Influence of Total Parenteral Nutrition on Tissue Lipoprotein Lipase Activity During Chronic and Acute Illness

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This study examines the influence of total parenteral nutrition (TPN) compared with 5% dextrose (D_5) infusion on skeletal muscle and adipose tissue lipoprotein lipase (LPL) activity in nutritionally depleted, injured and infected patients. The plasma concentrations of glucose, free fatty acid (FFA), triglyceride and insulin were also measured. During TPN, nutritionally depleted subjects showed an increase in adipose tissue LPL activity, "fat cell size," and plasma insulin concentration. Skeletal muscle LPL activity and plasma FFA concentration decreased. In comparison, trauma patients showed a less marked rise in adipose tissue LPL activity and skeletal muscle LPL activity increased. Infected patients had a much smaller rise in adipose tissue LPL activity than either of the other groups, and muscle activity rose. The depleted and injured patients showed a linear relationship between adipose tissue LPL activity and plasma insulin concentration and an inverse hyperbolic relationship between adipose tissue LPL activity and plasma FFA concentration.

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RECENT ADVANCES IN TOTAL parenteral nutrition (TPN), including the availability of artificial fat emulsions as an energy source, have given impetus to the study of fat metabolism as it relates to the nutritional management of chronically and acutely ill patients. The proper place of intravenous fat emulsions in a nutritional armamentarium is still controversial.[1-7] The purpose of this study is to describe the changes in skeletal muscle and adipose tissue lipoprotein lipase (LPL) activity associated with nutritional depletion, trauma and infection, and to determine the influence of TPN in each of these clinical settings.

Lipoprotein lipase is the rate limiting enzyme and a major determinant of the tissue uptake of fatty acid from circulating triglyceride (TG).[8] Its hydrolytic action at the lumenal surface of the capillary endothelium provides the major pathway by which exogenous, as well as endogenous, TG rich particles are cleared from the bloodstream. Although this enzyme is found in most extrahepatic tissues,[8-12] approximately 75% of exogenously administered fat emulsion is removed in skeletal and cardiac muscle and subcutaneous adipose tissue.[13] The remainder is removed by the extrahepatic sphlanchnic tissues, including omental and mesenteric adipose tissue. Therefore, muscle and adipose tissue are primarily responsible for removal of circulating TG from the bloodstream.

Materials and Methods

Subjects

Nutritionally depleted patients were chosen on the basis of recent weight loss (at least 10% of normal body weight), and most had gastrointestinal abnormalities precluding adequate oral alimentation, but were not acutely ill (Table 1). Trauma patients had either experienced severe accidental injury or had undergone a major operative procedure. Infected patients were chosen on the basis of fever and clinical evaluation. In most cases, a specific infection was confirmed by positive blood cultures or demonstration of an abscess cavity.

Protocol

Fifteen nutritionally depleted patients, 18 injured patients and 12 infected patients were studied either during infusion of 5% Dextrose solution (D_5), or after four to five days of TPN. Of these patients, seven nutritionally depleted, three injured and three infected were studied twice, once under each dietary condition. Studies were performed on injured patients during D_5 infusion two to six days following injury and during TPN five to nine days following injury.

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TABLE 1. *Subject Characteristics*

Diagnosis, Sex Age	Number of Patients
Nutritionally Depleted (11 M, ages 30–76, 4F, ages 64–82)	
partial small bowel obstruction	3
S/P radiotherapy for bladder carcinoma	1
S/P esophagogastrectomy, anastomotic stricture	1
chronic pancreatitis, inactive	4
gastric outlet obstruction	1
chronic urinary tract infection	1
malabsorption syndrome	2
radiation enteritis or esophagitis	2
Trauma (11 M, ages 19–69, 7 F, ages 21–82)	
fractured hip, flail chest	1
stab wound abdomen	1
multiple gunshot wounds, including chest or abdomen	3
multiple stab wounds, back and flank	1
auto accident, multiple fractures	3
colon resection, gastric polypectomy	1
total hip replacement	4
radical cystectomy	4
Infected (12 M, ages 24–79)	
subphrenic abscess	1
pancreatic abscess	1
urinary sepsis	1
empyema	1
retroperitoneal abscess following gunshot wound	3
subphrenic abscess following gunshot wound	2
infected uroma following gunshot wound	1
pneumonia following gunshot wound	1
wound infection following multiple fractures	1

The results for the tissue LPL activity in injured and infected patients on D_5 have been previously reported.[14] These data are repeated in this communication in order to provide a basis for comparison to injured and infected patients receiving TPN.

