Metabolic Utilization of Intravenous Fat Emulsion During Total Parenteral Nutrition

JORGEN NORDENSTRÖM, M.D., YVON A. CARPENTIER, M.D., JEFFREY ASKANAZI, M.D., ARNOLD P. ROBIN, M.D., DAVID H. ELWYN, PH.D., TERRY W. HENSLE, M.D., JOHN M. KINNEY, M.D.

The effect of nutritional therapy on the utilization of an intravenous fat emulsion was studied in patients with injury, infection, and nutritional depletion using 1-^{14}C-trioleate labeled Intralipid. The plasma fractional removal rate and ^{14}C-Intralipid oxidation rate was 55% and 25% higher, respectively, in patients following trauma and during periods of infection receiving 5% dextrose than in healthy control subjects. Total parenteral nutrition (TPN) was administered as either 1) nonprotein calories given as glucose (Glucose System) or 2) equal proportions of glucose and intravenous fat emulsion (Lipid System). In comparison to TPN with the Lipid System, administration using the Glucose System resulted in higher plasma clearance rates and lower oxidation rates in both acutely ill and depleted patients. There was no correlation between the rates of plasma removal and oxidation of the intravenous fat emulsion ($r = -0.04$; NS) indicating that the removal of exogenous fat from plasma cannot be used as an indicator of oxidation. A negative linear relationship was seen between the oxidation rate of intravenous fat and carbohydrate intake ($r = -0.92$; $p < 0.001$). Glucose intakes exceeding energy expenditure did not totally inhibit oxidation of the fat emulsion. The oxidation rate of ^{14}C-Intralipid was linearly related to net whole body fat oxidation calculated using indirect calorimetry ($r = -0.90$; $p < 0.001$) suggesting that the fat emulsion was oxidized in a similar manner to endogenous lipids.

This study suggests that intravenous fat emulsions are utilized as an energy substrate in patients with major injury, infection or nutritional depletion. This observation, along with a relative unresponsiveness to glucose in surgical patients suggests that fat emulsions may be useful as a calorie source in patients receiving parenteral nutrition.

From the Departments of Surgery, Anesthesiology, and Urology, Columbia–Presbyterian Medical Center, New York, New York

THE NONPROTEIN CALORIES of total parenteral nutrition (TPN) may be given as hypertonic glucose solution or as a combination of intravenous fat emulsion and glucose. Artificial fat emulsions have the advantage of a high caloric content and osmolarity near that of plasma, which can obviate the need for central venous catherization. Furthermore, substitution of part of the glucose calories with intravenous fat may reduce undesirable effects that are sometimes seen with hypertonic glucose such as hypoglycemia and hyperglycemia, excessive CO_2 production[1,2] and increased urinary excretion of norepinephrine.[32]

The soybean-based fat emulsion Intralipid is widely used as a source of essential fatty acids for patients who require parenteral nutrition and can also be used as a major calorie source. Intralipid resembles natural chylomicrons with respect to droplet size,[22] plasma removal kinetics,[21] and interaction with the enzyme lipoprotein lipase.[4] To characterize the kinetics of plasma removal of Intralipid an intravenous fat tolerance test (IVFTT) has been introduced.[5] Studies using the IVFTT have shown that subjects in the postoperative and fasted state have an increased clearance rate of fat emulsion from plasma.[21] Studies using the IVFTT have shown that subjects in the postoperative and fasted state have an increased clearance rate of fat emulsion from plasma.[21] However, clearance from plasma does not necessarily indicate that the fat emulsion is being utilized to meet energy requirements, since clearance from plasma may indicate storage rather than oxidation of the fat emulsion.

Indications of metabolic utilization of fat emulsions have, however, been provided by indirect calorimetry and nitrogen balance studies. Increases in oxygen consumption and decreases in respiratory quotient have been observed during Intralipid infusion,[13,34] indicating that the administered fat actually was oxidized. Nitrogen balance studies have shown that intravenous fat emulsion may have a protein-sparing effect similar to glucose in depleted[13,23] or postoperative patients.[3] Ni-

Presented in part at the 65th Clinical Congress of American College of Surgeons, Chicago, Il, October 1979

Supported in part by Public Health Service Grant No. GM 14546 and the U.S. Army Contract No. DA49-193-MD-2552.

Reprint requests: John M. Kinney, M.D., Professor of Surgery, Columbia University, College of Physicians and Surgeons, 630 West 168th St., New York, New York 10032.

The 1-^{14}C-trioleate Intralipid 10% was manufactured and kindly supplied by Dr. Ivan Håkansson, Vitrum AB, Stockholm, Sweden.

Submitted for publication January 25, 1982.

0003-4932/82/0800/0221 $01.35 © J. B. Lippincott Company

TABLE 1. *Injured and Infected Patients*

Patient No.	Sex/Age	Weight (kg)	Weight Loss (%)	Clinical Condition	Resting Energy Expenditure (kcal·kg^{-1}·day)	Resting Energy Expenditure (% of predicted)	Diet
1	M/59	84.0		Cystectomy	21.4	93	D*
2	M/46	52.7	15	Pancreatitis, intra-abdominal abscess	25.5	94	D
3	M/50	85.0		Leg, pelvic and lumbar fractures	29.6	133	D
4	M/78	85.0		Multiple long-bone & pelvic fractures	21.2	97	D
5	F/50	49.0		Cystectomy	35.1	117	D
6	M/31	69.0		Abdominal gunshot wounds; nephrectomy	28.7	113	D
7	M/54	78.0		Abdominal gunshot wounds; liver rupture	27.2	118	D
8	M/27	98.0		Abdominal gunshot wounds; intestinal resection	25.7	113	D
9	F/59	45.5	17	Abdominal abcess	29.4	104	D, L†
10	M/66	72.5	14	Pancreatic abscess, sepsis	25.1	108	D, G‡§
11	F/59	57.1	10	Pancreatectomy, sepsis	25.2	100	D, G
12	M/59	46.8	29	Intestinal resection, sepsis	28.1	94	L, L
13	M/61	86.9		Cystectomy	29.0	144	L
14	M/18	73.4	5	Abdominal gunshot wounds	29.8	108	L
15	M/69	88.8		Cystectomy	21.4	101	L
16	M/45	58.8	10	Gunshot & stabwounds, sepsis	27.1	97	L, G
17	M/47	51.0		Cystectomy	24.1	85	G
18	M/67	83.6		Cystectomy	22.2	101	G
19	M/29	95.5		Multiple long-bone fractures	23.1	109	G
20	M/76	47.0	34	Intestinal resection, colon carcinoma	26.4	92	G
Mean ± SEM:	53 ± 4	70.4 ± 4.0	7 ± 2		26.3 ± 0.8	106 ± 3	

* D = 5% dextrose.
† L = TPN, Lipid System.
‡ G = TPN, Glucose System.
§ Studies were performed during administration of TPN formulas in the order listed.

trogen balance studies and indirect calorimetry data strongly indicate that intravenous fat emulsions are metabolically utilized. However, little information is available regarding the rate of oxidation and how the simultaneous infusion of other nutrients influences utilization of intravenous fat.

