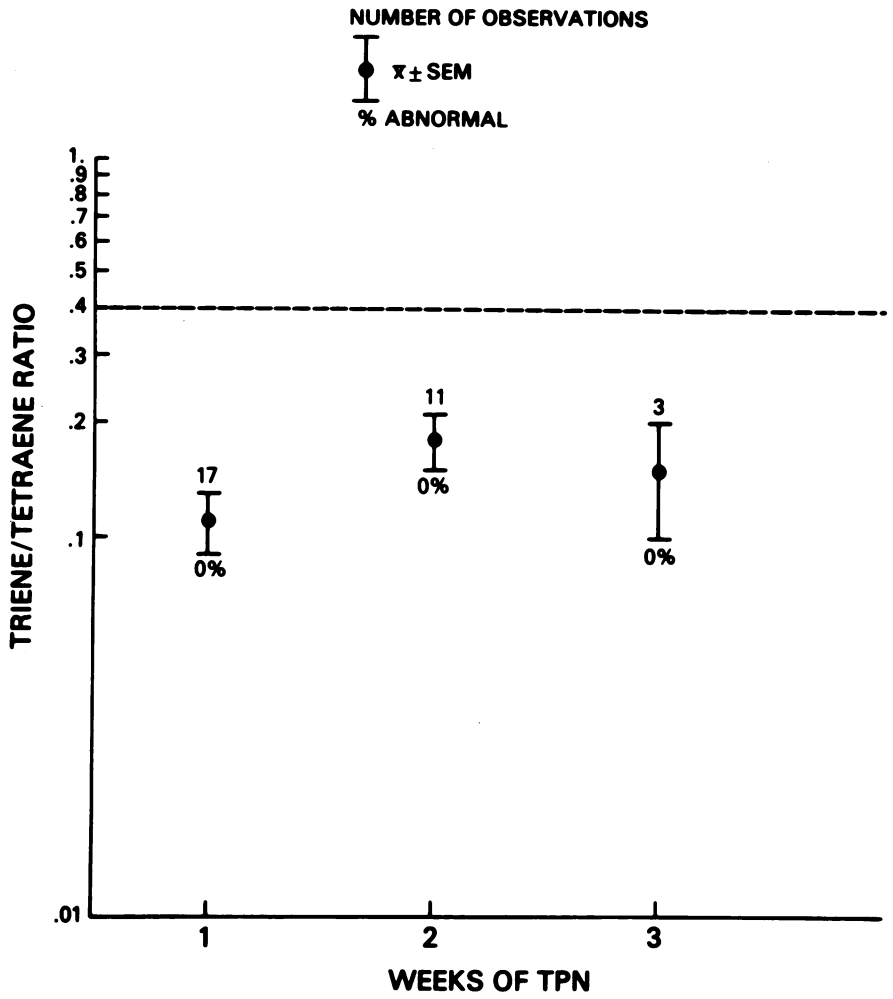

FIG. 6. Triene:tetraene ratios during TPN in ten patients who received greater than 15% of their calories as oral fat. There were no abnormal values over the three weeks of observation.

The role of continuous IV glucose in producing EFA deficiency is supported by the ability of fasting or intermittent feeding to return triene:tetraene ratios to normal.[22,25] The influence of glucose loads is also demonstrated in this study by the group of patients who, not on TPN, were able to remain normal with as little as 8.6% of calories as oral fat. Other studies, in dogs, have shown that the development of fat deficiency is related to the amount of food consumed.[26,27] Wiese found that Beagle puppies on a low-fat diet given 200 calories/kg/day developed symptoms of EFA deficiency in four to five months, whereas those given 100 calories/kg/day never developed clinical EFA deficiency.[26]

The rate of developing EFA deficiency is dependent on the amounts of linoleic acid in the diet, the amount

TABLE 2. *Triene:Tetraene Ratio at End of TPN**

Fat Intake	Total†	Abnormal‡	Per Cent
On TPN			
None	19	18	95
IV			
0.1–3%	8	7	88
>3%	17	1§	6
PO			
0.1–15%	22	14	64
>15%	10	0	0
No TPN			
PO 8.6–41.8%	9	0	0

* TPN given at least 14 days.
† Total number of TPN courses.
‡ Biochemical EFAD; triene:tetraene ≥ 0.4.
§ % IV fat = 3.1%.

