Clinical Evaluation of a 10% Intravenous Fat Emulsion for Parenteral Nutrition in Thermally Injured Patients

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EXTENSIVE WEIGHT loss and nitrogen depletion characterize the post-traumatic metabolic response following severe thermal injury. Vigorous nutritional support using enteral or combined enteral-parenteral feedings during this catabolic phase of trauma reduces body wasting and often produces caloric equilibrium and weight stabilization.[18] The complications of sepsis,[1] hyperglycemia, nonketotic hyperosmotic coma,[21] and central venous thrombosis[15] which have been related to the use of hypertonic nutritional solutions in severely ill patients limit the use of recently developed technics of parenteral feedings in patients with major injury. Fat emulsions which are isotonic and contain 1–2 calories/ml., may be administered by a peripheral vein, in order to avoid many of the harzards associated with central venous infusion of hypertonic dextrose solutions. The purpose of this study was to determine the safety and efficacy of a 10% soy bean oil emulsion, Intralipid, as an essential nutrient and caloric source in thermally injured patients.

Method and Materials

Acute Toxicity Studies

Single 500 ml. units of 10% soy bean emulsion were administered to 15 healed, convalescing controls and 12 hypermetabolic thermally injured patients. After 8 hours of fasting, the emulsion was infused at a constant rate over a 4-hour period by way of a forearm vein. Baseline body temperature, pulse rate, blood pressure, and respiratory rate were recorded prior to the infusion and then serially each hour for the next 12 hours. Fat clearance from the blood was determined by measuring plasma spectrophotometric optical density at 700 mμ before infusion and 4, 8, and 24 hours postinfusion. Complete blood count, total serum proteins, albumin, alkaline phosphatase, SGOT, total bilirubin and direct fraction were determined before infusion and 24 hours following administration of the single unit of fat.

Eight patients with normal cardio-respiratory function were given an intravenous bolus of ^{133}Xenon gas dissolved in saline, and serial pulmonary perfusion-diffusion scans made with a scintillation counter. The overall characteristics of the lung fields were determined by serial anterior-posterior scintigrams and the clearance rate of the gas was studied by measuring disappearance rates of the isotope from the lung fields.[9] Following the baseline xenon study, a 500 ml. unit of 10% soy bean emulsion was administered, and, at the end of the 4-hour infusion, a repeat ^{133}Xenon lung scan was performed.

Pulmonary diffusion capacity was determined in duplicate in five convalescing patients following a 12-hour fast. Before starting the infusion, duplicate measurements of diffusion capacity were made with the subjects sitting in the upright position, using a standard carbon monoxide rebreathing technic.[8] One unit (500 ml.) of 10% fat emulsion was administered over a 4-hour period and the diffusion capacity was again determined at the end of the infusion and 4 hours postinfusion, using the same rebreathing technic.

Single or multiple units of intravenous fat were ad-

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ministered to 20 additional severely burned individuals requiring supplemental or total parenteral nutrition. Arterial blood was drawn at the start of the infusion and at the end of infusion and analyzed for pH, pCO_2, and pO_2.

Red Cell Phospholipid Studies

Heparinized blood was drawn from 13 burn patients, two individuals with chronic enterocutaneous fistulae receiving prolonged fat-free intravenous feedings, and five age-matched normal subjects. Total lipid extraction from red cells and serum was performed with chloroform and methanol, according to the procedures of Way and Hanihan.[16] Red cell phospholipids were separated by thin-layer chromatography, using silicate gel H; plasma lipids were isolated by thin-layer chromatography using silicate gel G. The method of Dodge and Philip was followed for fatty acid analysis,[4] and final identification of the various fatty acids was by comparison with commercially available standards, cod-liver oil, fatty acid methylesters, and published chromatograms.

With the identification of fatty acid deficiency, the 10% fat emulsion was administered to two patients in whom enteral dietary support was inadequate or impossible. An oral diet, supplemented with polyunsaturated fatty acids, was used in the third individual, and a parenteral fat-free diet (hypertonic dextrose, protein hydrolysate, minerals, and vitamins) was continued in two patients. Serum and red cell fatty acid analysis was continued periodically during this supportive dietary therapy.

Long Term Studies

Intravenous fat emulsion was administrered for 5–46 days to 10 hypermetabolic burn patients who required extensive energy support because of associated injuries or complications following thermal injury (Table 1). In six individuals, the fat emulsion was administered along with other parenteral nutrients to supplement enteral feedings, but in the remaining four patients, fat emulsion was given in combination with dextrose and protein hydrolysate as total parenteral nutrition. The emulsion was administered through a Y-connector, infused simulataneously with a solution containing 5–15% dextrose, 4–5% protein hydrolysate, electrolytes, vitamins and minerals. Central venous cannulae were used for administration of the more hypertonic solutions but peripheral venous routes were frequently used to administer dextrose and amino acid solution containing less than 14% solute concentration. All urine was collected in 24-hour pools and analyzed for sodium, potassium, chloride, creatinine, urinary urea nitrogen, glucose, and total nitrogen. Douglas bag collections of expired gas were performed on selected patients to determine daily metabolic rates and allow calculation of metabolic fuel oxidation. Blood was drawn daily or when clinically indicated to determine blood count, serum electrolytes, glucose, blood urea nitrogen, blood gas pressure, liver and renal function studies.