The experimental protocol and any inherent risks were explained to all subjects and written informed consents were obtained. This experimental protocol has been approved by the Institutional Review Board of Columbia University.

Intravenous Diets

Total parenteral diets provided calories equivalent to 1.5–2.0 times the patient's measured resting energy expenditure (REE). The formulas contained approximately 12 mg nitrogen per kcal REE and 100 ml of 10% Intralipid per day. The remainder of nonprotein calories was in the form of hypertonic dextrose except in three cases (two depleted, one trauma) where one-half of nonprotein calories was provided as a 10% fat emulsion.

Biopsy Procedure and Tissue Preparation

Under local anesthesia, approximately 50 mg of adipose tissue was excised from the subcutaneous tissue through a 1 cm skin incision in the anterior thigh. Immediately afterward, 50 mg of vastus lateralis muscle was obtained through the same incision with the percutaneous needle biopsy technique of Bergström.[15] Tissue samples were immediately placed in ice-cold 0.25 M sucrose—1 mM EDTA buffer solution (pH 7.4). The muscle sample was carefully dissected to remove any fat or fibrous tissue, and blotted to remove excess water and weighed. The tissue was then placed in 1 ml sucrose-EDTA buffer and 25 units of heparin and incubated for one hour in a shaking water bath at 37 C in order to extract the soluble enzyme. The enzyme extract was stored at −80 C for later analysis of lipolytic activity. The fat sample was similarly dissected from any remains of dermis or fibrous tissue, blotted and weighed, and a 10–20% w/v homogenate was prepared in the sucrose-EDTA buffer. The homogenate was centrifuged in the cold (12,000 *g* for 15 minutes) and the fat free postmitochondrial supernatent was aspirated from below the fat cake layer and stored at −80 C for later analysis of lipolytic activity.

Lipoprotein Lipase Assay

LPL activity was determined from the rate of free fatty acid (FFA) release during incubation of the enzyme preparation with a triglyceride substrate in the presence of pooled human plasma activator.[16] The substrate was prepared using 3.0 μCi of ^{14}C-triolein, 10 mg of unlabelled triolein in benzene and 0.6 mg of lysolecithin in 3 ml of chloroform-methanol (2:1). The organic solvents were evaporated in water bath under a nitrogen flow and 2.55 ml of 0.2 M tris-HCl buffer (pH 8.0), 0.45 ml of 1% fatty acid free bovine serum albumin and 3.0 ml of thawed human serum (originally obtained after a 12 hour fast) were added and the mixture was sonicated in an ice bath. Nonspecific lipolysis was accounted for by adding 0.1 ml 2 M NaCl to the samples. Only the lipolysis inhibited by the addition of NaCl was designated as LPL activity. Duplicate samples, each containing 0.1 ml substrate were preincubated at 37 C for 30 minutes[16] and the reaction was started by adding 0.1 ml of enzyme preparation. The reaction was stopped after 30 min by adding 3.25 ml of a fatty acid extraction mixture, chloroform-methanol-heptane, 2–3:2.5:1.8.[17] To facilitate separation of the phases, 1.05 ml of 0.4 M sodium carbonate buffer, pH 10.5, was added[12,17] and the contents were mixed and centrifuged at 800 *g* for 20 minutes at room temperature. One milliliter aliquots of the upper phase containing released FFA were pipetted into scintillation vials, 10 ml Aquasol II was added and radioactivity was counted.

