Familial chylomicronemia due to a circulating inhibitor of lipoprotein lipase activity[1]

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Abstract A mother and her son who have lipoprotein phenotype I are described. They differed from subjects with lipoprotein lipase deficiency in that lipoprotein lipase was present in adipose tissue respectively at 30- and 2-fold the levels seen in normal subjects, and from subjects with apoprotein C-II deficiency in that apoprotein C-II was present in their plasma. They appeared to have an inhibitor to lipoprotein lipase activity in their whole plasma that inhibited that activity eluted from adipose tissue with heparin and that activity present in postheparin plasma of normals. The inhibitor was nondialyzable, heat-stable, sensitive to repeated freezing and thawing, and appeared to be present in the non-lipoprotein fraction of plasma. The presence of chylomicronemia and the plasma inhibitor in the mother and her son, and possibly in her father and grandson, argues against this being inherited as an autosomal recessive abnormality, as are lipoprotein lipase deficiency and apoprotein C-II deficiency.—**Brunzell, J. D., N. E. Miller, P. Alaupovic, R. J. St. Hilaire, C. S. Wang, D. L. Sarson, S. R. Bloom, and B. Lewis.** Familial chylomicronemia due to a circulating inhibitor of lipoprotein lipase activity. *J. Lipid Res.* 1983. **24:** 12–19.

Supplementary key words apoprotein C-III • gastric inhibitory polypeptide

Hyperlipoproteinemia with phenotype I is associated with marked hypertriglyceridemia due to the accumulation of chylomicrons in plasma. It is relatively rare and is associated with an abnormality in the lipoprotein lipase system for plasma triglyceride removal (1). This lipoprotein phenotype can be secondary to a number of acquired diseases (2) or may be due to one of several familial disorders. Total lipoprotein lipase deficiency, with absence of enzyme activity in adipose tissue (3, 4) and postheparin plasma (4, 5), may occur as an autosomal recessive disorder that usually presents in childhood. Selective tissue lipoprotein lipase deficiency may present in adults with isolated lack of enzyme activity in adipose tissue or other tissues (4).

Phenotype I can also occur in subjects with the familial absence of apoprotein C-II, a necessary cofactor for lipoprotein lipase activity (6–9). This report describes a family with ineffective lipoprotein lipase activity apparently due to the presence of an inhibitor of the enzyme activity in plasma (10).

METHODS

Subjects

The proband (subject 1) was a 47-year-old Caucasian female who was found to have massive hypertriglyceridemia (**Table 1**) after developing eruptive xanthomas on the outer aspects of both feet. There were no other xanthomas or xanthelasma. She gave a history of recurrent undiagnosed abdominal pain since the age of 16 years. Alcohol intake was minimal, and she was not taking any hormone preparations. On physical examination the spleen was palpable, but there was no hepatomegaly. She was not obese. There was no clinical evidence of atherosclerotic disease. Oral glucose tolerance was normal. Conventional biochemical indices of renal, thyroid, and hepatic function were also normal. There was no paraproteinemia. On an unrestricted diet, plasma lipoprotein fractionation by sequential preparative ultracentrifugation at densities of 1.006 and 1.063 g/ml (11) demonstrated: chylomicron triglyceride, 1813 mg/dl; VLDL triglyceride, 598 mg/dl; VLDL cholesterol, 74 mg/dl; LDL triglyceride, 158 mg/dl; LDL

cholesterol, 31 mg/dl; HDL triglyceride, 30 mg/dl; HDL cholesterol, 14 mg/dl. Nicotinic acid treatment (3 g/d) had no effect on plasma lipoproteins. Reduction of dietary fat intake to 5 g/day under metabolic ward conditions reduced chylomicron triglyceride by 80% after 48 hr; in contrast, VLDL triglyceride was unchanged.

The father of the patient died at age 39 years after having abdominal surgery for acute abdominal pain. Screening of other family members demonstrated normal lipid levels in the proband's mother, sister, brother, and husband (**Fig. 1**). However, her only son, aged 21 years, also had marked hypertriglyceridemia (subject 2 of Table 1). He had no xanthomas or hepatosplenomegaly, and was asymptomatic. Two years after these studies were performed, this son had a male child who was noted to have grossly lipemic plasma. At 4 months of age his triglyceride was 2400 mg/dl and his cholesterol was 246 mg/dl.