Results

No significant thermogenic response to the intravenous fat emulsion occurred in the group of control or burn patients. Pulse rate, respiratory rate, blood pressure, and body temperature remained normal in the control group of patients. Complete blood count and liver function studies were unchanged before and after infusion of one unit of intravenous fat (Table 2). Fat clearance curves demonstrated accelerated plasma disappearence rate of the emulsion in the acutely burned patients when compared with the

TABLE 1. *Characteristics of Patients Studied*

Patient	Age	Weight (kg)	Body Surface Area m²	Per Cent Total Burn	Per cent Third Degree	Associated Injuries or Complications
1	21	57	1.63	42	7	Stress ulcer bleeding requiring subtotal gastrectomy; postop bowel obstruction requiring lysis of adhesions.
2	41	53	1.65	60	40	Chronic alcoholism, muscular dystrophy.
3	19	77	1.98	75	50	Repeated sepsis; transferred to this unit for final wound coverage.
4	18	81	1.96	56	54	T-E fistula, stress ulcer requiring gastrectomy, respiratory failure, sepsis.
5	54	74	1.86	26.5	18	Hemiplegia, severe leg burns requiring A-K amputations, respiratory failure.
6	9	25	0.94	31	14	Cerebral edema, inhalation injury, stress ulcer requiring subtotal gastrectomy.
7	23	60	1.65	14.5	14.5	Electrical injury resulting in T-1 paralysis, required radical debridement of right neck, right arm & right upper thorax.
8	17	65	1.68	32	22	Head injury, associated fractures, respiratory failure
9	19	72	1.97	28	12.5	Stress ulcer bleeding requiring subtotal gastrectomy.
10	31	52	1.78	75	47	Severe burn required right A-K amputation; gastric fistula, respiratory failure.
Mean	25.2	61.6	1.71	44	27.9	

TABLE 2. *Hematologic Studies and Indices of Liver Function Before and 24 Hours Following Infusion of 500 ml. Soy Bean Emulsion in 15 Convalescing Thermally Injured Patients (Mean ± S.D.)*

	Before	After
Hematocrit	41 ± 5	42 ± 4
WBC(cu mm)	7,900 ± 2,200	7,700 ± 2,200
Total protein Gm./100 ml.	7.3 ± 0.5	7.6 ± 0.4
Albumin (Gm./100 ml.)	3.6 ± 0.6	3.7 ± 0.4
Alkaline phosphatase (K-A units)	13 ± 3	15 ± 4
SGOT (Karmen units)	30 ± 11	34 ± 9
Total bilirubin (Mg./100 ml.)	0.5 ± 0.3	0.5 ± 0.3
Direct bilirubin (Mg./100 ml.)	0.1 ± 0.0	0.0 ± 0.0

resting controls (Fig. 1). ^{133}Xenon perfusion-diffusion scans remained normal following the administration of the fat emulsion in the eight patients studied. No change in the distribution of the xenon or its rate of clearance from the lung fields was noted (Fig. 2).

Pulmonary diffusion capacity measured by carbon monoxide rebreathing technic demonstrated no alterations in the five patients studied (Table 3). Blood gas measurements carried out in 20 patients were unchanged following the infusion of 1 Gm./Kg., 2 Gm./Kg., and 3 Gm./Kg. body weight (Table 4). There was no evidence of cyanosis or respiratory insufficiency associated with the fat infusion.

Analysis of the total phospholipid distribution in the red cell revealed that the burn patients formed two distinct categories, those with normal phospholipid patterns and those with marked phospholipid alterations. Eight burn patients (mean age 33.8, burn size 41.1%, 28.4% full-thickness injury) had normal levels of red cell membrane phosphorus and normal distribution of phospholipids among the four major lipid classes (Table 5). On the other hand, five burn patients (mean age 29.2, burn size 45.6%, 23.7% third degree) revealed a marked reduction of red cell lipid phosphorus. Among

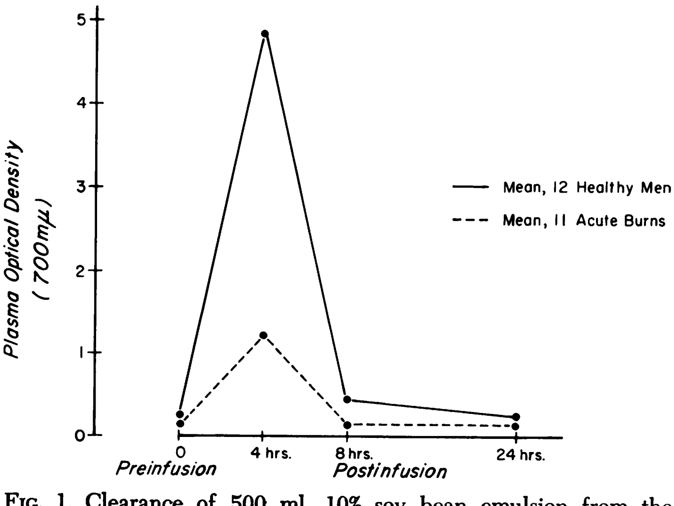

FIG. 1. Clearance of 500 ml. 10% soy bean emulsion from the blood stream following a 4-hour infusion (from 0 to 4 hours).