Direct evidence of oxidation may be obtained by use of radioactive labeled fat emulsions. We have used Intralipid labeled with ^{14}C-trioleate to determine rates of plasma clearance and oxidation in patients with major injury, infection and nutritional depletion. Studies were performed during infusion of 5% dextrose solution and during administration of TPN while the nonprotein calories were given entirely as glucose (Glucose System) or as approximately equal parts of glucose and fat (Lipid System).

Materials and Methods

Patients

Twenty patients with major trauma or evidence of clinical infection, six patients with nutritional depletion, and four healthy subjects were admitted to the study. Demographic parameters, clinical condition, resting energy expenditure (REE), and nutritional intake are shown in Tables 1 and 2. There was no significant weight loss in the patients with major injury except for patient no. 20 (Table 1). The patients studied during periods of infection had a significant weight loss (10–20%) before study. The mean REE was 6% above predicted in the combined traumatized/infected group. All of the depleted patients had a history of substantial weight loss (14–59%) with a REE that averaged 14%

TABLE 2. *Depleted Patients*

Patient No.	Sex/Age	Weight (kg)	Weight Loss (%)	Clinical Condition	Resting Energy Expenditure (kcal·kg^{-1}·day)	Resting Energy Expenditure (% of predicted)	Diet
1	F/67	38.8	26	Intestinal obstruction, radiation ileitis	20.9	71	G*
2	M/47	55.4	14	Chronic subileus	31.6	111	G
3	M/52	49.5	59	Duodenal stenosis, post gastrectomy syndrome	27.7	88	G, L†, G, G‡
4	F/52	39.1	25	Oesophageal stenosis	26.5	87	L, G
5	M/79	47.3	37	Intestinal obstruction	22.6	80	L, G
6	M/48	55.0	14	Oesophageal stricture	25.0	81	L, G, L
Mean ± SEM	58 ± 5	47.5 ± 3.0	29 ± 7		25.7 ± 1.6	86 ± 5	

* G = TPN, Glucose System.
† L = TPN, Lipid System.
‡ Studies were performed during administration of TPN formulas in the order listed.

below predicted values (Table 2). Four normal male subjects (age 54 ± 7 (SEM); weight 85.0 ± 3.6 kg) were studied in the postabsorptive state to obtain control data.

Protocol

Upon admission to the study, patients received an infusion of 5% dextrose solution. Daily measurements of O_2 consumption, CO_2 production, and nitrogen balance were instituted (see below). REE was calculated from measurements of gas exchange and N excretion using principles of indirect calorimetry. An intravenous fat tolerance test using labeled Intralipid (^{14}C-IVFTT) was performed during administration of 5% dextrose in 11 traumatized/infected patients. The initial ^{14}C-IVFTT in the patients with major trauma was performed within 1 to 2 days of the actual injury. In these patients it was felt that the resumption of oral intake would not occur in the first week and infusion of TPN was instituted on the second day following the injury. The patients considered to be infected had a temperature above 102°F, and either clinical evidence of localized infection or a positive blood culture. Following administration of the assigned nutritional regimen for a 4 to 6-day period, a repeat ^{14}C-IVFTT was performed on 14 occasions (seven during each nutritional regimen). The studies actually performed on each individual are shown in Table 1.

In the patients with nutritional depletion studies were continued for up to 4 weeks. Each ^{14}C-IVFTT was performed after 7 days of administration of the assigned dietary regimen. Eight studies were performed during administration of the Glucose System and five studies during administration of the Lipid System. The normal subjects were studied in the postabsorptive state.

The protocol of this study has been approved by the Institutional Review Board, Health Science Center, Columbia University. Written informed consent was obtained following explanation of the risks and benefits involved.

During the period of administration of 5% dextrose solution, energy intake averaged approximately 5 kcal·Kg^{-1}·day^{-1}. The energy and nitrogen content of the subsequently infused TPN formula was calculated on the basis of the REE of the patient measured during the administration of 5% dextrose. Two different TPN formulas were administered: the Glucose and Lipid System. With the Glucose System, all of the nonprotein calories were given as hypocaloric glucose solution. For the Lipid System, approximately half of the nonprotein calories were supplied by the triglyceride fraction of Intralipid 10% (Cutter, California), the rest being supplied by hypertonic glucose and the glycerol fraction of fat emulsion. Amino acids are given as Aminosyn 10%. Energy intake in the traumatized/infected group averaged 1.44 ± 0.05 (SEM) times the measured REE, while daily nitrogen intake averaged 19.2 ± 0.9 g. During administration of the Lipid System, the traumatized/infected patients received 47 ± 2% of the nonprotein calories as fat. The depleted patients received an energy intake of 1.61 ± 0.09 times REE. Daily nitrogen intake averaged 19.6 ± 0.9 g with both diets. Fat constituted 46 ± 1% of nonprotein calories during TPN with the Lipid System in the depleted patients. During administration of the Glucose System, essential fatty acids were supplied by a daily massage with one tablespoon of corn oil.[10] Appropriate quantities of vitamins, minerals, and trace elements were added. There was no oral intake other than trace elements and water. The

amino acids and glucose solutions were administered at a constant rate during the 24-hour period. Fat emulsions were infused in the late afternoon over a 6- to 8-hour period.

Measurements

Oxygen consumption and carbon dioxide production were measured using a rigid lucite head canopy system previously described.[25,39] Measurements were performed 4 to 6 times each for 30 to 40 minutes, evenly spaced throughout the day. Resting energy expenditure and rates of substrate oxidation were calculated by standard procedures.[12,41] Predicted normal values for REE were obtained by adding 10% to the values obtained from conventional tables of basal metabolic rate.[16]

The determination of nitrogen balance has been previously described in detail[10] and is briefly summarized. All intake, whether oral or infused, was measured by difference in weight of full and emptied containers. The amount of each constituent (H_2O, N, etc.) was calculated from the composition obtained from the manufacturer's specifications or by direct analysis in this laboratory, according to established procedures.[33] Energy contents of diets were calculated from published values.[29] Urine, feces, and drainages were collected and analyzed for total nitrogen. In addition, urea was determined in urine and drainage, creatinine was determined in urine, and glucose was determined in those urine samples in which qualitative tests (Ketodiastix®, Ames Co., Elkhart, Indiana) were positive. A manual, micro-Kjeldahl procedure was used for digesting samples for total nitrogen determination.