Included in this study, for comparison with subjects 1 and 2, were a 30-year-old Caucasian female with familial apoprotein C-II deficiency (subject 3) and a 29-year-old Caucasian male (subject 4) with lipoprotein phenotype I due to classical lipoprotein lipase deficiency (unmeasurable lipoprotein lipase activity in adipose tissue and in plasma during a prolonged, high dose heparin infusion). Data concerning subjects 3 (9) and 4 (4) have been published previously. Two additional subjects with documented familial lipoprotein lipase deficiency in whom lipoprotein apoproteins were measured also are included for comparison (Table 1). Subjects 1 to 4 were studied in the Metabolic Ward of St. Thomas' Hospital, London (numbers 1, 2 and 3), or the Clinical Research Center, University Hospital, Seattle (number 4). The subjects were all weight-stable, were taking no medications, and the studies were performed after an overnight fast of 12–14 hr unless otherwise stated.

The age- and sex-matched control subjects for apoprotein levels were employees of the Oklahoma Medical Research Foundation, and their relatives and friends living in the Oklahoma City area. All these subjects were healthy, asymptomatic Caucasians with no history of familial hyperlipoproteinemias or diabetes. Blood samples were obtained after an overnight fast of 12 hr. Blood was drawn by antecubital venipuncture and the sera were collected by low-speed centrifugation.
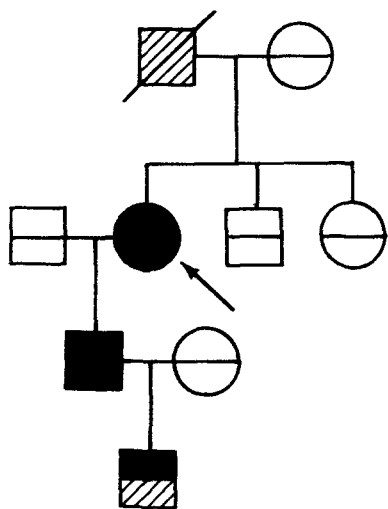
Adipose tissue lipoprotein lipase activity

AT-LPL was measured as the heparin-releasable enzyme as previously described (12). Adipose tissue specimens were obtained by suction needle biopsy of subcutaneous tissue in the area of the buttock. The tissue pieces were rinsed with 100 ml of cold Krebs-Ringer phosphate buffer (pH 7.4), dried on lipid-free sharkskin

TABLE 1. Subject characterization and plasma lipoprotein apoproteins

No.	Age/Sex	Wt	Ht	TG	Chol	Total Plasma[a]							Hepatic Lipase[b]
						A-I	A-II	B	C-II	C-III	D	E	
		kg	*cm*			*mg/dl*							*mU/ml*
1	47/F	65.7	156	3865	450	68.7	38.0	72.6	21.1	53.5	8.7	68.2	0.29 ± 0.04
2	21/M	55.7	166	3596	287	51.3	25.7	32.6	7.7	24.0	5.2	27.0	0.37 ± 0.03
3	30/F	59	170	2900	328	57.8	26.4	52.5	0	38.6	7.4	57.5	0.27 ± 0.02
4	29/M	66	175	3180	425								0.11 ± 0.01
Classical lipoprotein lipase deficiency (n = 2) { M						45.4	15.4	92.5	11.0	15.2	3.5	13.0	
F				2810	964	92.7	40.8	69.2	6.5	24.0	11.2	57.2	
Normals (n = 6)	40-49/F			210 ± 26	77 ± 22	139 ± 13	66 ± 8	112 ± 26	4.1 ± 0.7	8 ± 1.7	8.8 ± 1	14 ± 8	
Normals (n = 25)	20-39/M			184 ± 23	89 ± 38	118 ± 19	52 ± 7	114 ± 30	4.0 ± 1	8.4 ± 2.4	10 ± 4	10 ± 3	

[a] The quantitative determination of apoprotein levels was carried out in the Laboratory of Lipid and Lipoprotein Studies, Oklahoma Medical Research Foundation. Mean ± SD.
[b] Hepatic lipase in postheparin plasma. One mU is 1 neq FFA released per minute. Hepatic lipase activity in five normal individuals was 0.21 ± 0.05 mU/ml of plasma.