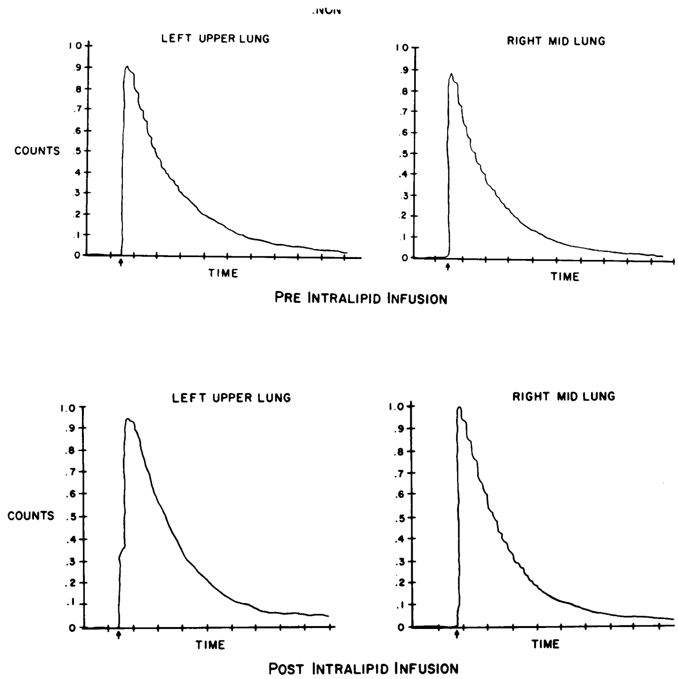

FIG. 2. No alteration in clearance of ^{133}Xenon was demonstrated when comparing total lung or regional isotope disappearance curves obtained before (top) and immediately following fat infusion (bottom).

the individual phospholipids, there was a relative increase in phosphatidylcholine and sphingomyelin, and a relative decrease in phosphatidylethanolamine. When calculated in terms of absolute changes, with the overall decrease of membrane phosphorus taken into consideration, these alterations of lipid classes corresponded to an absolute reduction of phosphatidylethanolamine (38% of normal), and phosphatidylserine (64% of normal). On this weight basis, phosphatidylcholine and sphingomyelin levels remained normal.

An analysis of the fatty acids derived from the total phospholipid extracts of the red cell revealed only minimal differences between normal red cells and those samples taken from the first group of burn patients (Table 6). However, measurement of fatty acid distribution in the deficient burn patients revealed a pronounced decrease in all polyunsaturated species. The most dramatic changes include a 70% decrease in the arachidonate (20:4n6), an 88% decrease in decosahexanoate (22:6n3), and a 36% decrease in linoleate (18:2n6)* Concurrently, there was a substantial increase in the saturated acids, notably 16:0, 18:1n9, 24:0, 24:1n9. When the realtive changes of fatty acids were

* The nomenclature for fatty acids is as follows: arachidonic acid, 20:4n6, where 20 is the total nubmer of carbon atoms, 4 is the number of methylene-bridged *cis* double bonds, and n6 is the position of the double bond nearest the terminal methyl group.

TABLE 3. *Diffusion Capacity (DL_{co}) before and after 500 ml. Soy Bean Emulsion in Convalescing Individuals*

Subject	Age	Height (inches)	Postburn Day Studied	Vital Capacity (Liters BTPS)	Diffusing Capacity in ml. CO/min/mm. Hg (Each Value = Mean of Two Measurements) Pre-Infusion	Immediately Post-Infusion	Four Hours Post-Infusion
1	18	72	97	6.41	36.32	36.32	—
2	20	72	109	6.92	32.92	32.54	33.91
3	21	74	78	5.81	35.04	33.04	35.07
4	21	70	20	5.55	35.99	33.73	35.99
5	20	73	78	4.71	41.00	42.60	38.99

converted from a weight distribution to molar distribution, then grouped according to structural similarities, the difference between the normal and deficient red cells was more clearly defined (Table 7). Specifically, decrease in all members of the n6 and n3 series, and an increase in all members of the n9 and saturated series, lead to a marked shift in the ratio of saturated to unsaturated fatty acids within the red cell membrane of the phospholipid deficient burn patients.

