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TREATMENT OF HYPERLIPIDEMIC STATES

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I. INTRODUCTION

Triglyceride, contained principally in adipose tissue, is an excellent form in which energy can be stored with the greatest economy of space. The body of a 70 Kg man contains an average of 15 Kg of triglyceride representing about 135,000 kcal of energy (1). The ability to store food energy for later use in believed to have played a significant role in that stage of man's evolutionary development when he was predominantly a hunter and therefore subject to varying periods of food excess or food scarcity (2). Though the problem is still unsettled, adipose tissue in man is not thought to be a quantitatively significant site of fatty acid biosynthesis (3) and the triglyceride stored there is largely delivered from both the intestine and liver in the form of lipoproteins, principally chylomicrons and very low density lipoproteins (VLDL). While modern man still retains the ability to store triglycerides this system of energy storage is no longer as critically important as it once was and in many causes it has become an outright nuisance. In addition, this system has developed a number of flaws and those flaws dealing with the transport phase of triglyceride and cholesterol through plasma will be the subject of today's discussion.

II. LIPOPROTEINS IN PLASMA

A. Definitions and Physical Characteristics.

Four major lipoprotein families, defined primarily by their density and electrophoretic behavior on paper, are found in plasma (Table I).

TABLE I

PHYSICAL CHARACTERISTICS OF MAJOR PLASMA LIPOPROTEIN FAMILIES

LIPOPROTEIN	DENSITY g/ml	S_f +	MOBILITY*	MOLECULAR WEIGHT	SIZE Å
[4]CHYLOMICRONS	<0.96	>400	Origin	10^3-10^4x10^6	750-10,000
[5]VLDL	0.96-1.006	20-400	Pre-beta	5-27x10^6	300-800
[5]LDL	1.006-1.063	0-20	beta	2.2-3.5x10^6	200-220
[6]HDL	1.063-1.21	----	alpha	1.5-2.6x10^5	70-95

+Svedberg flotation units (10^{-13} cm/sec/dyne/g) in sodium chloride solution of density 1.063 g/ml (26°C)

* paper electrophoresis

1) Chylomicrons - largest and lightest lipoproteins - normally not present after 14 hour fast. Increased plasma concentrations cause turbidity initially, followed by formation of a cream layer after overnight refrigeration.

2) Very Low Density Lipoproteins (VLDL) - also called prebetalipoprotein because of electrophoretic behavior. Elevated plasma levels cause turbidity. (Rarely called α_2 - VLDL).

3) Low Density Lipoprotein (LDL) - also called betalipoprotein. Because of smaller size, elevated plasma levels do not produce turbidity.

4) High Density Lipoproteins (HDL) - also called alphalipoprotein. Disorders attributable to high HDL levels have not been described.

Two abnormal lipoproteins occasionally found in plasma are listed below:

5) Floating BetaLipoprotein (FBL) - only found in disease states. Thought to represent an intermediate form between VLDL and LDL (20). (Occasionally called β-VLDL)

6) Lipoprotein-X (LP-X) - found in obstructive liver disease - not present normally - elevations produce hypercholesterolemia. Usually has beta mobility on electrophoresis (47).

B. Composition: Knowledge of lipoprotein composition assists in interpreting plasma cholesterol and triglyceride levels, (Fig. 1, Ref. 6,7).

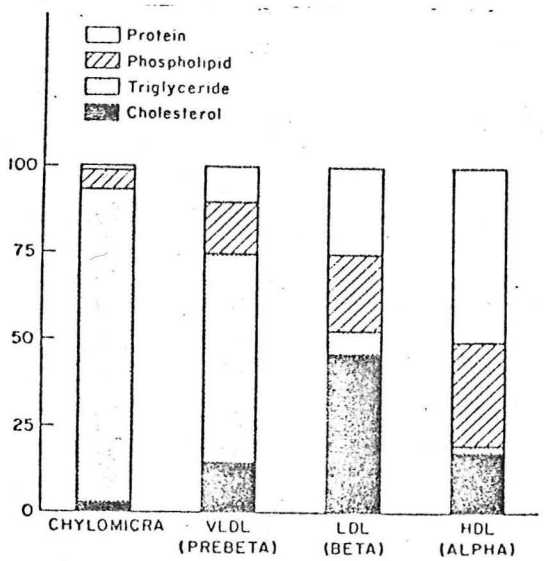


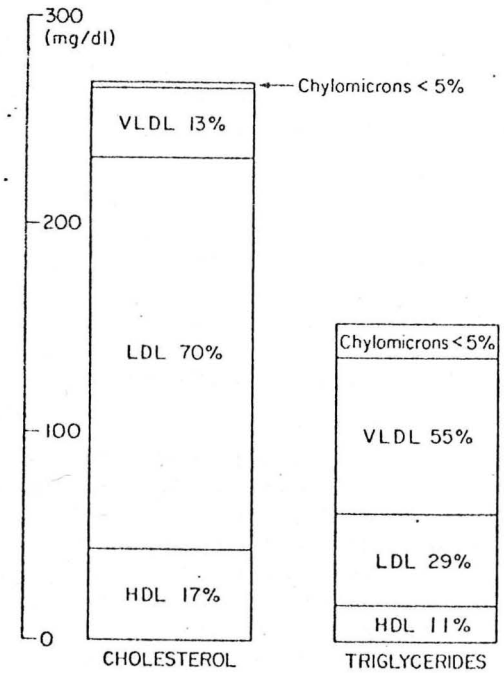
Figure 1

Average figures expressed as percent dry weight are listed below. Slight variation occurs among laboratories.

	Cholesterol	Triglyceride	
Chylomicrons	7%	80-95%	
VLDL	20%	55-65%	
LDL	45%	10%	
HDL	17%	8%	
*FBL	33%	39%	(44)
+LP-X	25%	3%	(47)

Based on these values, hypertriglyceridemia is due to an elevation of chylomicrons, VLDL and/or FBL. Hypercholesterolemia is due to an elevation of LDL, FBL or LP-X. Raised HDL levels in the presence of normal levels of all other plasma lipoproteins rarely causes the total plasma cholesterol to be abnormally elevated.

In the normal fasting state most of the plasma cholesterol is in LDL while the major portion of triglyceride is in VLDL. (Fig. 2, Ref. 45)



Contribution of Each Lipoprotein Class to Total Plasma Cholesterol and Triglycerides in the Normal Subject

Figure 2

C. Physiology: Metabolism of plasma lipoproteins is highly interdependent.

1) Chylomicrons (8, 9, 10, 11) (Fig. 3) - Synthesized in the intestine in response to ingestion of long chain triglycerides (C-14 and greater), these large particles travel via lymphatics to the thoracic duct where most directly enter plasma. A small portion are extracted from lymph by the liver. Here the TG is hydrolyzed to FFA which are re-esterified into new TG and secreted as VLDL. Plasma half-life of chylomicrons is about 15 minutes and most are gone in 8 hours following a test meal. The triglyceride portion is hydrolyzed by lipoprotein lipase at the capillary endothelial surface of many tissues but especially adipose tissue and muscle. Resultant FFA are taken up by these tissues (some FFA are released directly into plasma, bind with albumin, and return to the liver), and the cholesterol-rich "remnant" particle remaining is quickly taken up by the liver (12). Several hundred grams of triglyceride can be transported by this route daily (46). Hyperlipidemia caused by chylomicron excess is termed exogenous because the substrate directly driving chylomicron synthesis is derived from dietary fat.

2) VLDL (8, 9, 10, 11, 13) (Fig. 4) - VLDL is produced in the liver from FFA liberated from adipose tissue or synthesized from dietary glucose. Medium chain FFA (C-10 or less) ingested as medium chain triglycerides (MCT) are absorbed directly into the portal vein and upon delivery to the liver, are packaged into VLDL (14). Thus MCT bypass chylomicron production and are useful as an energy source for patients with abnormally high chylomicron levels. Normally VLDL transport about 20 gm of triglyceride daily (46).

Hypertriglyceridemia due to high VLDL levels is termed endogenous because the FFA substrate is largely derived from endogenous energy sources (glycogen and adipose tissue triglyceride).

After secretion from the liver (only small amounts are contributed by intestine), VLDL triglyceride is hydrolyzed by lipoprotein lipase in a way similar to that for chylomicrons. The plasma half-life of VLDL is from 2-6 hours.

3) LDL - results from VLDL degradation (13, 15) and no evidence supports independent entry of LDL into plasma though the matter is not completely settled. Interest in the origin of LDL resides in its potent atherogenic effect and much effort has been expended finding ways to lower its concentration. The LDL half-life in plasma is 3 to 4 days. Its catabolic routes are not completely known but it may filter into arterial walls and/or be taken up by cells of the reticuloendothelial system (R.E.S.). The liver may take up a considerable amount.