Fig. 1. Family pedigree of subjects 1 and 2. ▣⊖, Lipoprotein phenotype I; ⊟⊖, increased adipose tissue LPL activity with lipoprotein lipase inhibitor in plasma; ⊟⊖, normal plasma triglyceride and cholesterol level; ▨, presumed affected relatives, see text.

filter paper, and cut into pieces of uniform size. Approximately 45 mg of tissue was incubated in duplicate flasks for 45 min at 37°C in 2.5 ml of Krebs-Ringer buffer with heparin (2 U/ml). At the end of the incubation period, two 1-ml samples of heparin-eluted enzyme were taken from each flask for assay.

The substrate for the AT-LPL assay was prepared using 200 μl of unlabeled triolein solution (25 mg/ml in benzene); 100 μl (0.2 μCi) of tri-[^{14}C]oleoylglycerol (0.05 μCi/mg) in benzene; and 20 μl of purified egg lecithin solution (12 mg/ml in chloroform–methanol 1:1). These were combined and evaporated under nitrogen, and emulsified in 2 ml of a mixture of 10% fatty acid-free bovine serum albumin (pH 8.0), pooled human serum as a source of enzyme activator, 2 M Tris-HCl buffer (pH 8.2 at 37°C), and distilled water (4:1.5:5:9.5, vol/vol) for a total of 3 min with a Branson 125 Sonifier (Branson Sonic Power Co., Danbury, CT). The substrate was kept cool on ice during and after sonification for a minimum of 30 min before use. The 1-ml aliquot of the medium containing the heparin-eluted enzyme activity was added to 0.2 ml of substrate and incubated at 37°C in a metabolic shaker. The reaction was stopped at 45 min by adding Dole's reagent, and free fatty acids were extracted and the specific activity was determined. AT-LPL activity is expressed as milliunits per gram of adipose tissue, with one milliunit equal to one nanoequivalent of free fatty acids released per minute.

In some assays of adipose tissue LPL activity the usual pooled human serum was replaced by serum obtained from each of subjects 1 to 4, or with a mix of equal volumes of subjects and pooled human serum. Some

assays were performed in the presence of 1 M NaCl to inhibit LPL activity.

Heparin infusion studies

Plasma postheparin lipoprotein lipase activity and hepatic lipase (HL) activity were measured during a heparin infusion of 4–5 hr duration after an overnight fast. Initially a bolus of heparin was injected (2280 U/m² body surface area, approximately 60 U/kg). This was followed by an infusion of 2000 U/m²/hr (4). Postheparin plasma was incubated for 2 hr with serum containing antibody directed against human plasma postheparin HL activity (13); the remaining activity was then used as postheparin LPL activity. The enzymatic activity in postheparin plasma was tested by the above reported assay. The materials used in these assays were obtained as previously reported (12).

Inhibition assay of postheparin plasma lipolytic activity[6]

Plasma samples (6 ml) from patients 1 and 2 and a normal control were adjusted to density 1.25 g/ml by the addition of solid KBr and made up to a final volume of 13 ml by the addition of an aqueous KBr solution, d 1.25 g/ml. After centrifugation in a Ti50 rotor (Spinco model L-2 centrifuge) at 40,000 rpm for 44 hr, the supernatant fraction (lipoprotein fraction) was removed by a tube-slicing technique. The infranatant fraction was washed twice by the addition of the KBr aqueous solution, d 1.25 g/ml, and centrifuged at 40,000 rpm for 22 hr. The upper layer (1–2 ml) was removed and the lipoprotein-free plasma fraction, d > 1.25 g/ml, was concentrated by polyethylene glycol to a small volume (approximately 3 ml), dialyzed against 50 mM NH₄OH · HCl buffer, pH 8.5, and adjusted to the original plasma volume (6 ml). This lipoprotein-free plasma fraction had a protein concentration of approximately 50 mg/ml.

The lipase assay for these particular studies were performed using triolein emulsified in Triton X-100 (14). The assay was carried out in a buffer solution of 50 mM NH₄OH · HCl buffer, pH 8.5, containing 60 mg/ml of bovine serum albumin as fatty acid acceptor. The substrate concentration was 10 μmol/ml, 0.01 μCi/ml of triolein solution. Postheparin plasma (0.1 ml) from a normolipidemic subject was utilized as enzyme source. In the inhibition study, the assay mixture contained 0–0.4 ml of the lipoprotein-free plasma fraction, d > 1.25 g/ml, and the volume of the final assay mixture was 1.0 ml. After incubation at 37°C for 1 hr, the reaction was stopped by the addition of 4 ml of isopropanol–3 N

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[6] These assays were performed in Oklahoma City.