Isolation of the individual phospholipids by thin-layer chromatography, and interaction and quantification of the fatty acid composition of the individual components, demonstrated that sphingomyelin, with its high proportion of saturated and long chain fatty acids, was unaffected by the nutritional and thermal stress. However, phosphatidylethanolamine and phosphatidylserine were the major subcategories demonstrating the quantitative decrease in polyunsaturated fatty acid responsible for the alterations observed with the combined phospholipid analysis. Evaluation of the plasma lipid classes, carried out to determine the extent of the fatty acid alterations following thermal injuries, revealed no consistent difference in the fatty acid composition of the plasma phospholipids, triglycerides, or cholesterol esters. Two patients had a reduced level of plasma linoleate, but the others had normal or somewhat elevated quantities. At the same time, minimal fluctuations of arachidonic and n3 saturated and unsaturated acids were found. The appearance of 5-8-11 eicosatrienoate (20:3n9), which is absent in normal man, was observed in the plasma phospholipid fraction of three of the four deficient patients studied.

Studies of two patients with chronic enterocutaneous fistulas, with normal metabolic rates, who received fat-free parenteral diets for more than a month revealed no significant alterations in membrane phospholipid fatty acid (Table 6). Evaluation of one of these patients after 6 months of fat-free feeding demonstrated only a depressed level of linoleate with a normal distribution of arachidonate and decosahexanoate (Fig. 3).

Polyunsaturated fatty acids (the n6 and n3 fatty acid species) cannot be synthesized *de novo* in man, and therefore must be acquired by dietary intake. The soy bean lipid emulsion was used for replacement therapy in two patients, an oral diet supplemented with high quantities of polyunsaturated fats was used to treat one individual, and a fat-free parenteral diet was continued in two patients.

Following the administration of 10% soy bean emulsion, fatty acid imbalances were gradually corrected to normal levels. For example, patient 1 received 50, 500 ml., units of Intralipid over a 34-day period and patient 2 received 67 units over a 63-day interval. In the first individual, there was marked improvement of red cell polyunsaturated fatty acids after only 2 weeks of fat therapy (Fig. 4), and, simultaneously, palmitate and other saturated fatty acids were reduced to a normal level. Patient 2, on the other hand, progressed more gradually to a normal fatty acid distribution when placed on the intravenous fat feedings (Fig. 5). An essentially normal pattern was found on day 260, about 60 days following the onset of lipid infusion. One patient corrected his fatty acid red cell abnormalities following addition of polyunsaturated fats to his diet and the other two patients received hypercaloric fat-free feedings administered by central venous catheter (Table 6). After 68 days, no improve-

TABLE 4. *Effect of Intravenous Fat on Blood Gas Pressures and pH (Mean ± S.D.)*

	pO_2 (in mm. Hg) Before	After	pCO_2 (in mm. Hg) Before	After	pH Before	After
1 Gm./Kg.	91.6 ± 9.5	86.0 ± 9.4	26.9 ± 6.1	27.8 ± 4.4	7.448 ± 0.072	7.466 ± 0.066
2 Gm./Kg.	86.0 ± 22.9	89.7 ± 20.1	28.1 ± 6.5	30.6 ± 7.1	7.454 ± 0.040	7.460 ± 0.060
3 Gm./Kg.	75.2 ± 10.7	78.4 ± 12.5	32.3 ± 3.2	32.1 ± 4.3	7.444 ± 0.046	7.448 ± 0.037

TABLE 5. *Phospholipid Composition of Red Cells from Normal and Burned Subjects (Mean ± S.E.M.)*

	Normal Subjects (n = 4)	Burn Patients Group I (n = 8)	Burn Patients Group II (n = 5)
Lipid phosphorus*	0.119 ± 0.008	0.122 ± 0.004	0.094 ± 0.010
Phospholipid distribution (Weight per cent)			
Phosphatidylethanolamine	26.3 ± 1.3	26.4 ± 1.1	13.2 ± 1.0
Phosphatidylserine	13.0 ± 2.5	14.5 ± 0.8	11.8 ± 1.6
Phosphatidylcholine	29.7 ± 2.2	30.2 ± 1.3	37.8 ± 2.2
Sphingomyelin	30.7 ± 1.4	28.4 ± 0.9	37.2 ± 2.6

* mg./ml. packed cell

ment in erythrocyte fatty acid deficiency was noticed in one individual despite his relative improvement in terms of wound healing and gain in body weight, but the second patient died from infection and hemolysis before fat could be obtained for administration. Only transient alterations in serum fatty acid levels occurred following the Intralipid therapy.

Two hundred and twenty-two liters of the 10% intravenous fat emulsion were administered to 10 patients with large burns (average burn size 44% *total* body surface, 27.9 average per cent third degree burn) and associated injuries or complications secondary to their extensive thermal injuries. The emulsion was administered from five to 46 days (mean length of therapy 16.1 days). Although the average dose of the fat emulsion administered did not exceed 3.3 Gm./Kg./body weight/24 hours, daily variations occurred and several patients received as much as 2.5 liters of emulsion per day, or a dose of fat equal to 5 Gm./Kg. body weight/day. No untoward effects could be specifically related to the emulsion in this group of critically ill patients, although a transient plasma lipemia existed while the infusions were in progress. No febrile response was related to the emulsion, and no alterations in liver, renal, or pulmonary function were associated with the doses given to this group of patients. Four of these 10 individuals died, and autopsies obtained in all patients revealed no excess accumulation of fat in liver, lung, or other body tissues.