TABLE 2. *Effect of Total Parenteral Nutrition on Tissue LPL Activity, Fat Cell Size and Plasma Hormone and Substrate Concentrations in Nutritionally Depleted, Injured, and Infected Patients*

	Depleted		Trauma		Infected	
	D_5	TPN	D_5	TPN	D_5	TPN
Muscle LPL activity $\frac{\mu mol\ FFA}{g \cdot h}$	.069 ± .012 (9)	.053 ± .008 (6)	.050 ± .005 (10)	.081 ± .019* (3)	.038 ± .005† (7)	.081 ± .016* (4)
Adipose LPL activity $\frac{\mu mol\ FFA}{g \cdot h}$	.26 ± .04 (13)	3.11 ± .54*** (10)	.48 ± .08† (17)	2.42 ± .53*** (4)	.23 ± .05‡ (11)	.80 ± .26††,‡ (5)
"Fat cell size" $\frac{gm\ adipose\ tissue}{mg\ protein}$	0.08 ± .01 (13)	.10 ± .01 (10)	.08 ± .01 (17)	.10 ± .03 (4)	.12 ± .02‡‡ (11)	.10 ± .01 (5)
Insulin μU/ml	6.1 ± .8 (13)	45.2 ± 9.0*** (10)	9.5 ± 1.1†† (17)	36.9 ± 9.0*** (4)	13.2 ± 2.3† (11)	38.6 ± 18.2* (5)
Glucose mmol/l	6.0 ± .3 (13)	6.5 ± .6 (10)	7.0 ± .4 (17)	8.8 ± 1.5 (4)	6.3 ± .3 (11)	7.7 ± .7* (5)
TG mmol/l	1.2 ± .1 (13)	1.1 ± .1 (10)	1.3 ± .1 (17)	1.0 ± .2 (4)	2.0 ± .3††,‡‡ (11)	2.1 ± .5†,‡ (5)
FFA mmol/l	.55 ± .06 (13)	.36 ± .04* (10)	.55 ± .05 (17)	.37 ± .09 (4)	.54 ± .05 (11)	.54 ± .10 (5)

* Difference from D_5.
† Difference from depleted.
‡ Difference from trauma.

For symbols, 1 = $p < .05$, 2 = $p < .01$, 3 = $p < .001$.
Values given as mean ± SEM (# of subjects). Statistical analysis based upon the unpaired Student's t-test.

Chemical Analysis

Plasma FFA concentration was measured titrimetrically by the procedure of Dole and Meinertz.[18] Glucose measurements were made with a Beckman Glucose Analyzer. Plasma triglycerides were measured by the enzymatic method of Bucola and David.[19] Insulin was measured by radioimmunoassay, using Pharmacia kits. Protein content of adipose tissue was determined by the Bio-Rad protein assay.[20] Since protein content per cell remains relatively constant over a wide range of adipocyte size,[21] the weight of adipose tissue per protein content is considered a rough indicator of fat cell size.

Results

Effect of TPN in Nutritionally Depleted Patients

During TPN, depleted patients showed a ten-fold rise in adipose tissue LPL activity, a seven-fold rise in plasma insulin level, and a 30% decrease in plasma FFA concentration (Table 2, Fig. 1). There were small decreases in skeletal muscle LPL activity and increases in fat cell size, which were not statistically significant. There was no effect on plasma glucose or triglyceride concentration.

Effect of TPN in Trauma Patients

As compared with depleted patients, trauma patients had higher LPL activity in adipose tissue while on D_5 and the rise during TPN was less marked, although still highly significant (Table 2, Fig. 1). Plasma insulin levels followed a similar pattern, beginning higher than in the depleted group, and rising less markedly during TPN. Skeletal muscle LPL activity rose and there was a tendency for fat cell size to increase, plasma glucose concentration to increase and plasma FFA concentration to decrease.

Effect of TPN in Infected Patients

While on D_5, this group of patients had low LPL activity in both tissues as compared to trauma patients without superimposed infection (Table 2). During TPN, adipose tissue LPL activity rose, but to a much lesser degree than was observed with either the depleted or the trauma group (Fig. 1). Plasma insulin levels rose significantly although the concentrations while on D_5 and the changes during TPN were much more variable than with either of the other groups. Skeletal muscle LPL activity increased during TPN, as did the plasma glucose concentration. The average TG concentration was higher than in any of the other groups, and no change was seen during TPN.