CHYLOMICRON METABOLISM

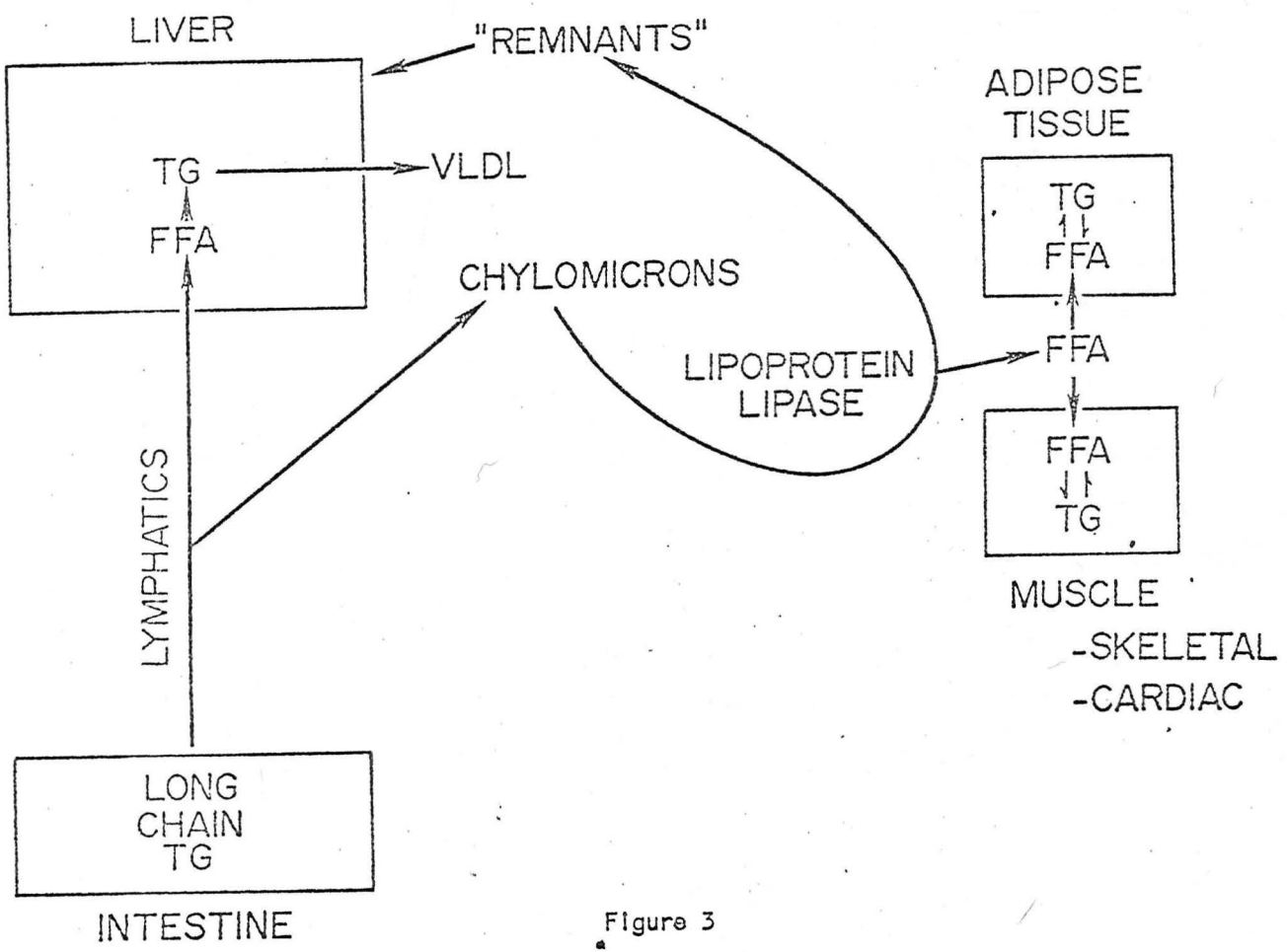


Figure 3

VLDL METABOLISM

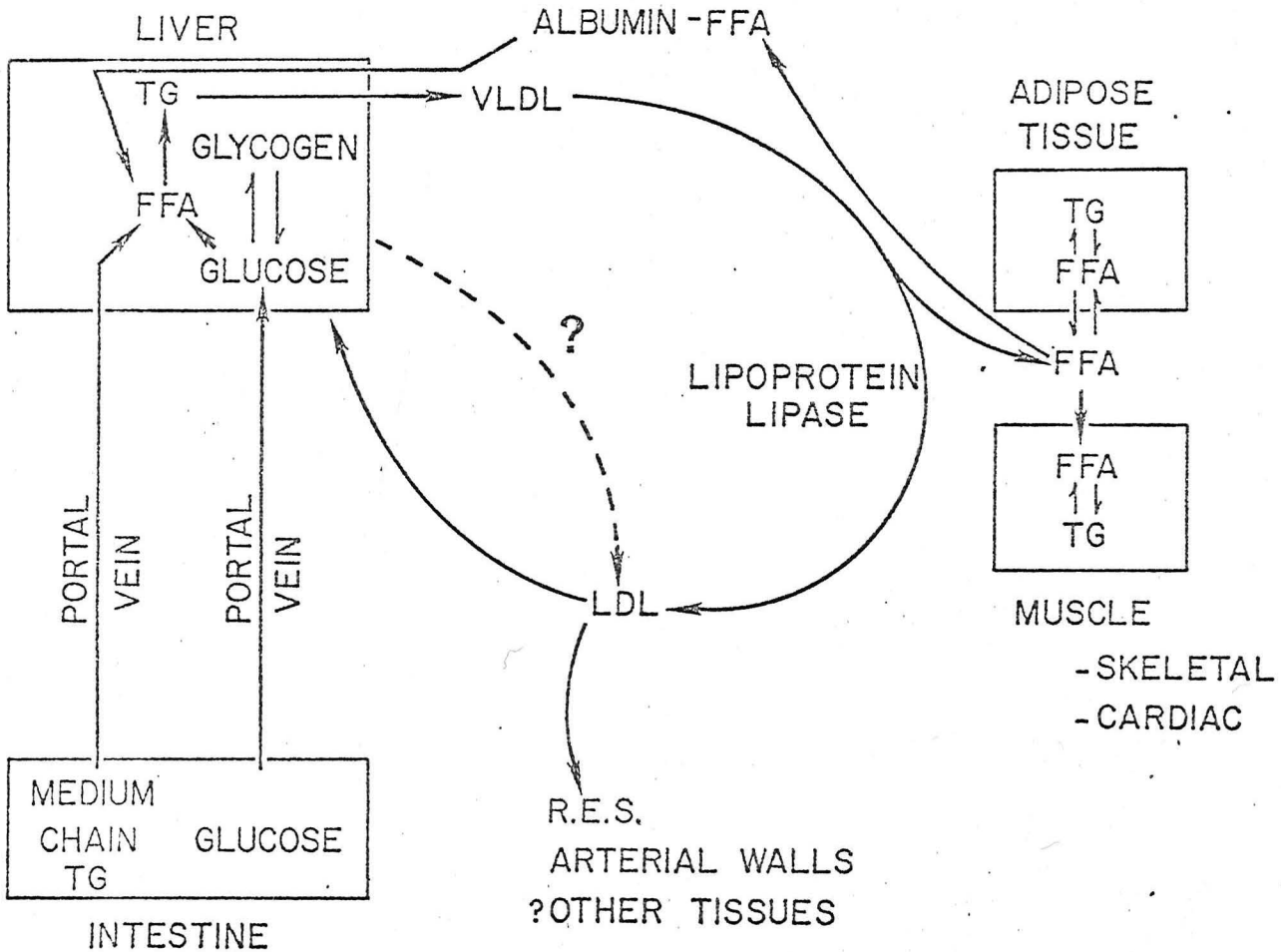


Figure 4

4) HDL (16) - Though not implicated in hyperlipidemia, HDL plays a central role in lipoprotein catabolism (Fig. 5).

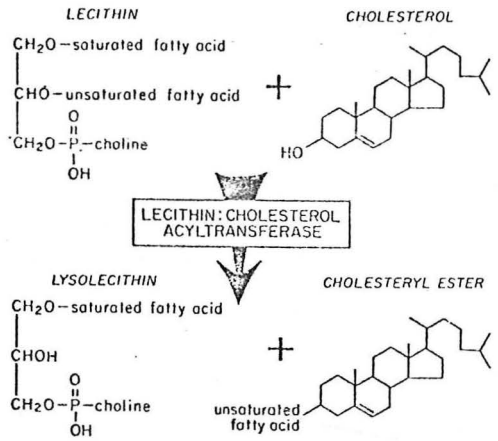
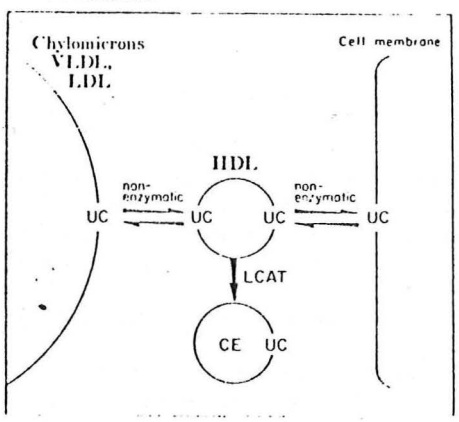


Figure 5

It functions in close association with a plasma enzyme called lecithin: cholesterol acyltransferase (LCAT) which transfer a fatty acid from lecithin to the hydroxyl group on the 3-position of cholesterol.

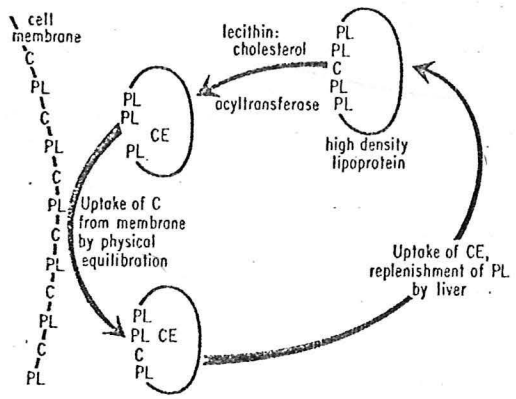
The hypothesis regarding the function of HDL and LCAT is as follows:



Schematic illustration showing equilibria between the unesterified cholesterol (UC) of plasma lipoproteins and plasma membranes and the effect of coupling these equilibria to the formation of HDL cholesteryl ester (CE) by the LCAT reaction.

Figure 6-a

Both chylomicrons and VLDL have their surfaces covered with phospholipid and protein that serve to function as detergent which permits the non-polar triglyceride cargo to be transported through the polar aqueous plasma. Unesterified cholesterol is closely associated with the phospholipid at the surface. As VLDL and chylomicrons reduce in size during hydrolysis of their triglyceride content, the excess protein and phospholipid surface material transfer directly to HDL while unesterified cholesterol is first esterified by LCAT before HDL accepts it. HDL thus functions as a "sink" or reservoir for the excess surface coat material. It is noteworthy that in Tangier Disease (congenital near-absence of HDL) (17) and in Familial LCAT Deficiency (16) lipoprotein metabolism is abnormal and both disease are associated with elevations of triglyceride - containing lipoproteins of an unusual type. These observations support the HDL-LCAT Hypothesis.



Postulated role of LCAT reaction in transporting cholesterol from peripheral tissues to the liver: LCAT reacts with HDL to form cholesteryl esters (CE) from unesterified cholesterol (C) and lecithin (PL); the HDL subsequently pick up unesterified cholesterol from cell membranes and release cholesteryl esters to the liver. (From Ref. 1.)

Figure 6-b

HDL may also function to remove unesterified cholesterol from cell membranes and HDL is believed responsible for transport of cholesterol from many body tissues to the liver where the sterol can be converted to bile acids or excreted directly into bile.

III. HYPERLIPIDEMIA AND HYPERLIPOPROTEINEMIA

A. Definition of Normal - normal values for cholesterol and triglyceride are nearly impossible to determine since large population studies reveal a broad range of values for these plasma lipids without division into normal and abnormal groups. (18, 19). Cholesterol and triglyceride values increase with

age through 60 years and differ in the sexes. For experimental and large population studies, the 95th percentile of control population levels has been used as the upper normal limit. Values from two such studies are shown in Table 2-a (20) and 2-b (21).

TABLE 2-a

PLASMA LIPID CONCENTRATIONS, MG PER 100 ML, IN NORMAL* SUBJECTS

Age, yr	Cholesterol, mean and 90 percent limits	Triglyceride, 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 (160-330)	95 (10–190)

* The population sample is derived from a total of 511 normal subjects (279 males, 232 females) and includes the smaller sample previously described [65]; the criteria for acceptance of patients were no evidence of metabolic disease or family history of hyperlipoproteinemia, and plasma triglyceride levels less than 200 mg per 100 ml; all samples were obtained 12 to 16 hr after the last (evening) meal. Some significant differences between the sexes were ignored [49, 68, 69].