The average daily caloric intake in the 10 patients studied was 3,770 kcal/day, and 19.2 Gm. nitrogen/day, with the fat emulsion contributing an average of 38% of the total calories received by these patients (Table 8). Nitrogen retention, determined by comparing nitrogen intake with urinary nitrogen loss, indicated posi-

TABLE 7. *Molar Fatty Acid Distribution of Red Cell Phospholipids from Normal and Burned Subjects*

	Normal Subjects	Burn Patients Group I	Burn Patients Group II
Saturated fatty acids			
Palmitate (16)	28.5	27.8	35.3
Stearate (18)	16.9	16.7	17.4
Lignocerate (24)	4.4	4.0	6.7
Total	49.8	48.5	59.4
Unsaturated fatty acids			
Oleate series (n9)			
Oleate (18)	16.8	18.6	21.6
Nervonate (24)	4.4	6.1	7.1
Total	21.2	24.7	28.7
Linoleate series (n6)			
Linoleate (18)	9.7	9.4	6.2
Arachidonate (20)	15.8	12.9	3.6
Total	25.5	22.3	9.8
Linolenate series (n3)			
Decosahexanoate (22)	2.7	2.2	0.4
Total unsaturated, including Palmitoleate (16:ln7)	50.3	51.6	40.5
Ratio (saturated/unsaturated)	0.99	0.94	1.47

TABLE 6. *Fatty Acid Composition of Total Phospholipid from Rec Cells (Mean ± S.E.M.)*

	Number of Patients	16:0	16:1n7	18:0	18:1n9	18:2n6	20:4n6	22:6n3	24:0	24:1n9
		Fatty Acid (g/100 g)								
Normals	5	24.9 ±1.3	0.8 ±0.3	16.6 ±0.6	16.5 ±0.4	9.5 ±0.5	17.2 ±0.8	3.2 ±0.5	5.8 ±0.6	5.7 ±0.2
Burns Normal fatty acids	8	24.2 ±0.8	2.1 ±0.2	16.3 ±0.3	18.1 ±0.3	9.1 ±0.3	14.0 ±0.4	2.7 ±0.3	5.4 ±0.2	8.0 ±0.6
Burns Essential fat deficient	5	31.0 ±1.8	1.5 ±0.4	17.3 ±0.5	21.4 ±0.6	6.1 ±0.6	4.1 ±0.6	0.4 ±0.2	8.9 ±0.8	9.3 ±0.3
Deficient burns following IV fat	2	24.3	0.8	19.5	16.2	10.2	15.9	4.1	6.6	6.4
Deficient burn following fat-free IV diet	1	34.5	0.7	17.3	15.0	8.1	3.8	0.8	10.6	9.1
Deficient burn following high fat oral diet	1	23.8	1.9	15.9	16.8	10.7	16.4	2.4	5.5	6.7
Fistula patients following fat-free IV diet	2	25.0	2.0	15.1	18.9	7.4	13.0	2.6	6.6	9.2

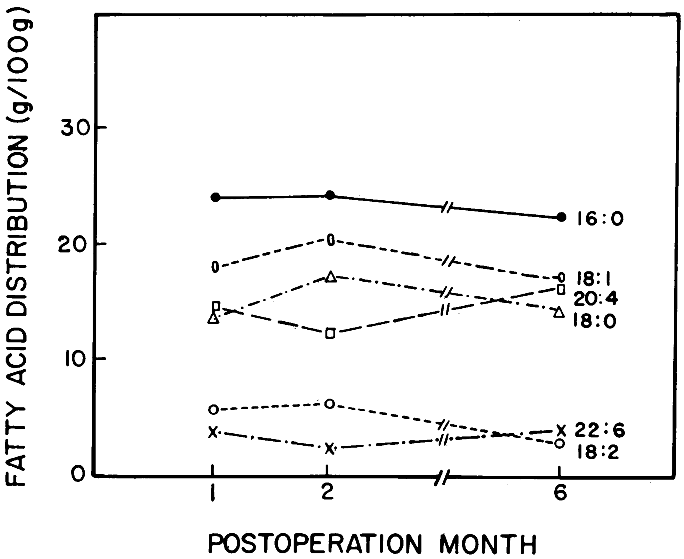

FIG. 3. Distribution of selected fatty acids from the erythrocyte phospholipids from a 26-year-old women with multiple enterocutaneous fistulae. Her metabolic rate was measured at normal predicted levels and she was maintained by total fat-free intravenous nutrition for 6 months with minimal alterations in polyunsaturated fatty acids.

tive nitrogen balance in four individuals (patients 2, 3, 6, and 10), nitrogen equilibrium in three patients (patients 4, 5, and 8), and diminution of the post-traumatic net nitrogen loss in the remaining three individuals. Moreover, vigorous caloric support contributed to stabilization of body weight or actual weight gain, and a good correlation existed between weight change and positive caloric balance.