TABLE 3. *Triene:Tetraene Ratios at End of TPN**

IV + PO Fat Total†	Number	Abnormal‡ (Per Cent)	Per Cent Fat	
			IV	PO
2.0–5%	4	3 (75)	0.8–2.2	0.8–3.3
5.1–10%	7	0 (0)	1.9–8.3	1.9–5.0
10.1–15%	5	2 (40)	0.9–8.7	2.7–13.1
>15%	5	0 (0)	7.2–10.1	7.5–11.6

* TPN given at least 14 days.
† Per cent of total non-protein calories given as fat.
‡ Biochemical EFAD; triene:tetraene ≥ 0.4.

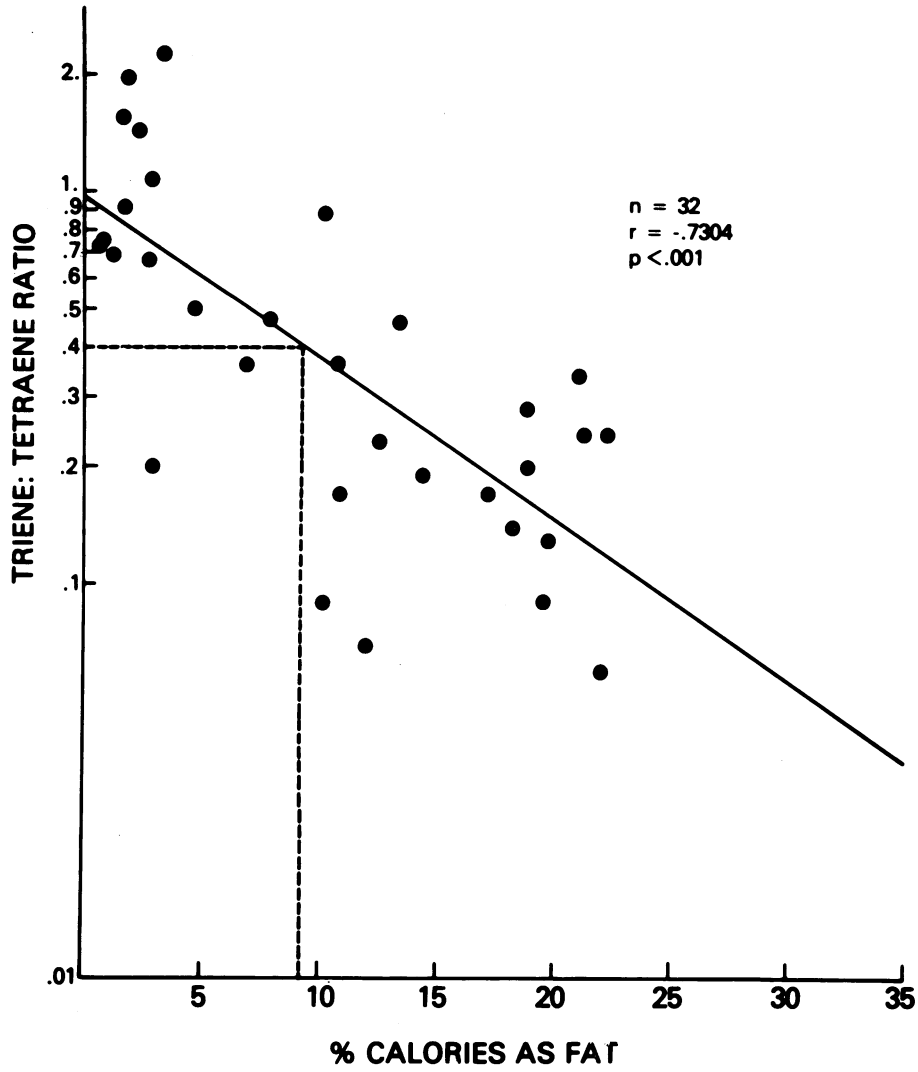

FIG. 7. Correlation of the percent of total nonprotein calories given as oral fat with the triene:tetraene ratio at the end of each TPN course. No abnormal values (≥0.4) noted when at least 13.5% of calories given as oral fat. N = 32. r = ⁻.7304. p < 0.001.

