Metab

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D I S O R D E R S O F P L A S M A T R I G L Y C E R I D E M E T A B O L I S M

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TABLE OF CONTENTS

I. Introduction

Hypertriglyceridemia is encountered fairly frequently in the general population and in general medical practice. In any given patient, hypertriglyceridemia may be a sporadic finding, an expression of a familial lipoprotein disorder, or the secondary manifestation of another disease such as diabetes mellitus or the nephrotic syndrome.

The medical consequences of hypertriglyceridemia may include eruptive xanthomas, pancreatitis, and premature atherosclerosis. Of these, pancreatitis is the most dramatic problem and severely hypertriglydermic patients are prone to die from hemorrhagic pancreatitis. The link of hypertriglyceridemia with premature atherosclerosis is debated but there is no question that certain types of hypertriglyceridemia are associated with a higher-than-normal frequency of myocardial infarction.

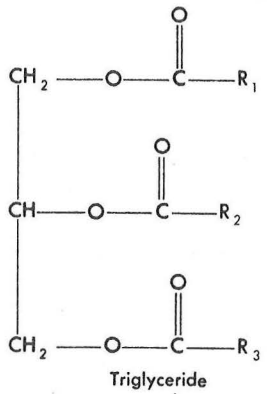
Several distinct hypertriglyceridemic disorders have been identified but the techniques needed to distinguish one from another are too specialized for routine clinical use. Consequently, the clinician cannot usually pursue the specific diagnosis of a hypertriglyceridemic individual but he or she must nevertheless devise a treatment program to control the condition.

In this grand rounds, a brief summary of the specific hypertriglyceridemic syndromes will be given and then a general approach to the management of hypertriglyceridemia will be outlined.

II. Triglyceride Metabolism in the Plasma

The triglyceride molecule consists of 3 fatty acids attached to glycerol by ester bonds (Figure 1).

Figure 1



Triglyceride

The fatty acids in triglycerides arise either from endogenous biosynthesis (largely in the liver) or from the ingestion of dietary fat.

The packaging of triglycerides into lipoproteins provides a mechanism by which this nonpolar lipid can be transported through plasma.

While triglyceride is present to some degree in all families of lipoproteins, only chylomicrons and Very Low Density Lipoproteins (VLDL or prebetalipoproteins) transport triglyceride to any significant extent (Table 1). It follows, therefore, that hypertriglyceridemia is caused by hyperchylomicronemia and/or hyperprebetalipoproteinemia (elevated VLDL).

Table 1. Composition of Plasma Lipoproteins (% dry weight)+

Constituent	Chylomicrons	VLDL*	LDL*	HDL*
Triglyceride	80-95	45-65	4-8	2-7
Unesterified Cholesterol	1-3	4-8	6-8	3-5
Esterified Cholesterol	2-4	16-22	45-50	15-20
Phospholipid	3-6	15-20	18-24	26-32
Protein	1-2	6-10	18-22	45-55

* VLDL = Very Low Density Lipoprotein; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein.

\+ from Ref. 1.

A great deal has been learned in recent years about the factors governing chylomicron and VLDL metabolism. An especially important role is played by the proteins contained in these lipoproteins. For example, a protein called C-II that is found normally in both chylomicrons and VLDL activates the enzyme responsible for the initial degradation of both these lipoproteins. Another protein called E (or apoE) is responsible for the normal uptake of chylomicron remnants by specific receptors found in the liver. The major plasma apoproteins and their presumed or established functions are given in Table 2 and the apoprotein composition of human plasma lipoproteins is presented in Table 3.

The metabolic pathways for chylomicrons and VLDL are summarized in Figure 2. The scheme is constructed using data from a variety of experiments in both humans and animal models.

The term 'chylomicron' refers to a lipoprotein synthesized in the intestine in response to the ingestion of dietary fat. Only the longer chain dietary fatty acids (>12 carbons), of both the saturated and unsaturated variety, are transported in these particles. Chylomicrons are not of one unique size but actually represent a spectrum of particles that overlap with VLDL in terms of size and composition. Although chylomicrons contain mostly triglyceride and only a small amount of cholesterol (Table 1), chylomicrons also represent the major route by which dietary cholesterol is absorbed.

Table 2. Characteristics of Human Plasma Apoproteins*

Apoprotein	Mol. Wt.	Carbohydrate	Function	Site of Synthesis
A-I	23,300	+	LCAT activation	Intestine, liver
A-II	17,000	±	?	Intestine, liver
B	549,000	∿ 5%	Triglyceride transport	Liver, intestine, kidney (?)
B_I§	264,000	?	Chylomicron triglyceride transport	Intestine (?)
C-I	6,331	0	?	Liver, Intestine
C-II	8,837	0	Lipoprotein lipase activation	Liver, intestine
C-III	8,764	+	? Inhibits uptake of triglyceride-rich lipoproteins by the liver	Liver, intestine
E	33,000	?	? Recognition site for uptake of chylomicron remnants by liver.	Liver, ? intestine

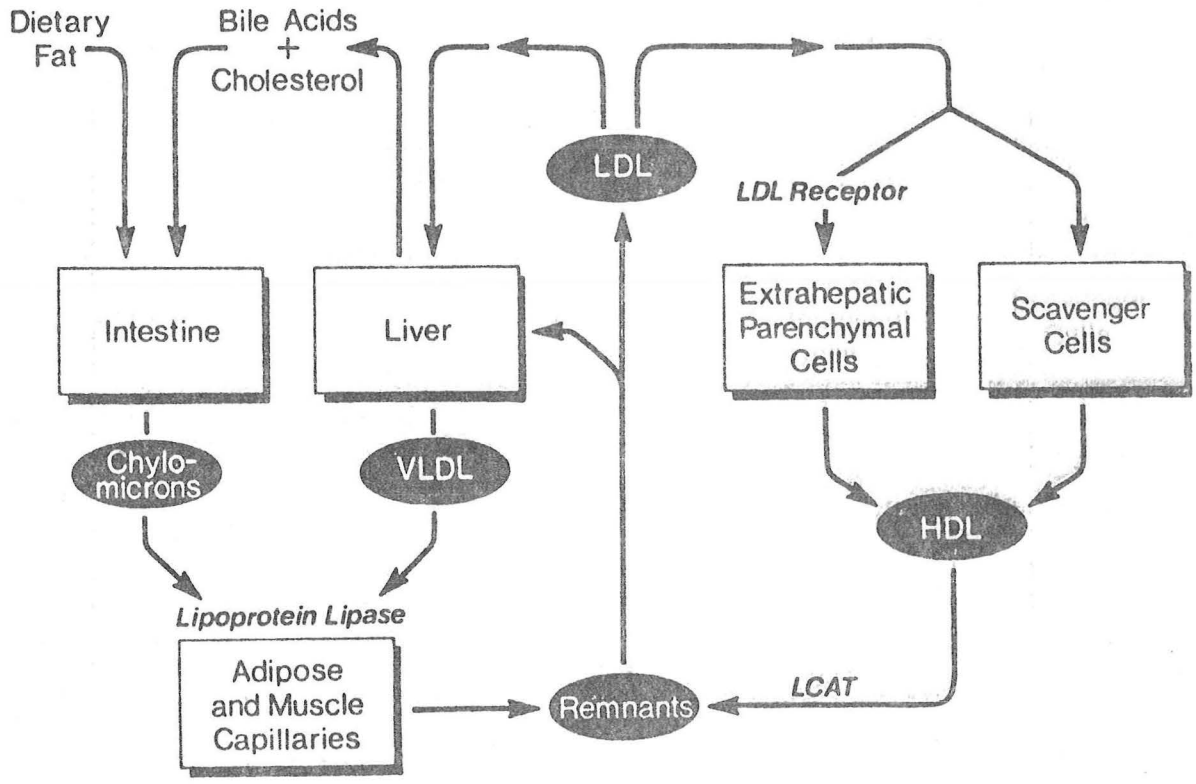
* From references 3-9. Some apoproteins of questionable significance have been omitted (e.g. apoD and apoH).
§ B_I refers to apoB derived from the intestine (8).

Table 3. Apoprotein Composition of Human Plasma Lipoproteins+

Content	Chylomicrons	VLDL	LDL	HDL
Major apoproteins	A-I B B_I*	B C-I C-II C-III E	B	A-I A-II
Minor apoproteins	A-II E§ C-I C-II C-III	A-I A-II	C	C-I C-II C-III E

* B_I refers to apoB derived from the intestine (8).
§ apoE is minor in terms of quantity but plays an important role in chylomicron remnant uptake by the liver.
+ From references 3-7.

Figure 2



For clinical purposes, it is helpful to know that the chylomicrons are larger and less dense than plasma; therefore plasma rich in chylomicrons is opaque or lactescent and if such plasma is refrigerated, the chylomicrons coalesce and float to the surface to form a cream layer. Inspection of refrigerated plasma is therefore useful in detecting the presence of chylomicrons in plasma.

Following ingestion of dietary fat, chylomicrons are synthesized in intestinal epithelial cells and then secreted into the lymph. They are carried by the lymphatics to the venous system where they enter the plasma space. Once in the general circulation, they interact with lipoprotein lipase (LPL), an enzyme found in many tissue capillary beds but especially in adipose tissue, muscle (skeletal and cardiac), lung and lactating mammary gland (3,14,15). This enzyme digests the triglyceride in the chylomicrons, liberating fatty acids which can either be used immediately for energy or stored for later use. After about 75% of the triglyceride is removed from chylomicrons, the remnant particles are quickly removed from the circulation by the liver (14,16).

This overall pathway has several features which tend to prevent chylomicron metabolism from becoming chaotic:

1) Newly secreted chylomicrons have a greater affinity for lipoprotein lipase and much less affinity for hepatic receptors (16-19).

2) Newly secreted chylomicrons acquire apoC-II from HDL by simple exchange (14). ApoC-II is known to activate lipoprotein lipase; thus chylomicrons carry a trigger mechanism for their own catabolism (20,21).

3) Chylomicron remants have a much greater affinity for hepatic receptors and much less affinity for lipoprotein lipase than do chylomicrons (17-19). Presumably, an apoE binding site is uncovered when chylomicrons are converted to remnants and this binding site is responsible for the rapid uptake of remnants by the liver (22-24). The appearance of the apoE binding site may partly be related to the loss of apoC from chylomicrons as the triglyceride is removed from the core (13,25).

Another lipase, distinct from lipoprotein lipase (26), is found on the endothelial surface of hepatic sinusoids. It is called hepatic triglyceride lipase and it is thought to play a role in HDL metabolism (27-29). Thus far, this enzyme has not been implicated in the pathogenesis of any hypertriglyceridemic syndromes.

The metabolism of VLDL (Figure 2) is similar but not identical to that of chylomicrons (7,30). VLDL is secreted from the liver and functions to transport triglyceride from this organ to extrahepatic tissues during the post-absorptive state. VLDL triglyceride is also hydrolyzed by lipoprotein lipase and a remnant,often called Intermediate Density Lipoprotein (IDL), is formed (30). Normally IDL is converted to LDL by an, as yet, unknown reaction but hepatic triglyceride lipase has been implicated in the process (34,35). In hyperlipemic states, IDL may be catabolized directly without conversion to LDL (31,32). Unfortunately, in hyperlipemic syndromes, chylomicron remnants may be present and are indistinguishable from VLDL particles; thus the alleged direct catabolism of IDL may actually represent catabolism of chylomicrons and not VLDL remnants. This issue is unresolved.

LDL is the metabolic product of VLDL catabolism. LDL contains most of the plasma cholesterol and its function is to transport this sterol from the liver to extrahepatic tissues where it is taken up by a well-described specific receptor mechanism (33).

In summary, both chylomicrons and VLDL transport triglyceride in the plasma and the triglyceride in both is hydrolyzed by lipoprotein lipase. The chylomicron remnant resulting from the action of lipase is catabolized rapidly by a specific receptor mechanism in the liver and the recognition site on the remnant is apoE. The VLDL remnant termed 'IDL' is rapidly converted to LDL and then cleared more slowly throughout the body by a specific receptor mechanism; the recognition site or LDL is apoB. Current evidence favors the hypothesis that a single receptor recognizes both apoE and apoB (24,36).

