MEDICAL GRAND ROUNDS

October 19, 1972

GENETICS OF HYPERLIPIDEMIA IN CORONARY HEART DISEASE

By Joseph L. Goldstein, M. D.

I. Familial Aggregation in Coronary Heart Disease

1. Osler, W. Lectures on Angina Pectoris and Allied States. D. Appleton and Company, New York. 1897.
2. Gertler, M. M., and P. D. White. Coronary Heart Disease in Young Adults: a Multidisciplinary Study. Harvard University Press, Boston. 1954.
3. Thomas, C. B., and B. H. Cohen. The familial occurrence of hypertension and coronary heart disease, with observations concerning obesity and diabetes. Ann. Intern. Med. 42:90, 1955.
4. Slack, J., and K. A. Evans. The increased risk of death from ischemic heart disease in first degree relatives of 121 men and 96 women with ischemic heart disease. J. Med. Genet. 3:239, 1966.

Osler was the first to emphasize the importance of genetic factors in the pathogenesis of coronary heart disease. He described several remarkable family pedigrees in which the grandfather, father, and son had each died of "heart pain" before age 40 years (Reference 1). As a result of a number of carefully conducted recent studies on the familial aggregation of coronary heart disease (2,3,4), it is generally believed that:

1) if an individual has a myocardial infarction before age 60 years, his first-degree relatives,(i.e., parents, siblings, and children) show a 6 fold increased risk for myocardial infarction as compared to that of the general population.
2) if an individual has his first myocardial infarction at or after age 60 years, the risk to his first-degree relatives is 2 fold over that of the general population.

II. Coronary Heart Disease as a Multifactorial and Heterogeneous Disorder

5. Epstein, F. H., and L. D. Ostrander, Jr. Detection of individual susceptibility toward coronary heart disease. Progr. Cardiovas. Dis. 13:324, 1971.
6. Epstein, F. H. Epidemiologic aspects of atherosclerosis. Atherosclerosis. 14:1, 1971.
7. Epstein, F. H. Risk Factors in coronary heart disease: Environmental and hereditary influences. Israel J. Med. Sci. 3:594, 1967.
8. Kannel, W. B., W. P. Castelli, T. Gordon, and P. M. McNamara. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. Ann. Intern. Med. 74:1, 1971.

9. Ostrander, L. D., Jr., B. J. Neff, W. D. Block, T. Francis, Jr., and F. H. Epstein. Hyperglycemia and hypertriglyceridemia among persons with coronary heart disease. Ann. Intern. Med. 67:34, 1967.

As a result of many large-scale epidemiological investigations (5-9) a number of genetically-determined and environmentally-influenced factors ("risk factors") are now recognized to play an important role in the etiology of coronary heart disease (see Table 1). Since four of these "risk factors" - hypercholesterolemia, hypertriglyceridemia, hypertension, and diabetes mellitus - are importantly influenced by genetic factors, it is likely that much of the familial aggregation of coronary heart disease is determined by the familial occurrence of hyperlipidemia, diabetes mellitus, and hypertension.

III. Hypertriglyceridemia as an Independent Risk Factor for Coronary Heart Disease

10. Albrink, M. J., J. W. Meigs, and E. B. Man. Serum lipids, hypertension, and coronary heart disease. Amer. J. Med. 31:4, 1961.
11. Brown, D. F., S. H. Kinch, and J. T. Doyle. Serum triglycerides in health and in ischaemic heart disease. New Eng. J. Med. 273: 947, 1965.
12. Havel, R. J., and L. A. Carlson. Serum lipoproteins, cholesterol and triglycerides in coronary heart disease. Metabolism. 11: 195, 1962.
13. Carlson, L. A., and L. E. Bottiger. Ischaemic heart disease in relation to fasting value of plasma triglycerides and cholesterol. Lancet. i:865, 1972.

Albrink was the first to emphasize the importance of the plasma triglyceride level as a predictor of coronary heart disease (10). Althcugh the level of plasma cholesterol has generally been thought to be a more significant risk factor than the level of plasma triglyceride, the more recent Swedish epidemiological investigations of Carlson (13) indicate that the fasting triglyceride value is a more informative and important risk factor than the cholesterol value. It is unfortunate to note that neither of the two major American epidemiological studies on coronary heart disease - i.e., the Tecumseh study and the Framingham study - obtained fasting blood specimens for measurement of the triglyceride level.

IV. Genetic Studies of Hyperlipidemia and Coronary Heart Disease

14. Murphy, E. A. Some difficulties in the investigation of genetic factors in coronary artery disease. Canad. Med. Assn. J. 97:1181, 1967.

This article (14) clearly outlines the problems which preclude a precise genetic analysis of coronary heart disease. These include: 1) delayed and variable age of onset of the disorder; 2) high frequency of the disorder in the population; 3) heterogeneity of "risk factors" which predispose to development of coronary atherosclerosis; and 4) absence of knowledge of basic metabolic defects and hence absence of specific genetic markers for identifying asymptomatic individuals who may carry gene(s) predisposing to coronary disease.

15. Slack, J. Risks of ischaemic heart-disease in familial hyperlipoproteinemic states. Lancet ii: 1380, 1969.
16. Fredrickson, D. S. and R. I. Levy. Familial hyperlipoproteinemia. In The Metabolic Basis of Inherited Disease. J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson. McGraw-Hill, New York. 3rd edition. 595, 1972.
17. Slack, J., and N. C. Nevin. Hereditary aspects of hyperlipidemic states. In Treatment of the Hyperlipidemic States. H. R. Casdorph, Editor. Charles C. Thomas, Springfield, Illinois. 121, 1971.
18. Miettinen, T. A., I. M. Penttila and E. Lampainen. Familial occurrence of mild hyperlipoproteinaemias. Clin. Genetics 3:271, 1972.
19. Schrott, H. G., J. L. Goldstein, W. R. Hazzard, M. M. McGoodwin, and A. G. Motulsky. Familial hypercholesterolemia in a large kindred: Evidence for monogenic mechanism. Ann. Intern. Med. 76:711, 1972.
20. Nevin, N. C., and J. Slack. Hyperlipidaemic xanthomatosis. II. Mode of inheritance in 55 families with essential hyperlipidaemia and xanthomatosis. J. Med. Gen. 5:9, 1968.
21. Patterson, D., and J. Slack. Lipid abnormalities in male and female survivors of myocardial infarction and their first-degree relatives. Lancet i:393, 1972.

Although a number of recent studies have unequivocally demonstrated a relationship between the familial occurrence of hyperlipidemia and coronary heart disease (15-21), none of these investigations was carried out on unselected and consecutively studied patients who are representative of the general population. Therefore, from these data one cannot determine the true frequency of the familial hyperlipidemias in "garden-variety" patients with coronary heart disease nor can one accurately quantitate the magnitude of the contribution of the genetic forms of hyperlipidemia to the overall pathogenesis of coronary heart disease.