Plasma free fatty acid (FFA) concentration was measured according to Dole and Meinertz.[9] The radioactivity in unesterified fatty acids (^{14}C-FFA) was measured by counting of the aqueous phase of Dole extract suitably washed in a Mark II scintillation counter (Nuclear Instruments, Chicago, Illinois). Plasma Triglyceride (TG) concentration was determined by an enzymatic method and radioactivity in total plasma lipids was measured by scintillation counting of a Folch extract.[17] Plasma glucose concentration was measured by an automated procedure (Glucose Analyzer, Beckman Instruments, Inc., Fullerton, California). Plasma insulin was measured by radioimmunoassay using Pharmacia Kits. Plasma glucagon was measured with a 30 K antibody.[15] Blood urea nitrogen was measured by an automated enzymatic procedure (BUN analyzer, Beckman Instruments, Inc., Fullerton, California).

Measurements of Rates of Plasma Removal and Oxidation of ^{14}C-Intralipid

Catheters were inserted into each antecubital vein: one for injection of the fat emulsion and the other for withdrawal of blood samples. Both were maintained for the duration of the study with isotonic saline. Baseline blood samples were obtained (at least 40 minutes after catheter placement) for determination of free fatty acids (FFA), glucose, triglycerides (TG), insulin, glucagon, blood urea nitrogen, and baseline radioactivity. A bolus dose of 1 ml per kg body weight of Intralipid 10%, containing 36 μCi of 1-^{14}C-trioleate labeled Intralipid, was injected over a 60-second period. Blood samples for the determination of FFA, TG, ^{14}C-FFA and ^{14}C-TG, were obtained at 2, 4, 6, 8, 12, 20, 40, and 60 minutes after the midpoint of the Intralipid infusion. Studies in patients receiving the Lipid system were performed before the daily administration of the unlabelled fat emulsion. Expired air was collected using the canopy system[25,39] which measures expired radioactivity as well as the total excretion of unlabelled CO_2. Expired air was collected for five to six periods averaging 30 to 40 minutes each, within the first 450 minutes following the injection.

The 1-^{14}C-Triolein labelled Intralipid was prepared by Vitrum AB (Stockholm, Sweden). The labelled triolein was added to the soy bean oil before incorporation into the fat emulsion. Specific activity was 4.0 μ Ci/100 mg triglyceride, with more than 99% of the radioactivity in the triglyceride fraction.

Plasma clearance of intravenous fat was determined by the rate of disappearance of radioactivity in plasma TG. The rate constant for the fractional removal of the injected isotopic triglyceride was calculated from the computed least squares regression line (Ln ^{14}C-TG *vs.* time).

The rate of oxidation of ^{14}C-Intralipid was calculated from the cumulative $^{14}CO_2$ production which was obtained by integration under the curve of expired radioactivity. This rate is expressed as the fraction of administered dose oxidized within 450 minutes (% · 450 min^{-1}).

Statistical Methods

Student's t test was used for the statistical analysis using the paired t test when applicable. Coefficients of correlation were determined by standard procedure.[38] Variance of the mean is expressed as the standard error of the mean (SEM).

Results

The results for the injured and infected patients were similar and, therefore, are presented together.

Plasma Clearance of Intralipid Fat Emulsion

The disappearance of plasma TG radioactivity was found to follow first order kinetics for the first 15 min-

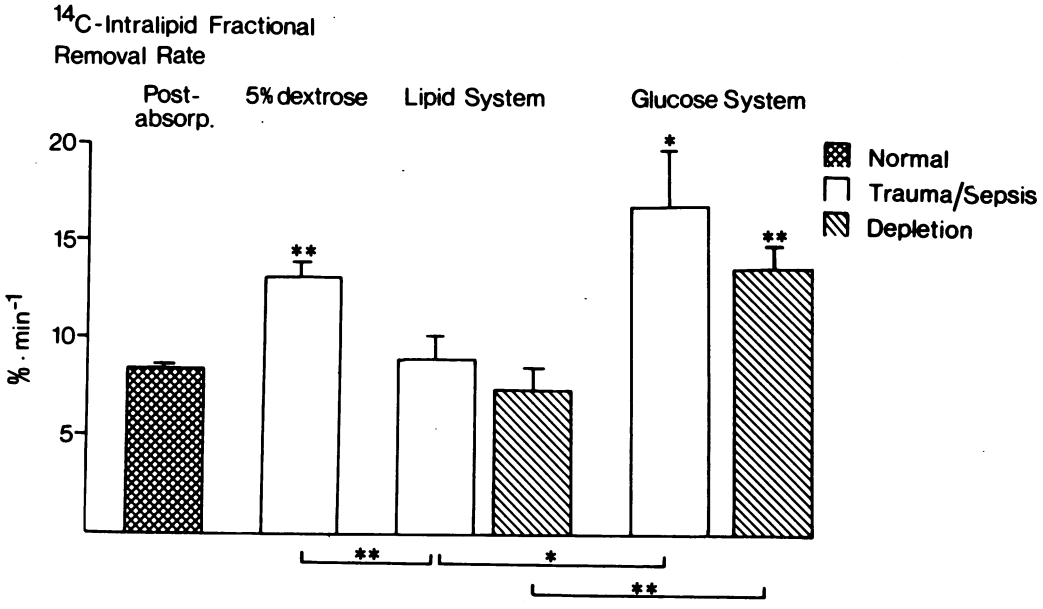

FIG. 1. Fractional removal rate of 1-^{14}C-triolate labelled Intralipid in healthy postabsorptive subjects, traumatized/infected patients receiving 5% dextrose or TPN and depleted patients receiving TPN. Asterisks above columns are for comparison with the normal postabsorptive value. Statistical significance: *$p < 0.05$, **$p < 0.01$.

utes following the infusion. Correlation coefficients ranged between 0.99 and 0.95 in all the cases included in the results. Two studies were excluded since technical problems precluded interpretation of curves based on first order kinetics model.