III. The Normal Triglyceride Level: A definition of the "normal" triglyceride level in the North American population is undergoing some change. For a long time, the accepted normal triglyceride level was that established by the National Heart Lung and Blood Institute (Table 4) (2).

Table 4. Suggested "Normal Limits" for Plasma Lipid Concentrations, mg/dl.

Age, yr	Cholesterol, mean and 90 percent limits	Triglycerides, mean and 90 percent limits
0-19	175 (120-230)	65 (10-140)
20-29	180 (120-240)	70 (10-140)
30-39	205 (140-270)	75 (10-150)
40-49	225 (150-310)	85 (10-160)
50-59	245 (160-370)	95 (10-190)

Similar but slightly higher values were observed in the Seattle Study where an age-adjusted mean ±1 SD (at age 45) for triglyceride was 94 ± 52 mg/dl for women and 97 ± 50 mg/dl for men (37).

However recently published results from the Lipid Research Clinics Program Prevalence Study indicate that the "normal range" (statistically defined) may be much higher than was previously thought (tables 5,6 and 7) (38,39). In men, the upper 95th percentile for triglyceride peaks at 327 mg/dl during ages 45-49 (Table 5). Levels are slightly lower in white women not taking steroids; the peak 95th percentile in this group is 262 mg/dl during ages 55-59 (Table 6). Values are slightly higher in women taking sex hormones (Table 7).

Table 5. *Plasma Triglyceride (mg/dl) for White Males—Lipid Research Clinics Program Prevalence Study, Visit 1*

Age (years)	n	Mean	SD	Percentiles 5	10	50	90	95
0–4	238	56.4	24.2	29	33	51	84	99
5–9	1253	55.7	22.7	30	33	51	85	101
10–14	2278	65.6	30.6	32	37	59	102	125
15–19	1980	78.0	38.1	37	43	69	120	148
20–24	882	100.3	56.4	44	50	86	165	201
25–29	2042	115.8	104.3	46	54	95	199	249
30–34	2444	128.3	121.2	50	58	104	213	266
35–39	2320	144.9	120.8	54	62	113	251	321
40–44	2428	151.4	146.8	55	64	122	248	320
45–49	2296	151.7	115.8	58	68	124	253	327
50–54	2138	151.8	117.8	58	68	124	250	320
55–59	1621	141.4	88.1	58	67	119	235	286
60–64	905	142.3	94.4	58	68	119	235	291
65–69	750	136.7	142.2	57	64	112	208	267
70–74	484	129.5	70.8	57	68	112	217	258
75–79	244	129.1	69.1	59	65	112	206	267
80+	122	132.1	120.6	55	64	105	182	255
Total	24,425							

Table 6. *Plasma Triglyceride (mg/dl) for White Females Not Taking Sex Hormones—Lipid Research Clinics LRC Program Prevalence Study, Visit 1*

Age (years)	n	Mean	SD	Percentiles				
				5	10	50	90	95
0–4	186	63.9	24.3	34	38	59	96	112
5–9	1118	60.3	25.3	32	36	55	90	105
10–14	2080	75.4	30.9	37	44	70	114	131
15–19	1911	72.4	32.5	39	44	66	107	124
20–24	778	72.4	35.3	36	41	64	112	131
25–29	1329	74.7	37.0	37	42	65	116	144
30–34	1569	78.5	40.1	39	44	69	123	150
35–39	1606	86.2	49.0	40	46	73	137	176
40–44	1583	98.4	82.0	45	51	81	155	191
45–49	1515	104.5	69.5	46	53	87	170	214
50–54	1257	114.8	69.6	52	59	97	186	233
55–59	1112	125.0	76.7	55	63	106	203	262
60–64	723	126.9	88.5	56	64	105	202	239
65–69	593	131.3	110.1	60	66	112	204	243
70–74	411	133.8	112.1	60	69	113	205	231
75–79	207	127.9	101.0	57	69	106	195	242
80+	130	135.2	103.8	60	70	112	211	242
Total	18,108							

Table 7. *Plasma Triglyceride (mg/dl) for White Females Taking Sex Hormones—Lipid Research Clinics Program Prevalence Study, Visit 1*

Age (years)	n	Mean	SD	Percentiles				
				5	10	50	90	95
10–14	7	62.9	17.4					
15–19	167	106.3	50.0	49	54	95	162	200
20–24	788	105.3	41.5	55	63	98	155	176
25–29	855	110.4	47.9	57	64	101	164	191
30–34	579	115.8	47.7	58	67	106	179	206
35–39	406	126.0	58.1	56	66	112	200	241
40–44	466	128.9	73.2	58	67	113	205	237
45–49	627	129.6	90.9	53	63	111	210	260
50–54	729	130.0	97.2	57	65	110	200	248
55–59	577	126.5	65.7	62	68	110	203	238
60–64	341	126.0	64.5	57	64	112	197	240
65–69	224	129.5	66.6	60	65	110	201	234
70–74	95	110.0	55.3	54	66	113	198	224
75–79	26	110.0	34.4					
80+	11	115.9	41.1					
Total	5,898							

The evolution of the statistical normal level for triglyceride does not significantly affect our assessment of the hypertriglyceridemic syndromes since they are typically associated with fasting plasma triglyceride levels clearly in excess of the LRC Prevalence Program 95th percentile cut points.

IV. The Primary Hypertriglyceridemic Syndromes

Currently six primary hypertriglyceridemic syndromes can be identified (Table 8) but it is likely that more will emerge as additional genetic defects are discovered. Each one will be briefly discussed below.

Table 8

Primary Hypertriglyceridemic Syndromes

1. Familial Lipoprotein Lipase Deficiency
2. Familial Apolipoprotein C-II Deficiency
3. Familial Dysbetalipoproteinemia
4. Familial Endogenous Hypertriglyceridemia
5. Familial Type 5 Hyperlipidemia
6. Familial Multiple Lipoprotein-Type Hyperlipidemia
7. Sporadic Hypertriglyceridemia

1. Familial Lipoprotein Lipase Deficiency

(Familial Type I Hyperlipoproteinemia, Bürger-Grütz Syndrome) (2,3,40).

Clinical picture: This is a rare form of hyperlipoproteinemia. Patients present with fasting hyperchylomicronemia when consuming a diet containing ordinary amounts of fat. Age of onset is variable and the diagnosis has been made in an 8-day-old infant (41). The major clinical feature of the disease is recurrent pancreatitis. Hepatosplenomegaly is also common as are eruptive xanthomas; obesity is unusual. Foam cells have been described in various tissues (42,43) but atherosclerosis is unusual. Plasma is lipemic and will contain a cream layer with a slightly turbid or clear infranatant; the blood may appear as "cream-of-tomatoe soup". Lipemia retinalis may be observed.

Biochemical defect and pathogenesis: Patients lack the enzyme, lipoprotein lipase, which is responsible for the normal catabolism of chylomicrons and VLDL. However, only chylomicron levels are severely elevated while VLDL may be normal or only slightly increased. Recent evidence suggests that the lipase deficiency may represent a heterogeneous group of disorders (44). The plasma level of apo-

C-II, the activator of lipoprotein lipase, is normal or increased in patients with primary lipase deficiency (46). Pancreatitis is thought to result from hyperchylomicronemia when pancreatic lipase acts locally within the pancreas to liberate fatty acids which in turn produce local irritation (45).

Diagnosis: The diagnosis is suggested when severe fasting hyperchylomicronemia is observed in a young child or in a non-obese young adult. The diagnosis is confirmed by showing that lipoprotein lipase levels are virtually absent with one of several conventional assays. However, the assays are only done in a few research labs.

Treatment: Dietary fat (both saturated and unsaturated) must be restricted to no more than 30 gm/day. Medium chain triglyceride may be used for dietary supplementation. On this regimen, fasting plasma triglycerides may drop to about 500-1000 mg/dl at which attacks of pancreatitis are relatively uncommon. There is no known effective drug treatment.

2. Familial Apolipoprotein C-II Deficiency

(Familial Lipoprotein Lipase Cofactor Deficiency)

Clinical picture: This interesting disorder was first described in 1978, and nearly 20 cases have already been detected (47,51,52). The disease usually presents as severe hyperchylomicronemia often complicated by pancreatitis (47,50) and several cases have been initially misdiagnosed as having Familial Lipoprotein Lipase deficiency (49). The age of detection is variable and ranges from 6 to 49 years. The major clinical features observed in 14 cases is shown in Table 9.

Table 9.

Homozygotes for apo CII Deficiency
(8 males & 6 females, ages 16-64 years)[a,b]

N	Findings
14	chylomicronemia
9[a]	pancreatitis 1 diabetes & malabsorption 1 pseudocyst
2	peptic ulcer
3	splenomegaly
0	hepatomegaly
0	xanthomata
1	corneal arcus, age 62
8	anemia
3	hypertension (age 39,41,63 Yr.)
2	CHD (age 59 & 62)
2	cataracts (age 59 & 62)
2	peripheral pain at rest
3	chronic rashes
1	ecchymoses
2	obese

[a] In addition to these, one sib of a homozygote died of acute pancreatitis prior to this study and presumably was a homozygote.
[b] Mean age of onset: symptoms at 10 years, detection of lipemia at 14 years.

Although the hyperchylomicronemia is severe, eruptive xanthomas have not been observed, nor has there been any hepatosplenomegaly detected (49,50); these observations differ from those noted with classic Familial Lipoprotein Lipase Deficiency. Obesity and diabetes are uncommon.

Typical plasma lipid levels in homozygotes are shown in Table 10.

Table 10.

Homozygotes with Apolipoprotein C-II Deficiency.

Pedigree No.	Sex	Present Age	Age at Onset of Pancreatitis	MA*	DM†	Plasma Cholesterol	Plasma Triglycerides
		yr	*yr*			*mg/dl*	
V-13 (proband)	M	62	+ (20)	+	+	980	9,473
V-5	M	60	+ (37)	–	–	520‡	5,866‡
V-6	F	55	?	–	–	330	2,050
VI-1	F	23	–	–	–	151	1,310
VI-3	M	20	–	–	–	176	1,760
VI-6	M	18	+ (6)	–	–	530	5,220
VI-7	F	41	+ (36)	–	–	240‡	2,417‡
VI-11	M	44	+ (39)	–	–	500	3,660

*Malabsorption syndrome. †Diabetes mellitus.

‡Not fasting; all others 12 hr or longer fast.

Biochemical Defect and Pathogenesis: Patients homozygous for apo-C-II deficiency are not able to activate lipoprotein lipase and the metabolism of triglyceride-rich lipoproteins is impaired. In this respect, patients phenotypically resemble patients with familial lipoprotein lipase deficiency. However, apoC-II-deficient patients have detectable LPL when normal plasma containing apoC-II is added to their post-heparin plasma (47,51) and patients transfused with normal blood or plasma respond by promptly clearing their hypertriglyceridemia to a significant degree (Figure 3) (47).

Figure 3

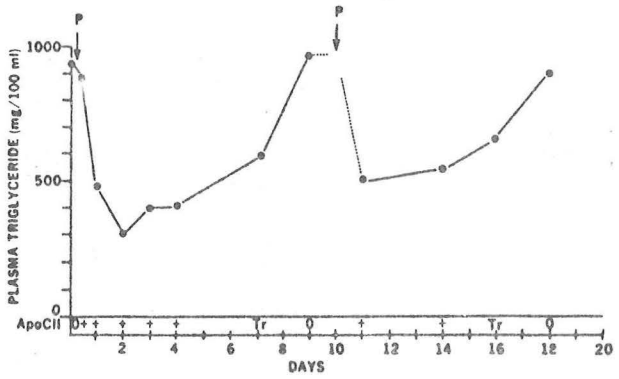


Figure 5. Effect of Transfusions of Normal Plasma on the Plasma Triglyceride Concentrations of a Patient with Apolipoprotein C-II Deficiency.