V. The Seattle Study - A Genetic Analysis of Hyperlipidemia in Coronary Heart Disease

22. Goldstein, J. L., W. R. Hazzard, H. G. Schrott, E. L. Bierman, and A. G. Motulsky. Genetics of hyperlipidemia in coronary heart disease. Trans. Assoc. Am. Physicians. 85: In press. 1972.
23. Goldstein, J. L., W. R. Hazzard, H. G. Schrott, E. L. Bierman and A. G. Motulsky. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J. Clin. Invest. Submitted for publication. 1972.
24. Goldstein, J. L., H. G. Schrott, W. R. Hazzard, E. L. Bierman and A. G. Motulsky. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder: combined hyperlipidemia. J. Clin. Invest. Submitted for publication. 1972.
25. Hazzard, W. R., J. L. Goldstein, H. G. Schrott, A. G. Motulsky, and E. L. Bierman. Hyperlipidemia in coronary heart disease. III. Lipoprotein phenotyping of 156 genetically defined survivors of myocardial infarction. J. Clin. Invest. Submitted for publication. 1972.

The above articles (22-25) contain the data from the Seattle study. Portions of these data are reproduced in Tables 2-13 and Figures 1-19 of this protocol.

VI. Diagnostic Approach to the Individual Hyperlipidemic Patient with Coronary Heart Disease

26. Gofman, J. W., L. Rubin, J. P. McGinley, and H. B. Jones. Hyperlipoproteinemia. Amer. J. Med. 17:514, 1954.
27. Thannhauser, S. J. Lipidoses: Diseases of the Intracellular Lipid Metabolism. Grune & Stratton, New York. 3rd edition. 1958.
28. Ahrens, E. H., Jr., J. Hirsch, K. Oette, J. W. Farquhar and Y. Stein. Carbohydrate-induced lipemia. Trans. Assoc. Amer. Physicians. 74: 134, 1961.
29. Fredrickson, D. W., R. I. Levy, and R. S. Lees. Fat transport in lipoproteins--an integrated approach to mechanisms and disorders. N. Engl. J. Med. 276:32, 94, 148, 215, 273, 1967.
30. Beaumont, J. L., L. A. Carlson, G. R. Cooper, Z. Fejfar, D. S. Fredrickson, and T. Strasser. Classification of hyperlipidemias and hyperlipoproteinemias. Bull. World Health Org. 43:891, 1970.
31. Havel, R. J. Typing of hyperlipoproteinemias. Atherosclerosis 11:3, 1970.

Over the past 2 decades, several different systems have emerged for classification of the hyperlipidemias:

1) Gofman, in 1954, proposed the use of analytical ultracentrifugation of plasma lipoproteins as a method for classification (26). However, this proved too difficult for routine clinical use and was quickly abandoned.
2) Thannhauser, in 1958 and even earlier, classified patients according to type of xanthomas (i.e., tendinous, tuberous, or eruptive) and according to the predominant lipid elevation (i.e., hypercholesterolemia or hypertriglyceridemia) (27).
3) Ahrens, in 1961, added a refinement to the Thannhauser classification by subdividing hypertriglyceridemic states into 2 broad categories - endogenous (or carbohydrate-induced) and exogenous (or fat-induced) (28).
4) Fredrickson, in 1967, introduced lipoprotein electrophoresis and originally recognized 5 types of hyperlipidemia (29). The Fredrickson method has since been modified by the World Health Organization (30) and in its present form, 6 types of hyperlipidemia are recognized - types I, IIa, IIb, III, IV, and V.

   With the exception of type I hyperlipidemia which generally reflects the presence of the rare autosomal recessive disorder of lipoprotein lipase deficiency, none of the other lipoprotein types are specific for a single genetic disorder; conversely, none of the genetic lipid disorders is specified by a single lipoprotein type (see data of Tables 11 and 13 and Fig. 19). Thus, classification by lipoprotein typing has no valid genetic basis and for this reason it is probably an unphysiologic clinical approach.

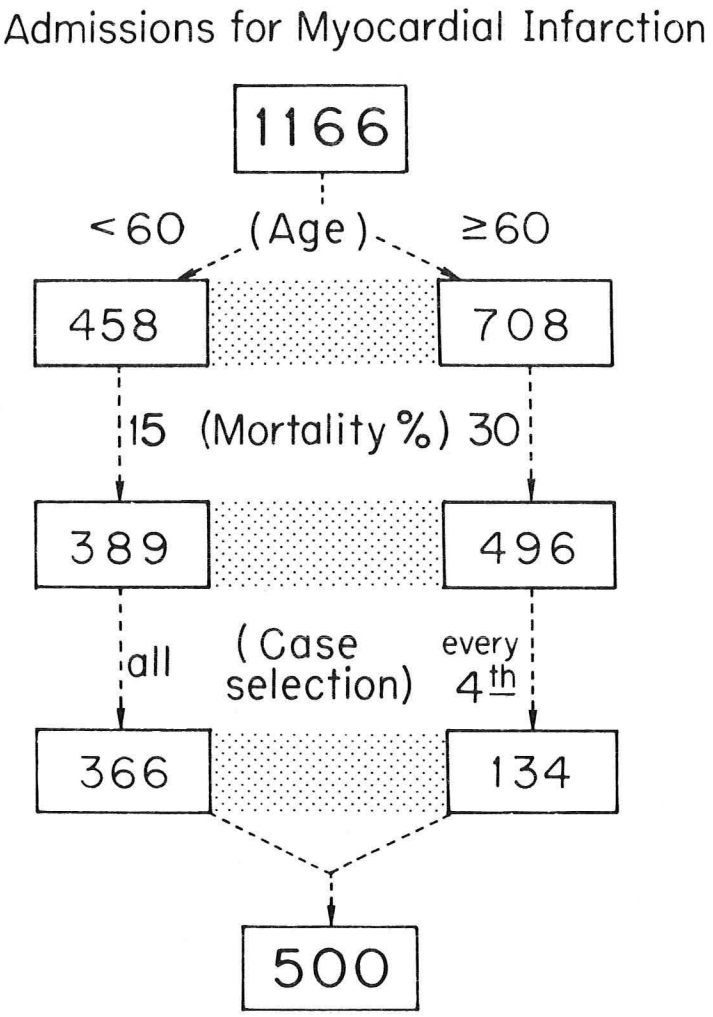
5) Havel has suggested that a measurement of the levels of whole plasma cholesterol and triglyceride in the fasting state provides the clinician with as much useful information as that obtained from lipoprotein phenotyping (31).
6) From the data of the Seattle study (22-25), it would appear that the most currently rational and physiologic way to classify patients with hyperlipidemia (until definitive and specific genetic markers become available) is by analysis of the fasting levels of whole plasma cholesterol and triglyceride of the relatives of the given subject. This approach offers the additional advantage of identifying at an early age young members of the population who are hyperlipidemic and are therefore at risk for the development of premature coronary atherosclerosis. Lipoprotein quantification and phenotyping may be helpful in rare circumstances, such as diagnosing the occasional patient with the type III lipoprotein pattern (found in less than 1% of the 500 consecutively studied survivors of myocardial infarction in the Seattle study {25}).