H₂SO₄ 40:1 (v/v) and the fatty acids were extracted as described by Schotz et al. (14) for measuring the radioactivity.

Determination of gastrointestinal polypeptide hormones

For hormone estimations 10 ml of blood was taken into chilled heparin tubes containing 1000 Kallikrein inhibitory units per ml aprotinin (Trasylol: Bayer Co., West Germany). This blood was immediately centrifuged for 5 min at 1500 g at 4°C; the plasma was decanted and stored at −20°C until assayed. Insulin was measured using ^{125}I-labeled insulin (1M 38: The Radiochemical Centre, Amersham, UK). Standard curve tubes were set up in plasma stripped of endogenous insulin by charcoal adsorption. The sensitivity of the assay was 6 pmol/l. GIP was estimated by radioimmunoassay using a mid C-terminal reacting antiserum (GIP 19) raised in a rabbit using carbodiimide condensation of GIP to haemocyanin (15). Radiolabeled antigen (^{125}I-labeled GIP) was prepared by lactoperoxidase oxidation (16). The specific activity was approximately 65 Bq/fmol. In the absence of added cold GIP, the antiserum used, at a final dilution of 1:96,000, bound approximately 50% of 1.5 fmol of ^{125}I-labeled GIP added to each assay tube. Standard curve plasma was prepared by specific immunoadsorption (17). GIP 19 recognizes two major immunoreactive forms of GIP when analyzed by gel permeation chromatography. The first elutes shortly after cytochrome C (Kav 0.3 ± 0.02) and the other peak co-elutes with pure porcine standard (Kav 0.67 ± 0.02). The antibody demonstrated no cross-reactivity with any other gastrointestinal or pancreatic hormones with the exception of glucagon where it was less than 1%. The sensitivity of the assay allowed changes of 3 pmol of GIP/1 to be detected between individual adjacent plasma samples with 95% confidence.

Determination of lipoprotein apoproteins

Plasma samples from patients 1, 2, and 3 were preserved with merthiolate (0.1 mg/ml) and maintained at 4°C during transportation by air to Oklahoma City. The quantitative determination of plasma apoproteins was carried out by previously described procedures for apoproteins A-I and A-II (18), B (19), C-II (20), C-III (21), D (22), and E (23).

Statistics

Results are reported as mean ± SD. Data were analyzed with Students t test and linear regression analysis.

RESULTS

As seen in patients with classical lipoprotein lipase deficiency (patient 4, Table 1) or familial apoprotein C-II deficiency (patient 3, Table 1), both patients ultimately demonstrated to have a serum inhibitor of lipoprotein lipase (patients 1 and 2, Table 1) have very high levels of serum triglycerides and total cholesterol. All of these type I patients have very characteristic apoprotein profiles. In comparison with normolipidemic subjects, they have significantly decreased levels of apoproteins A-I, A-II, and B, normal concentrations of D, and increased levels of apoproteins C-II, C-III, and E. The only exception are patients with familial apoprotein C-II deficiency characterized by the absence of C-II, but with high levels of C-III and E.

Adipose tissue LPL activity was found to be extremely high in subject 1 (173 mU/g) and moderately elevated in subject (9.2 mU/g) as compared to normal controls (5.6 ± 2.4 mU/g; n = 12) (**Table 2**) when their

TABLE 2.   Adipose tissue lipoprotein lipase activity in lipoprotein phenotype I subjects

Subject	Disease[a]	Enzyme Source				
		Subject	Subject	Normal	Subject	Subject
		Plasma Activator Source				
		Normal	Normal 1 M NaCl	Subject	Subject	Normal and Subject
		mU/g				
1	"Inhibitor"	173	—[b]	—	—	—
2	"Inhibitor"	9.2	—	—	—	—
3	C-II = 0	117	—	—	—	108
4	LPL = 0	—	—	4.2	—	—