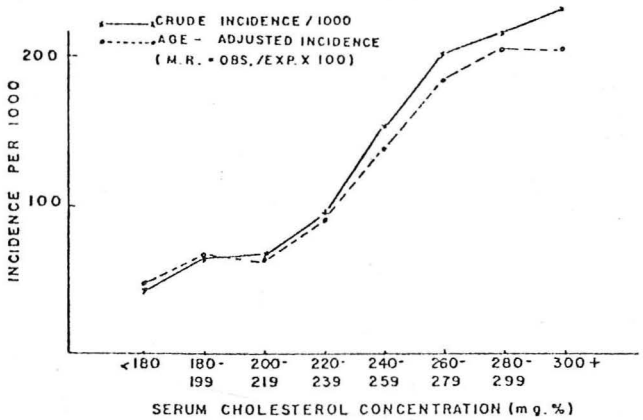
TABLE 2-b

Unadjusted Plasma Lipid Levels in Controls

Age range	No.	950 Spouse controls	
		Cholesterol	Triglyceride
		Mean±SD	Mean±SD
yr		*mg/100 ml*	*mg/100 ml*
Men			
15–19	13	168±27	53±22
20–29	43	192±33	76±37
30–39	62	212±34	92±56
40–49	116	226±43	101±47
50–59	85	239±42	109±58
60–69	51	226±39	103±58
70–79	24	200±39	98±43
80–89	6	169±21	98±19
Total	400		
Women			
15–19	11	183±17	71±27
20–29	47	199±36	79±40
30–39	88	196±39	73±38
40–49	168	215±42	87±46
50–59	162	238±43	107±55
60–69	55	250±49	98±47
70–79	19	230±32	146±78
Total	550		

Evidence from the Framingham Study (22) suggests the 95th percentile values are too high. The incidence of heart disease in men aged 30-49 at entry into the study rises steeply with 20 mg% increments in plasma cholesterol from 200 mg% to 300+ mg% (Fig. 7).

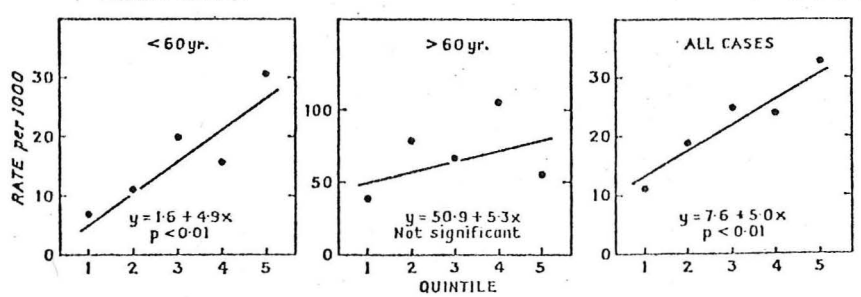
Figure 7



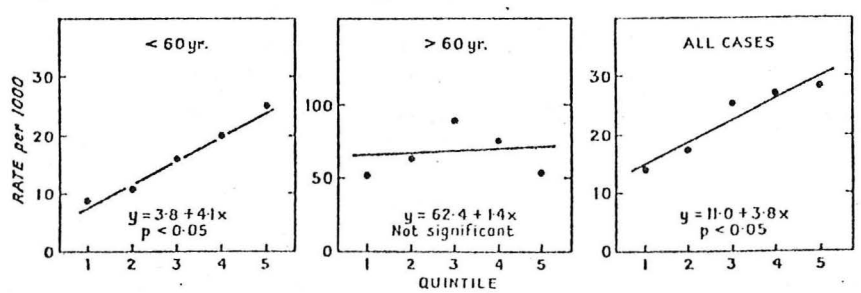
Risk of coronary heart disease (14 years) according to serum cholesterol concentration. Men aged 30 to 49 at entry. Framingham Study.

Forty percent of coronary disease in men developed in individuals with cholesterol values in the upper quartile of the distribution of lipids in the general population (between 250 and 350 mg%) (19). In other words, men in the upper 25% of the distribution curve for cholesterol values experienced 40% of the myocardial infarctions.

Similar results for triglyceride levels were obtained by Carlson and Böttiger (23). They observed an increased rate of new events, particularly in individuals less than 60 years old, as the triglyceride rose from low to high levels (Fig. 8).



Linear regression analysis of the rate of new events in the prospective group of I.H.D. (per 1000) in relation to plasma-triglyceride quintiles.



Linear regression analysis of the rate of new events in the prospective group of I.H.D. (per 1000) in relation to plasma-cholesterol quintiles.

Figure 8

This study is especially important because:

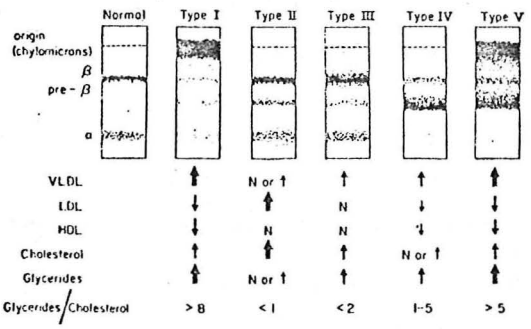
1) It established elevated TG as a coronary risk factor.

2) It suggests the age-associated rise in plasma cholesterol and triglyceride may be abnormal.

Selection of upper normal limits is arbitrary in the absence of a clear-cut normal population. Fredrickson suggests that cholesterol values exceeding 220 mg% at any age may require attention (24), but this would require treatment of a majority of the population. We may eventually do that but at present, an upper limit of 250 mg% seem reasonable since it would focus attention on those individuals in the upper quartile who are most at risk for coronary disease (19).

The upper limit of normal for triglyceride in adults is generally taken at 150 mg% (24).

B. Classification: Gofman and co-workers first focused attention on the lipoproteins as carriers of lipids in plasma and devised methods of isolation and measurement of lipoproteins based on their density characteristics (25, 26, 27, 28). Elevations of LDL and VLDL were found in atherosclerotic individuals and Gofman's results stimulated a cooperative study (29) to investigate the predictive role of lipoprotein levels in coronary disease. The 2-year study suggested that neither lipoproteins nor cholesterol were of predictive value in atherosclerosis. Interest diminished until 1963, when Lees and Hatch described a simple paper electrophoretic method for plasma lipoprotein separation (30). Using this method, Fredrickson and Lees described 5 predominating types of lipoprotein patterns in their highly select hyperlipidemic patients at the National Institutes of Health (31) (Fig. 9).



Electrophoretic Patterns, Lipid and Lipoprotein Changes in Hyperlipoproteinemia.

The width of the arrows is proportional to the extent of the deviation from normal, and the direction of the arrows indicates increase or decrease of lipids. The usual glyceride-cholesterol ratio is given as an aid to diagnosis.

Figure 9

Lipoprotein elevations in each type are illustrated in Table 3.

TABLE 3

THE MAJOR ABNORMAL LIPOPROTEIN PATTERNS [a] AND THEIR TYPE NUMBERS

Type	Chylo-microns	LDL (β-lp)	VLDL (pre-β-lp)	Floating β-lipopro-teins [b]
I	+			
IIa		+		
IIb		+	+	
III				+
IV			+	
V	+		+	

[a] + indicates which lipoprotein "family" (families) occurs in concentration above "normal" in the different abnormal patterns.
[b] Also known as "broad β-lipoproteins".

The simple typing system was attractive in a field filled with memory-taxing names and general confusion. In 5-years time, it was widely employed and in 1970, the World Health Organization (WHO) adopted it in modified form for global use (Table 3) (33).

The lipoprotein typing system was initially thought to have the following advantages:

1) Fairly simple and relatively inexpensive.

2) Definition of hyperlipidemia based on lipoprotein elevations was more physiologic.

3) Better classification would permit conduct of more accurate clinical and genetic studies.

4) Dietary treatment could be outlined by physiologic principles.

5) Drug treatment could be specified by type.

6) Prognosis might be predictable by type.

After a period of critical appraisal, not all the advantages of this extensively used clinical tool have held up.

1) Lipoprotein typing is often uncertain. Pries, et.al. (37) found that five observers independently typing 20 lipoprotein electrophoretograms agreed in only six cases. The observers were "correct" in only 55-75% of the cases.

2) Goldstein and co-workers (35) studied clinical, genetic and biochemical characteristics of a large group of hyperlipidemic survivors of myocardial infarction initially chosen only by cholesterol and triglyceride values. They were able to delineate three monogenic disorders (Fig. 10).

Summary of Clinical, Genetic, and Biochemical Characteristics of Hyperlipidemic Survivors of Myocardial Infarction

Disorder	Typical Lipid Level		Lipoprotein Types	Mode of Inheritance	Expression in Children
	Cholesterol (mg/100 ml)	Triglyceride (mg/100 ml)			
Monogenic Familial hypercholesterolemia	353	126	IIa, IIb	Autosomal dominant	Yes
Familial hypertriglyceridemia	241	267	IV, V	Autosomal dominant	Rarely
Combined hyperlipidemia	300	241	IIa, IIb, IV, V	Autosomal dominant	Rarely
Polygenic hypercholesterolemia	308	287	IIa, IIb	Polygenic	Not applicable
Sporadic hypertriglyceridemia	233	243	IV, V	Nongenetic	Not applicable

Figure 10

After families were identified lipoprotein typing was performed and multiple lipoprotein types were found in each of the genetic disorders. Four lipoprotein types were found in families with combined hyperlipidemia. Though this disorder proved most common in the myocardial infarction survivors, its existence as an entity was not discovered by lipoprotein typing.

Similar reports from Finland (36) also illustrate the wide variability of lipoprotein types in families.

The genetic studies help explain earlier reports indicating failure to clearly separate on clinical or biochemical ground types III and IV (38) and types IV and V (39, 40, 41) as distinct entities.

Since multiple lipoprotein types may be found in the same family with monogenic hyperlipidemia:

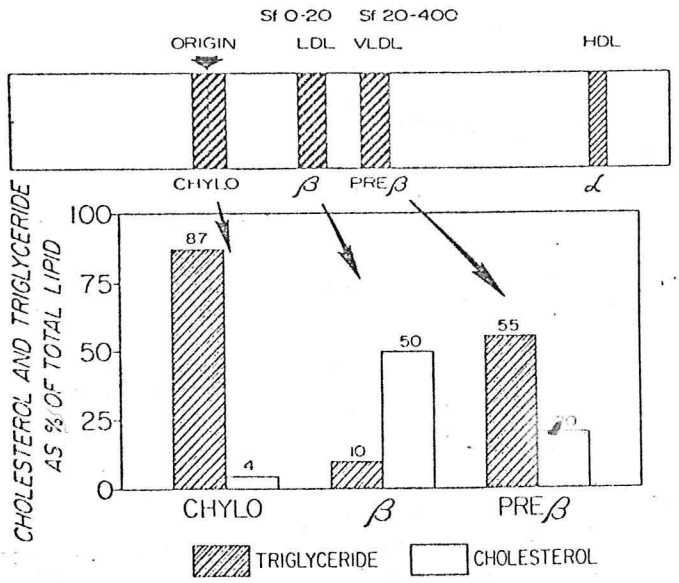
1) Diet treatment by lipoprotein type may be difficult with regard to preparation of meals.