At the times indicated by P, 1 unit of plasma was infused intravenously over a two-hour period. Apolipoprotein C-II was detectable as indicated by +, Tr (trace) and 0 (not detectable) by the analyses of the apolipoproteins by polyacrylamide-gel electrophoresis and by the activation of guinea-pig lipoprotein lipase.

Genetics: The available evidence is compatible with inheritance of an autosomal recessive trait (48,49). Consanguinity was present in both well-studied pedigrees. Furthermore, while obligate heterozygotes have plasma apoC-II concentrations about 30-50% of normal, their plasma lipid and lipoprotein concentrations are either normal or only minimally elevated (48.49,51).

Diagnosis: The diagnosis should be considered in anyone with marked hypertriglyceridemia and pancreatitis and/or an apparent deficiency of lipoprotein lipase. Confirmation of the diagnosis requires special techniques to measure both the plasma level of apoC-II and the post-heparin lipoprotein lipase activity before and after addition of normal C-II. A presumptive diagnosis could be made if hypertriglyceridemia improves dramatically following the transfusion of normal plasma.

Treatment: A low fat diet similar to that used in Familial Lipoprotein Lipase Deficiency is required to treat patients with apoC-II deficiency. There is no known effective drug treatment.

3. Familial Dysbetalipoproteinemia

(Familial Type 3 Hyperlipidemia, Broad-beta Disease)

Clinical Picture (2,3,53-57): The full-blown clinical syndrome including hyperlipidemia, xanthomas and atherosclerosis is relatively rare. The hyperlipidemia results from the accumulation in the plasma of an abnormal lipoprotein which is relatively enriched in cholesterol and depleted of triglyceride when compared to normal VLDL (58-60). These lipoproteins are actually thought to represent the abnormal accumulation of metabolic "remnants" of chylomicron and VLDL catabolism. A summary of the clinical and biochemical features of the patients in one large study is presented in Table 11 (53).

Table 11.

Comparison of Clinical and Biochemical Data on Patients with Type III Hyperlipoproteinemia

	Present Study	Borrie (6)	Mishkel (7)
Patients			
Total, *no.*	47	18	16
Age range, *yrs*	23-70	24-53	26-59
Mean cholesterol, *mg/100 ml*	453	429	465
Mean triglyceride, *mg/100 ml*	699	600	733
	←	*% of patients*	→
Xanthomas			
Palmar xanthomas (xanthoma striata palmaris)	64	72	44
Tendinous xanthomas	23	17	38
Tuberous xanthomas (xanthoma tuberosum)	51	100	88
Eruptive xanthomas	4	28	
Xanthelasma	6	6	25
Corneal arcus	6	11	31
Ischemic heart disease	37	28	31
Peripheral vascular disease	29	11	31

The most medically significant complication of Familial Dysbetalipoproteinemia is atherosclerosis which affects both the coronary and peripheral vasculature. The atherosclerosis is premature and men are affected at a younger age than are women (Table 12).

Table 12.

Age of Onset of Vascular Disease In Patients with Type III Hyperlipoproteinemia*

	Ischemic Heart Disease	Peripheral Vascular Disease	Cerebral Vascular Disease
Men	38.1 ± 3.4 (11)	38.1 ± 4.8 (8)	57.5 ± 0.5 (2)
Women	49.7 ± 2.9 (7)	50.5 ± 3.9 (4)	53.7 ± 7.9 (3)

* Numbers in parentheses represent number of patients in each group. Age is in years (mean ± SEM).

Xanthomas are frequently observed and 2 types of xanthomas are fairly unique to this disorder. Lipid deposition in the palmar creases (xanthoma striata palmaris) are characteristic but do not occur in all patients. Tuberous xanthomas and tubero-eruptive xanthomas are orange or yellow-orange lesions on the elbows, knees, or other pressure points. Both of these xanthomatous deposits disappear when appropriate therapy is given.

Associated abnormalities include hyperuricemia (40%), abnormal glucose tolerance (55%) and obesity (53,55). There is no evidence for a primary insensitivity to either insulin or glucagon in patients with this disease (61).

Expression of the full-blown disease in childhood is unusual and most affected individuals are detected when they are young or middle-aged adults (53,56). Hypothyroidism also accentuates the expression of the disease (57).

Biochemical Defect and Pathogenesis: The disease results from a genetic mutation affecting apolipoprotein E. Patients are homozygous for a mutant allele which results in increased plasma levels of an abnormal form of apoE (62-73). It was initially thought that the defect was a deficiency in one of the polymorphic forms of apoE (apoE-3 deficiency) (66) but very recent evidence indicatesthat no deficiency exists; instead, the mutant allele codes for a structurally abnormal form of apoE (72). In the isolated perfused rat liver system, artificial lipid-protein complexes made with apoE from patients with Familial Dysbetalipoproteinemia are taken up much more slowly by the hepatocytes than are complexes made with normal apoE (73). These results are compatible with the hypothesis that remnant lipoproteins accumulate in these patients because the abnormal structure of apoE renders them less susceptible to uptake by specific hepatic receptors (73). Lipoprotein turnover studies using radiolabeled lipoproteins indicate that the catabolism of both chylomicron and VLDL remnants is impaired (31,74-76), thereby lending further support for the above hypothesis. Adipose tissue lipoprotein lipase is normal in this disease (77).

Genetics: ApoE consists of multiple forms in the plasma. Patients with Clinical Familial Dysbetalipoproteinemia are homozygous for a mutant allele and as a result they produce a structurally abnormal form of apoE. Pedigree and population studies indicate that this homozygous state is required but not sufficient to produce the full-blown clinical syndrome. It appears that the homozygous apoE abnormality is fairly common (∿ 1% of the population) but by itself does not lead to hyperlipidemia unless an additional abnormal gene for hyperlipidemia is present in an individual (Figure 4) (68-70,78).

Figure 4

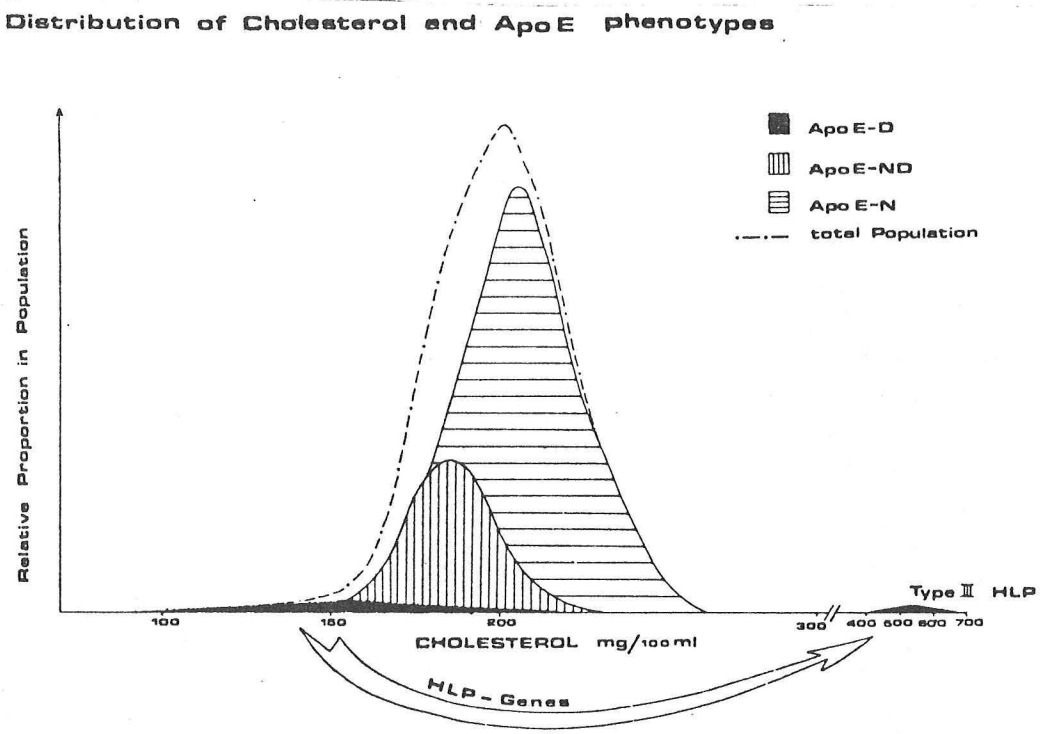


Fig. 3. Schematic representation demonstrating the presence of the three overlapping cholesterol distributions in the population that are determined by the Apo E phenotypes, and of the interaction of phenotype Apo E-D and "hyperlipidemia genes" in producing severe hyperlipoproteinemia type III.

Thus the clinical expression of the disease may vary somewhat depending on the nature of the additional abnormal hyperlipidemia gene.

Diagnosis: On clinical grounds, the presence of tuberous, tuberoeruptive or palmar xanthomas is highly suggestive. Another clue is the presence of hypercholesterolemia and hypertriglyceridemia to about the same degree (e.g. ∿ 500 mg/dl each).

Another way to test for the diagnosis is to measure the VLDL cholesterol/total triglyceride ratio since it has been shown that when the total plasma triglyceride level is between 150 and 1000 mg/dl, a ratio of 0.25 suggested the diagnosis of Familial Dysbetalipoproteinemia and a ratio of 0.3 or more is diagnostic of the disorder (54). Unfortunately most clinical laboratories are not able to perform this analysis.

The diagnosis is confirmed by demonstrating the presence of the abnormal forms of apoE using 2-dimensional polyacrylamide gel electrophoresis (72). Unfortunately this technique is only available in a few research laboratories at the present time.

In a general medical setting, therefore, it is only possible to make a presumptive diagnosis based on clinical grounds.

Treatment: Diet therapy with weight loss is very effective in reducing the plasma lipid levels. Several lipid-lowering diets can be used but in one study using a 40% fat ($P/S = 2$), 40% carbohydrate, 20% protein diet restricted in calories and alcohol, the results were impressive (Table 13) (53).

Table 13. Response of Plasma Lipids to Therapy in Familial Dysbetalipoproteinemia

	Cholesterol	Triglyceride
	mg/dl	
Before diet therapy	453 ± 21	699 ± 77
After diet therapy	185 ± 6	131 ± 7

Patients who do not follow or respond to the diet very well can be treated with clofibrate at a dose of 2 gm b.i.d. (2,80). Nicotinic acid is also useful. It has been shown, using plethysmography, that the control of hyperlipidemia in this disease can result in improved peripheral circulation (79).

Women show a significant hypolipidemic response to estrogen therapy but estrogen should only be tried if the diagnosis of Familial Dysbetalipoproteinemia is firm (81,82).

4. Familial Endogenous Hypertriglyceridemia

(Familial Hypertriglyceridemia, Primary or Familial Type 4 Hyperlipoproteinemia)

Clinical Picture (2,3,83): Familial Endogenous Hypertriglyceridemia is a genetic disorder affecting plasma VLDL metabolism. It is inherited as an autosomal dominant trait (85) and full expression of the abnormality does not occur until individuals reach their early 20's (84-86). Typical plasma lipid levels in heterozygotes are as follows: cholesterol 241 mg/dl, triglyceride 267 mg/dl (85); in fact, the range for triglyceride levels is considerable, varying from about 240 to 900 mg/dl or more (87). Individuals homozygous for this condition have not been recognized.

Several additional abnormalities, including obesity, insulin resistance, fasting hyperinsulinemia, glucose intolerance, hypertension, and hyperuricemia, have been found with apparent increased frequency in patients

with hypertriglyceridemia but their presence in these patients is not a constant feature, indicating that they are not causally related to the hypertriglyceridemia. It is possible, however, that these associated conditions may aggrevate the hypertriglyceridemia (87).

Familial Endogenous Hypertriglyceridemia was initially thought to be associated with premature atherosclerosis (2,85) but Brunzell and co-workers have presented evidence to show that the frequency of myocardial infarctions in living hyperlipidemic relatives with familial hypertriglyceridemia is no greater than it is in either normolipidemic relatives or spouse controls (Table 14) (88).

Table 14.