Regulatory Influence of Insulin and FFA

For nutritionally depleted and injured patients, average adipose tissue LPL activity was well correlated with the average plasma insulin concentration (Table 2. Fig. 1). Only the infected patients did not follow this trend. Adipose tissue LPL activity was plotted against plasma insulin concentration for each patient. There was a linear relationship with a highly significant cor-

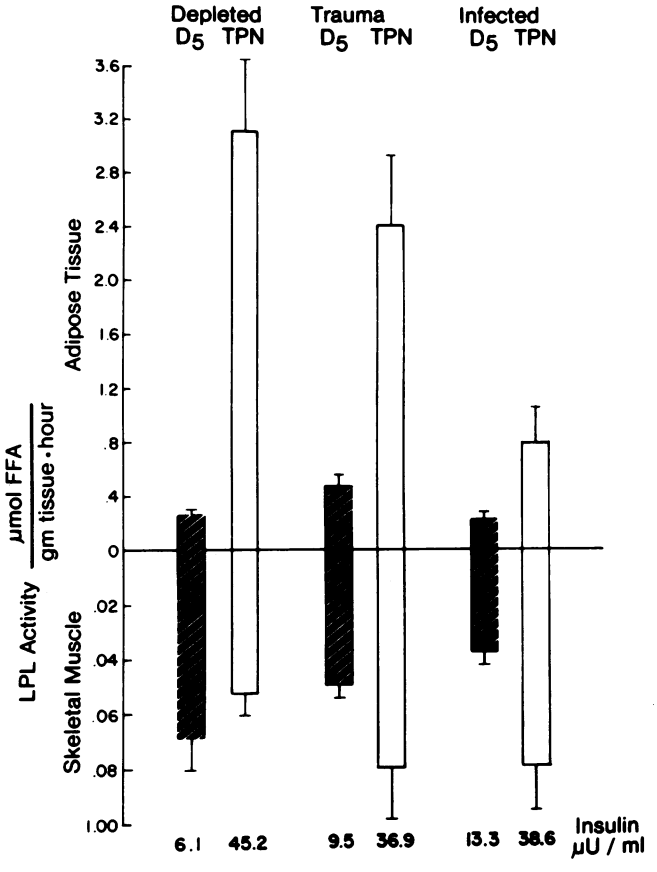

FIG. 1. Adipose tissue and skeletal muscle LPL activity and plasma insulin concentration; influence of total parenteral nutrition.

relation (Fig. 2). There was an inverse hyperbolic relationship between plasma FFA concentration and adipose tissue LPL activity (Fig. 3). No relationship was found between skeletal muscle LPL activity and any of the plasma hormone or substrate concentrations measured.

Discussion

Effect of TPN

Depleted patients on D_5, when compared with normal postabsorptive subjects*[14] had low LPL activity in adipose tissue, high activity in skeletal muscle, and low plasma insulin levels. This pattern probably reflects their ongoing state of malnutrition, and indicates that, in the absence of sufficient exogenous calories, the patients are mobilizing fat from adipose tissue to be used for oxidative metabolism. These data are in agreement with animal studies which, during periods of starvation, show a decrease in adipose tissue LPL activity and an increase in cardiac and skeletal muscle activity.[22,23] The changes in skeletal muscle may be peculiar to red muscle fibers involved in oxidative metabolism.[24]

During TPN, in nutritionally depleted patients, a marked rise in adipose tissue LPL activity and a small, but reproducible, decrease in skeletal muscle activity was observed. This reciprocal relationship is teleologically sound, channeling circulating TG to muscle for oxidative metabolism during starvation and to adipose tissue for storage in the fed state.[25,26] The concomitant increase in fat cell size and decrease in plasma FFA concentration suggests that during TPN depleted patients tended to replete adipose tissue triglyceride stores.

In comparison, injured patients had higher activity in adipose tissue before TPN, probably related to the higher insulin levels (9.5 vs 6.1 μU/ml), and the increase during TPN was less marked. In this group, skeletal muscle LPL activity rose during TPN, probably reflecting a continuing need for fat and fat derived fuels in this tissue.

Hypertriglyceridemia during experimental or clincial infection has been reported in laboratory animals as well as in man.[27-29] Some investigators have attributed this response to increased hepatic production,[27,29,30] while others point out the importance of defective mechanisms for clearing circulating TG from the bloodstream.[31,32] The most noticeable aspect of the infected group in the present study is that adipose tissue LPL activity began low and did not respond to TPN in a manner quantitatively similar to the other groups. These patients also had a higher average TG level than any other group. These results suggest that impaired clearing mechanisms do play some role in producing the hypertriglyceridemia associated with sepsis. However, this is a study of tissue enzyme activity, which is only one determinant of whole body lipid clearing capacity. Therefore, one must exercise caution in recommending or condemning the use of intravenous fat emulsion in various clinical settings based upon the above data.