The mean fractional removal rate of ^{14}C-Intralipid for the traumatized/infected patients receiving 5% dextrose was significantly higher ($13.2 \pm \cdot 7\% \cdot min^{-1}$) than in the healthy subjects in the postabsorptive state ($8.5 \pm \cdot 0.1\% \cdot min^{-1}$; $p < 0.01$) (Fig. 1). Plasma fractional removal rates were higher in the traumatized/infected patients than in the depleted patients receiving the comparable TPN formula, but these differences were not statistically significant. In the traumatized and infected group of patients, administration of TPN with the Lipid System was associated with a significantly decreased plasma clearance of lipid as compared with clearance during administration of 5% dextrose or the Glucose based regimen (Table 3). An increased fractional removal rate was observed with the Glucose System as compared with 5% dextrose infusion, but the results were not significant. The higher fractional removal rate observed during TPN with the Glucose System as compared with the Lipid System was also observed in the depleted patients (Table 4). Figure 2a shows the rate of elimination of TG radioactivity in plasma for the depleted patients. In the depleted patients in whom the ^{14}C-IVFTT was performed during administration of both nutritional regimens, fractional removal rates were higher during administration of the Glucose System. From this figure it is also evident that the elimination of ^{14}C-Intralipid follows first order kinetics during the 15 minutes. An increase in TG radioactivity is seen in some cases thereafter, probably caused by the appearance of recycled ^{14}C-FFA in plasma TG. There was a statistically significant correlation between fractional

TABLE 3. *Effect of Total Parenteral Nutrition on Intralipid Metabolism, Plasma Substrate, and Hormone Concentration in Traumatized and Infected Patients*

	Before TPN (5% dextrose)	TPN, Lipid System	TPN, Glucose System
^{14}C-Intralipid fractional removal rate, % · min^{-1}	13.2 ± 0.7	9.0 ± 1.2**	16.9 ± 2.9†
^{14}C-Intralipid oxidation rate, % · 450 min^{-1}	37.0 ± 1.1	26.1 ± 2.4***	13.8 ± 2.0***;††
Carbohydrate intake kcal · kg^{-1} · day^{-1}	4.6 ± 0.8	17.2 ± 1.2***	28.8 ± 2.0***;†††
Glucose concentration mmol · l^{-1}	5.4 ± 0.3	8.6 ± 1.2*	10.6 ± 1.3**
Triglyceride concentration mmol · l^{-1}	0.94 ± 0.11	1.72 ± 0.45*	1.03 ± 0.20
Free fatty acid concentration μmol · l^{-1}	731 ± 63	464 ± 67*	356 ± 54***
Insulin concentration μU · ml^{-1}	6.9 ± 1.3	25.9 ± 5.8***	52.9 ± 10.8***
Glucagon concentration pg · ml^{-1}	226 ± 30	371 ± 115	283 ± 40

Mean values ± SEM

	$p < 0.05$	$p < 0.01$	$p < 0.001$
Before TPN vs During TPN:	*	**	***
Glucose System vs Lipid System:	†	††	†††

TABLE 4. *Intralipid Metabolism, Plasma Substrate, and Hormone Concentration During Total Parenteral Nutrition in Depleted Patients*

	TPN, Lipid System	TPN, Glucose System
^{14}C-Intralipid fractional removal rate % · min^{-1}	7.5 ± 1.1	13.8 ± 1.1††
^{14}C-Intralipid oxidation rate % · 450 min^{-1}	22.1 ± 2.8	9.1 ± 1.0†††
Carbohydrate intake kcal · kg^{-1} · day^{-1}	17.6 ± 1.9	30.8 ± 1.7††
Glucose concentration mmol · l^{-1}	6.5 ± 0.3	7.3 ± 0.7
Triglyceride concentration mmol · l^{-1}	0.28 ± 0.08	0.54 ± 0.17
Free fatty acid concentration μmol · l^{-1}	383 ± 57	332 ± 33
Insulin concentration μU · ml^{-1}	6.5 ± 1.4	19.0 ± 3.4†
Glucagon concentration pg · ml^{-1}	182 ± 27	182 ± 21

Mean values ± SEM	p < 0.05	p < 0.01	p < 0.001
Glucose System vs Lipid System	†	††	†††

removal rate and carbohydrate intake in the nutritionally depleted group of patients ($r = 0.74$, $p < 0.01$) but not in the traumatized/infected group of patients ($r = 0.25$, $p < 0.05$). Plasma clearance rate of ^{14}C-Intralipid did not correlate with glucose concentrations in either patient category.

Oxidation of ^{14}C-Intralipid

Radioactivity appeared in expired CO_2 within 20 minutes after administration of ^{14}C-Intralipid in all cases with a gradual rise in both $^{14}CO_2$ excretion and specific activity during the following 40 to 100 minutes. At 450 minutes excretion of $^{14}CO_2$ had decreased to 20% of the peak rate.

While receiving 5% dextrose, the patients with trauma or infection had significantly higher oxidation rates of ^{14}C-Intralipid (37.0 ± 1.1%) than healthy postabsorptive controls (29.5 ± 2.0% · 450 min^{-1}, $p < 0.01$). Changes in clearance and oxidation of the labelled fat emulsion responded in a qualitatively similar manner in both the trauma/septic and nutritionally depleted patients. However, quantitatively, the oxidation of ^{14}C-Intralipid tended to be lower on any given diet in the nutritionally depleted patients (Fig. 3). In all patients, the oxidation of intravenous fat was greater with the lipid than the Glucose System. Figure 2b shows the actual data for ^{14}C-Intralipid oxidation in nutritionally depleted patients. In all patients, a higher oxidation rate of intravenous fat was seen with the Lipid System than with the Glucose System. The oxidation of ^{14}C-Intra-

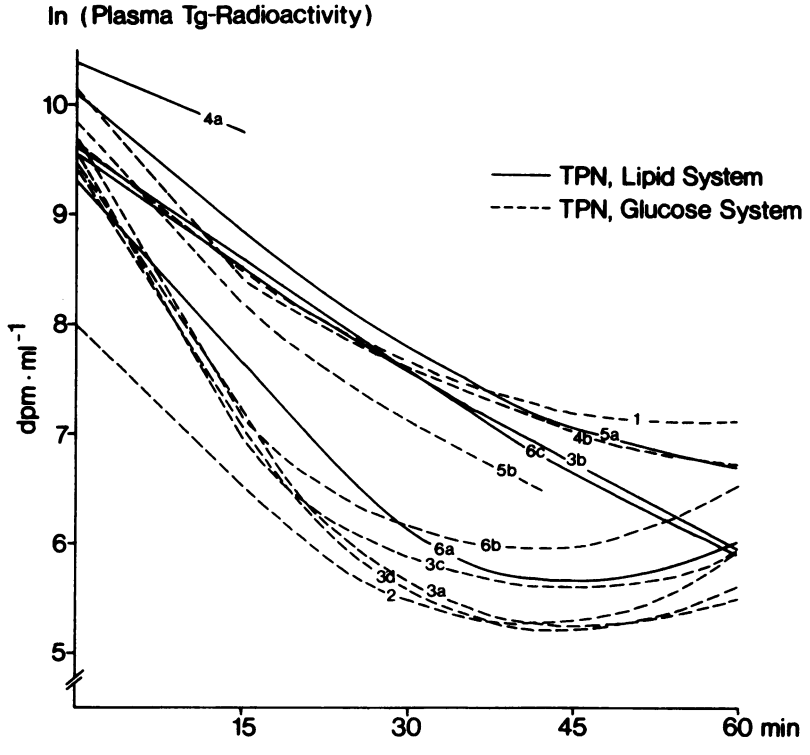

FIG. 2a. Plasma clearance of ^{14}C-Intralipid in depleted patients. The numbers in the figure correspond to the patients listed in Table 2. When some patients were studied more than once, small characters indicate the chronological order of the intravenous fat tolerance test.