TABLE 1

MULTIFACTORIAL BASIS OF CORONARY HEART DISEASE

1. Sex - Male > Female
2. Hypercholesterolemia
3. Hypertriglyceridemia
4. Diabetes Mellitus
5. Hypertension
6. Smoking
7. Obesity
8. Type A Personality
9. Physical Inactivity
10. Blood Group - Type A (Thrombosis only)

FIGURE 1



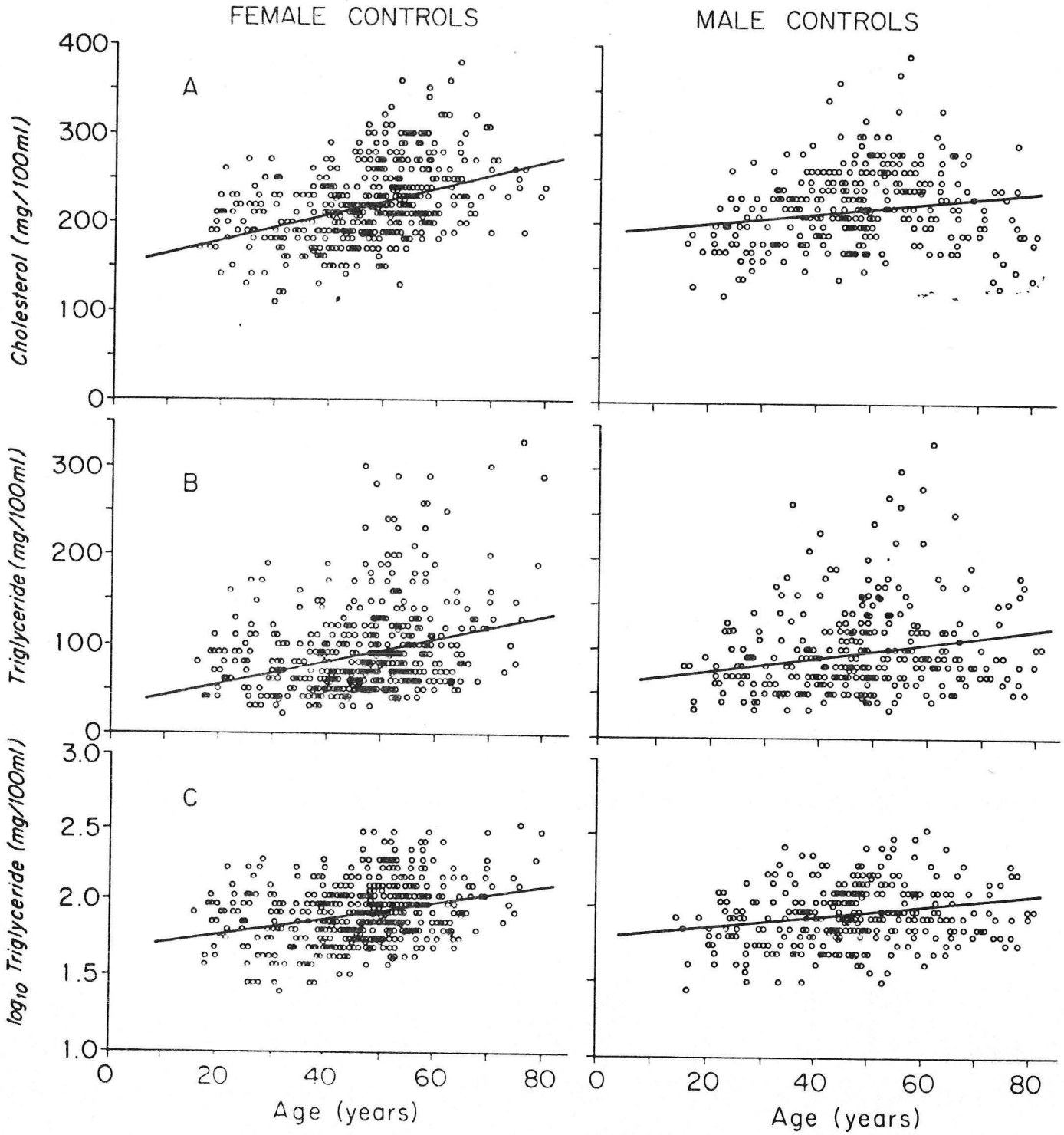
Method of Selection of Survivors of Myocardial Infarction

TABLE 2

Unadjusted Plasma Lipid Levels in Controls

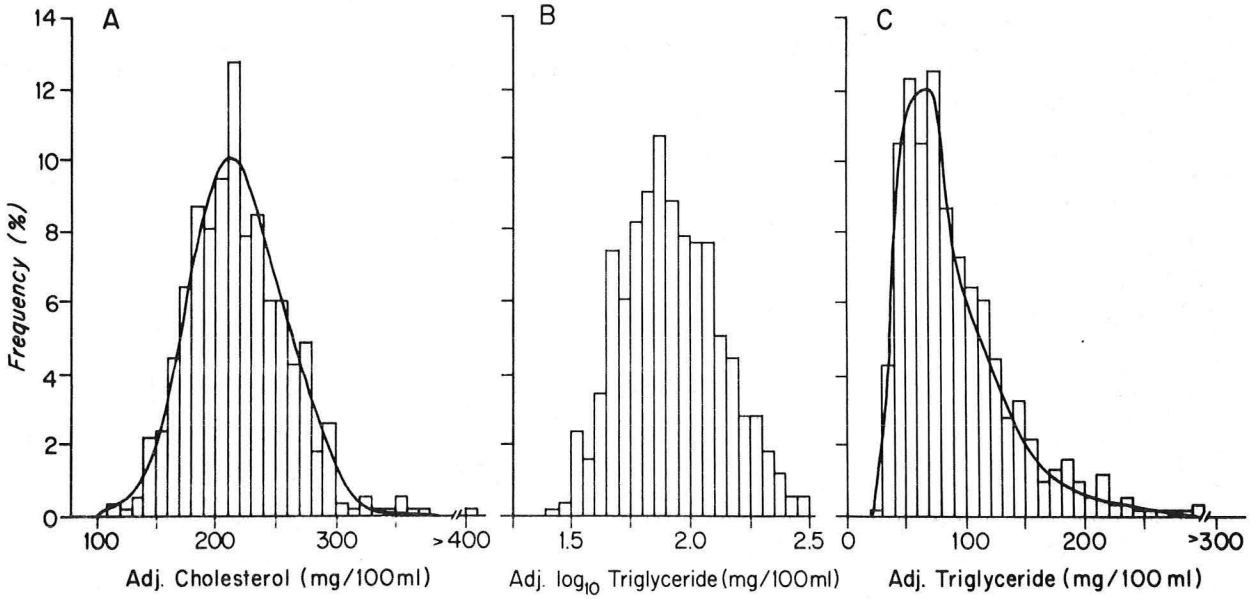
Age Range (years)	950 Spouse Controls		
	No.	Cholesterol (mg/100 ml)	Triglyceride (mg/100 ml)
Men		Mean ± S.D.	Mean ± S. D.
15 - 19	13	168 ± 27	53 ± 22
20 - 29	43	192 ± 33	76 ± 37
30 - 39	62	212 ± 34	92 ± 56
40 - 49	116	226 ± 43	101 ± 47
50 - 59	85	239 ± 42	109 ± 58
60 - 69	51	226 ± 39	103 ± 58
70 - 79	24	200 ± 39	98 ± 43
80 - 89	6	169 ± 21	98 ± 19
	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
	550		

FIGURE 2



Relation between age and the levels of plasma cholesterol (A), triglyceride (B), and $\log_{10}$ triglyceride (C) in controls. The female data consist of the lipid values determined for the first 400 consecutively studied individuals of a total female control group of 550. The male data consists of the lipid values determined for the first 300 consecutively studied individuals of a total male control group of 400.