Myocardial Infarction in Living Relatives

	Age, years (x ± S.D.)	Males	Females	Total	p = *
Familial combined hyperlipidemia (24 families)					
Hyperlipidemic relatives	50.4 ± 12.7	7/27	3/30	10/57 (17.5%)	
Normolipidemic relatives	47.0 ± 12.8	2/45	3/49	5/94 (5.3%)	p = 0.017
Familial hypertriglyceridemia (19 families)					
Hyperlipidemic relatives	49.3 ± 13.3	1/18	1/25	2/43 (4.7%)	p = 0.045
Normolipidemic relatives	54.4 ± 15.8	1/22	1/39	2/61 (3.3%)	p = 0.011
Spouse Controls	47.1 ± 9.9	5/68	3/87	8/155 (5.2%)	p = 0.007

*As compared to hyperlipidemic relatives with familial combined hyperlipidemia.

*The age of 29 years was used since full penetrance of the familial disorders involving triglyceride metabolism is found after that age.[4] No myocardial infarctions were seen before the age of 30 yr.

Despite this evidence, many specialists in this area still believe that hypertriglyceridemia is associated with premature atherosclerosis.

Familial endogenous hypertriglyceridemia is not associated either with pancreatitis or xanthomas, but an increased frequency of gallstones has been observed (108,109).

Biochemical Defect and Pathogenesis: No biochemical defect has been found in this disorder and it is possible that familial endogenous hypertriglyceridemia encompasses several disorders. Lipoprotein lipase is usually normal both in vivo and in vitro (94-97).

A number of investigators have argued that hyperinsulinemia often observed in patients with endogenous hypertriglyceridemia is actually involved in the pathogenesis of the hypertriglyceridemia by stimulating the liver to secrete VLDL (91,93). Others argue that the hyperinsulinemia is actually associated with co-existing obesity and is therefore a secondary event (90,92). The role of the hyperinsulinemia is the pathogenesis of hypertriglyceridemia cannot be resolved at the moment.

Glucose intolerance is also noted with increased frequency in patients with endogenous hypertriglyceridemia and for a time these two ab-

normalities were thought to be linked together in some fashion. However Brunzell and co-workers have shown through family studies that diabetes mellitus and hypertriglyceridemia appear to be independently inherited and they conclude that hypertriglyceridemia, per se, does not carry an increased risk for diabetes (Table 15) (89).

Table 15.

Prevalence of Diabetes in Genetic Hypertriglyceridemia

	Diabetes	No Diabetes	Total
Hypertriglyceridemic Propositi	*n* = 25	*n* = 66	*n* = 91
Relatives >39 yr old			
Hyperlipidemic	3/23 (13.0%)	5/80 (6.2%)	8/103 (7.8%)
Normolipidemic	5/34 (14.7%)	5/125 (4.0%)	10/159 (6.3%)
Total	8/57 (14.0%)	10/205 (4.9%)	

Prevalence of diabetics in spouse controls 4/232 (1.8%).

Investigators have attempted to define the pathogenesis of hypertriglyceridemia kinetically in terms of either lipoprotein overproduction or impaired catabolism or a combination of both (98-103). Results of such studies have been either inconclusive (98,100,103) or contradictory (99,102). Obesity, per se, is associated with triglyceride overproduction (100) but hypertriglyceridemia doesn't result unless catabolic processes are also impaired in some way (100). Often, VLDL turnover studies in hypertriglyceridemic individuals indicate that overproduction, impaired catabolism, or a combination of both occur (100,103).

Genetics: The disorder is inherited as an autosomal dominant trait (85,86). Patients homozygous for this condition have not been recognized.

Diagnosis: A specific diagnosis in the individual patient is not possible because these patients have no unique clinical or biochemical features to distinguish them from patients with other genetic or non-genetic forms of hypertriglyceridemia. The diagnosis can only be made with certainty when the patient has relatives affected with the same abnormality (2,3).

Treatment: The initial form of treatment is diet therapy. The composition of the diets used by different groups vary somewhat but all agree that calories should be restricted to achieve ideal body weight. The carbohydrate content varies from 40-50% of the calories, the fat from 30-40%, and the protein from 15-20%. Daily cholesterol intake is usually limited to 300 mg/day and the polyunsaturate/saturate fat ratio varies from 1 to 2 (104-107, 110,111). Alcohol is known to aggrevate hypertriglyceridemia so it should not be included in the diet.

If weight loss is either not achieved or does not lower the lipids adequately, therapy with either clofibrate or nicotinic acid can be employed. At times, both drugs are effective when used in combination.

Exercise also has a beneficial effect in lowering plasma triglyceride levels (113,114).

5. Familial Type 5 Hyperlipoproteinemia

Clinical Picture: It is not clear that this disorder is distinct from Familial Endogenous Hypertriglyceridemia and there is an increasing tendency to consider them together as different manifestations of a similar abnormality (3,87,115). The hyperlipoproteinemia consists of hyperchylomicronemia and hyperprebetalipoproteinemia. As a consequence, the triglycerides are typically > 1000 mg/dl and lipemic plasma with a cream layer is evident. The cholesterol may also be elevated but the triglyceride elevation exceeds it by 6 to 10 fold.

The major clinical abnormality associated with this problem is pancreatitis (115-119, 126-129) and the attacks begin to appear when the hypertriglyceridemia exceeds the range of 1000-2000 mg/dl. Atherosclerosis is not a common manifestation of this disorder (115,116) but it does appear to be accelerated in some patients (120,123,125).

The hypertriglyceridemia is made worse by weight gain, estrogens, alcohol consumption and poorly controlled diabetes (115,116). Both hyperuricemia and diabetes appear more prevalent in these individuals.

Lipemia retinalis and eruptive xanthomas are fairly common (3,116,134), as is hepatosplenomegaly (40,121). The clinical abnormalities found in type 5 hyperlipoproteinemia are shown in Table 16 (121).

Table 16.

The proportion of patients, expressed as percentages, with Type V hyperlipoproteinaemia experiencing clinical abnormalities in the series of Fredrickson & Levy (1972) compared with the present series

	Abnormal glucose tolerance	Ischaemic heart disease	Peripheral vascular disease	Eruptive xanthoma	Hepatosple-nomegaly	Abdominal pain	Pancrea-titis	Hyperuri-caemia
Fredrickson & Levy (1972)	82	4·5	0	45	32	75	41	41
Present series	55	0	0	100	44	33	10	55

Biochemical Defect and Pathogenesis: No consistent biochemical defect has been identified. Lipoprotein lipase levels are reported to be low or normal (97,116). It is well recognized that patients may show varying lipoprotein patterns, often shifting repeatedly between type 4 and type 5 patterns. Also the triglyceride levels may show wide swings from time to time. The reason for this variability is thought to relate to the saturability of the lipoprotein lipase clearing system (133). Normally the lipolytic rate increases as the plasma triglyceride increases up to about 500 mg/dl. Between 500-1000 mg/dl, the lipolytic rate begins to level off and does not increase significantly as triglycerides exceed 1000 mg/dl (Figure 4).

Figure 4

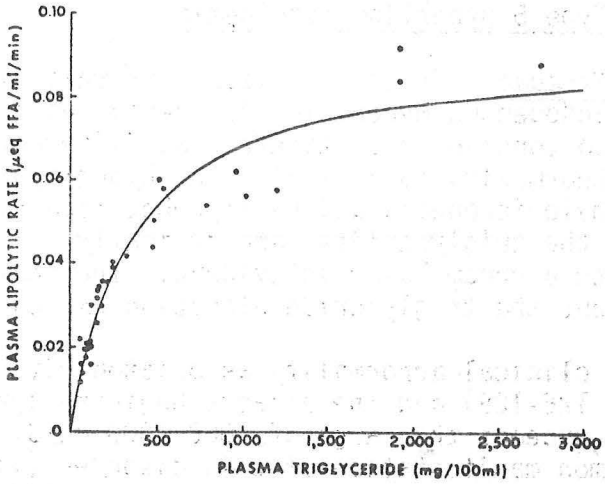


FIGURE 3 Plasma lipolytic rate and plasma triglyceride concentration at equilibrium during heparin infusion obtained from studies in multiple subjects (8–17, Table I), studied sequentially before and after caloric manipulation on a fat-free diet. Hyperbola calculated as best fit by least squares after Woolf linear transformation.

Thus, simple dietary factors can be manipulated sufficiently to change plasma lipoprotein patterns from type 4 to 5 and vice versa (Figure 5).

Figure 5

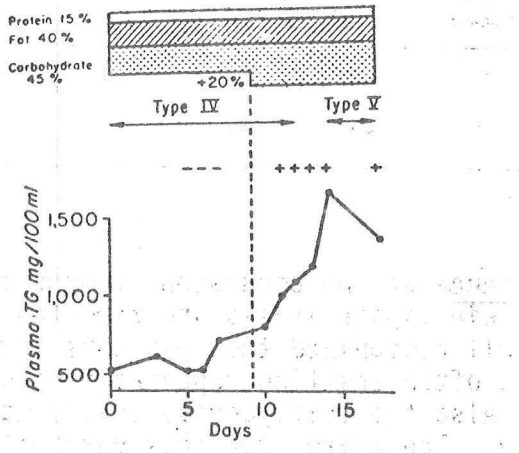


FIGURE 1 Effect of carbohydrate overfeeding on plasma triglyceride in a subject with a Type IV pattern (no. 3, Table I) on constant fat diet. Presence of chylomicrons in fasting plasma indicated by PVP flocculation (— not present, + present).

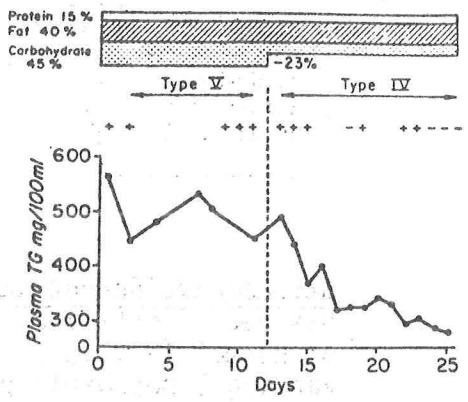


FIGURE 2 Effect of carbohydrate restriction on plasma triglyceride in a subject with a Type V pattern (no. 6, Table I) on constant fat diet. Presence of chylomicrons in fasting plasma indicated by PVP flocculation (+ present, — not present).

Genetics: The genetics of this disorder are not conclusively established but it is tentatively considered to be transmitted as an autosomal dominant trait (3). It is well recognized that patients with "type 5" hyperlipidemia usually have relatives with "type 4" or endogenous hyperlipidemia, thereby lending weight to the suggestion that type 5 hyperlipidemia is a more severe form of Familial Endogenous Hypertriglyceridemia (115,116,121,124).

Diagnosis: The picture of severe hypertriglyceridemia, eruptive xanthomas, lipemia retinalis, and a cream layer on the plasma is classic. Patients with pancreatitis should be checked for this disorder. Individuals with poorly controlled diabetes should be aggressively treated to establish the degree to which the severe hyperlipemia is related to the degree of diabetic control. In some instances the hyperlipemia may become insignificant after diabetic control is achieved.

Treatment: Weight loss and therapy with a total fat-restricted diet are needed (104). Drug treatment with nicotinic acid (131) and/or clofibrate are helpful. Norethindrone acetate is useful in treating women with this disease (132). Effective therapy can reduce or abolish the attacks of pancreatitis.

6. Familial Multiple Lipoprotein-Type Hyperlipidemia

(Previously called Familial Combined Hyperlipidemia) (37,85,86, 135-139)

Clinical Picture: This disorder has only recently been identified because the patterns of lipid elevation in the affected relatives of families vary considerably. About one-third of the affected relatives have hypercholesterolemia (2a pattern), one-third have hypertriglyceridemia (type 4 pattern) and one-third have hypercholesterolemia plus hypertriglyceridemia (2b pattern) (Figure 6) (135).