Regulatory Mechanisms

Our data support the relationship between adipose tissue LPL and plasma insulin concentration reported by others[25,33,34] showing a linear relationship between the parameters. However, the relationship was disrupted by severe infection. Adipose tissue LPL activity was also inversely related to plasma FFA concentration

* In this laboratory, corresponding values for normal postabsorptive subjects are as follows[14]:

Adipose tissue LPL:	.51 ± .08 (SEM)	$\frac{\mu mol\ FFA}{gm \cdot hour}$
Skeletal muscle LPL:	.057 ± .012 (SEM)	$\frac{\mu mol\ FFA}{gm \cdot hour}$
Insulin:	8.6 ± 1.1 (SEM)	$\frac{\mu U}{ml}$

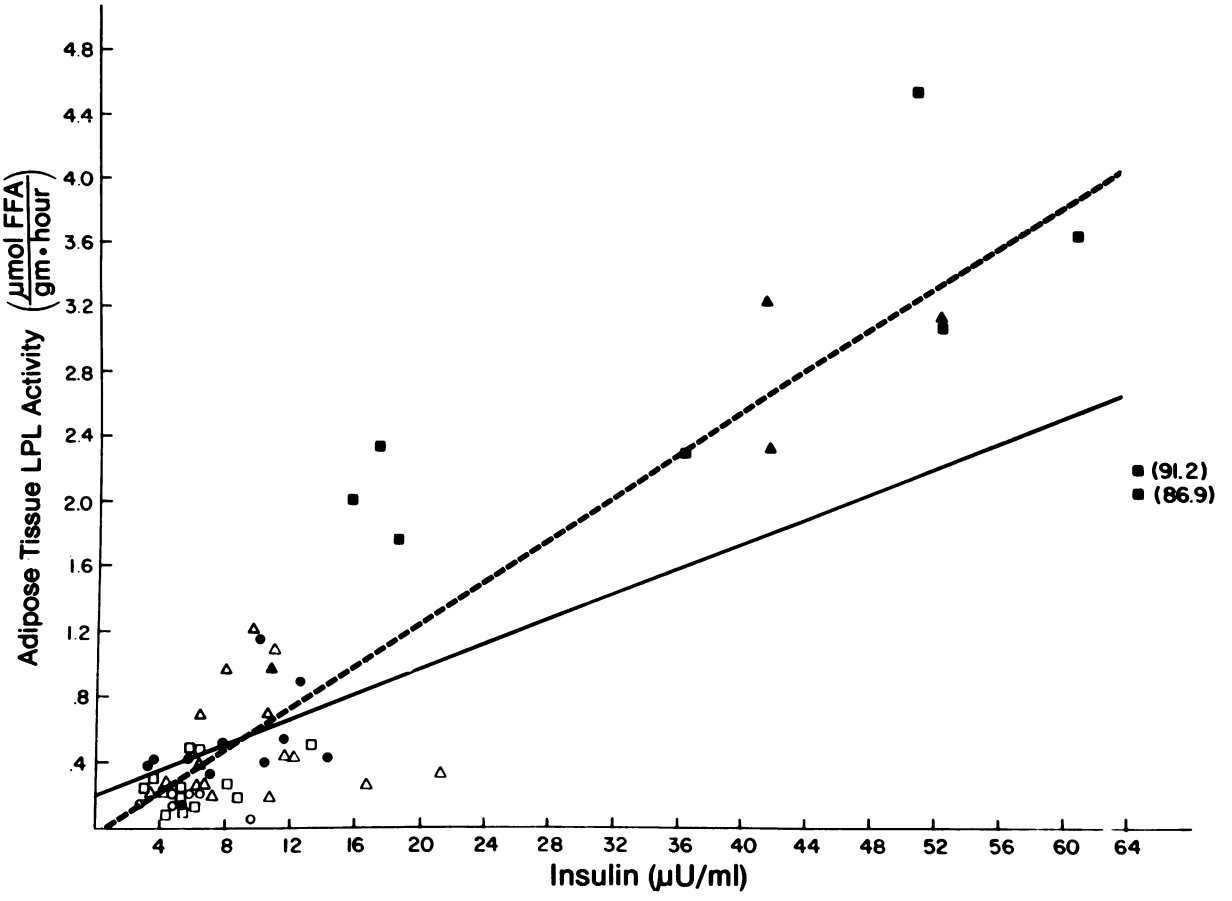

FIG. 2. Adipose tissue LPL activity vs. plasma insulin concentration. Sixteen normal subjects (14) are included. Infected patients are excluded; N = 59, r = .79; p < .001. Broken line shows the relationship when the two subjects with plasma insulin concentrations >85 μU/ml are excluded; N = 57, r = .91, p < .001. ○: Normal, D_5. ●: Normal, postabsorption. □: Depleted, D_5. ■: Depleted TPN. △: trauma, D_5. ▲: Trauma, TPN.

(Fig. 3). This relationship may be explained on the basis of the simultaneous effects of insulin of stimulating LPL and inhibiting fatty acid release from adipose tissue in the following manner. In the presence of glucose and insulin, FFA re-esterification is promoted in the adipocyte.[35,36] Insulin also acts on the adipocyte to inhibit the catecholamine stimulated, cAMP mediated, activation of hormone sensitive lipase,[36,37] thus, diminishing the rate of lipolysis of stored triglyceride. It is likely, therefore, that the relationship between adipose tissue LPL activity and FFA concentration is linked to the regulatory influence of insulin, and that this relationship can become uncoupled under certain pathological conditions such as severe infection.