[a] C-II = 0, subject with familial apoprotein C-II deficiency (9); LPL = 0, subject with classical lipoprotein lipase deficiency of adipose tissue and postheparin plasma (4).
[b] Activity in assay was immeasurable. Adipose tissue LPL activity in twelve normal subjects with normal pooled serum was 5.6 ± 2.4 mU/g (mean ± SD).
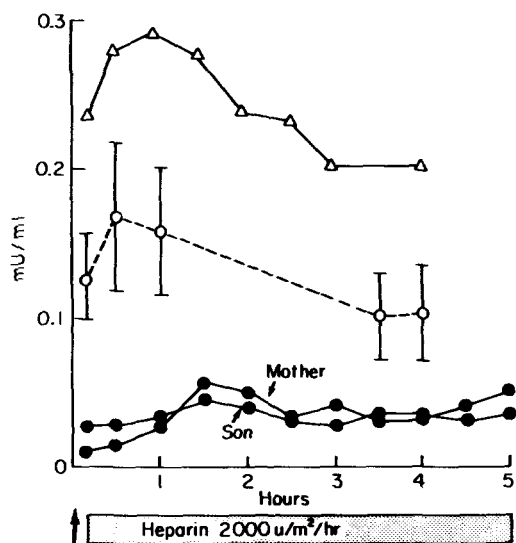
Fig. 2. Postheparin plasma lipoprotein lipase activity during prolonged, high dose heparin infusion in six normal subjects (O) (mean ± SD), in subjects 1 and 2 (●), and in subject 3 with apoprotein C-II deficiency (△). Postheparin plasma was incubated with rat serum containing antibody to human postheparin plasma hepatic lipase.

adipose tissue enzyme was assayed against substrate activated with pooled normal plasma as the source of apoprotein C-II. This lipolytic activity did not appear to be some other triglyceride lipase since it was totally inhibited by NaCl at a final concentration of 1 M. Adipose tissue LPL activity was also very high (117 mU/g) in subject 3 with apoprotein C-II deficiency, while the activity in subject 4, with classical lipoprotein lipase deficiency, was unmeasurable.

No measurable LPL activity was present when plasma from subjects 1, 2, or 3 was used to activate their own adipose tissue enzyme or the enzyme obtained from a normal individual (Table 2). This failure to activate LPL was not due to the high triglyceride content of these plasmas, since the enzyme was activated by plasma obtained from subject 4 with classical LPL deficiency. When a one-to-one mix of the plasma from subject 3 with apoprotein C-II deficiency and normal pooled plasma was used to activate the assay substrate, adipose tissue LPL activity from this subject was found to be increased (108 mU/g) to a level similar to that when only pooled normal plasma was used. This was compatible with the replacement of the small amount of apoprotein C-II required for LPL to hydrolyze the triglyceride substrate. In contrast, the enzyme activity in the adipose tissue from subjects 1 and 2 remained unmeasurable when a similar one-to-one mix of their plasma and normal pooled plasma was used, compatible with the presence of an inhibitor of LPL in their plasma samples.

Postheparin plasma (PHP) LPL activity was low in subjects 1 and 2 throughout the duration of a prolonged, high dose, heparin infusion (**Fig. 2**). In contrast, PHP-LPL activity was elevated in subject 3 with apoprotein C-II deficiency. (These assays were performed in the presence of exogenous apoprotein C-II, since this was present in the rat antiserum used to inhibit PHP hepatic lipase.) PHP hepatic lipase activity appeared to be normal in all four subjects (Table 1).

To further characterize the "inhibitor" in the plasma of subjects 1 and 2, their plasma was separated into a lipoprotein fraction and a lipoprotein-free fraction by ultracentrifugation at density 1.25 g/ml. The lipoprotein fraction from subjects 1 and 2 inhibited lipolytic activity present in PHP obtained from normal subjects, but this inhibition was no different from that produced by lipoproteins from normal subjects. The lipoprotein-free fraction of normal plasma had no effect on the lipolytic activity seen in normal PHP, whereas lipoprotein-free plasma from subjects 1 and 2 inhibited lipolytic activity in postheparin plasma (**Fig. 3**) and that eluted from human adipose tissue (**Table 3**). Chylomicron-free plasma of subjects 1 and 2 also inhibited human adipose tissue LPL activity when mixed with normal plasma to activate the assay substrate (Table 3). The inhibitor was still present after dialysis of chylomicron-free plasma for 24 hr at 4°C (average pore size 24 Å) and after heating for 2 hr at 55°C. However, the inhibitor was no longer present after freezing at −20°C and rethawing (three times) (Table 3).