Figure 6

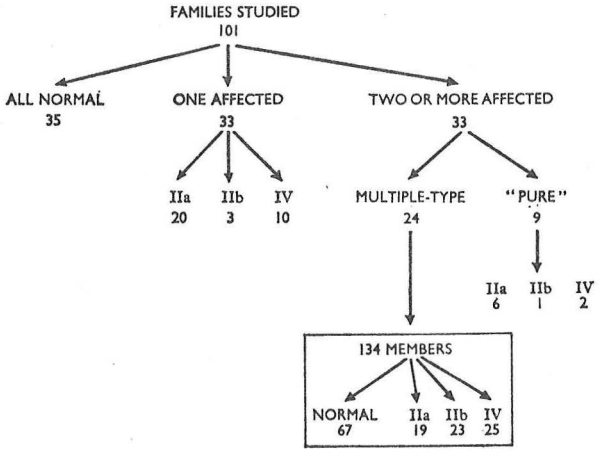


Fig. 3—Distribution of families of survivors of myocardial infarction according to the number and phenotype of members with serum-lipid abnormality.

Box indicates the individual type distribution of members in the families with multiple-type hyperlipoproteinæmia. Index patients are not included.

In a study of survivors of myocardial infarction, this disorder was seen in nearly 10% of the MI victims (85). For reasons outlined by Havel et al. this disorder appears to be distinct from either Familial Hypercholesterolemia or Familial Endogenous Hypertriglyceridemia (3). The disease is not expressed in children and it first makes its appearance, usually as hypertriglyceridemia, in the 3rd decade of life.

There are no unique clinical features associated with this disorder other than the characteristic lipid levels in the affected relatives. Xanthomas are not observed.

Biochemical Defect and Pathogenesis: Unknown.

Genetics: The disease is thought to be inherited as an autosomal dominant trait. However, this conclusion is tentative until the basic defect is identified and evaluated in family studies. It is possible that several disorders are included under this heading.

Diagnosis: A specific diagnosis in the individual patient is not possible because these patients have no unique clinical or biochemical features that set them apart from other individuals with hyperlipidemia. The diagnosis can only be made with certainty following family screening.

Treatment: Treatment has not been standardized. Therapy with a modified low fat, low cholesterol diet is the initial step. Weight loss is recommended if obesity is present. Drug therapy is empirical and the two most frequent agents employed are clofibrate and nicotinic acid. In one study, patient response to a clofibrate-like drug was variable (139).

7. Sporadic Hypertriglyceridemia:

Individuals with hypertriglyceridemia who either have no affected relatives or have too few relatives to test fall into this category. Thus, it represents a heterogeneous group of individuals. It was found in 5% of the survivors of myocardial infarction in one series (85). It is not currently possible to distinguish patients with Sporadic Hypertriglyceridemia from those patients with single-gene forms of primary hypertriglyceridemia. Therapy is non-specific and drug therapy if the diet alone has not been satisfactory.

V. A General Approach to Therapy of the Hypertriglyceridemic Patient

Most of the hypertriglyceridemic syndromes outlined in section IV are associated with significant pathological consequences such as eruptive xanthomas, pancreatitis, and coronary heart disease. However, as indicated in Table 17, the diagnosis of these disorders requires either special laboratory techniques or family testing and usually neither is available to the practicing physician.

Table 17. Diagnostic Procedures in the Hypertriglyceridemic Syndromes

Disorder	Diagnostic Procedure
Familial Lipoprotein Lipase Deficiency	Lipoprotein Lipase Assay
Familial Apolipoprotein C-II Deficiency	Lipoprotein Lipase Assay and PAGE*
Familial Dysbetalipoproteinemia	Analysis of VLDL by IEF§ on PAGE, or two-dimensional PAGE
Familial Endogenous Hypertriglyceridemia	Family Pedigree
Familial Type 5 Hyperlipidemia	Family Pedigree, Lipoprotein Lipase Assay, PAGE
Familial Multiple Lipoprotein-type Hyperlipidemia	Family Pedigree
Sporadic Hypertriglyceridemia	Family Pedigree

* PAGE = Polyacrylamide Gel Electrophoresis
§ IEF = Isoelectric Focussing

Nevertheless, the physician will often be required to treat the patient to control the clinical manifestations mentioned above. It is therefore useful to have a general therapeutic approach to the hypertriglyceridemic patient which provides adequate care in the absence of a specific diagnosis. In this general approach, attention must be given to those common factors which aggrevate or ameliorate the hypertriglyceridemia and these are obesity, alcohol, diabetes mellitus, estrogens, and hypolipidemic drugs.

1. Obesity: The beneficial effects of weight reduction on hypertriglyceridemia were shown clearly in careful studies by Olefsky et al. (140). These investigators studied a group of 36 patients with varying degrees of obesity whose plasma triglyceride levels ranged from 88 to 906 mg/dl. Patients were fed a liquid formula diet with a calorie breakdown as follows: 43% carbohydrate, 15% protein, 42% fat with a $^{P}/_{S}$ ratio of 0.21.

   The mean drop in fasting plasma triglyceride after weight reduction was 139 mg/dl (from 319 to 180 mg/dl). The cholesterol also dropped from 282 to 223 mg/dl (Figure 7) (140).

Figure 7

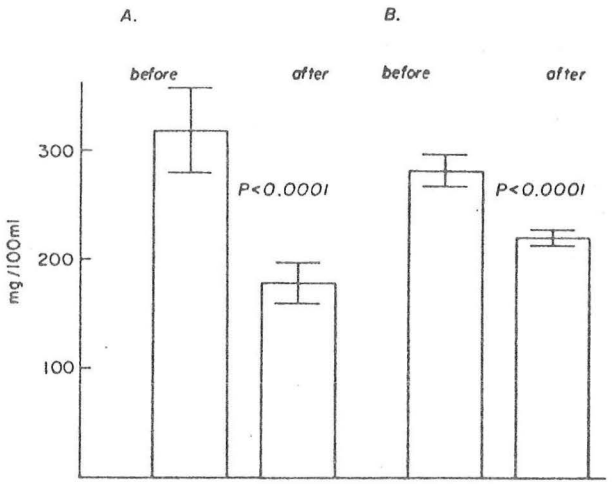


FIGURE 2 Plasma TG (A) and cholesterol (B) concentrations in 36 patients before and after weight reduction. Data are given as means±SEM.

The percent decrease was greater in those individuals who initially had the highest triglyceride levels (Table 18) (140).

Table 18.

Decrease in plasma TG and cholesterol levels in subjects divided into quartiles

Plasma TG range per quartile	Mean ±SE plasma TG levels*				Mean ±SE plasma cholesterol levels			
	Before	After	Absolute decrease	Percentage decrease	Before	After	Absolute decrease	Percentage decrease
1st quartile (71–147)	115±8	96±9	19	17	239±16	215±13	24	10
2nd quartile (159–228)	182±8	139±20	43	24	269±12	223±15	46	17
3rd quartile (254–357)	312±13	172±13	140	45	303±24	232±16	71	23
4th quartile	658±60	311±35	347	53	324±35	223±17	101	31

* The 36 subjects are divided into quartiles (9 in each quartile) on the basis of their plasma TG concentrations before weight reduction.
Of the nine subjects in the 1st quartile, six were classified as normal, and three had Type IIa hyperlipoproteinemia.
Of the nine subjects in the 2nd quartile, one was classified as Type IIa, three as Type IIb, and five as Type IV.
Of the nine subjects in the 3rd quartile, three were classified as Type IIb, one as Type III, and five as Type IV.
Of the nine subjects in the 4th quartile, two were classified as Type III and seven as Type IV.

This reduction in plasma triglyceride following weight loss was at least partly due to a decrease in the production of VLDL-triglyceride as measured by VLDL-TG turnover studies (Figure 8) (140).

Figure 8

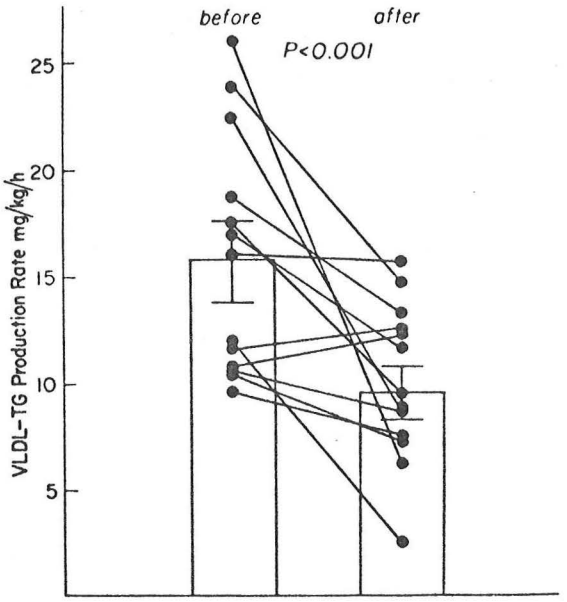


FIGURE 6 VLDL-TG production rates in 13 patients before and after weight reduction. The lines connect each patient's before and after value. Data are given as means±SEM.

In addition, similar degrees of triglyceride lowering were obtained when comparing the results in very obese subjects with those in less obese subjects (Table 19) (140).

Table 19. *Comparison of Effects of Weight Reduction in the Five Most Obese and the Five Least Obese Men**

	Weight	Adiposity	Insulin response‡	Glucose response‡	Plasma TG level§	Plasma cholesterol§
	kg	%				
Most obese						
Before	108.70	41.94	434	462	319	257
After	96.9	36.46	226	401	188	212
Difference	11.8	5.48	208	61	131	45
Decrease, %	11	13	48	13	41	18
Least obese						
Before	86.36	24.61	283	425	338	266
After	75.78	21.14	156	384	173	203
Difference	10.58	3.47	127	41	165	63
Decrease, %	12	14	45	10	48	24

* All numbers represent the mean of each observation in five subjects.
‡ Total area under the plasma response curve during the oral glucose tolerance test in each subject.
§ Mean of at least two fasting determinations in each subject.

Weight loss also results in improved glucose tolerance and less hyperinsulinemia (140).

The type of diet used to achieve weight loss should be nutritionally balanced. Most have calorie distributions as follows: 40-45% carbohydrate, 35-40% fat, 20% protein. Cholesterol intake varies from 300 to 500 mg/dl and the P/S ratio varies from 1 to 2 (104,107,111). It has recently been shown that diets containing less than 35% of the calories as fat are associated with lower all-day plasma triglyceride levels than are diets containing larger amounts of fat (141), suggesting that lower fat diets are theoretically better for treatment of hypertriglyceridemia.

Occasionally, lean patients with severe hypertriglyceridemia are encountered and in these cases, the dietary fat must be restricted to as little as 10% of the calories. Experience in one such patient is shown in Figure 9 (119). During period A, the patient was fed a 10% fat diet and her triglycerides were around 1000 mg/dl. When she was fed a 40% fat diet during period B, her triglycerides soared to > 4000 mg/dl.