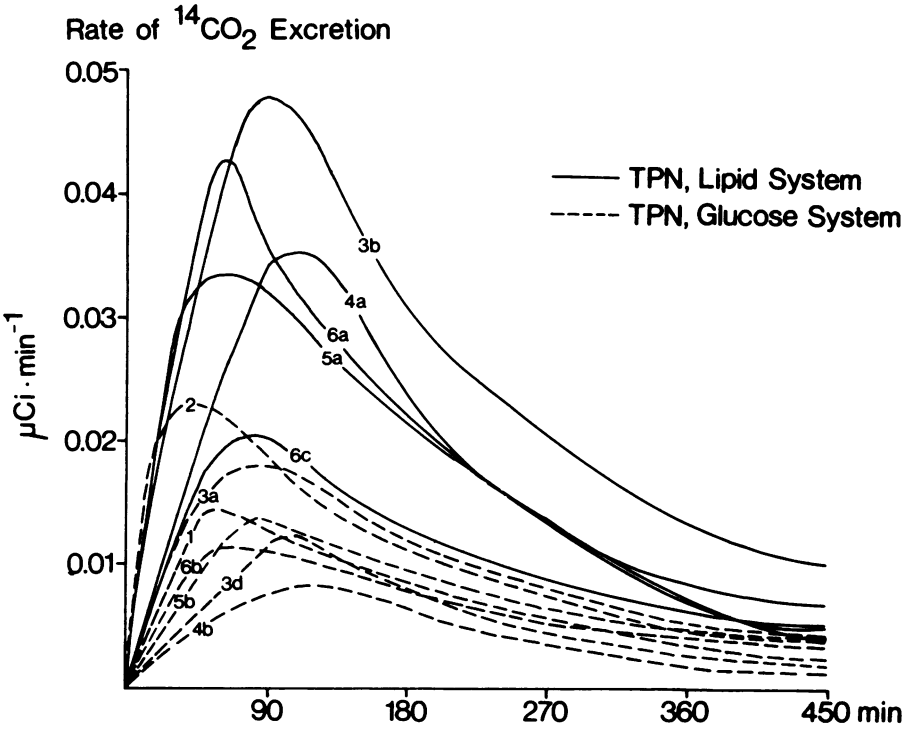

FIG. 2b. Oxidation rates of ^{14}C-Intralipid in depleted patients.

lipid was inversely related to carbohydrate intake but was never totally suppressed even when glucose calories were provided in excess of REE (Fig. 4). There was no correlation between oxidation and plasma clearance of exogenous fat (r = 0.04, NS).

Plasma Substrate and Hormone Concentrations

In traumatized and infected patients receiving 5% dextrose, concentrations of glucose and TG were in the upper normal range and FFA concentrations were mod-

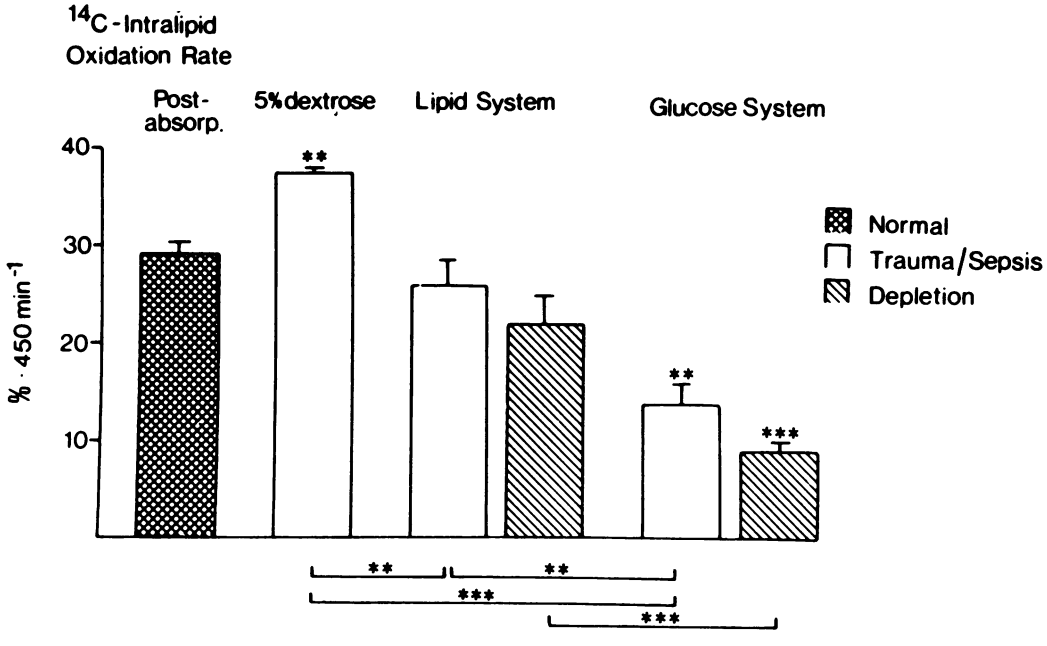

FIG. 3. Oxidation rates of 1-^{14}C-trioleate labelled Intralipid in healthy postabsorptive subjects, traumatized/infected patients receiving 5% dextrose and the effect of TPN in depleted as well as in traumatized patients. Mean values ± SEM. Statistical significance: **P < 0.01, ***P < 0.001.