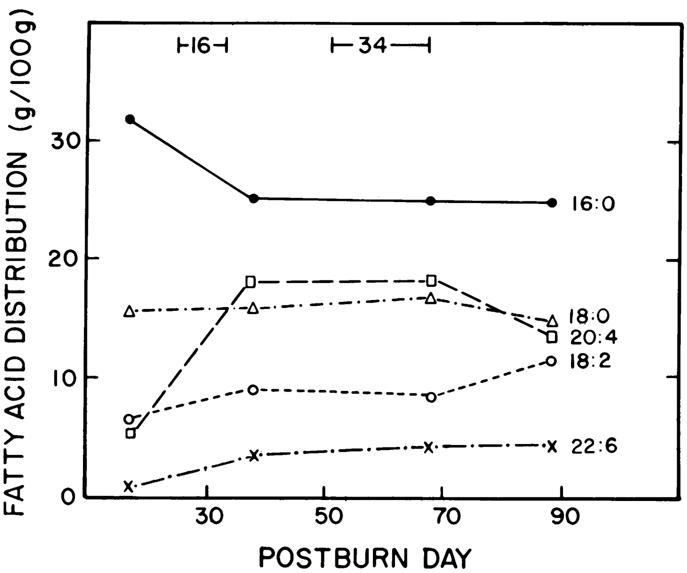

FIG. 4. A 40-year-old man with 60% total body surface burns corrected his essential fatty acid deficiency (18:2, 22:4, 22:6) with the infusion of 50 units soy bean emulsion. The dose and time relationship of the infused fat is shown at the top of the figure.

Discussion

Intralipid, the fat emulsion studied, contains soy bean oil, egg yolk-phosphatide, and glycerol as a 10% emulsion which provides 1,100 calories per liter. The particles are similar to naturally occurring emulsions (such as chyle), and their average diameter of 0.13 μm is similar to that of chylomicrons (diameter of 0.096–0.21 μm).[19] The emulsion is isotonic with body fluids and hence may be infused by peripheral vein, and, because of its relatively solute-free nature, provides a source of additional free water to the patient.

Early complications have been reported with other fat emulsions, including fever, dyspnea, cyanosis, flushing, nausea, vomiting, headache, and jaundice. Hyperlipemia, alterations in blood coagulation, liver dysfunction, anemia, and deposition of intravenous fat were late complications associated with the use of other fat emulsions.[20] In this study, the emulsion tested did not demonstrate discernible thermogenic reactions, with units taken from 10 different manufacturing batches. Complete blood counts and indices of liver function were unchanged following a one-unit infusion, and critically ill patients given multiple-unit infusions did not demonstrate abnormalities that could be directly related to the emulsion. A report of dyspnea and cyanosis associated with the administration of fat emulsions,[6] prompted our assessment of the effect of Intralipid on pulmonary function. These studies demonstrated no changes in xenon perfusion-diffusion scans or clearance of the isotope from the lung fields after infusion of a single unit of fat emulsion. Pulmonary diffusion capacity was unaltered in the five individuals studied, and no changes in blood gas values have been detected after administration of single or multiple units of the fat emulsion.

Prior to wound coverage, the hypermetabolic burn patient demonstrated increased clearance of the intravenous soy bean emulsion from the blood stream. Fat clearance, dependent on concentrations of lipoprotein lipase, is increased following starvation and stress, and may be further accelerated by heparin or insulin. In control adult subjects following an overnight fast, clearance rates have been estimated at 3.8 Gm. fat/Kg. body weight/24 hours.[19] While clearance cannot be directly equated with fat utilization, previous studies have documented favorable weight gains and nitrogen retention with the administration of intravenous fat emulsions in animals and man. There is a shift in respiratory quotient toward that of fat oxidation following the administration of the soy bean emulsion, suggesting utilization of the fat.[5] Histologic examination of specimens from our patients showed no lipid accumulation in tissue. Of the series of 10 patients receiving long-term infusion, four died (patients 4, 7, 8, 10), and no abnormalities of fat distribution or lipid accumulation were found. Because the hypermetabolic response to thermal injury provides a neuroendocrine environment favoring triglyceride and fatty acid mobilization and utilization,[2] the emulsion apparently equilibrates with available body lipid for utilization or storage as a basic fuel substrate.

Essential fatty acid deficiency occurred in five of the 13 burn patients studied, with a marked decrease in linoleate, arachidonic, and decosahexanoic acids (polyunsaturated fatty acids which cannot be synthesized by the body and hence must be repalced by dietary fat). Although it has been stated that the diet should include approximately 4% of the nonprotein calories as polyunsaturated fat,[3] essential fatty acid deficiencies seldom occur in man, as demonstrated by our two patients with enterocutaneous fistulas, who received fat-free diets for 4 and 7 months with only minor alterations in plasma and red cell polyunsaturated fatty acids. However, the stress of injury in addition to inadequate dietary fat appears to result in a deficiency state, which can also be produced in the stressed young animal or growing infant receiving fat-free feedings.[12] Following major injury, the increased energy demands result in increased mobilization and oxidation of body fat. This study suggests that this increase in fat oxidation is sufficient, when combined with a diet inadequate in polyunsaturated fat, to result in essential fatty acid deficiency. Administering essential fat (Intralipid® 10% contains 43 Gm. of linoleic acid and 6.5 Gm. linolenic acid per liter) to our patients who had been maintained on carbohydrate-rich, fat-free, parenteral feedings resulted in return of the red cell membrane fatty acids to normal. That the lipid emulsion played a specific role in correcting the fatty acid deficiency is seen in the patient who received an isocaloric but fat-free intravenous diet and failed to correct the essential fat deficiency, which persisted for 2 months. Finally, in the patient in which total intravenous support is unnecessary, a diet high in calories containing polyunsaturated fatty acids should correct the characteristics of the essential fatty acid denficiency, as illustrated by the patient who responded to appropriate oral therapy.