Figure 9

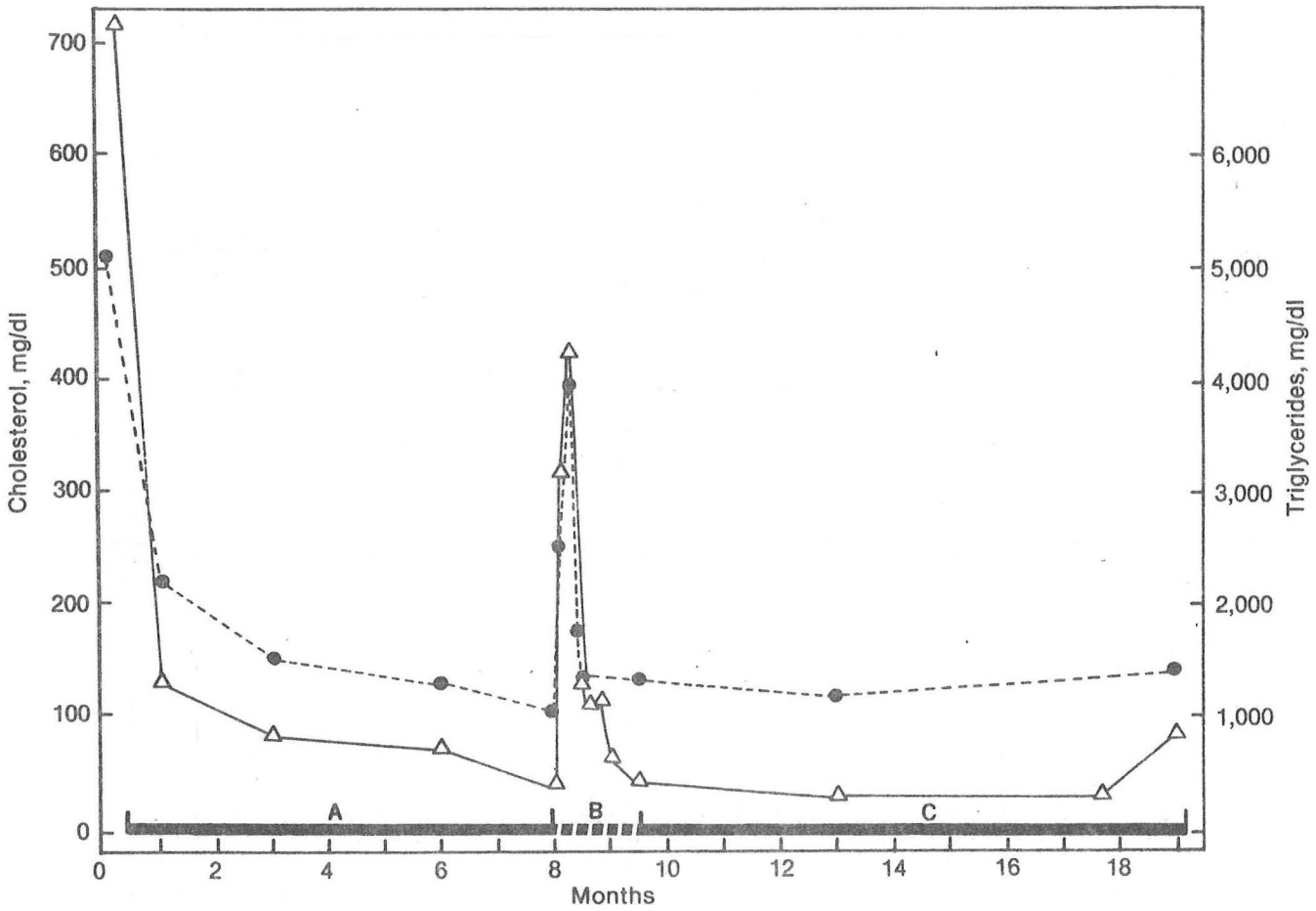


Fig 1.—Effect of diet on plasma lipid concentrations. During periods A and C, patient received a modified type I diet. During period B she received normal diet. Solid line indicates triglyceride levels; dashed line, cholesterol levels.

The amount of dietary fat such subjects can tolerate must often be established by trial and error but hyperchylomicronemic patients must usually drop their fat intake to 25% or less of total calories (104).

2. Alcohol: It is well established that alcohol will aggrevate hypertriglyceridemia (142-144) and alcohol-induced hypertriglyceridemia, if severe, may lead to pancreatitis (145). A steady daily alcohol intake of about 7½ oz. of whiskey will raise fasting triglyceride levels in both normal and hypertriglyceridemic individuals but the rise is proportionately greater in the hypertriglyceridemic subjects (Figure 10) (144).

Figure 10

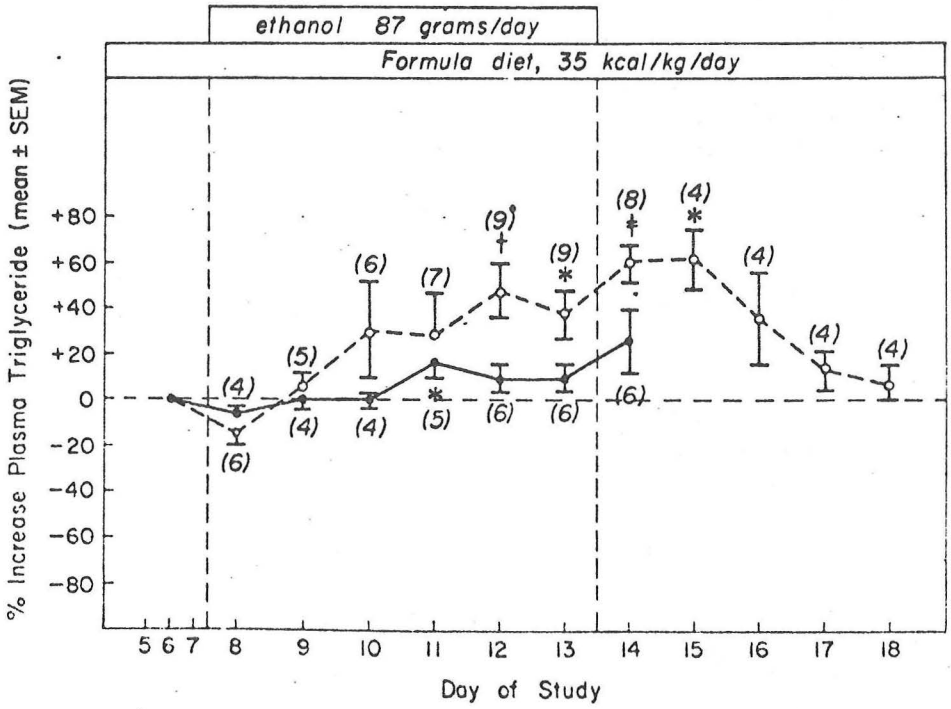


Figure 2. Daily percent rise (group mean ± SEM) versus the control period value of plasma triglyceride levels during and after the addition of alcohol to the diet. The mean of a person's fasting values on days 5 to 7 was used as the control value in calculating the percent rise for that person. The number of persons in each sample is shown in parentheses. Hypertriglyceridemic patients = O—O; normal persons = ●—●; * = $P < 0.05$; † = $P < 0.01$; ‡ = $P < 0.001$.

Thus, the response of triglycerides to alcohol ingestion depends on baseline triglyceride levels and this fact was shown most clearly by Mendelson and Mello. These workers studied 3 groups of alcoholics under controlled conditions; one group had normal triglycerides, another had fasting hypertriglyceridemia ("Familial Type IV") and a third group displayed hypertriglyceridemia only when challenged with carbohydrate ("carbohydrate-induced Type IV"). Participants of the 3 groups were allowed to drink up to 32 oz. of whiskey per day over a 11-12 day period. During this time, the hypertriglyceridemia and blood alcohol levels were monitored. The results are shown in Figure 11 (142). Normal subjects did not raise their triglycerides significantly in response to alcohol but subjects with either carbohydrate-induced or "familial" hypertriglyceridemia did respond and the effect was dose-related (Figure 11). Of note, the familial type IV patients were most

sensitive to the hypertriglyceridemic response of alcohol.

Figure 11

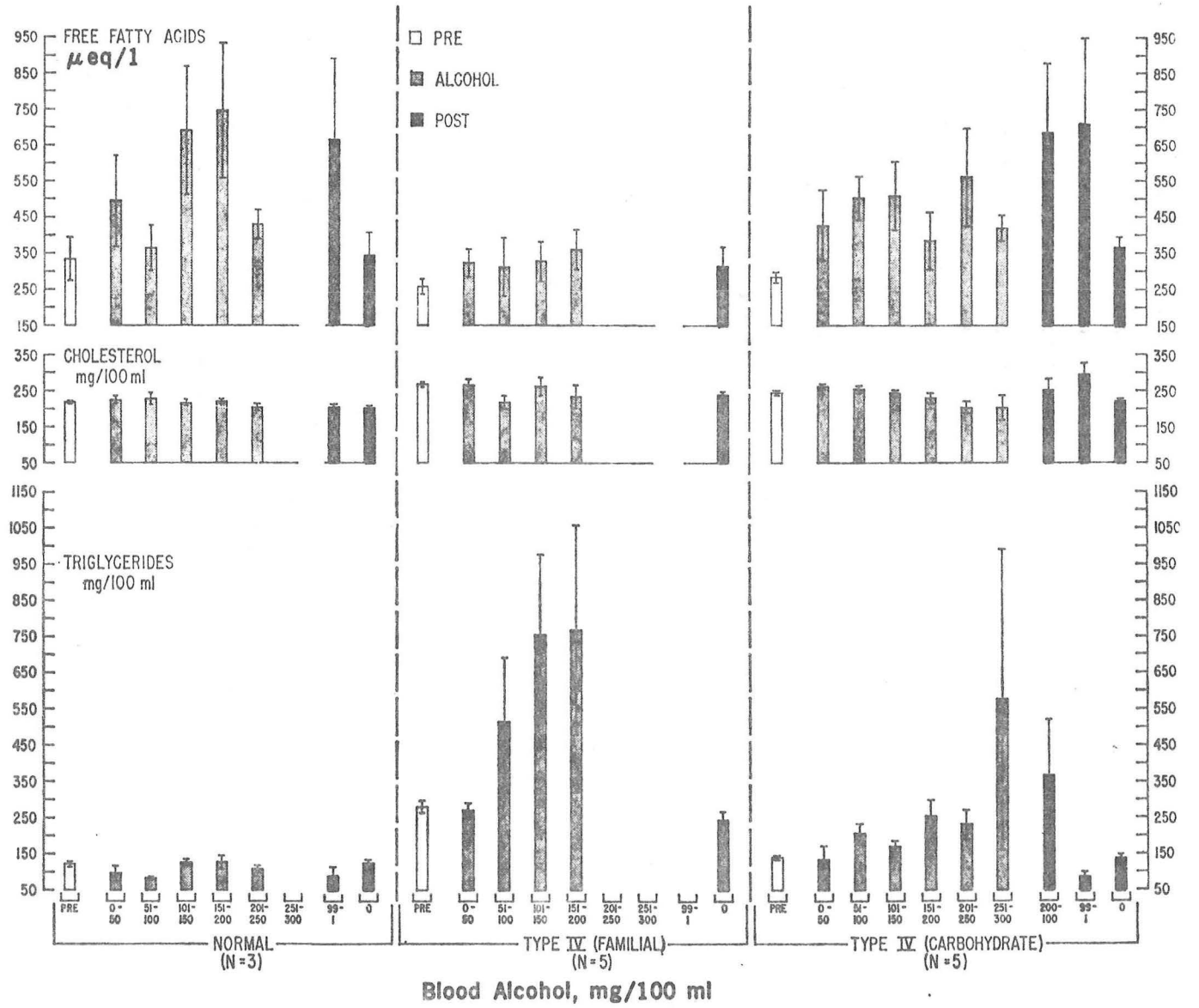


Fig. 1. Serum lipid levels (mean ± standard error) are presented for each of three groups of subjects: normal, type IV primary, and type IV carbohydrate induced.

Actually the alcohol, per se, may not cause hypertriglyceridemia. The extra calorie load in the alcohol may be the true culprit, as has been suggested by Witzum et al (107). These investigators studied a group of hypertriglyceridemic men before and during weight loss with a standard diet (Figure 12) (107).