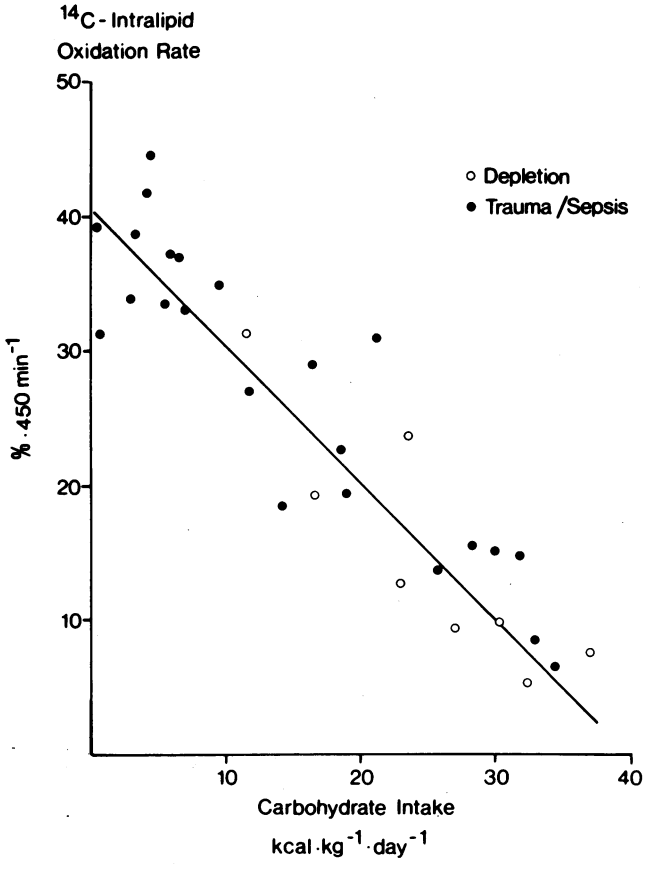

FIG. 4. Effect of carbohydrate intake on ^{14}C-Intralipid oxidation rate. $y = -0.955x + 40.5$; $n = 31$ $r = -0.92$; $p < 0.001$.

erately elevated (Table 3). Glucose levels increased significantly and FFA concentrations decreased during TPN. There was no significant difference in glucose, FFA, or TG levels between the two TPN diets in either group of patients (Tables 3 and 4). During administration of TPN, insulin levels rose significantly from the values observed during the administration of 5% dextrose solution. The highest concentration, as expected, were observed during administration of the Glucose System. Insulin concentration was closely correlated to carbohydrate intake both in the traumatized/septic ($r = 0.73$, $p < 0.01$) and in the depleted patients ($r = 0.64$, $p < 0.001$). However, the depleted patients had significantly lower insulin levels than the traumatized/infected patients both with the Lipid System ($p < 0.05$) and the Glucose System ($p < 0.001$). Furthermore plasma glucose, FFA and TG levels tended to be lower in the depleted patients than in the traumatized/infected patients despite comparable carbohydrate intakes. Glucagon concentration was more than twice normal during 5% dextrose infusion in the traumatized/infected group of patients as compared with reference values obtained in normal postabsorptive subjects,[15] and did not significantly change during TPN with either system (Table 3). The depleted patients also had substantially elevated glucagon levels during TPN as compared with normal postabsorptive patients with no change during administration of the two dietary regimens.

Effect of TPN on Substrate Oxidation as Measured by Indirect Calorimetry

With administration of TPN to the traumatized/infected patients, REE with the Lipid System increased

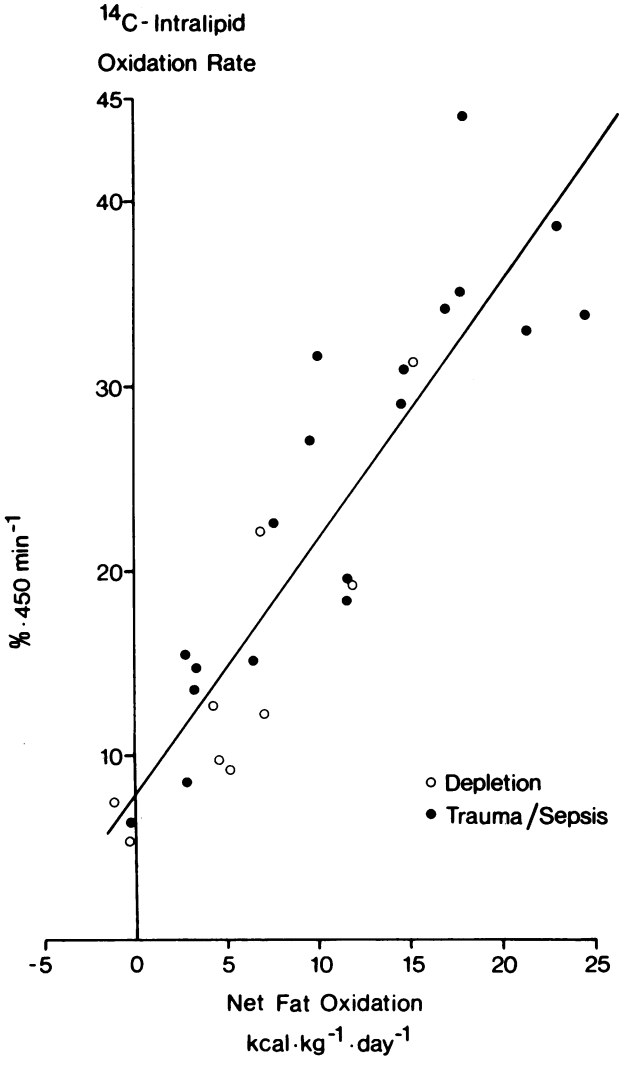

FIG. 5. Relationship between ^{14}C-Intralipid oxidation rate and net fat oxidation calculated by indirect calorimetry. Negative values for net fat oxidation are indicative of whole body net lipogenesis. $y = 1.39x + 7.96$, $n = 28$; $r = 0.90$; $p < 0.001$.

from 27.5 ± 1.3 to 29.4 ± 1.5 kcal · Kg^{-1} · day^{-1}, and from 24.4 ± 0.6 to 25.9 ± 0.8 ($p < 0.05$) with the glucose system. Net fat oxidation during 5% dextrose infusion was 20.2 ± 1.3 kcal · Kg^{-1} · day^{-1}, significantly higher than during TPN with the Lipid System (12.0 ± 0.8, $p < 0.001$), or with the Glucose System (3.7 ± 1.0, $p < 0.001$). Resting energy expenditure in the depleted patients averaged 26.0 ± 1.2 kcal · Kg^{-1} · day^{-1} during administration of the Lipid System and 29.2 ± 2.0 kcal · Kg^{-1} · day^{-1} during infusion of the Glucose System ($p < 0.05$). Net fat oxidation in the depleted patients was significantly higher ($p < 0.01$) with the Lipid System (11.2 ± kcal · Kg^{-1} · day) than with the Glucose System (2.7 ± 1.2). There was a close negative correlation between net fat oxidation and carbohydrate intake both in the traumatized/infected patients $r = -0.90$, $p < 0.001$) and in the nutritionally depleted patients $r = -0.94$, $p < 0.001$). Net fat oxidation was linearly correlated to plasma insulin levels in the traumatized/infected patients ($r = -0.79$, $p < 0.001$) but not in the depleted patients ($r = -0.35$, $p > 0.05$). A linear relationship for all patients was observed between Intralipid oxidation and net fat oxidation calculated by indirect calorimetry (Fig. 5).