Summary

Nutritionally depleted patients on D_5 had a low level of lipolytic activity in adipose tissue and a high level in skeletal muscle. During TPN, LPL activity rose markedly in adipose tissue and dropped in skeletal muscle. This pattern indicates a reciprocal relationship, permitting utilization of circulating TG of oxidative metabolism in muscle in the starved state and storage

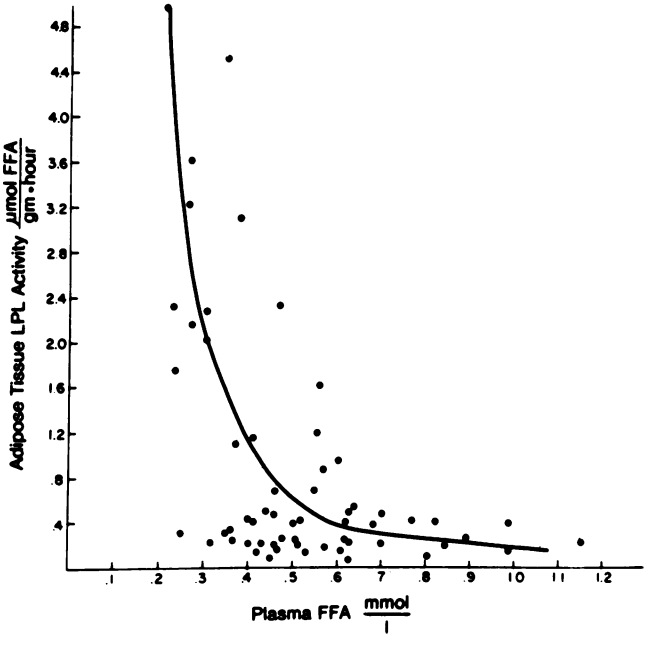

FIG. 3. Adipose tissue LPL activity vs. plasma FFA concentration. Sixteen normal subjects (14) are included. Infected patients are excluded. N = 59; y = (x + a)/(bx + c); for best computer fit a = 589, b = 3,679; c = −682, r = −.77, p < .001.

in adipose tissue in the fed state. On D_5, trauma patients had higher LPL activity in adipose tissue and higher plasma insulin level. During TPN, both of these parameters rose markedly, but in contrast to the depleted patients, skeletal muscle LPL activity also increased. Infected patients showed low LPL activity in both tissues while on D_5, possibly contributing to the high plasma TG concentration in this group. The response of infected patients to TPN was extremely variable, and the increase in adipose tissue LPL was dampened as compared to the other groups. In depleted patients and injured patients, adipose tissue LPL activity was positively correlated to plasma insulin concentration and inversely correlated to plasma FFA concentration.

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