Figure 12

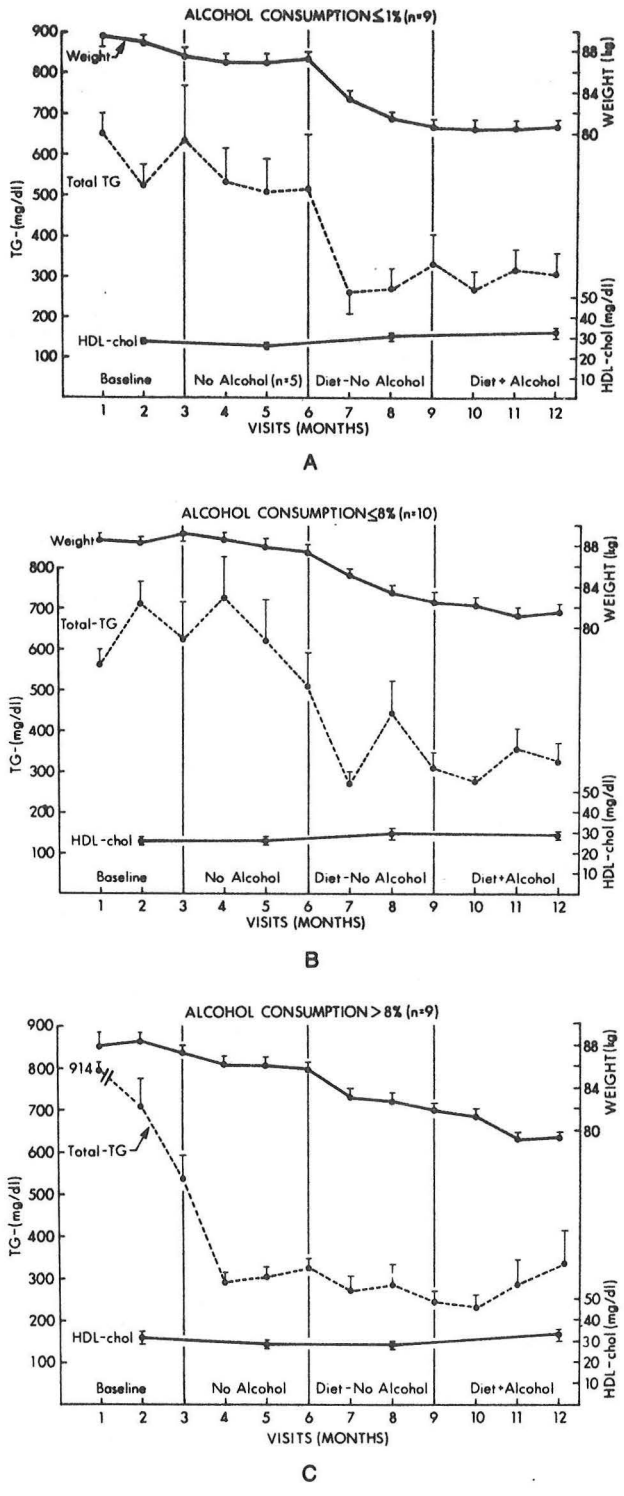


Figure 2. Effect of Dietary Changes on Subjects Consuming Various Quantities of Alcohol.

A refers to subjects whose alcohol consumption was ≤1% of their daily caloric intake; B, to those whose alcohol consumption was ≤8% of daily calories; and C, to those whose alcohol consumption was >8% of daily calories. Note that only subjects whose alcohol consumption was >8% of daily calories had a significant reduction in triglycerides when alcohol was discontinued. Data are reported as mean ±S.E.M. TG denotes triglycerides.

After weight loss was achieved, alcohol was added isocalorically to the diets to determine if hypertriglyceridemia would result. As seen in panel B of Figure 12, if less than 8% of the calories were consumed as alcohol, no significant hypertriglyceridemia resulted but if consumed in greater amounts (> 8% of calories, panel C), then hypertriglyceridemia began to re-appear.

Individual patients can't be carefully studied in this way and in general practice it is best to suggest nearly total elimination of alcohol consumption.

Careful attention to the medical history with regard to alcohol consumption is very helpful in the management of selected patients as shown by the following case:

> E.H., a 35-year-old WM, was referred for management of hypertriglyceridemia. Between 7/75 and 2/80, his fasting triglyceride varied between 389 and 1435 mg/dl and his cholesterols ranged from 194 to 256 mg/dl. He received various treatments including an AHA diet, nicotinic acid and clofibrate but none of the regimens seemed to work well. The remainder of his blood chemistries and thyroid function were normal, and he was not significantly obese (ht. 6 ft, 2 inch; wt. 192 pounds). He gave a history of drinking one quart of wine per day with meals. He was advised to continue the AHA diet but to discontinue all alcohol. In 2 months, his triglyceride dropped from 1188 mg/dl to 205 mg/dl. No additional treatment was required.

This case illustrates that relatively simple measures may be effective in lowering triglycerides in the well-motivated patient.

3. Diabetes Mellitus: When diabetes mellitus is present in hypertriglyceridemic patients, the degree of diabetic control has a strong influence on the fasting triglyceride levels (89, 146-148). Present data indicate that the untreated hypertriglyceridemic diabetic patient has a decreased capacity to remove triglyceride from the plasma (148). Since it is known that tissue lipoprotein lipase activity depends on the presence of insulin, the impaired ability to catabolize triglyceride in untreated or poorly-treated diabetics probably reflects low levels of tissue lipoprotein lipase activity. There is little evidence to indicate that triglyceride overproduction causes the hypertriglyceridemia (148).

   Appropriate treatment of the diabetes will lower the triglyceride levels significantly (Figure 13) (89), but they may not return to normal.

   Of note, Brunzell et al. suggest that diabetic subjects with fasting triglycerides greater than 400 mg/dl often have an independent familial form of hypertriglyceridemia (148).

Figure 13

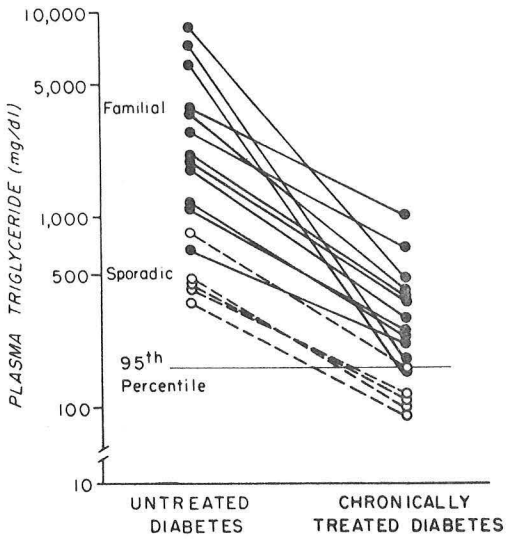


Fig. 1. Plasma triglyceride levels in index diabetic subjects before and after long-term therapy with oral sulfonylureas or insulin. e—e: Index subjects with concomitant familial form of hypertriglyceridemia. o---o: Index subjects with nonfamilial hypertriglyceridemia. Age-adjusted plasma triglyceride in log scale on ordinate compared to value for 95th percentile (horizontal line) of spouse control population.[14]

The response of the hypertriglyceridemia to diabetic therapy in the diabetic patient may be remarkable as shown by the following 2 cases:

C.J., a 42-year-old LAF, suffers from diabetes mellitus and hypertriglyceridemia. She initially refused insulin therapy and was therefore treated with diet and Orinase (3 gm/day). During 1980, her triglycerides ranged from 601 to 940 mg/dl, her cholesterol ranged from 159 to 229 mg/dl and her fasting blood sugars ranged from 221-319 mg/dl. One month after starting insulin therapy, her blood sugar was 205 mg/dl, her cholesterol was 201 mg/dl and her triglyceride was 193 mg/dl. At present, her only therapy is diet control and insulin.

W.S., a 47-year-old WM, was referred for evaluation of eruptive xanthomas and lipemic plasma in 6/80. He was in good health until 10/79, when he was noted to be diabetic on a routine company physical exam. Diet therapy was prescribed but he did not do well; he developed polyuria and lost weight from 270 to 218 pounds. On 2/80, he developed eruptive xanthomas first on the knees and later on the elbows. In May, 1980, his plasma cholesterol was 738 mg/dl, the triglycerides were 6156 mg/dl and the FBS was 219 mg/dl. In that one-month period he followed his diabetic diet closely and when first seen here, his FBS was 214 mg/dl, his cholesterol was 487 mg/dl, and his triglyceride was 1835 mg/dl. Orinase therapy was prescribed and in 6 weeks (7/22/80), his cholesterol dropped to 231 mg/dl and his triglycerides were 160 mg/dl. The FBS was 207 mg/dl.

It must be recognized that not all patients with both hypertriglyceridemia and diabetes respond this well and some will require drug therapy for the hyperlipidemia. This will be discussed in a later section.

4. Estrogens: Estrogen therapy may produce profound changes in the plasma lipid levels in susceptible patients. Small changes in patients are seen widely (149) but individuals with genetic forms of hypertriglyceridemia may respond to estrogen treatment by developing hyperchylomicronemia and pancreatitis (150-152). While most reported cases were in women, the same abnormal response was observed in a man receiving post-prostatectomy estrogen treatment (150). Withdrawal of the estrogen is associated with a gradual decline in the plasma lipid levels over several months (Figure 14) (152).

Figure 14

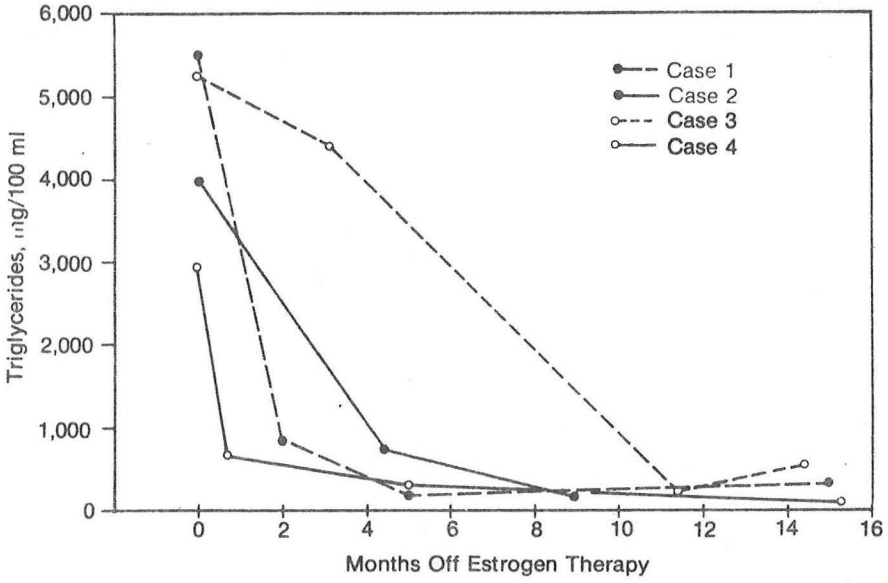


Fig 1.—Decrease in serum triglyceride levels following cessation of oral contraceptive or postmenopausal estrogen therapy.

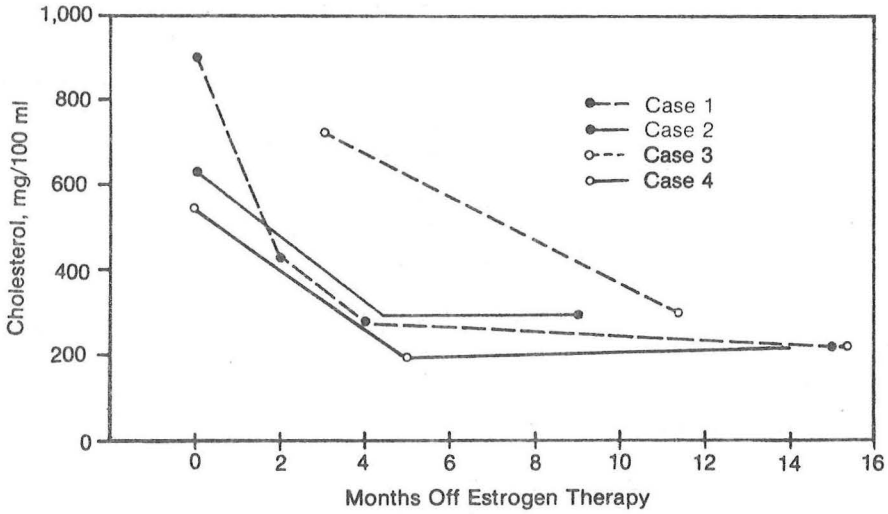


Fig 2.—Decrease in serum cholesterol level following cessation of oral contraceptive or postmenopausal estrogen therapy.

The cause of the hypertriglyceridemia induced by estrogens is thought to be overproduction of VLDL by the liver (153,154).

Estrogen treatment may also have a less profound but still potentially harmful effect on plasma lipids as illustrated by the following case.

> B.E., a 55-year-old WF, was referred for evaluation of hyperlipidemia. Her medical history was otherwise unremarkably except for mild hypertension under treatment. She had taken Premarin 0.675 mg/day for 3 years, presumably to control menopausal symptoms. Her height was 5 ft. 3 inches and she weighed 128 pounds. Her laboratory data are summarized below:

Date	Cholesterol (mg/dl)	Triglyceride (mg/dl)	Drug
12/75	365	317	Premarin 0.625 mg/day
2/76	300	226	No treatment
5/76	252	162	Clofibrate 1 gm b.i.d.