2) It may be possible that one drug is useful for all the types in a given family. Thus drug prescription by type may not always be necessary.

3) Prognosis would be indicated more by the genetic disorder than by the lipoprotein type.

In summary, lipoprotein typing has not proved as useful as anticipated but it was immensely helpful in focusing attention on lipoproteins as the transport vehicles for plasma lipids. It remains useful as a short-hand description of lipoprotein abnormalities in patients. It is most important to remember that lipoprotein types are not diseases and a given type is not unique for a given disease.

A simplified means of estimating lipoprotein levels in hyperlipemic patients has been proposed by Havel (43). First recall the cholesterol-triglyceride content of the major lipoproteins (Fig. 11, Ref. 42).



Location of lipoproteins separated by paper electrophoresis with cholesterol and triglyceride content listed as a percentage of total lipid.

Figure 11

Combining this information with the knowledge of the plasma cholesterol, triglyceride and appearance of chilled plasma permits a reasonable assessment of lipoprotein elevation in a given patient (Fig. 12).

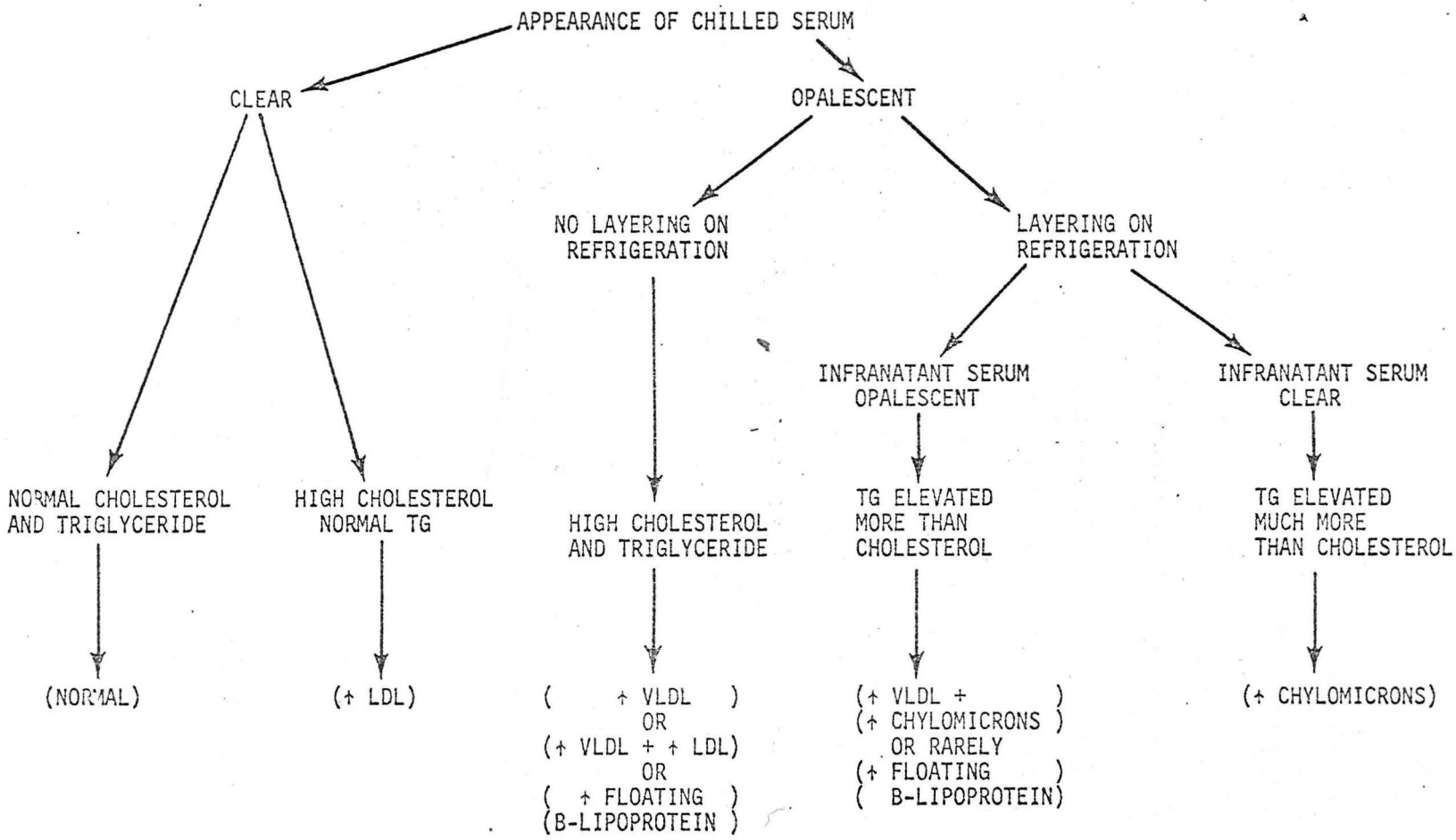

APPEARANCE OF CHILLED SERUM
CLEAR
OPALESCENT
NO LAYERING ON REFRIGERATION
LAYERING ON REFRIGERATION
INFRANATANT SERUM OPALESCENT
INFRANATANT SERUM CLEAR
NORMAL CHOLESTEROL AND TRIGLYCERIDE
HIGH CHOLESTEROL NORMAL TG
HIGH CHOLESTEROL AND TRIGLYCERIDE
TG ELEVATED MORE THAN CHOLESTEROL
TG ELEVATED MUCH MORE THAN CHOLESTEROL
(NORMAL)
(↑ LDL)
(↑ VLDL) OR (↑ VLDL + ↑ LDL) OR (↑ FLOATING B-LIPOPROTEIN)
(↑ VLDL + ↑ CHYLOMICRONS) OR RARELY (↑ FLOATING B-LIPOPROTEIN)
(↑ CHYLOMICRONS)

Figure 12

COMMENTS

1) Blood collected using EDTA anticoagulant (Lavender top vacutainer tubes) works best. Serum is less satisfactory since clot formation will trap many chylomicrons.

2) Rough estimates of triglyceride concentration are as follows:

150-250 mg% - clear at room temperature, turbid at 4°C .

> 250 mg% - turbid at room temperature.

3) Obstructive liver disease patients with LP-X usually have clear plasma and high cholesterol levels.

4) Layering upon refrigeration is considered an excellent test for chylomicrons and it is often more helpful than lipoprotein electrophoresis in detecting these particles.

5) Further definition of hyperlipidemia with regard to VLDL, LDL, and FBL requires more specialized techniques than are usually available and is not required for general clinical purposes.

C. Differential Diagnosis:

GENETIC HYPERLIPIDEMIA (PRIMARY)

Familial Hypercholesterolemia (monogenic)
Familial Hypertriglyceridemia
Familial Combined Hyperlipidemia
Broad Beta Disease (Familial Dysbetalipoproteinemia)
Familial Hypercholesterolemia (polygenic)
Lipoprotein Lipase Deficiency

SECONDARY HYPERLIPIDEMIA (ENDOCRINE RELATED)

Diabetes Mellitus
Corticosteroid Treatment
Hypothyroidism
Hypopituitarism
Estrogen or Oral Contraceptive Treatment

SECONDARY HYPERLIPIDEMIA (NON-ENDOCRINE)

Dietary and sporadic
Renal Disease - Nephrotic Syndrome, Uremia
Alcoholism
Dysglobulinemia
  -Systemic Lupus Erythematosis
  -Lymphoma
  -Multiple Myeloma
Congenital Lipodystrophy
Biliary Cirrhosis
Hepatoma

Lipoprotein-related findings for the primary and secondary hyperlipidemias are summarized in Tables 3, 4, and 5 (adapted from Blerman and Glomset, Ref. 48). These are for reference and illustrate the variability of lipoprotein changes in different disorders and in the same disorder at varying levels of severity. (eg. Diabetes Mellitus)

D. Primary Hyperlipidemias:

Two of these disorders -- lipoprotein lipase deficiency and broad beta disease are rare and will not be discussed here. They are well covered in Reference 20. Only broad beta disease is associated with atherosclerosis. Discussion will focus on the monogenic disorders associated with atherosclerosis.

1. Clinical Features - The monogenic hyperlipidemias have only recently been described (21). Consequently clinical studies of patients grouped this way are lacking. Previous clinical descriptions based on lipoprotein type alone (20) are now less valid from a genetic point of view. Certain general points can be made however.

a) The frequency of certain atherosclerotic risk factors - diabetes mellitus, obesity and hypertension - is significantly higher in hypertriglyceridemic survivors of myocardial infarction (Table 6) (21).

Table 6

Frequency of Risk Factors in Normolipidemic and Hyperlipidemic Survivors‡

Risk factor	Frequency			
	All survivors (n = 500)	Normolipidemic survivors (n = 343)	Hypercholesterolemic survivors§ (n = 78)	Hypertriglyceridemic survivors§ (n = 118)
	%			
Diabetes mellitus‖	12.6	11.1	11.5	18.6
Hypertension¶	15.4	13.4	16.6	21.2*
Obesity**	17.2	14.0	25.5*	*24.5*
Hyperuricemia‡‡	13.8	13.1	14.1	19.5
Excessive smoking§§	39.5	38.5	44.0	40.8

* Denotes statistical level of significance at 0.05 (italicized number denotes 0.01) using Chi-square test to compare proportion with risk factor in hyperlipidemic with that in normolipidemic group.
‡ 95th percentile values used to define hyperlipidemia.
§ Independent of level of other plasma liquid.
‖ Diagnosed if one of two criteria fulfilled: (*a*) survivor taking either insulin or an oral antihyperglycemic medication; or (*b*) fasting plasma glucose >120 mg/100 ml.
¶ Considered present if past history of specific treatment with antihypertensive drug therapy. Frequency of hypertension by same criterion in controls was 6.2%.
** Weight in excess of 125% of ideal body weight by criteria of Metropolitan Life Insurance Company tables (51). Frequency of obesity by same criteria in controls was 16.8%.
‡‡ Plasma uric acid ≥7.0 mg/100 ml in women and ≥8.0 mg/100 ml in men (52).
§§ More than 20 cigarettes per day. Frequency of excessive smoking by same criterion in controls was 10.0%.

b) In the monogenic disorders childhood expression is seen in familial hypercholesterolemia but rarely in the other two disorders (Fig. 10). Therefore, family screening should include children but failure to find hyperlipidemia in a child from an affected family is no guarantee that the child has been spared since the lipids may rise when he or she becomes an adult.