FIGURE 3



Frequency distributions of adjusted cholesterol (A), $\log_{10}$ triglyceride (B), and triglyceride (C) levels in 950 controls. The smooth curve represents a nonparametric density estimate of the distribution.

TABLE 3

Estimated Upper Percentile Values for Sex and Age-Adjusted Plasma Lipids in Controls

(Adjustment to Age 45 Years)

Plasma Lipid	Upper Percentiles		
	90th	95th	99th
		mg/100 ml	
Cholesterol	270	285	314
Triglyceride	147	165	200

Percentile values were computed from the mean and standard deviation estimates of the respective normal distributions of adjusted cholesterol and adjusted $\log_{10}$ triglyceride.

TABLE 4

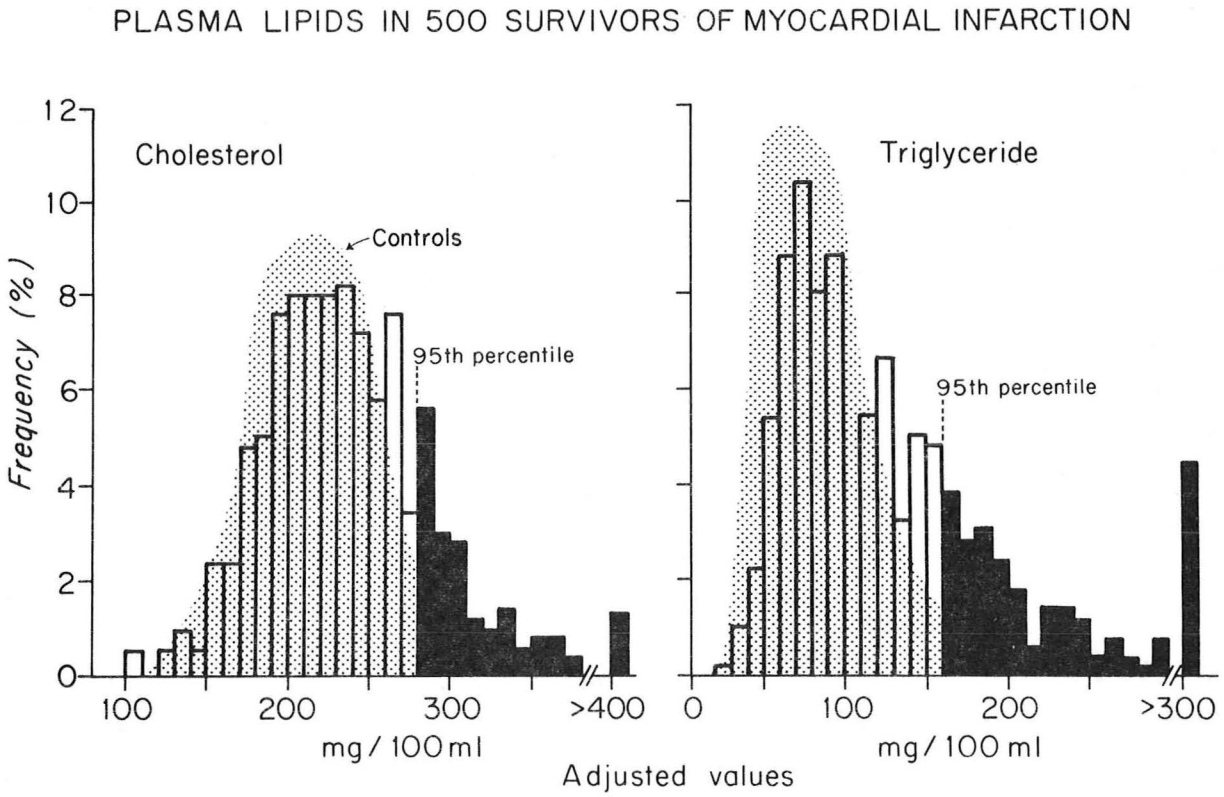
Age and Sex Composition of 500 Survivors of Myocardial Infarction

Age Range, (years)	500 Survivors	
	Men (no.)	Women (no.)
30 - 39*	23	2
40 - 49*	88	19
50 - 59*	199	35
60 - 69†	57	18
70 - 79†	24	19
80 - 89†	10	6
	401	99

* Represents virtually complete ascertainment of three-month survivors of myocardial infarction.

† Represents a randomly chosen group of three-month survivors of myocardial infarction (1 out of 4 selected).

FIGURE 4



Comparison of frequency distributions of adjusted plasma lipid levels in survivors of myocardial infarction and controls.

TABLE 5

Comparison of Hyperlipidemia in 500 Survivors and 950 Controls

Percentile of Controls	Adjusted Cholesterol*			Adjusted Triglyceride*		
	Expected†	Observed§	Observed / Expected	Expected†	Observed§	Observed / Expected
	%	%		%	%	
80th	20	33.8	1.7	20	42.2	2.1
90th	10	22.2	2.2	10	32.2	3.2
95th	5	15.4	3.1	5	23.5	4.7
99th	1	6.8	6.8	1	14.3	14.3
99.9th$^{\Pi}$	0.1	3.8	38.0	0.1	8.0	80.0

* Independent of level of other plasma lipid.

† Expected = % controls with plasma lipid level equal to or exceeding indicated percentile.

§ Observed = % survivors with plasma lipid level equal to or exceeding indicated percentile.

Π 99.9th percentile for adjusted cholesterol = 342 mg/100 ml and for adjusted triglyceride = 245 mg/100 ml.