Associated with the decrease in the polyunsaturated fatty acid is an increase in saturated acids to abnormally elevated levels. In addition, abncrmal fatty acids appear and one component to which significance is attached is 5-8-11 eicosatrienoate (20:3n9), which is absent from most normal tissues.[7] During deficiency states, this abnormal oleate-derived acid appeared in three out of the four deficient patients examined, and in severe deficiency may account for the major proportion of all polyunsaturated lipid. The contribution of previous dietary history to red cell lipid abnormalities, though difficult to assess, may be an important contribution in the development of this deficiency state. Although all five patients appeared to be in good health prior to injury, two individuals reported a high consumption of alcohol. Chronic alcholism may progress to a condition of plasma hyperlipidemia, with an increase of both cholesterol and phospholipid fractions of red cell membrane in chronic alcoholics.[17] While our findings are not entirely compatible with this state, it seems unreasonable to assume that the major disproportions of saturated and unsaturated fatty acids observed in patient number 4 on the second postburn day are simply a result of his thermal injury. It therefore appears that the patient susceptible to fatty acid deficiency is the one who has a previous dietary history of low essential fatty acid intake with marginal stores of polyunsaturated fat, is then maintained on a fat-free diet, and has increased essential fatty acid needs as a result of the stress of injury or the need for body repair or growth.

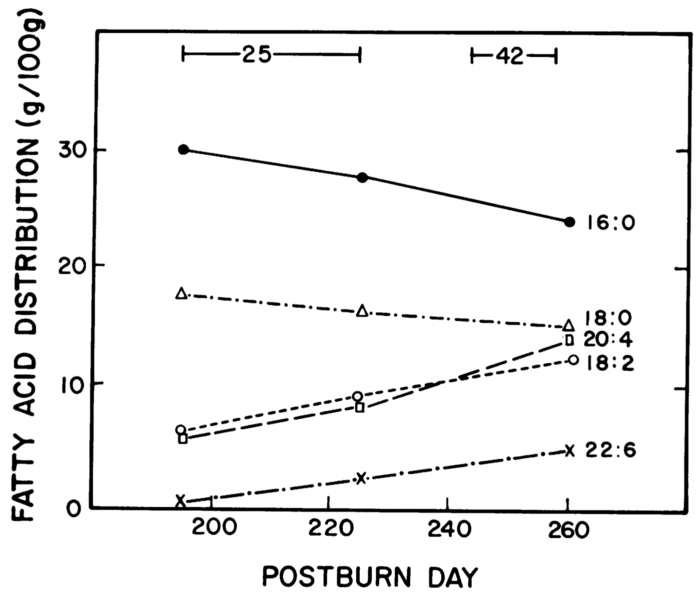

FIG. 5. Gradual correction of the polyunsaturated fatty acid deficiency was accompanied by return to normal of the unsaturated fats (16:0, 18:0) with the inclusion of intravenous soy bean emulsion in the diet of this 19-year-old man with a 75% total body surface burn.

The observed essential fatty acid denficiency may influence the response to the stress of thermal injury. Fat is an essential component of cell membranes and the proportions of saturated to polyunsaturated fat determine membrane fluidity and, hence, effect transport of water, ions, and other essential nutrients through cell wall and mitochondrial membranes. These observations of altered phospholipid and fatty acid com-

TABLE 8. *Dietary Support and Metabolic Response*

Patient	PBD* Diet Started	No. Days Studied	10% Fat Emulsion: Total Dose (Liters)	10% Fat Emulsion: Av. Daily Caloric Contribution Kcal/Day	Other Nutrient Support (Exclusive of Fat): Enteral Feedings Total Kcal/Day	Enteral Feedings N (Gm./Day)	Parenteral Feedings Kcal/Day	Parenteral Feedings N (Gm./Day)	Total Nutritional Intake Kcal/Day	Total Nutritional Intake N (Gm./Day)	Urinary Excretion of Nitrogen Gm./Day	Weight Change Kg./Day
1	41	26	38.0	1650	0	0	1566	17.0**	3216	17.0	21.7	+0.076
2	74	14	19.5	1532	1831	11.9	455	8.3	3818	20.2	10.7	+0.206
3	245	14	11.5	904	3682	22.8	265	8.7	4851	31.4	10.6	+0.129
4	18	10	9.5	1045	1424	11.9	1226	2.2	3695	14.1	10.3	+0.030
5	15	7	10.5	1650	2041	11.6	0	0	3541	11.6	10.6	+0.171
6	30	14	16.8	1320	0	0	1200	16.3	2928	16.3	13.2	+0.280
7	10	12	20.0	1833	0	0	2136	15.9	3969	15.9	29.6	—
8	12	5	7.5	1600	1632	13.0	690	9.6	3922	22.6	20.9	—
9	31	16	18.5	1217	0	0	1295	13.9**	2860	13.9	14.3	0.00
10	89	46	70.0	1711	1957	13.2	1234	15.6**	4902	28.8	21.3	+0.152