TABLE 3

GENETIC HYPERLIPIDEMIA

NAME	CHYLOMICRONS	VLDL	LDL	*FBL	CHOL	TG	WHO TYPE
FAMILIAL HYPERCHOLESTEROLEMIA (MONOGENIC)		↑ (Chance)	↑		↑	N or ↑	IIa, IIb
FAMILIAL HYPERTRIGLYCERIDEMIA	N or ↑	↑			N or ↑	↑ or ↑↑	IV, V
FAMILIAL COMBINED HYPERLIPIDEMIA	N or ↑	N or ↑	↑		↑	↑	IIa, IIb, IV, V
BROAD BETA DISEASE	N or ↑			↑	↑	↑	III
FAMILIAL HYPERCHOLESTEROLEMIA (POLYGENIC)		↑ (Chance)	↑		↑	N or ↑	IIa, IIb
LIPOPROTEIN LIPASE DEFICIENCY	↑↑				↔	↑↑	I

* FLOATING BETA LIPOPROTEIN

N = Normal

TABLE 4

SECONDARY HYPERLIPIDEMIA (ENDOCRINE RELATED)

CAUSE	CHYLOMICRONS	VLDL	LDL	*FBL	CHOL	TG	WHO TYPE
ENDOCRINE							
DIABETES							
Severe	↑	N or ↑			N or ↑	↑↑	I, V
Moderate	N or ↑	N or ↑	N or ↑	N or ↑	N or ↑	↑ or ↑↑	IIb, III, IV, V
Mild	N or ↑	N or ↑	N or ↑	N or ↑	N or ↑	↑ or ↑↑	IIb, III, IV, V
CORTICOSTEROID RX							
High Dose	N or ↑	N or ↑			N or ↑	↑ or ↑↑	IV, V
Low Dose or Cushing's Syndrome		N or ↑	N or ↑		N or ↑	N or ↑	IIa, IIb, IV
HYPOTHYROIDISM	N or ↑	N or ↑	N or ↑	N or ↑	↑	N, ↑ or ↑↑	IIa, IIb, III, IV, V
HYPOPITUITARISM	N or ↑	N or ↑			N or ↑	↑ or ↑↑	IV, V
ESTROGEN OR ORAL CONTRACEPTIVE RX	N or ↑	N or ↑			N or ↑	↑ or ↑↑	IV, V

*FBL = Floating Beta Lipoprotein

N = Normal

TABLE 5

SECONDARY HYPERLIPOPROTEINEMIA (NON-ENDOCRINE)

CAUSE	CHYLOMICRONS	VLDL	LDL	*FBL	CHOL	TG	WHO TYPE
NON-ENDOCRINE							
RENAL DISEASE							
Nephrotic Syndrome	N or ↑	N or ↑	N or ↑		N or ↑	N, ↑ or ↑↑	IIa, IIb, IV, V
Uremia	N or ↑	N or ↑			N or ↑	↑ or ↑↑	IV, V
ALCOHOLISM	N or ↑	N or ↑			N or ↑	↑ or ↑↑	IV, V
DYSGLOBULINEMIA -Systemic Lupus Erythematosis -Lymphoma -Multiple Myeloma	N or ↑	N or ↑	N or ↑	N or ↑	N or ↑	N, ↑ or ↑↑	I,IIa, III, V
GLYCOGEN STORAGE DISEASE	↑	N or ↑			N or ↑	↑↑	I, V
CONGENITAL LIPODYSTROPHY	N or ↑	N or ↑					IV, V
BILIARY CIRRHOSIS	Abnormal lipoprotein termed LP-X present.				N or ↑	↑	---
HEPATOMA	Hypercholesterolemia - ? due to LP-X or LDL				↑	?	---

c) Certain signs and symptoms relate to the lipoprotein or groups of lipoproteins elevated in plasma. Table 7 summarizes this information. Note, for example, that pancreatitis, lipemia retinalis and hepatosplenomegaly occur when chylomicrons are elevated but rarely, if ever, occur with elevation of other lipoproteins. In contrast various types of xanthomas occur with LDL and FBL elevations but only eruptive xanthomas have been definitely linked to chylomicrons.

Lipoproteins can also influence certain diagnostic tests. Some reported changes in hyperlipemic patients are listed in Table 8. Liver scan and UGI radiologic reports are not very convincing and the recommended approach in ascribing one of these abnormalities to hyperlipidemia is to do so by exclusion.

2. Dietary treatment: Over the years, studies have shown that lipoproteins generally respond to certain dietary factors in the following way:

a) High carbohydrate feeding = ↑ VLDL levels.

b) High saturated fat, high cholesterol = ↑ LDL levels.

c) Fat (saturated or unsaturated) = ↑ chylomicron production but high levels are not sustained in normal subjects.

d) Hypercaloric intake = ↑ VLDL (occasionally chylomicrons form if VLDL levels become very high in hyperlipemic patients) (41).

Based on lipoprotein elevations and the above information, Fredrickson and co-workers devised 5 different diets to be used with the 5 lipoprotein types (24) (Table 9).

Summary of Diets for Types I to V Hyperlipoproteinemia — Table 9

Factor	Type I	Type II	Type III*	Type IV*	Type V
Dietary prescription	Low-fat, 25 to 35 g	Low-cholesterol, polyunsaturated fat increased	Low cholesterol approximately: 20% cal. protein 40% cal. fat 40% cal. CHO	Controlled CHO (approximately 40 to 45% calories); moderately restricted cholesterol	Restricted fat (30% calories), controlled CHO (50% calories), moderately restricted cholesterol
Calories	Not restricted	Not restricted, except in type IIb where weight reduction is often indicated	Achieve and maintain "ideal" weight—reduction diet if necessary	Achieve and maintain "ideal" weight—reduction diet if necessary	Achieve and maintain "ideal" weight—reduction diet if necessary
Protein	Total protein intake not limited	Total protein intake not limited	High protein	Not limited other than control of patient's weight	High protein
Fat	Restricted to 25 to 35 g; kind of fat not important	Saturated fat intake limited; polyunsaturated intake increased	Controlled to 40% to 45% calories (polyunsaturated fats recommended in preference to saturated fats)	Not limited other than control of patient's weight (polyunsaturated fats recommended in preference to saturated fats)	Restricted to 30% calories (polyunsaturated fats recommended in preference to saturated fats)
Cholesterol	Not restricted	Less than 300 mg or as low as possible; only source of cholesterol is meat	Less than 300 mg, only source of cholesterol is meat	Moderately restricted to 300 to 500 mg	Moderately restricted to 300 to 500 mg
Carbohydrates	Not restricted	Not restricted (may be controlled in type IIb)	Controlled; most concentrated sweets eliminated	Controlled; most concentrated sweets eliminated	Controlled; most concentrated sweets eliminated
Alcohol	Not recommended	May be used with discretion	Limited to 2 servings (substituted for carbohydrate)	Limited to 2 servings (substituted for carbohydrate)	Not recommended

* Cal. = calories; CHO = carbohydrate.

TABLE 7

SIGNS + SYMPTOMS RELATING TO LIPOPROTEIN ELEVATION

	CHYLOMICRONS	VLDL	LDL	FBL
XANTHELASMA			+	RARE
XANTHOMAS				
TENDON			+	+
TUBEROUS			+	+
TUBERO-ERUPTIVE		Occasional		+
ERUPTIVE	+	Occasional		
PLANAR			+	+
PLANAR-PALM CREASES				+
SUBPERIOSTEAL			+	+
ARCUS CORNEAE			+	+
HEPATOMEGALY	+	Occasional		Occasional
SPLENOMEGALY	+			?
LIPEMIA RETINALIS	+			
PANCREATITIS + ABDOMINAL PAIN	+	Occasional		Rare
ARTHRITIS		?	+	
TENDONITIS			+	
RETINAL CHANGES				
HEMORRHAGES	+			
EDEMA	+			
YELLOW DEPOSITS	+			
DETACHMENT	+			
VESSEL DILATATION	+			
XANTHOMAS			+	

+ indicates that a sign or symptom occurs frequently when a particular lipoprotein is elevated.

TABLE 8

INFLUENCE OF LIPOPROTEINS ON DIAGNOSTIC TESTS

	CHYLOMICRONS	VLDL	LDL	FBL
ESR		+	+	
ABNORMAL LIVER SCAN	+	+	?	?
UGI RADIOLOGIC FINDINGS -Mucosal Thickening -Antral Deformity -Bulbar Deformity -Pyloric Prolapse of Gastric Mucosa		+	?	?
FALSE DEPRESSION OF LABORATORY VALUES	+	+		?

Diets for the Type II, III and IV diet are nearly identical with only small differences in cholesterol intake. The Type V diet contains a 10% reduction in fat and a 10% increase in carbohydrates to help reduce chylomicron formation.

Although the diets make sense physiologically, it is cumbersome to work with four slightly different diets and no data is available to indicate that these small dietary differences significantly alter lipoprotein levels any more than a balanced diabetic diet would.

In most cases, therefore, a diabetic diet restricted in fats and low in cholesterol is satisfactory. It is virtually identical to the Type III diet of Fredrickson and its general composition is as follows:

	Calorie Distribution
Protein	20%
Carbohydrate	40%
Fat	40%
Cholesterol content	300 mg
P/S ratio	∿ 1.5 to 2

(enriched in polyunsaturated fats.)

Calories must be adjusted to achieve weight loss when necessary.

Diets are modestly effective in lowering lipids as illustrated in Table 10. Six representative studies are summarized. Fat content varied between 30-40% and all were enriched in polyunsaturated fats and restricted in cholesterol content. Taken together, these studies indicate that cholesterol levels can be reduced an average of 12% using such diets. Triglyceride results ranged from variable with but a slight average decrease to sizeable reductions of 11 to 17%. Triglyceride reduction was greatest in studies where weight loss occurred during dietary treatment and in general, TG reduction was greatest in those patients with higher initial levels.

Several problems and controversies exist with regard to these diets:

a) Prevalence of cholelithiasis is increased in men ingesting serum cholesterol-lowering diets (55).

b) Cancer incidence in men consuming high polyunsaturated fat diets was reportedly increased (56). This study was subsequently refuted (57) and controversy rages on.

c) Some investigators (58) feel safety of polyunsaturated fatty acids (PUFA) has not been adequately proven and cite the following:

I) Effectiveness of PUFA to reduce mortality from coronary disease is not convincing.

II) PUFA given as corn oil can cause cancer in mice.