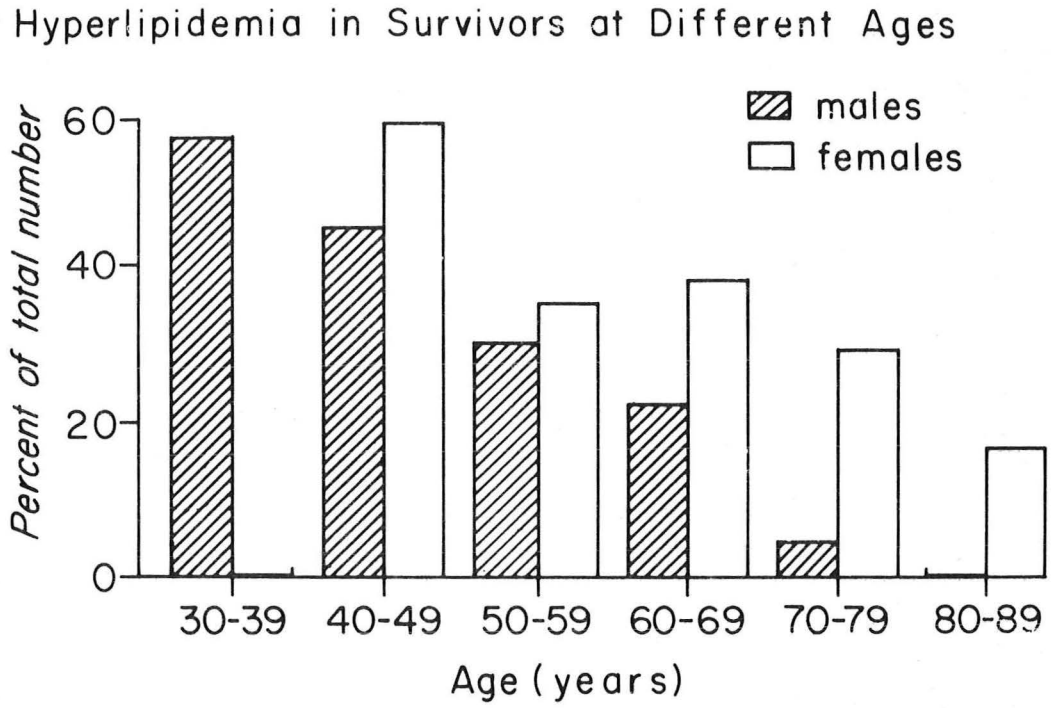
TABLE 6

Overall Frequency of Hyperlipidemia in 500 Survivors

Lipid Elevation	Frequency	
	Number	Percentage
Hypercholesterolemia alone		
Adjusted Cholesterol ≥ 285 mg/100 ml Adjusted Triglyceride < 165 mg/100	38	7.6
Hypertriglyceridemia alone		
Adjusted Cholesterol < 285 mg/100 ml Adjusted Triglyceride ≥ 165 mg/100 ml	78	15.6
Both		
Adjusted Cholesterol ≥ 285 mg/100 ml Adjusted Triglyceride ≥ 165 mg/100 ml	41	7.8
Total	157*	31.0

* This total become 162 (32%) if 5 normolipidemic survivors who were taking clofibrate for previously diagnosed hyperlipidemia had been included.

FIGURE 5



Relation between frequency of hyperlipidemia and age and sex of survivors. The number of survivors in each age and sex category is indicated in Table 4.

TABLE 7

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[Π]	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[x]	39.5	38.5	44.0	40.8

* Denotes statistical level of significance at 0.05 (** denotes 0.01) using Chi-square test to compare proportion with risk factor in hyperlipidemic to that in normolipidemic group.

† 95th percentile values used to define hyperlipidemia.

§ Independent of level of other plasma liquid.

Π Diagnosed if 1 of 2 criteria fulfilled: 1) survivor taking either insulin or an oral antihyperglycemic medication; or 2) fasting plasma glucose > 120 mg/100 ml.

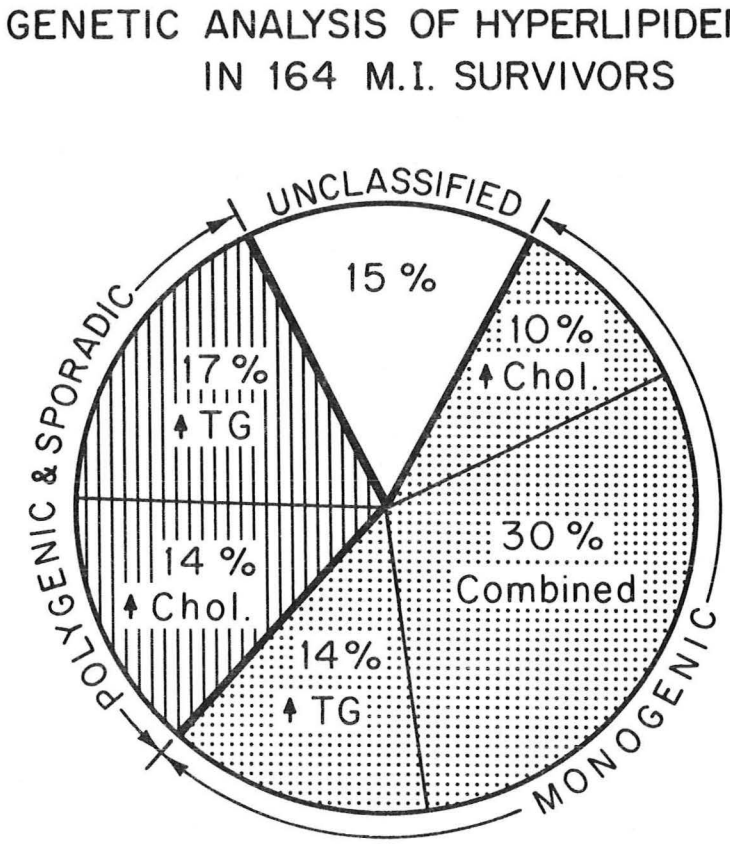
¶ Considered present if past history of specific treatment with antihypertensive drug therapy. Frequency of hypertension by same criterion in controls was 6.2%.

\# Weight in excess of 125% of ideal body weight by criteria of Metropolitan Life Insurance Company tables. Frequency of obesity by same criteria in controls was 16.8%.

§§ Plasma uric acid $\geq$ 7.0 mg/100 ml in women and $\geq$ 8.0 mg/100 ml in men.

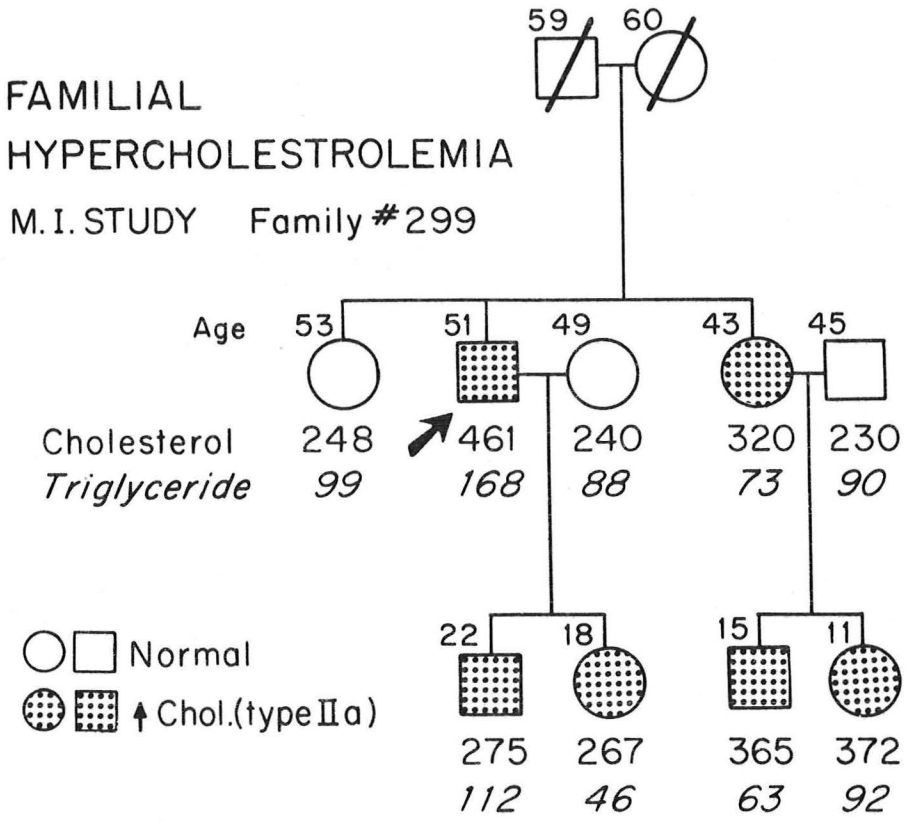
x More than 20 cigarettes per day. Frequency of excessive smoking by same criterion in controls was 10.0%.