* PBD—Postburn day.
** Albumin administered but not included in nitrogen intake.

position of the red cell membrane are similar to those described for a wide variety of red cell disorders.[11] Reduced linoleate levels are associated with hereditary spherocytosis, leptocytosis, certain acquired hemolytic anemias, and acanthocytosis. Investigation into these disease states has resulted in a definition of altered physiology assocaited with the biochemical derangement of the red cell membrane. Altered osmotic fragility, abnormal sodium and potassium transport, and a decreased cellular half life, have all been associated with similar membrane alterations described in other disease states.[13] Our preliminary evidence suggests similar correlation between specific lipid abnormalities and functional changes of the red cell membrane in these patients, and further investigations are continuing in this area.

The specific role of fat on protein metabolism must be defined, for fat administered to fasting man may prevent weight loss but apparently has little effect on protein catabolism. Monroe,[10] in an extensive and thorough review of interaction between carbohydrate and fat calories in the diet, points out that an essential amount of dietary carbohydrate is required for nitrogen sparing, but, over and above this quantity, fat and carbohydrate can be interchanged to provide additional calories with similar effects on metabolism. Fat emulsions provide an isotonic high-caloric fuel source which seems ideal for the burn patient, who requires additional solute-free water because of the marked increase in evaporative water loss from the damaged integument and needs caloric support because of the hypermetabolism associated with thermal injury. Glucose and amino acids can be constituted as 10–14% solutions and delivered simultaneously with the fat emulsion by peripheral vein. Using fat emulsion combined with other feeding technics, nitrogen equilibrium was achieved in these patients with the administration of approximately 15 Gm. nitrogen/m^2/24 hours and 2,000–2,200 cal/m^2/day, an estimate comparable to the nitrogen and caloric requirements previously determined at this Institute.[14]

Side effects in noninjured patients have frequently been related to the increased plasma lipid that occurs following fat infusion, and accelerated lipid clearance following trauma may account for the relative safety of the fat emulsion following injury. Most of these studies were performed in previously healthy young individuals and specific guidelines for use of the emulsion in the noninjured patient during states of resting starvation and in patients with metabolic derangements of fat and carbohydrate metabolism remain to be defined. However, in burn patients, the intravenous fat emulsion provided a ready caloric source with minimal hazard and could be used to supplement other feeding technics.

Summary

Single unit infusions of a 10% soy bean emulsion (Intralipid) were evaluated in convalescing men and hypermetabolic thermally-injured patients. No significant thermogenic responses to the emulsions occurred in either group. Vital signs, CBC, and liver function studies remained unchanged. Fat clearance curves demonstrated an accelerated plasma disappearance of the emulsion in the acutely burned patients. ^{133}Xenon perfusion-diffusion studies were normal, and pulmonary diffusion capacity, using the carbon monoxide rebreathing technic, was also normal following the infusion. Blood gas levels did not change following infusion of single or multiple units of Intralipid.

An essential fatty acid deficiency of the red cell membrane was identified in five patients, with a marked decrease in linoleate, arachidonic, decosahexanoic acids, all members of the polyunsaturated fatty acid series which cannot be synthesized *de novo.* All patients had extensive burns, and most were on long term, fat free, parenteral diets before this essential fatty acid deficiency occurred. Infusing quantities of soy bean emulsion high in polyunsaturated fatty acids corrected the fatty acid deficiency in the red cell membranes. Administering an isocaloric fat-free diet to an individual for 2 months resulted in weight gain and wound healing but failed to correct the compositional fatty acid deficiency. Thus, the fatty acid deficiency in red cell membranes appears to be a combination of the stress of thermal injury and nutritional inadequacies, and can be successfully treated by the inclusion of polyunsaturated fatty acids in the diet.

Finally, fat emulsion was administered, along with other caloric support, to 10 critically injured individuals. The fat appeared to be utilized without complication, and the fat emulsion contributed 38% of the total caloric intake in this group of patients. The nitrogen and caloric support of these patients resulted in protein sparing in all, as manifested by varying degrees of nitrogen retention related to both extent of injury and the degree of nutritional support. The availability of this emulsion as an isotonic, high caloric, noncarbohydrate, energy source increases the flexibility of the surgeon's repertoire for nutritional support in the severely injured patient.

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Discussion

Dr. John M. Kinney (New York City): I think we are indebted to Dr. Wilmore and his associates for a contribution which is of both practical and immediate significance because surely fat emulsions will become commercially available soon and also for some potential questions which may open new avenues of therapy for the future.