The increase in adipose tissue LPL activity in subjects 1, 2, and 3 might be an adaptive response to the inability of their enzyme to hydrolyze their triglyceride-rich lipoproteins. Since several gastrointestinal polypeptides,
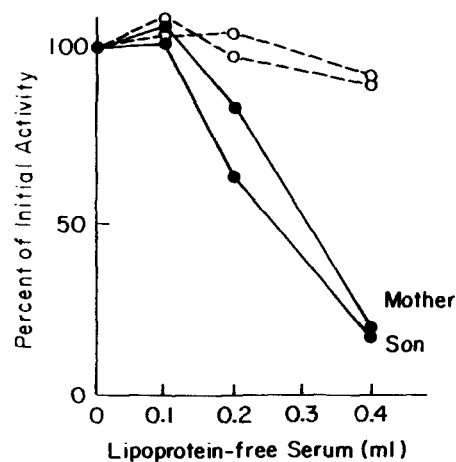
Fig. 3. Inhibition of normal postheparin plasma lipolytic activity with increasing volumes of lipoprotein-free serum added to normal serum as activator for assay substrate. Normal controls (O), subjects 1 and 2 (●).

TABLE 3. Characterization of inhibitor[a]

Activator Source	Perturbation	Activity[b]	
		Subject 1	Subject 2
		% of control	
1:1 Mix of normal pooled serum and subject's whole plasma	None	2.4	6.9
1:1 Mix of pool and subject's chylomicron-free plasma	None	0	0
1:1 Mix of pool and subject's chylomicron-free plasma	Dialysis of subject's plasma	0.7	0
1:1 Mix of pool and subject's chylomicron-free plasma	Heating of subject's plasma at 55°C for 2 hr	91.2	92.0
1:1 Mix of pool and subject's chylomicron-free plasma	Freezing and thawing of subject's plasma ×3	0	0
1:1 Mix of pool and subject's lipoprotein-free plasma	None	0.1	2.0

[a] Enzyme source, activity eluted from normal human adipose tissues with heparin. Normal control values for these studies ranged from 2.31 ± 0.57 to 3.76 ± 0.36 mU/g.
[b] Each study was performed in quadruplicate. Control value, 100%.

e.g., insulin, glucagon, and gastric inhibitory polypeptide (GIP), have been suggested to be involved in the regulation of LPL activity, they were measured in plasma after an overnight fast and following a standard breakfast (24). Basal GIP levels were higher in subjects 1, 2, and 3 (16, 20, and 30 pmol/l, respectively) than in six normal subjects (10.6 ± 4.4 pmol/l) (15) (**Fig. 4**). This elevation in GIP levels persisted after the ingestion of a standard breakfast. When subject 3 was given a 200-ml infusion of fresh frozen plasma over 30 min, there was an 84% fall in plasma triglyceride levels (9). Adipose tissue LPL activity measured 96 hr after the plasma infusion had fallen 62% (from 117 to 47 mU/g) with a fall in plasma GIP levels at all time points before and after a repeat standard breakfast (26 to 43% decrease).

Plasma levels of insulin, enteroglucagon, pancreatic glucagon, motilin, and pancreatic polypeptide were normal in the basal state and after the standard breakfast in all three subjects (data not presented).

DISCUSSION

The lipoprotein phenotype I with marked chylomicronemia is present in subjects with the classical form of lipoprotein lipase deficiency and in subjects with apoprotein C-II deficiency, a lack of the necessary cofactor for lipoprotein lipase. An additional abnormality characterized by the lipoprotein phenotype I is reported here in two subjects who appear to have an inhibitor to lipoprotein lipase activity in their plasma. The similarity in the apoprotein patterns among patients with phenotype I seems to be the logical consequence of the inability of lipoprotein lipase to hydrolyze triglyceride-rich lipoproteins caused by different underlying factors. Apoprotein profiling can be used to differentiate familial apoprotein C-II deficiency from familial lipoprotein lipase deficiency or familial presence of serum in-

hibitor, but cannot be applied to differentiation of the latter two disorders.