FIGURE 6



Summary of genetic analysis in 164 hyperlipidemic survivors of myocardial infarction. The unclassified category represents those hyperlipidemic survivors in whom family study was not possible because of lack of availability of at least three relatives. Type III hyperlipidemia (not included here) was identified in four, or 2.4%, of these 164 hyperlipidemic survivors.

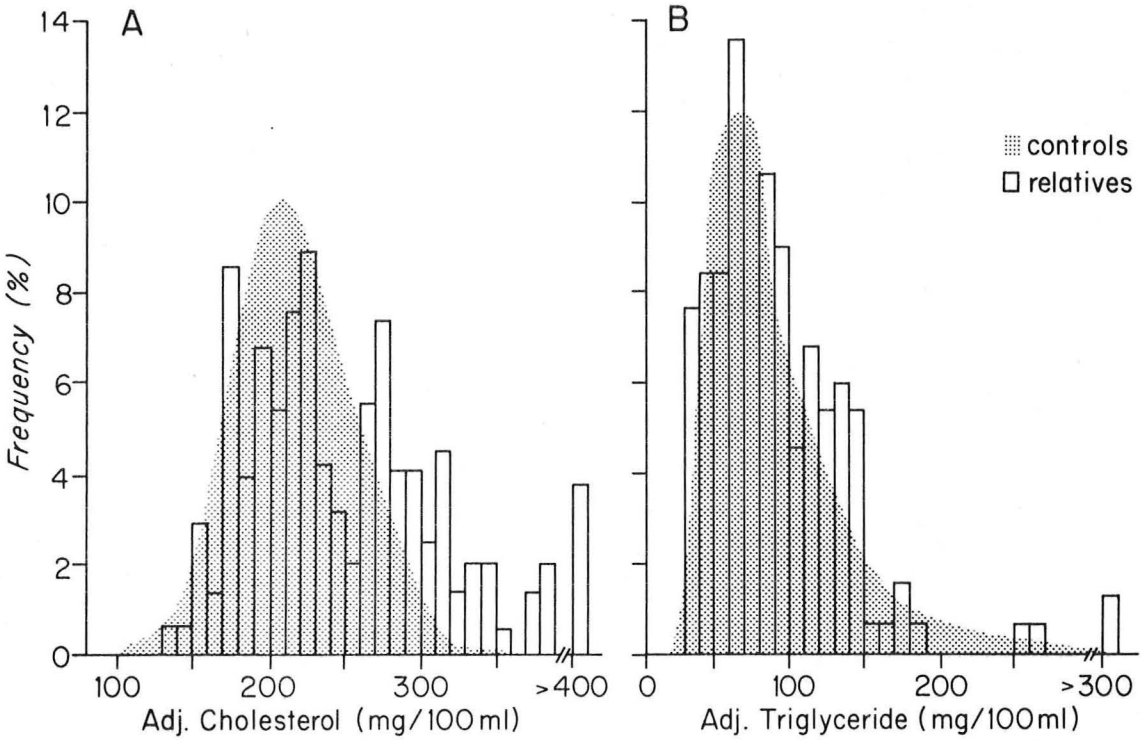
FIGURE 7



Pedigree of a typical family with familial hypercholesterolemia. The lipid levels shown represented unadjusted (i.e., actual) values.