III) Potentially carcinogenic lipid peroxides easily form in PUFA by auto-oxidation.

TABLE 10

EFFECTS OF DIET ON PLASMA LIPIDS

STUDY		DIET	CHOL	TG	COMMENT	WEIGHT
DIET-HEART (1968)	A)	30% Fat, Low Chol ↑ P/S Ratio	-11%	Variable Most ↓	20-25% Poor Adherence	Stable
	B)	40% Fat, Low Chol ↑↑ P/S Ratio	-12%	Variable Most ↓		Stable
OSLO DIET-HEART (1970)		Low Fat, ↑ P/S Ratio 300 mg Chol/Day	-17%	--	↓ MI Mortality	--
BIERENBAUM, ET.AL. (1973)		28% Fat, ↑ P/S Ratio in half. 400 mg Chol/Day	-7.3 to 9.7%	Slight ↓	↑ P/S did not improve results 17% greater survival rate.	Yes
HALL, ET.AL. (1972)		20% Protein, 30% Fat P/S 1.25, 300 mg Chol/Day	-12.1%	-17.3%	2 year study	5.3% ↓
WILSON, ET.AL. (1971)		16% Protein, 43% Chol 40% Fat P/S = 1.6 Chol 227 mg/Day	- 9.6%	-11.7%	6 month study	0.8% ↓
MEITTINEN, ET.AL. (1972)		30-32% Fat ↑ P/S Ratio Chol ∿ 250 mg/Day	-12 to 18%	Variable ↓	Diet trial in two mental hospitals over 12 years. CHD mortality ↓ in men but only suggestive in women.	

iv) Heating PUFA may produce carcinogenic substances such as polycyclic and aromatic hydrocarbons.

v) PUFA (unheated) may potentiate tumor-inducing properties of other carcinogens.

vi) PUFA ingestion may increase nutritional requirements for vitamin E and other vitamins.

These areas are under investigation but no conclusions can be drawn.

Several advantages to diet in general can be cited:

a) Weight reduction will reduce plasma triglyceride levels, triglyceride production rate, insulin resistance and hyperinsulinism (59).

b) Lipid lowering diets produce regression of coronary artery atheromas in experimental atherosclerosis in the Rhesus mokey (60).

c) Several human diet trials report reduced mortality from coronary artery disease in patients following lipid lowering diets (50, 51, 54).

d) Certain coronary risk factors (cholesterol, blood pressure, blood glucose and uric acid) are reduced by weight loss with a concomitant improvement in chances of avoiding a heart attack (61) (Table II).

Table II

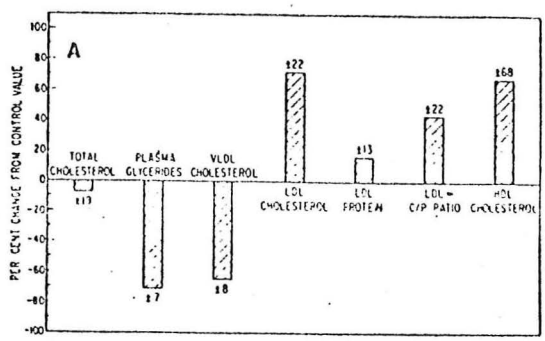
CORONARY HEART DISEASE RELATIVE ODDS RATIOS CORRESPONDING TO GIVEN CHANGES IN RELATIVE WEIGHT

	Males		Females	
Age:	35–44	45–54	35–44	45–54
Change in relative weight				
−20	0.57	0.62	0.62	0.83
−10	0.76	0.80	0.80	0.94
+10	1.38	1.31	1.31	1.20
+20	1.86	1.68	1.69	1.35

COMMENTS:

1) In general patients do better who are counseled by a nutritionist. Simply handing a diet manual to a patient is usually ineffective.

2) A weight-reduction diet alone in a hypertriglyceridemic patient often raises the LDL level in association with a decrease in VLDL levels, (62) (Fig. 13).



Effect of weight reduction on lipoprotein levels.

Figure 13

For this reason, caloric restriction is usually combined with a low cholesterol-high polyunsaturated fat diet.

3) Patients with persistent hyperchylomicronemia may require replacement of part of their regular dietary fat by medium chain triglyceride (MCT).

4) The following reference information may be useful in diet therapy:

I) Cholesterol content of foods (63).
II) Use of medium chain triglycerides (64).
III) Diets that Lower Plasma Lipids in man (65).

3) Drug Treatment - A variety of drugs are available for use in treating hyperlipidemia. The four most commonly used drugs are outlined here. None of the drugs is very specific and they vary with respect to their influence on lipoprotein levels as follows:

Nicotinic Acid - lowers VLDL and LDL
Clofibrate - lowers VLDL, variable effect on LDL
Cholestyramine - lowers LDL, may increase VLDL
D-Thyroxine - lowers LDL, little effect on VLDL

Major features of these drugs are summarized in Table 12 (Ref. 24).

a) Nicotinic Acid: Also termed niacin to avoid confusion with the completely unrelated compound, Nicotine. Nicotinic acid and Nicotinamide are effective in Pellagra but only Nicotinic acid lowers plasma lipids. (Nicotinamide was effective in one patient [67]). Liver function should be monitored during use. Reduction in cholesterol may range from 17-39%. Triglyceride reductions range between 30 and 90% (68, 69). Best results are seen in the most lipemic patients. For general discussion see references 68, 69, 24. Reference 70 is a lengthy treatise.

TABLE 12

HYPOLIPIDEMIC DRUGS*

	NICOTINIC ACID (NICALEX)	CHOLESTYRAMINE (QUESTRAN)	D-THYROXINE (CHOLOXIN)	CLOFIBRATE (ATROMID-S)
EFFECT ON PLASMA LIPOPROTEINS	↓ VLDL, ↓ LDL ↓ LDL synthesis	↓ LDL, may ↑ VLDL ↑ LDL catabolism	↓ LDL, little effect on VLDL, ↑ LDL catabolism	↓ VLDL, effect on LDL variable
INITIAL DOSE	100 mg orally, three times daily	4 gm orally four times daily	1 mg orally, daily. Increased by 1-2 gm at monthly intervals	0.5 - 1.0 gm twice daily
MAINTENANCE DOSE	1-2 gm orally, three times daily with meals	4-8 gm orally, four times daily	4-8 gm orally, daily	1 gm orally, twice daily
ADVERSE EFFECTS	Flusing, pruritis, hyperuricemia, ↓ glucose tolerance, hepatotoxicity	Constipation, bloating, nausea, fat malasorption at doses > 24 gm/day	Signs of hypermetabolism, may ↑ angina. Potentiate effects of Warfarin + epinephrine. May ↑ glucose in diabetics	Nausea, weight gain, myositis, alopecia, agranulocytosis. Abnormal liver function
CAUTION	Peptic ulcer patients. Safe use in pregnancy not established	Drug binds Warfarin, digitalis, thyroxin, + possibly thiazides. Safe use in pregnancy not established	↓ Warfarin dose. Avoid in patients with multiple ectopic premature beats. Extreme caution in patients with coronary disease Safe use in pregnancy (?)	Potentiates effects of Warfarin. Safe use in pregnancy not established
USE	↑ VLDL, LDL + Floating beta lipoprotein levels (Types IIa, IIb, III, IV, V)	↑ LDL levels. (Type IIa, ? type IIb in combination)	↑ LDL, ↑ Floating beta lipoprotein. (Type IIa, III, ? IIb)	↑ VLDL, Floating beta lipoprotein (Types III, V, ?IIb in combination)

b) Cholestyramine: A quaternary ammonium anion exchange resin, with basic groups attached to a styrene-divinyl-benzene copolymer by carbon-to-carbon bonds. Molecular weight is greater than one million and it is neither digested nor absorbed from the GI tract. It binds bile salts tightly in the intestine, thereby promoting their increased rate of loss from the gut. All links between bile salt loss and cholesterol metabolism are not yet known.

Anticoagulation with Warfarin is difficult to control and another drug should be substituted for cholestyramine if clear-cut indications for anti-coagulation are present (24). It is most effective in lowering cholesterol in doses of 16-24 gm/day. An average 20% reduction in LDL cholesterol can be achieved in Familial Hypercholesterolemia. Rarely, doses of 32 gm may be needed (in homozygous familial hypercholesterolemia). Doses should be given 1/2 to one hour before meals and at bedtime. In some patients, mild hypertriglyceridemia results during treatment but this is no reason to stop its use in moderate to severe hypercholesterolemia. Weight reduction or clofibrate can be used if TG levels go above 200 mg%. Some patients require laxatives to overcome the constipating effect of cholestyramine. For references, see 24, 71, 72, 76, and 73. Treated hypothyroid patients requiring cholestyramine need periodic monitoring of thyroid function because thyroxine binds to cholestyramine and may not be absorbed (74).

c) D-Thyroxine: Dextrorotatory form of thyroxine which retains its cholesterol-lowering effects while its calorigenic effects are much reduced but still present (24). Cardiac effects can be controlled by simultaneous treatment with propanolol (75). Though effective in reducing cholesterol (76), data from the coronary drug project (a large scale and long term study of drug regimens influencing lipid metabolism in men aged 30 to 64 years, who have recovered from one or more myocardial infarctions) indicated that after 36 months, patients receiving dextrothyroxine had an 18.4% higher proportion of deaths than did the placebo group. Mortality increased progressively with duration of treatment. In addition to higher rates of death from coronary and all other cardiovascular causes, there was also a higher proportion of patients suffering recurrent non-fatal myocardial infarctions. Dextrothyroxine was discontinued from the study (77). It is still available as a hypocholesterolemic agent but it is contraindicated in patients with:

I) Any known organic heart disease.
II) Hypertension
III) Advanced liver or kidney disease.

Maximum dose in patients receiving digitalis is 4 mg/day. Because of the cardiovascular contraindications, use of this drug is severely limited.

d) Clofibrate (Atromid-S): Probably the most widely used hypolipidemic drug. Its mechanism of action is uncertain but cholesterol balance data suggests that it may promote increased excretion of cholesterol stored in tissues (78). It has been used for long periods with good patient tolerance and few side effects (79, 80). In familial hypercholesterolemia (Type II) it produces only a 7% reduction in cholesterol (24). It is far more effective in hypertriglyceridemic states (81).

The results of three trials of clofibrate treatment in Ischemic Heart Disease have recently appeared, (82, 83, 84). These studies concluded that clofibrate had a favorable effect on morbidity in coronary heart disease which was not correlated with the hypolipidemia it produced. It was suggested that this beneficial effect might instead be due to some influence on one or several parameters of blood clotting, such as, platelet aggregation or fibrinolytic activity (81). These clinical trials have been critized by several biostatisticians who in general conclude that a beneficial effect of clofibrate on coronary heart disease morbidity is suggested but not conclusively shown by the data in these studies, (85, 86, 87). As a result, bigger and better studies are being proposed to settle this issue. Whatever the results, clofibrate remains an effective lipid-lowering drug with a good safety record.