The patient's plasma lipids dropped significantly when her Premarin was discontinued but they did not become normal.

In general, the withdrawal of estrogen therapy is an important first step in management of the hyperlipidemic patient. Estrogen therapy may actually be beneficial in women with Familial Dysbetalipoproteinemia (81,82). However, if this diagnosis cannot be made with certainty, it is better to adopt the general rule of avoiding estrogen use in all hypertriglyceridemic (and hypercholesterolemic) patients.

5. Hypolipidemic Drugs: A number of drugs have been used to treat hypertriglyceridemia and these include clofibrate, nicotinic acid, norethindrone acetate (132) and oxandrolone(155-157). Norethindrone acetate and oxandrolone have only been used to a limited extent and often in special circumstances. For that reason, these two drugs are not recommended for general therapy of the hypertriglyceridemic individual.

   Nicotinic acid and clofibrate, in contrast, have been used widely and do have a place in the treatment of hypertriglyceridemic disorders. Both can be effective when used separately and when given together, their effects are synergistic (158-161).

   Clofibrate (Atromid-S) will lower plasma triglycerides from 20 to 50% (165, 169 - 172) but its effects on cholesterol are variable, and it may actually raise cholesterol levels in certain individuals (182). With regard to its action on individual lipoproteins, it will lower chylomicron and VLDL levels, (165,173,178) but it exerts variable and somewhat unpredictable effect on LDL and HDL levels (171,175). It is an effective drug with which to treat hypertriglyceridemic diabetic patients (176). No specific mechanism of action for the therapeutic effect of clofibrate has been defined but it is known to

decrease triglyceride production, enhance triglyceride clearance, and stimulate lipoprotein lipase activity (162,177-179). The usual therapeutic dose is 1 gm twice daily and patient acceptance of this drug is good.

Nicotinic acid may be equally effective in treating hypertriglyceridemia. With regard to individual lipoproteins, this drug lowers chylomicron, VLDL, and LDL levels while it may increase or leave unchanged the plasma HDL level (163,165). Thus it is effective as both a hypotriglyceridemic and hypocholesterolemic agent. Its use in diabetes is limited by the fact that it causes deterioration of glucose tolerance (166) but it has not been shown to produce diabetes (165). Nicotinic acid actually is useful in the hyperlipemic, insulin-requiring diabetic and it does not seem to impose any problems of diabetic control. Patient acceptance of this drug is limited because it has several uncomfortable side-effects (165) including a cutaneous flush and gastric irritation. Mild abnormalities of liver function commonly occur but serious liver damage is rare (165,167,168). Nicotinic acid lowers plasma triglycerides by reducing VLDL production by the liver (162,164,165).

The usual starting dose of nicotinic acid is 250 mg P.O. three times daily with meals. The dose is gradually increased every 3-4 days to the range of 500-1000 mg t.i.d. The hypocholesterolemic dose of nicotinic acid may go up to 2000 mg t.i.d.

Of the two drugs, nicotinic acid has a more predictable effect in terms of therapeutic effect whereas clofibrate may be very effective in some hypertriglyceridemic patients and not in others (165,169). The reasons for this variability are not known but because of it, clofibrate therapy must be considered as a therapeutic trial in every patient. If it does not produce a significant reduction in plasma lipid levels after 3-6 months of therapy, its use should be discontinued.

Since the hypertriglyceridemic syndromes are primary metabolic defects, they must be controlled chronically. If dietary control is not adequate, the patient is then subjected to prolonged treatment with drugs. The need for prolonged treatment raises difficult questions about the long-term safety of the drugs we use and this issue is actively under discussion at the present time. Over the last two years, the results of a major epidemiological study (the W.H.O. Study) using clofibrate have appeared; the information from this study contains both good and bad news about the benefits of our attempts to lower plasma cholesterol in high risk patients. Similar questions apply regarding hypertriglyceridemia.

The W.H.O. Study (180-183) was designed to test the hypothesis that reducing plasma cholesterol levels in high risk men has a beneficial effect with regard to subsequent cardiovascular mortality. The investigators happened to use clofibrate because it was well tolerated and considered safe. About 15,000 men were enrolled into the study and they divided into 3 groups of approximately 5,000 each. The design of the study is shown in Figure 15 (182).

Figure 15

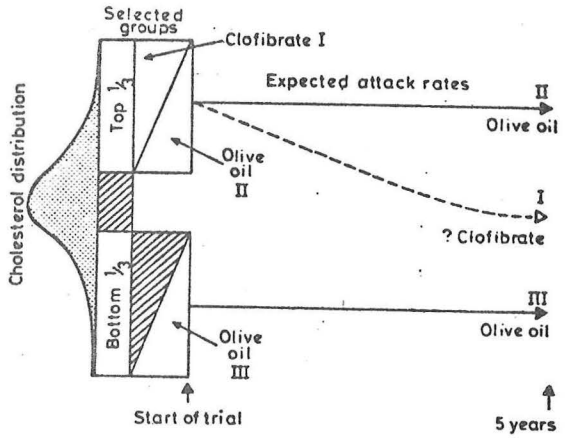


Fig. 1 *Design of the trial (broken line represents hypothetical effect of clofibrate on serum cholesterol and IHD attack rates).*

Two groups had cholesterols in the top third of the cholesterol distribution (groups I and II). Group I received clofibrate and group II received olive oil placebo. The third group (group III) was taken from the lower third of the cholesterol distribution; half of this group received placebo and half took nothing. The trial lasted 5 years and the results can be summarized as follows:

1) The mean cholesterol reduction in the treated groups was 9%.

2) The incidence of ischemic heart disease was reduced by 20% ($p < 0.05$) and this fall was confined to non-fatal heart attacks.

3) The incidence of fatal heart attacks was similar in the two high cholesterol groups (I and II).

4) The reduction of myocardial infarction in the clofibrate-treated group was greatest in men who responded well to the drug (e.g. who had the best therapeutic response).

5) Those who benefited most were men who also smoked and who had hypertension.

6) The crude mortality rates from all causes in the clofibrate-treated group significantly exceeded those in the high cholesterol control group but age-standardized mortality rates were no different.

7) Gallstone formation and cholecystectomy were more common in the clofibrate-treated group but cancer was not.

The good news from this study is that it demonstrated that lowering plasma cholesterol in middle-age men can reduce the incidence of ischemic heart disease. The bad news was that the overall mortality in the clofibrate-treated group was not improved and may actually have been slightly increased during the 5 years of treatment.

The investigators concluded that clofibrate could not be recommended as a lipid-lowering drug for community-wide primary prevention of ischemic heart disease. They did not mean that the drug should not be used in high risk individuals with primary hyperlipemic syndromes.

Follow-up of the groups continued through 4 more years after the trial was completed and that information was just published (183). There were 25% more deaths in the clofibrate-treated group than in the comparable high cholesterol control group (Figure 16) (183).

Figure 16

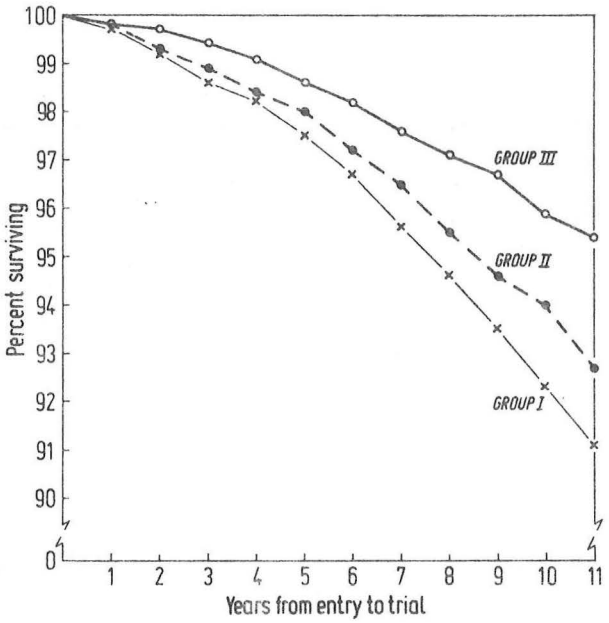


Fig. 1—Life-table analysis.

Deaths from all causes by group and time from entry. Group I *v.* group II, $p<0.01$.

	Number of men, at year from entry					
Group	*0*	*2*	*4*	*6*	*8*	*10*
I	5331	5288	5235	5157	4648	1559
II	5296	5261	5210	5150	4669	1613
III	5117	5100	5071	5027	4552	1599

There were more death from ischemic heart disease, stroke, cancer, and other major diseasesbut death from any one cause was not significantly different from that in the control groups. This excess mortality was also not related to the degree of cholesterol reduction or the length of time on clofibrate.

The cause for these findings is unknown and it is recognized that they are bizzare. Possible reasons for the findings include (1) a non-specific toxic effect of clofibrate, (2) a beneficial effect of olive oil placebo, (3) a possible adverse effect related to lowering tissue cholesterol pools, or (4) chance.

It is somewhat but not totally reassuring that other major therapeutic trials with clofibrate have not observed this phenomenon (184,185,187, 188). Nevertheless, clofibrate should be used selectively in only those patients who show the greatest chance for benefit.

Similar findings have not been reported for nicotinic acid (184).

Thus, clofibrate should be used to treat hypertriglyceridemic syndromes under the following circumstances:

1) Patients prone to develop pancreatitis. This group includes severely hyperlipemic diabetic subjects with adequately treated diabetes.

2) Hypertriglyceridemic patients with other cardiovascular risk factors (e.g. hypertension, smoking).

3) Hypertriglyceridemic patients with a strong family history of heart disease.

4) Hypertriglyceridemic patients who also have high-risk cholesterol levels (e.g. above 250 mg/dl).

There are no firm data to use as a guide for defining medically significant hypertriglyceridemia and opinions vary, but most suggested cut-off points fall within the range of 300-400 mg/dl. However, the triglyceride should be assessed along with the cholesterol level. Thus, a person with a cholesterol of 200 mg/dl and a triglyceride of 350 mg/dl may not be treated at all or at most may be given diet therapy. A patient with a cholesterol of 280 mg/dl and a triglyceride of 350 mg/dl is really different from the first one, may have Familial Multiple Lipoprotein-type Hyperlipidemia, and should be treated.

VI. Summary and Conclusion:

The bulk of epidemiological evidence seems to indicate that fasting triglyceride levels in the general healthy population are not a strong risk factor for ischemic heart disease (189). On the other hand, repeated observations have correlated premature atherosclerosis with hypertriglyceridemic syndromes (37,53,85,88,115,190-192). Furthermore, certain groups of hypertriglyceridemic individuals are plagued by other significant problems including pancreatitis and eruptive xanthomas. The complete evaluation of hyperlipidemia requires the measurement of the fasting plasma triglyceride level; inspection of the refrigerated plasma is also useful (Table 20).

Table 20. Value of the Triglyceride Measurement in Evaluating Hyperlipidemia

Patient	Cholesterol	Triglyceride	Diagnosis
	mg/dl		
1	350	100	Familial Hypercholesterolemia
2	350	500	Familial Dysbetalipoproteinemia
3	350	3,500	Familial Endogenous Hypertriglyceridemia (type 4-5)

The hypertriglyceridemic syndromes are challenging problems for the clinician to treat. Although specific diagnoses cannot often be made, a general approach involving diet, weight loss, abstinence from alcohol, treatment of diabetes when present, avoidance of certain drugs (estrogens) and the judicious use of other drugs (clofibrate, nicotinic acid) will usually bring about control of the hyperlipidemia. Effective therapy should reduce or abolish attacks of pancreatitis and promote the resolution of eruptive xanthomas. The effect of treatment on the prevention of ischemic heart disease is not established but it should be undertaken in high-risk individuals.

Secondary forms of hyperlipidemia were not covered in this protocol but they are well discussed in reference 3.

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