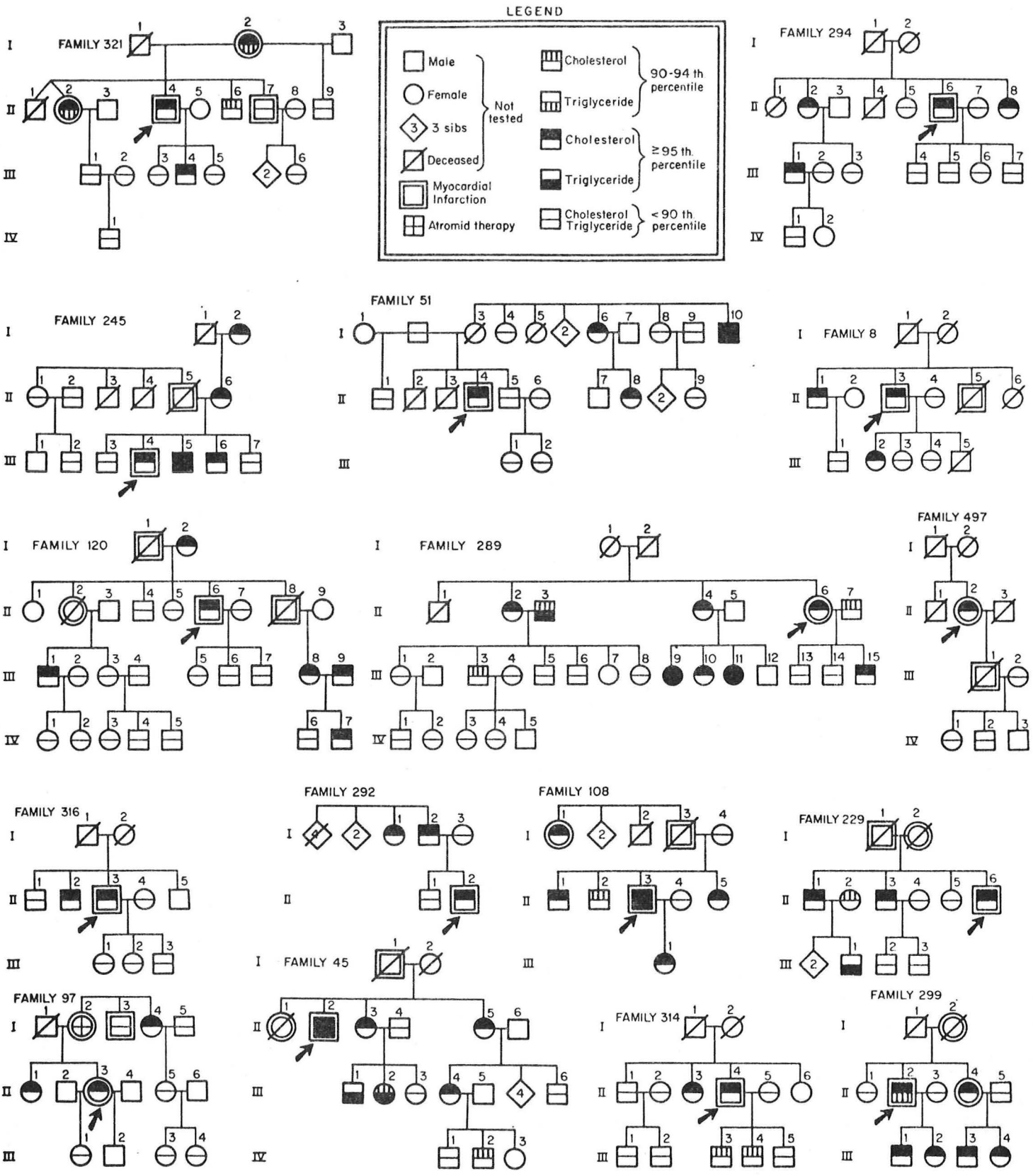
FIGURE 8

Familial Hypercholesterolemia



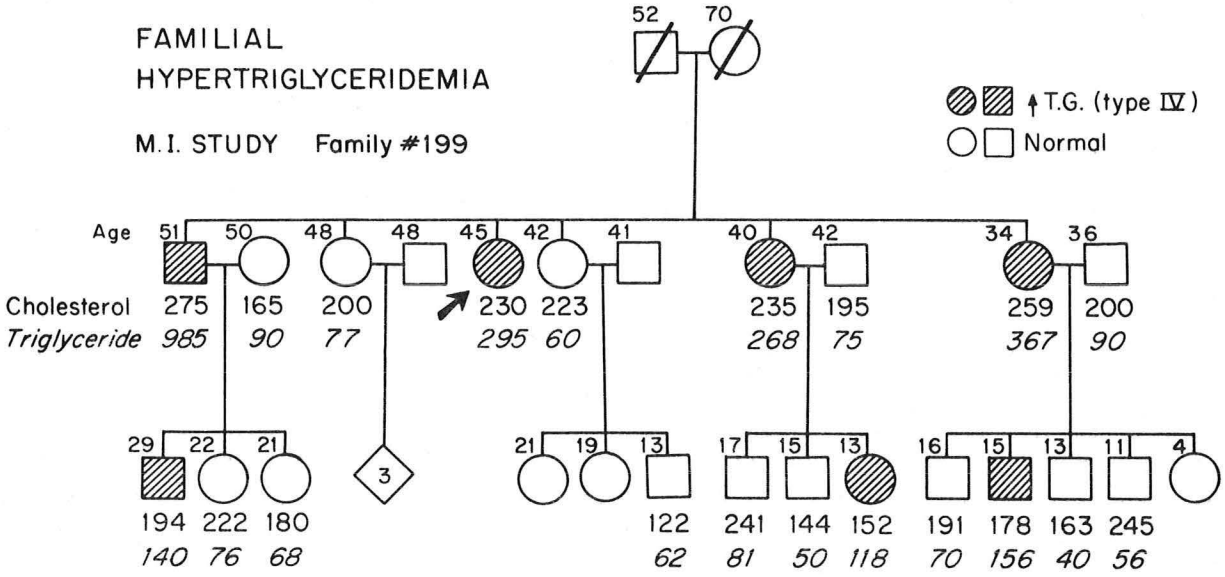
Frequency distributions of adjusted lipid levels in 132 near and distant relatives of 16 survivors with familial hypercholesterolemia. Included in this analysis were 68 first-degree, 44 second-degree, 18 third-degree, and 2 fourth-degree relatives. Forty-nine of the 132 relatives were between the ages of 6 and 20. The distribution is divided into increments of 10 mg/100 ml. The smooth stippled curve represents a non-parametric density estimate of the control distribution.

FIGURE 9



Composite showing the pedigrees of 16 families with familial hypercholesterolemia. The symbol ⊞ indicates that the family member was taking clofibrate (Atromid) and was normolipidemic when tested. The proband for each family is indicated by ↗. Spouses belonging to matings for which there were no data available for the offspring have been omitted from the pedigrees.

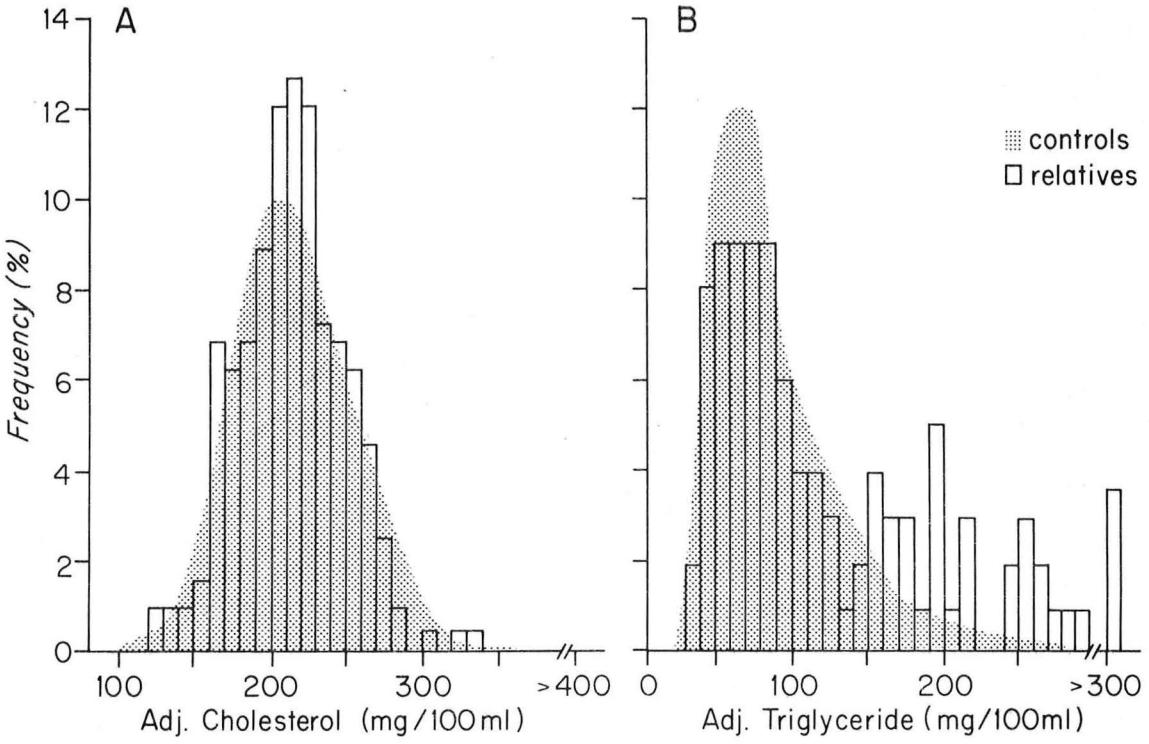
FIGURE 10



Pedigree of a typical family with familial hypertriglyceridemia. The lipid levels shown represent unadjusted (i.e., actual) values.