The inhibitor of LPL activity was heat stable, unstable to repetitive freezing and thawing, nondialyzable, and appeared to be present in the lipoprotein-free fraction of plasma. The inhibitor of LPL activity could be directed against the enzyme protein itself, or could be an anti-heparin agent indirectly causing inhibition of LPL activity in a way similar to protamine. From the data in this study it is not possible to differentiate these possibilities since heparin was present in both the samples of adipose tissue activity eluted with heparin and in the postheparin plasma. An anti-heparin agent would seem to be less likely due to the absence of any coagulation disorder in vivo or in vitro. Similarly no paraprotein abnormality was evident in these subjects as has been previously reported in some subjects with acquired lipoprotein phenotype I (25).

The presence of the inhibitor and the marked hypertriglyceridemia in the mother and son suggested this
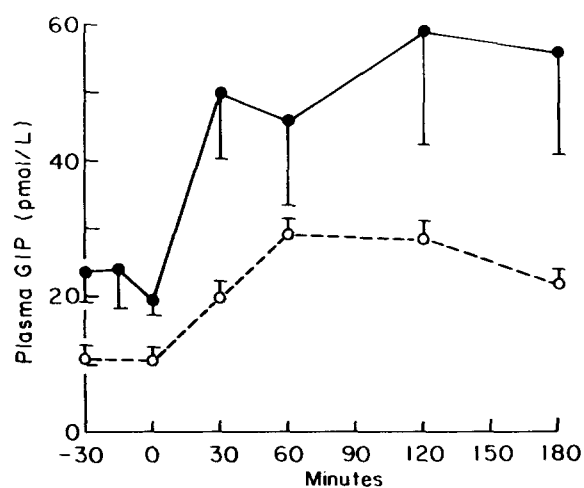

Fig. 4. Plasma GIP levels before and after standard breakfast in subjects 1, 2, and 3 (●) and six normal subjects (○) (15 (mean ±SEM).

factor was inherited. The mother of subject 1 had normal triglyceride levels, as did the husband of subject 1. The father of subject 1 died after abdominal surgery for acute abdominal pain at age 39. Although it cannot be substantiated, this man may have died from chylomicronemic-induced pancreatitis. The infant son of subject 2 was noted to be extremely lipemic. Thus, chylomicronemia was present in at least three generations. This is incompatible with the autosomal recessive pattern of inheritance seen in familial lipoprotein lipase deficiency or in familial apoprotein C-II deficiency, and would be more consistent with an autosomal dominant pattern of inheritance.

The inability of the enzyme in postheparin plasma to hydrolyze triglyceride-rich lipoproteins can account for the marked hypertriglyceridemia and lipoprotein phenotype I in the subjects with the familial LPL inhibitor and in the subject with apoprotein C-II deficiency. The increase in adipose tissue LPL activity in these conditions may be a physiological response to these defects in the interaction of their LPL with plasma triglyceride substrate. The decrease in adipose tissue LPL activity in the apoprotein C-II-deficient subject following apoprotein C-II replacement by plasma infusion supports the concept that adipose tissue LPL is under feedback control (12). Other evidence also supports the concept of feedback control of adipose tissue LPL activity. Obese subjects have a 3- to 4-fold increase in adipose tissue LPL activity when restudied in the isocaloric state after weight loss (12), an increase which seems to be persistent (26). Furthermore, some individuals who smoke cigarettes, and are below their usual or regulated weight, have a similar 3- to 4-fold increase in their adipose tissue LPL activity (27). In these weight-reduced individuals the increase in adipose tissue LPL activity may represent an attempt to return fat cell size or adipose mass to that level at which it is regulated (28).

If adipose tissue LPL is under feedback control, then an afferent and efferent loop must be present to and from the regulatory center that controls LPL activity. While insulin appears to be necessary as a permissive hormone for LPL activity, it may not be the primary regulator of LPL activity in adipose tissue (29). The normal insulin levels in the two subjects with the inhibitor and the apoprotein C-II-deficient subject are consistent with this contention. The simultaneous elevations of adipose tissue LPL activity and GIP levels in subjects with the inhibitor or with apoprotein C-II deficiency and the decrease in both LPL and GIP following administration of whole plasma as a source of apoprotein C-II suggest that GIP may play a role in the regulation of adipose tissue LPL in humans as it does in the cultured mouse 3T3-L1 preadipocyte (30). GIP levels also are elevated in obese individuals and the increase in basal GIP persists after weight loss (31). Thus, GIP could also mediate the increase in adipose tissue LPL activity in these ex-obese individuals. It is also likely that substrates and other components of the neuroendocrine system are important in the regulation of human adipose tissue lipoprotein lipase activity.▮

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