Discussion

Plasma removal rate of intravenous fat was increased more than 50% in the traumatized and infected patients receiving hypocaloric dextrose infusions compared with normal postabsorptive patients. This increase in plasma clearance of fat emulsion after trauma is in agreement with the findings of Hallberg[21] and the authors' previous studies.[35] Plasma clearance of exogenous fat was also increased in the infected patients taken separately, and was not significantly different from that seen in the traumatized patients, in agreement with our previous findings.[35] It has been suggested that the hypertriglyceridemia associated with various infections may be secondary to a decreased removal of fat from the circulation.[20] Experimental sepsis following endotoxin administration has been shown to decrease postheparin plasma lipolytic activity and to impair plasma clearance of intravenous fat emulsion.[24] Recent studies have furthermore shown that septic patients have low lipoprotein lipase activity in muscle and adipose tissue.[36] The lipid clearance capacity of intravenous fat emulsion during infection is thus variable and may be related to differences in infection agent, stage, and severity of the disease, nutritional status of the host as well as differences between various species.

It has been suggested that the IVFTT may be a useful tool in such diseases as atherosclerosis, hypertriglyceridemia,[14] and diabetes.[26] However the IVFTT is of limited value in the study of energetics of lipid metabolism since it provides no information regarding the oxidation of intravenous fat emulsion. The use of a fat emulsion that has been radioactively labeled in its fatty acid moiety offers unique possibilities since final oxidation product, $^{14}CO_2$, may be determined. The present study shows that $^{14}CO_2$ appears within a few minutes after the injection of ^{14}C-Intralipid indicating that this fat emulsion is readily used as an energy substrate. Mean oxidation rate of ^{14}C-Intralipid after trauma and during infection was approximately 25% higher than in healthy control subjects. Thus, trauma and infection may not only be associated with an accelerated plasma clearance but also an increased oxidation of intravenous fat emulsion.

During TPN, intravenous fat emulsion may be infused together with glucose and amino acids in order to reduce complications caused by high osmolarity of the latter two solutions. Little information is available, however, concerning the influence of the simultaneous infusion of other nutrients in the metabolism of intravenous fat emulsions during TPN. In the present study, patients receiving TPN with the Glucose System had higher plasma clearance rates of intravenous fat than had the healthy postabsorptive subjects. Studies by others have shown that healthy subjects also have increased plasma removal of intravenous fat emulsion during glucose absorption.[30] During TPN with the Lipid System, rates of fat emulsion were of similar magnitude as in the healthy postabsorptive controls (Fig. 1).

For all patients, a close negative correlation was seen between intravenous fat oxidation and carbohydrate intake (Fig. 4). In normals glucose and insulin effectively decrease the the oxidation of chylomicrons[18] and circulating plasma FFA.[19] Previous studies from this laboratory have shown that traumatized and infected patients have a continued oxidation of plasma FAA and whole body net fat oxidation despite the administration of glucose above energy requirements.[1,31] In the present study, oxidation of intravenous fat was also not entirely suppressed despite the administration of carbohydrate calories in excess of REE. Three patients receiving TPN with the Glucose System continued to oxidize ^{14}C-Intralipid despite a net fat synthesis (indicated by negative values for net fat oxidation) (Fig. 5).

The observation that TPN with the glucose System increased the clearance of Intralipid but decreased oxidation indicates that the fat emulsion was removed from the circulation predominately for storage. The rate-determining enzyme for the clearance of fat emulsions as well as chylomicrons and very low density lipoproteins is lipoprotein lipase located at the luminal

surface of the capillary endothelium of most extrahepatic tissues.[6] The activity of lipoprotein lipase is increased in adipose tissue related to muscle in the absorptive state, whereas the opposite effects are seen during conditions of negative energy balance.[6,40] In the postabsorptive state, Intralipid particles are predominantly removed by skeletal muscle and only to a minor extent by subcutaneous adipose tissue.[37] The administration of TPN to both postoperative and depleted patients induces a pronounced increase in adipose tissue lipoprotein lipase with little or no change in skeletal muscle lipoprotein lipase activity.[42] Our finding that the Glucose System is associated with increased plasma clearance of Intralipid may therefore be explained by an increased adipose tissue lipoprotein lipase activity. Together with such increased removal of Intralipid by adipose tissue during glucose infusion, a secondary decrease in oxidation would also be expected because of increased storage of triglyceride in muscle which provides substrate for oxidation in the future. Thus, during administration of hypertonic glucose the removal of circulating lipids may be shifted from removal by skeletal muscle (for oxidation) to removal by adipose tissue (for storage).

It has often been questioned whether the fate of exogenous fat emulsions after clearance from plasma is the same as for endogenously synthesized chylomicrons. In the present study there is a very close correlation between rates of oxidation of labelled Intralipid and whole body fat over a wide range of values and conditions. This indicates that exogenous fat emulsions are handled[15] in the same way after clearance from plasma as are endogenous fat stores and chylomicrons. Depleted as well as acutely ill patients have a metabolic status, directed toward the mobilization and oxidation of endogenous lipid stores.[1,31] Traumatized and infected patients furthermore display a relative unresponsiveness to glucose with respect to net fat oxidation,[1] plasma FFA turnover and oxidation,[31] and continued gluconeogenesis.[11] As shown in this study, intravenous fat emulsion is readily utilized and oxidized similarly to endogenous lipids. This observation, together with a relative glucose intolerance, suggests that a balanced intravenous nutritional support of glucose, exogenous fat, and amino acids may be a preferable approach for surgical patients in need of TPN.