Clofibrate has an ADH-like action (88) but significant water retention and weight gain have not been problematical. Use of clofibrate in nephrotic syndrome hyperlipidemia has been complicated by muscular pain, stiffness and general malaise (89). Those patients receiving maintainance Frusemide therapy developed a pronounced diuresis when clofibrate therapy was started. Most patients were hypoalbuminemic and it was postulated that reduced albumin binding sites lead to higher unbound clofibrate levels in sera with resultant toxic effects. The diuresis was thought due to displacement of Frusemide from its albumin-binding sites by the clofibrate. It was recommended that the clofibrate dosage not exceed 0.5 gm for each one gram percent serum albumin concentration.

e) Combination Drug Treatment: Experience is limited but several reports indicate combinations such as clofibrate + cholestyramine (or colestipol) or Nicotinic acid + cholestyramine work synergistically (90, 91). The latter combination is especially useful in homozygous familial hypercholesterolemia (24, 92). Additional combinations are found in references 93 and 94. In order to keep treatment programs simple, combinations should not be used except in very resistant cases of hyperlipidemia.

Mention of additional drugs can be found in reference 24 and in a recent review from the NIH group (95).

f) Surgery: Ileal bypass surgery has been proposed as an effective therapy for hypercholesterolemia and details are reviewed in reference 96.

The surgery promotes increased fecal loss of bile acids and may also cause a certain degree of malabsorption and diarrhea. Cholestyramine is the medical counterpart. I favor intensive medical treatment and consider surgery a last resort in hypercholesterolemic patients who, for one reason or another, are resistant to medical therapy.

Portacaval shunt surgery reportedly produced excellent results in a familial homozygous hypercholesterolemic child who was near death from atherosclerotic complications (97). Not only was cholesterol lowered considerably but xanthomas regressed as did atherosclerotic lesions. Much more information is needed but the results are promising.

SUMMARY - Suggested approach to Hyperlipidemia

1. Indications for testing lipids in a patient:

   A. Family History of: Atherosclerosis before age 55
      Diabetes Mellitus
      Xanthomas or xanthelasmas
      Hyperlipidemia

   B. Personal History of: Atherosclerosis before age 55
      Xanthomas or xanthelasmas
      Diabetes Mellitus or abnormal GTT
      Obesity
      Gout
      Hypertension
      Hypothyroidism
      Unexplained abdominal pain
      Alcoholism
      Turbid or milky plasma.

A routine test of plasma lipids is recommended as part of a general medical exam.

2. Conditions for base - line testing

   A. Fasting 12-14 hours

   B. Stable weight for 2 weeks

   C. Ordinary diet

   D. No medications known to affect plasma lipids.

   E. No myocardial infarction within 2-3 months (98)

3. Indications for treatment: Treatment should be considered in anyone with a cholesterol level greater than 250 mg% and/or a triglyceride level greater than 150 mg%. In my opinion, secondary hyperlipidemias of chronic duration should also be treated.

4. Treatment plan: Estimates of lipoprotein elevation should be made using the scheme in Figure 12.

A. DIET: The first step in treatment. A balanced diet (20% protein, 40% fat, 40% CHO) with a 300 mg cholesterol content and high P/S ratio (1.5 to 2) is generally successful. Caloric restriction is beneficial, particularly in hypertriglyceridemic states where obesity is more common. Severe hyperchylomicronemia may require further reduction in dietary fat from the above proportions. Cholesterol and FFA content of foods are given in Table 14 and ideal height/weight charts are reproduced in Tables 15-a and 15-b.

B. Drug therapy is usually withheld for 4 to 6 weeks after starting diet treatment since lipid values may normalize on diet alone, particularly in

CHOLESTEROL CONTENT OF FOODS[a]

(mg/100 gm product)

Beef		
Chuck Roast		55
Round Steak		68
Rump Roast		58
Tallow		56
Cheeses		
American		92
American Process		87
Blue		157
Cheddar		98
Cottage Cheese		
Dry or Rinsed		1
Creamed		15
Cream Cheese		140
Gouda		33
Limburger		92
Mozarella (part skim)		61
Parmesan		74
Roquefort		73
Swiss		91
Chicken		
Dark meat		76
Light meat		54
Dairy Products		
Butter		249
Cream		
Thick		140
Thin		40
Egg		
white		0
yolk		1370
Milk		
Buttermilk		6
Fortified Skim (1% Butterfat)		5
Skim	less than	1
Whole		14
Fats		
Lard		65
Margarine (vegetable)		0
Oils, vegetable		0
Peanut butter		0
Fish		
Codfish		46
Haddock		64
Halibut		33
Herring		75
Mackerel		80
Perch		63
Pike		71
Salmon		55
Trout		57
Tuna		51
Lamb		
Chops		66
Mutton		77
Pork		
Chops		55
Ham		42
Tenderloin		57
Shellfish		
Clams		49[b]
Crab		99
Lobster		83
Oysters		60[b]
Scallops		30[b]
Shrimp		161
Turkey		
Dark meat		96
Light meat		61
Variety meats		
Brains, Calf		1810
Kidney		300
Liver, Beef		320
Sweetbreads		280
Veal		71

[a]Laboratory analysis by Connor.

COMPOSITION OF VARIOUS FATS AND OILS PER 100 GM PRODUCT

	Total fat (gm)	*Saturated (gm)*	*Monounsaturated (gm)*	*Polyunsaturated (gm)*	*P-S Ratio*	*Iodine Number*	*Source[b]*
I. Vegetable oils							
A. Cocoa Butter(the fat in chocolate)	100	56	37	2	0.04	37	1
B. Coconut	100	86	7	—	—	6	1
C. Corn	100	10	28	54	5.4	123	1
D. Cottonseed	100	25	21	50	2.0	109	1
E. Olive	100	11	76	7	0.6	81	1
F. Peanut	100	18	47	29	1.6	95	1
G. Safflower	100	8	15	72	9.0	144	1
H. Soybean	100	15	20	63	4.2	132	1
II. Partially hydrogenated vegetable oil	100	14	46	40	2.9	114	2
III. Vegetable margarines							
A. Diet—Representative of available products	40	8	16	16	2.0	108	4, 5
B. Soft							
1. Safflower oil	80	11	19	51	4.6	137	3
2. Representative of other available products	80	17	35	29	1.7	105	4, 5, 6
C. Stick—Representative of available products	80	17	48	15	0.9	88	4, 5, 6, 7
D. Whipped—Representative of available products	80	17	48	15	0.9	88	5, 7
IV. Vegetable shortenings	100	25	46	29	1.2	94	2, 4
V. Animal fats							
A. Butter	80	45	27	3	0.1	37	1
B. Lard	100	38	46	11	0.3	61	1
VI. Peanut butter	50	12	23	15	1.3	96	2, 5, 7, 8

[b]See source sheet.

Sources (for Table 8-III)

1. Home Economics Research Report #7.
2. Procter and Gamble: Crisco Oil®, Crisco shortening®, Jif Peanut Butter®.
3. Anderson-Clayton and Company: Chiffon® tub margarine.
4. Lever Brothers: Diet Imperial® margarine, Soft Spread Imperial® margarine, Good Luck® stick margarine, Spry® vegetable shortening.
5. Standard Brands: Diet Fleischmann's® margarine, Soft Blue Bonnet® margarine, Soft Fleischmann's® margarine, Blue Bonnet® stick margarine, Fleischmann's® stick margarine, Whipped Blue Bonnet® margarine, Planter's® peanut butter.
6. Kraft Foods: Soft Parkay® margarine, Parkay® stick margarine.
7. Best Foods Products Company: Mazola® stick margarine, Whipped Nucoa® margarine, Skippy® peanut butter.
8. Derby Foods: Peter Pan® peanut butter.

TABLE 15A

Desirable Weights* Women of Ages 25 and Over

Weight in Pounds According to Frame (in Indoor Clothing)

Height (with shoes on) 2 inch heels				
Feet	Inches	Small Frame	Medium Frame	Large Frame
4	10	92-98	96-107	104-119
4	11	94-101	98-110	106-122
5	0	96-104	101-113	109-125
5	1	99-107	104-116	112-128
5	2	102-110	107-119	115-131
5	3	105-113	110-122	118-134
5	4	108-116	113-126	121-138
5	5	111-119	116-130	125-142
5	6	114-123	120-135	129-146
5	7	118-127	124-139	133-150
5	8	122-131	128-143	137-154
5	9	126-135	132-147	141-158
5	10	130-140	136-151	145-163
5	11	134-144	140-155	149-168
6	0	138-148	144-159	153-173

For girls between 18 and 25, subtract 1 pound for each year under 25.

Editor's Note: These body weights have been observed to be associated with the lowest mortality rates

TABLE 15B

Desirable Weights* Men of Ages 25 and Over

Weight in Pounds According to Frame (in Indoor Clothing)

Height (with shoes on) 1-inch heels				
Feet	Inches	Small Frame	Medium Frame	Large Frame
5	2	112-120	118-129	126-141
5	3	115-123	121-133	129-144
5	4	118-126	124-136	132-148
5	5	121-129	127-139	135-152
5	6	124-133	130-143	138-156
5	7	128-137	134-147	142-161
5	8	132-141	138-152	147-166
5	9	136-145	142-156	151-170
5	10	140-150	146-160	155-174
5	11	144-154	150-165	159-179
6	0	148-158	154-170	164-184
6	1	152-162	158-175	168-189
6	2	156-167	162-180	173-194
6	3	160-171	167-185	178-199
6	4	164-175	172-190	182-204

*From Metropolitan Life Insurance Company: New Weight Standards for Men and Women. Statistical Bulletin, Vol. 40, 1959, p. 3.

hypertriglyceridemic patients. As a rough guide, cholesterols over 280 mg% and/or triglycerides over 250 mg% during diet treatment indicate that drug therapy is needed.

As a rule, hypercholesterolemia responds to cholestyramine 16 to 24 gm/day. Patients respond to a lesser degree to Atromid-S and an occasional patient responds very well to Atromid-S for reasons unknown.

Hypertriglyceridemia may respond to Atromid-S or Nicotinic acid. Atromid-S, in contrast to Nicotinic acid, is well tolerated and I usually start with it in doses of 1 gm twice daily.

5. General: Encourage weight reduction and cessation of smoking. Mild exercise may be helpful if coronary status permits. Control hypertension. These are all added risk factors.

6. Family studies should be performed whenever possible to detect other hyperlipidemic subjects.

7. Treatment in children: No control studies available. Generally diet alone is used until adolescence, at which time drugs are added if lipids increase. Familial Homozygous Hypercholesterolemia requires aggressive treatment from early age but fortunately this condition is rare. Though hyperlipidemic females develop atherosclerosis about a decade later than similarly affected males, I favor dietary treatment of affected females in childhood.