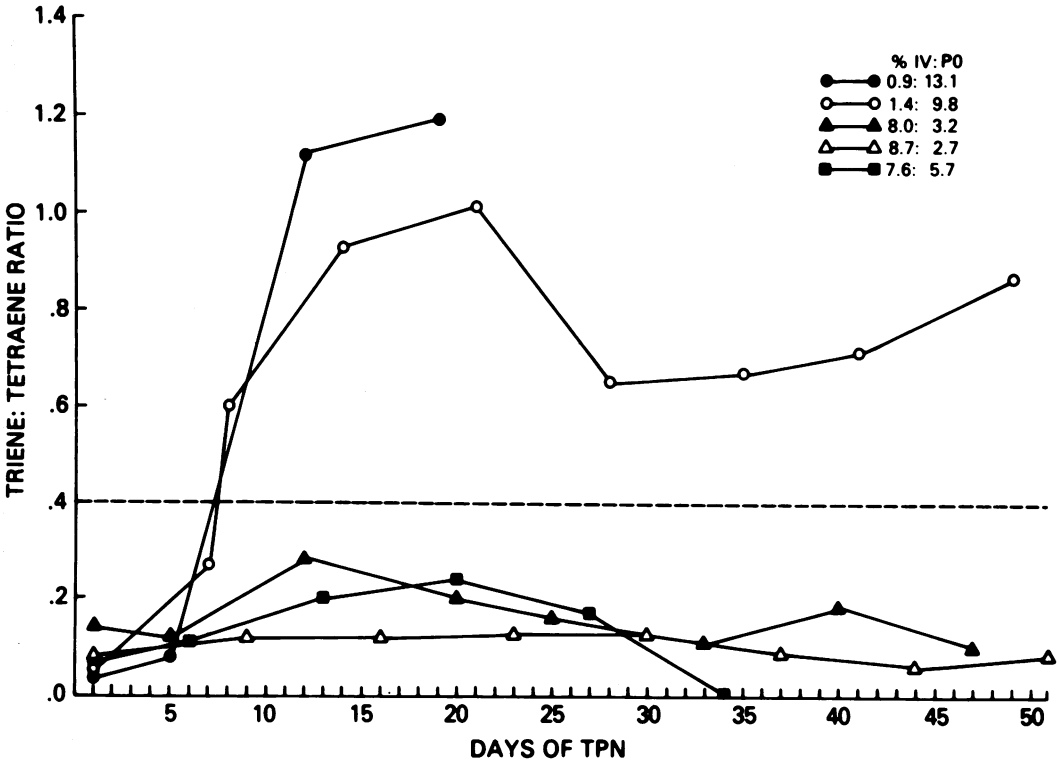

FIG. 8. Triene:tetraene ratios during TPN of 5 patients who received a total of 10.1–15% of calories from intravenous and oral sources. EFA deficiency developed in the two patients who had insufficient fat from either source.

of endogenous fat available, the rate of growth or weight gain and, when given by mouth, the ability to absorb the ingested fat. Elevated eicosatrienoic acid can be found in 24 hours, in well nourished adults put on fat-free TPN.[22] Seventy per cent of infants on fat-free TPN diets will develop triene:tetraene ratios greater than 0.4 by day 7, and all will develop dry, scaly thickened skin by three months.[6,19] Older children and adults, as in this study, develop biochemical EFA deficiency during TPN over a longer period of time, usually three to five weeks, with appearance of skin changes delayed up to two years.[5,8,28–30] Extensive intestinal resection may predispose to development of EFA deficiency. Press reported three adult patients with extensive small bowel resection, who developed EFA deficiency without having been on TPN.[31]

In the present study, all patients without fat supplement were EFA-deficient by 21 days of TPN. When at least 15% of calories by mouth, or 3.2% of calories intravenously were given, EFA deficiency was prevented. Although lesser amounts of fat decreased the rate of developing EFA deficiency, it did not prevent it from occurring. An adequate source of linoleic acid to prevent EFA deficiency can be obtained from 1000 ml per week of a 10% soybean oil emulsion.

Acknowledgments

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