References

1. Askanazi J, Carpentier YA, Elwyn DH, et al. Influence of total parenteral nutrition on fuel utilization in injury and sepsis. Ann Surg 1980; 191:40.
2. Askanazi J, Elwyn DH, Silverberg PA, et al. Respiratory distress secondary to a high carbohydrate load: a case report. Surgery 1980; 87:596.
3. Bark S, Holm I, Håkansson I, Wretlind A. Nitrogen sparing effect of fat emulsion compared with glucose in the postoperative period. Acta Chir Scand 1976; 142:423.
4. Boberg J, Carlson LA. Determination of heparin-induced lipoprotein lipase activity in human plasma. Clin Chim Acta 1964; 10:420.
5. Boberg J, Carlson LA, Hallberg D. Application of a new intravenous fat tolerance test in the study of hypertriglyceridemia in man. J Atheroscler Res 1969; 9:159.
6. Borensztajn J. Lipoprotein lipase. In: Scanu AM, Wissler RW, Getz GS, eds. The Biochemistry of Atherosclerosis. New York: Marcel Dekker, 1979; 321.
7. Brennan MF, Moore FD. An intravenous fat emulsion as a nitrogen sparer: comparison with glucose. J. Surg Res 1973; 14:501.
8. Bucola G, David H. Quantitative determination of serum triglycerides by use of enzymes. Clin Chem 1973; 19:476.
9. Dole VP, Meinertz H. Microdetermination of long-chain fatty acids in plasma and tissues. J Biol Chem 1960; 235:2595.
10. Elwyn DH, Gump FE, Munro HN, et al. Changes in nitrogen balance of depleted patients with increasing infusions of glucose. Am J Clin Nutr 1979; 32:1597.
11. Elwyn DH, Kinney JM, Jeevanandam M, et al. Influence of increasing carbohydrate intake on glucose kinetics in injured patients. Ann Surg 1979; 190:117.
12. Elwyn DH, Kinney JM. A unique approach to measuring total energy expenditure by indirect calometry. In Kinney JM, ed. Assessment of energy metabolism in health and disease. Report of the first Ross Conference on Medical Research, Columbus, Ohio, Ross Laboratories. 1980; 54.
13. Elwyn DH, Kinney JM, Gump FE, et al. Some metabolic effects of fat infusions in depleted patients. Metabolism 1980; 29:125.
14. Ericsson M, Rossner S. Correlation between intravenous fat tolarance and serum lipoproteins in normal and atherosclerotic subjects. Atherosclerosis 1979; 33:89.
15. Faloona GR, Unger RH. Radioimunassay methods. New York: Academic Press, 1974; 317.
16. Fleisch A. LE metabolism basal standard et sa détermination au moyen du "Metabolcalculator". Helv Med Acta 1951; 18:23.
17. Folch J, Lees M, Stanley GHS. A simple method for the isolation and purification of total lipides from animal tissue. J Biol Chem 1957; 226:497.
18. Fredrickson DS, McCollester DL, Ono K. Role of unesterified fatty acid transport in chylomicron metabolism. J Clin Invest 1958; 37:1333.
19. Frederickson DS, Gordon RS, Jr. The metabolism of albumin-bound C14-labeled unesterified fatty acids in normal human subjects. J Clin Invest 1958; 37:1504.
20. Gallin JI, Kay D, O'Leary WM. Serum lipids in infection. N Engl J Med 1969; 281:1081.
21. Hallberg D. Studies on the elimination of exogenous lipids from the blood stream. Acta Physiol Scand 1964; 62:407.
22. Hallberg D, Wersall J. The electron-microscopic investigation of chylomicrons and fat emulsions for intravenous use. Acta Chir Scand Suppl 1964; 325:23.
23. Jeejeebhoy KN, Anderson GH, Nakhooda AF, et al. Metabolic studies in total parenteral nutrition with lipid in man. Comparison with glucose. J Clin Invest 1976; 57:125.
24. Kaufmann RL, Matson CF, Rowberg AH, Beisel WR. Defective lipid disposal mechanisms during bacterial infection in rhesus monkeys. Metabolism 1976; 25:615.
25. Kinney JM, Morgan AP, Domingues FJ, Guildner KJ. A method for continuous measurement of gas exchange and expired radioactivity in acutely ill patients. Metabolism 1964; 13:205.
26. Lewis B, Mancini M, Mattock AP, et al. Plasma triglyceride and fatty acid metabolism in diabetes mellitus. Eur J Clin Invest 1972; 2:445.
27. Long JM, Wilmore DW, Mason AD Jr, Pruitt BA Jr. Effects of carbohydrate and fat intake on nitrogen excretion total intravenous feeding. Ann Surg 1977; 185:417.
28. Macfie J, Smith RC, Hill GL. Glucose of fat as a nonprotein energy source. Gastroenterology 1981; 80:103.
29. Merrill AL, Watt BK. Energy value of foods. Agriculture Hand-

book, no. 74, March 1955. Washington DC: United States Government Printing Office.
30. Nestel PJ, Barter PJ. Triglyceride clearance during diets rich in carbohydrate or fats. Am J Clin Nutr 1973; 26:241.
31. Nordenstrom J, Carpentier YA, Askanazi J, et al. Turnover and oxidation of free fatty acids during total parenteral nutrition (abstr). J Parent Ent Nutr 1980; 4:427.
32. Nordenstrom J, Jeevanandam M, Elwyn DH, et al. Increasing glucose intake during total parenteral nutrition increases norepinephrine excretion in trauma and sepsis. Clin Physiol 1981; 1:525.
33. Official Methods of Analysis. 9th ed. Washington DC: Association of Official Agriculture Chemists, 1963.
34. Reid DJ. Intravenous fat therapy II; changes in oxygen consumption and respiratory quotient. Br J Surg 1967; 54:204.
35. Robin AP, Nordenström J, Askanazi J, et al. Plasma clearance of fat emulsion in trauma and sepsis: use of a three-stage lipid clearance test. J Parent Ent Nutr 1980; 4:505.
36. Robin AP, Askanazi J, Greenwood MRC, et al. Lipoprotein lipase activity in surgical patients: influence of trauma and infection. Surgery 1981; 90:401.
37. Rossner S. Studies on an intravenous fat tolerance test. Methodological, experimental and clinical experiences with Intralipid. Acta Med Scand 1974; Suppl 564:1.
38. Snedecor GW, Cochran WG. Statistical Methods. 6th ed. Ames, Iowa: Iowa State University Press, 1967; 593.
39. Spencer JL, Zikria BA, Kinney JM et al. A system for the continuous measurement of gas exchange and respiratory functions. J Appl Physiol 1972; 33:523.
40. Steinberg D, Mayer SE, Khoo JC, et al. Hormonal regulation of lipase, phosphorylase, and glycogen synthase in adipose tissue. Adv Cyclic Nucleotide Res 1975; 5:549.
41. Swift RW, French CE. Energy Metabolism and Nutrition. Washington DC.: Scarecrow, 1954.
42. Taskinen M-R. Tulikoura I, Nikkila EA, Ehnholm C. Effect of parenteral hyperalimentation on serum lipoproteins and on lipoprotein lipase activity of adipose tissue and skeletal muscle. Eur J Clin Invest 1981; 11:317.