NOTE: A number of studies suggest that diet or drug treatment is beneficial with regard to improved morbidity and/or mortality from coronary heart disease. There is no conclusive proof that diet and/or drug treatment is beneficial. The recommendations above are made on the basis of epidemiologic studies of large populations. At present, it is the best information we have to use for guidelines.

Secondary Hyperlipidemia: Evidence is beginning to accumulate that certain forms of secondary hyperlipidemia may actually represent subclinical forms of familial hyperlipidemia that are unmasked by drug treatment or another superimposed illness. We will briefly comment on several secondary hyperlipidemias from this point of view. One hospital's experience regarding causes of hypertriglyceridemia are shown in Table 16, (105).

Table 16

—NUMBERS OF PATIENTS WITH HYPERTRIGLYCERIDÆMIA OF IDENTIFIED CAUSE AT HAMMERSMITH HOSPITAL IN 1971

Cause	No.
Familial	62
Diabetes mellitus	43
Alcoholism	31
Chronic renal disease	20
Hypothyroidism	14
Gout	11
Hypopituitarism	10
Acromegaly	7
Cholestasis	4
Malabsorption	3
Oral contraceptives	3
Cushing's syndrome	1
Addison's disease	1
Gram-negative septicæmia	1
Total	211

A. Hypothyroidism: In one series hypercholesterolemia (>300 mg%) was found in 81% of 147 cases of hypothyroidism (99). Only 6% of the cases had cholesterols less than 250 mg%. This high degree of hyperlipidemia suggests that hypothyroidism has profound general affects on lipid metabolism irrespective of the presence or absence of a genetic predisposition to hyperlipidemia.

B. Diabetes Mellitus: Nikkila has recently summarized the incidence of hyperlipidemia in diabetic patients in the diabetic clinic of Helsinki University Hospital (100). He found that hyperlipidemia varied with the state of diabetes as follows:

1) Diabetic ketoacidosis - 91% had elevated triglyceride levels. Gross hyperlipidemia was not very common. Hyperlipidemia responded to insulin treatment.

2) Insulin-treated juvenile diabetes - 20% exceeded the 90th percentile limit of a normal control population. Frequency of hypertriglyceridemia was twice that of controls.

3) Adult - onset non-insulin treated diabetes - 35% had triglyceride levels exceeding the 90th percentile of an age - matched basic population. Triglyceride levels correlated poorly with glucose levels but fairly well with the degree of obesity. The association of obesity with hypertriglyceridemia in patients with diabetes mellitus has been stressed by Bierman and Porte (101). Reason for the association remains unknown and there is insufficient evidence to suggest the diabetes (or obesity) is unmasking a primary hyperlipidemia. The association has clinical importance since diabetics with coronary disease have a high prevalence for hypertriglyceridemia (102, 103). Because of this a more aggressive approach to the treatment of hyperlipidemia in adult onset diabetic is probably indicated, particularly with use of hypolipidemic drugs. Triglyceride metabolism in Diabetes Mellitus has recently been reviewed (104).

C. Alcoholism: Chait and co-workers reported that alcohol did not interfere with uptake of triglyceride by peripheral tissues (105), and this led them to suggest that alcohol promoted lipoprotein secretion by the liver. Hyperlipemic alcoholics might then be those with relative triglyceride clearance defects - those individuals with a genetic predisposition to hypertriglyceridemia, Ginsberg, et.al. (106) studied the influence of ethanol (7½ oz/day) on triglyceride levels in hypertriglyceridemic and normal subjects. They found that fasting triglyceride levels rose only in hypertriglyceridemic subjects and suggested that alcohol be avoided in treating hypertriglyceridemic subjects. Finally Mendelson and Mello (107) studied the influence of up to 32 oz. of alcohol daily on serum lipid levels in 3 groups of alcoholics - normals, carbohydrate - induced hypertriglyceridemics and familial hypertriglyceridemics. Results are shown in Figure 14. Triglyceride levels rose most sharply in the familial hypertriglyceridemic subjects to high levels. The authors suggest that several important features of alcoholism may be linked to this phenomenon.

1) Fatty liver and possibly cirrhosis may develop mostly in alcoholics with a genetic hyperlipidemia.

2) Pancreatitis may develop in alcoholics with a genetic hyperlipidemia.

3) Alcohol may be a coronary risk factor in the hypertriglyceridemic patient.

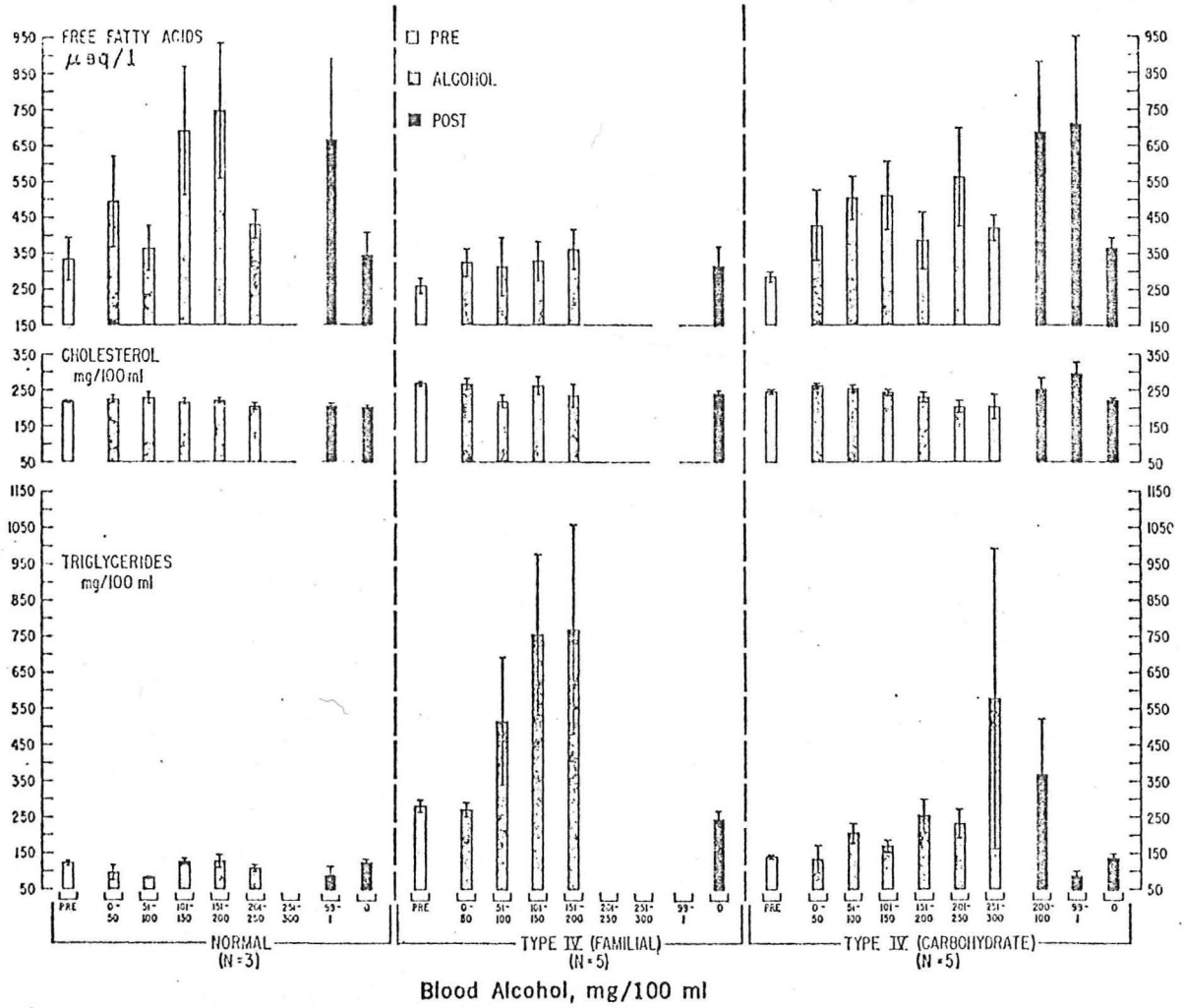


Figure 14

Families of hyperlipidemic alcoholics should be checked for evidence of genetic hyperlipidemia, particularly hypertriglyceridemia, to learn more about this issue.

D. Oral Contraceptives: These agents have a general effect on lipid metabolism which is exaggerated in certain patients with genetic lipid disorders. See reference 108 for review. Modest elevation of triglyceride is observed in large numbers of patients taking oral contraceptives and the degree of increase is dose-related to the estrogen content of the pill (Fig. 15) (109).

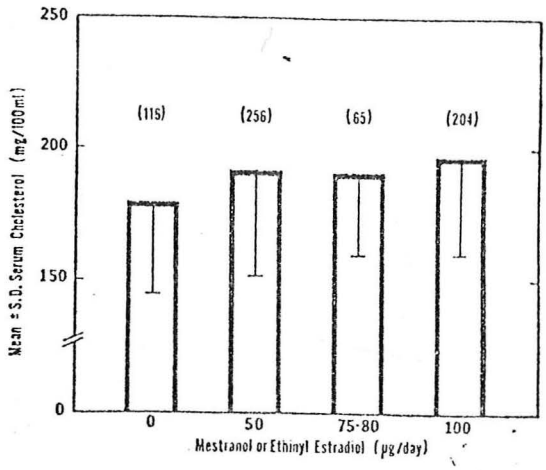


Figure 15

No change in serum triglyceride levels are seen when progesterone derivatives are used alone (110). In fact, progesterone derivatives can be effective in lowering plasma triglycerides in hypertriglyceridemic subjects presumably by increasing lipolytic activity (111). The estrogen component of oral contraceptives can produce massive hyperlipidemia, pancreatitis and death in susceptible individuals but this clinical situation may not be common (112, 113).

In light of this information several suggestions can be made:

1) Estrogen containing medications should be given with caution to hyperlipidemic patients - this also includes men receiving estrogen treatment for prostatic carcinoma. Optimally estrogen treatment should be avoided in such patients.

2) Hyperlipemic women requiring oral contraception should be given a progesterone - derivative.

3). Consideration should be given to obtaining baseline lipids on women about to receive oral contraceptives along with follow-up values sometime later during their use.

4) Consideration must be given to the possibility of increasing atherosclerotic risk in women receiving long-term treatment with oral estrogen - containing contraceptives.

Secondary hyperlipidemias, particularly those associated with chronic conditions, will be receiving increasing clinical attention in the future in view of the atherogenicity associated with these macromolecules. Hyperlipidemia in renal disease including that seen in chronic renal failure (114), following renal transplantation (115) and possibly during maintainance hemodialysis (116) are currently active fields of interest.

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