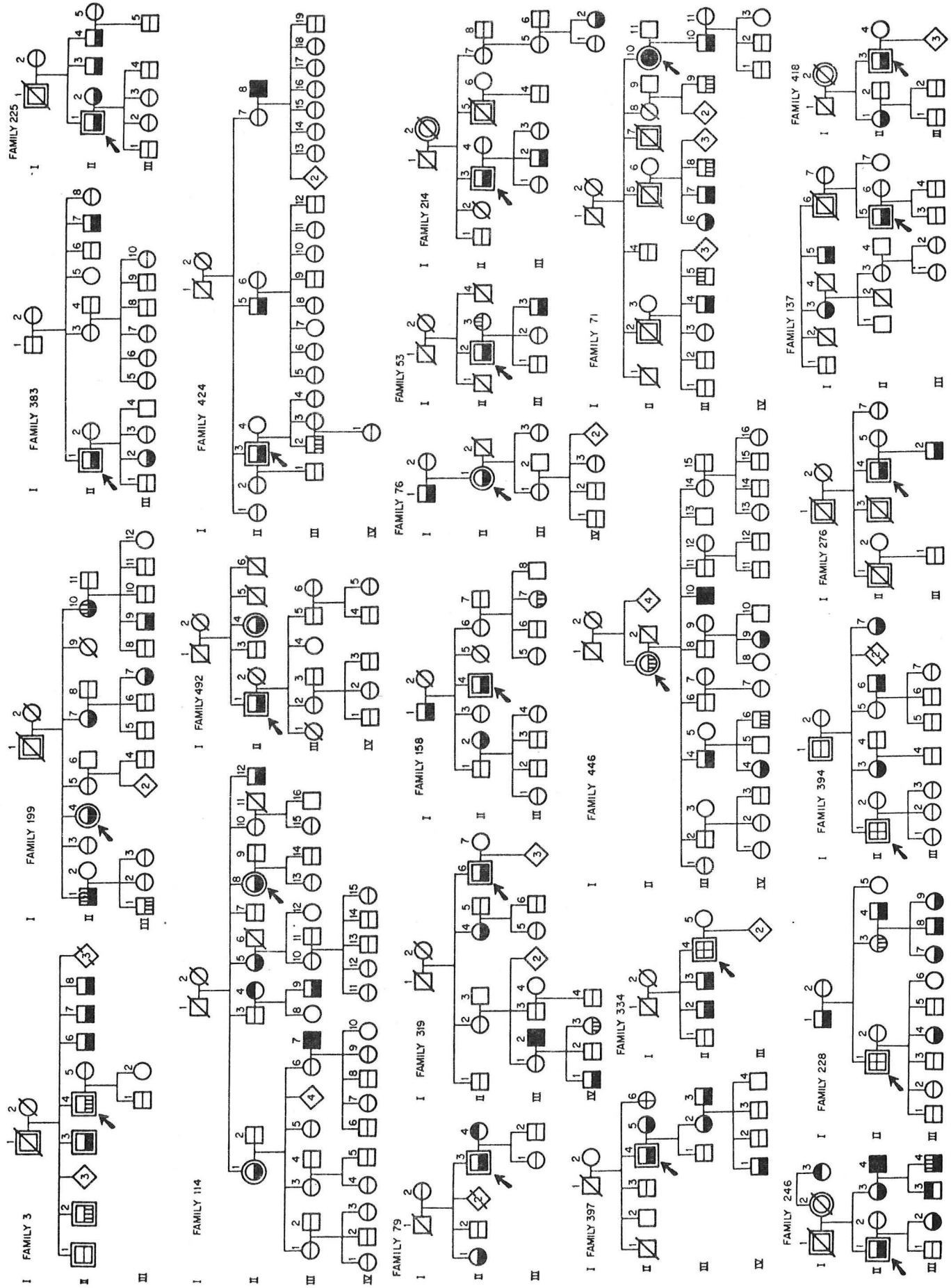
FIGURE 11

Familial Hypertriglyceridemia



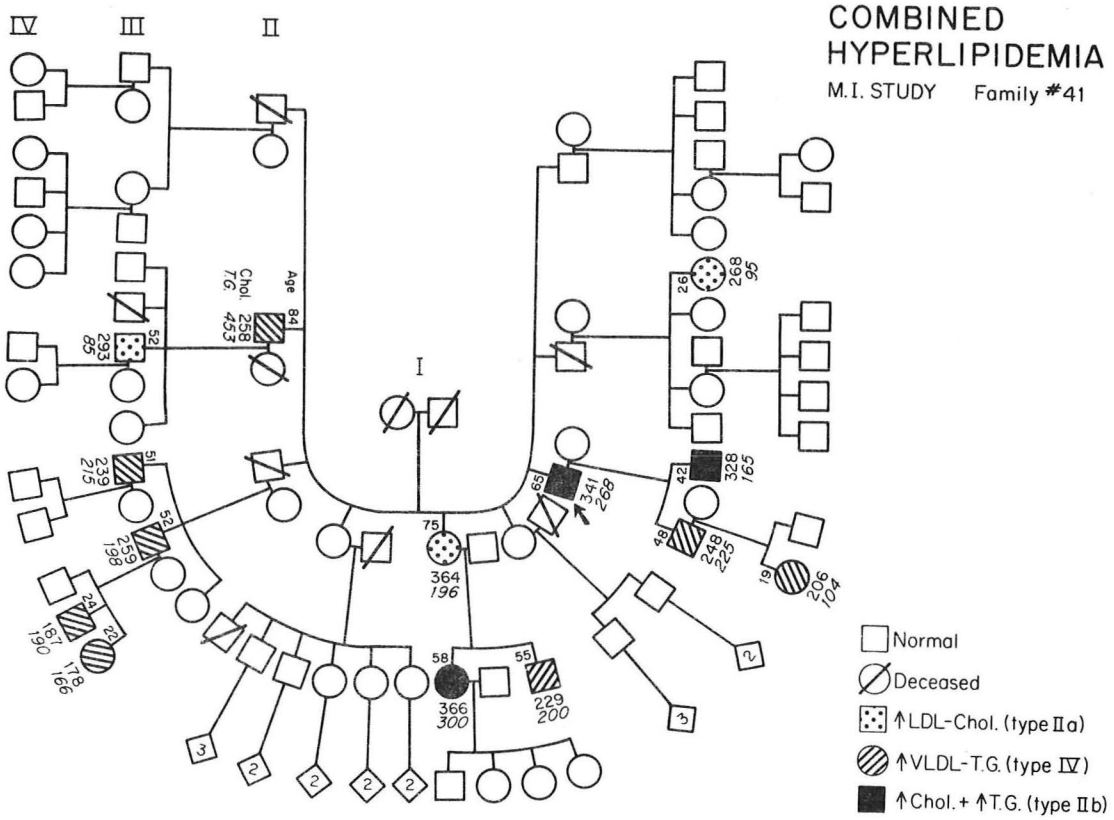
Frequency distributions of adjusted lipid levels in 132 adult (> 20 years of age) relatives of 23 survivors with familial hypertriglyceridemia. Included in this analysis were 90 first-degree relatives, 30 second-degree relatives, and 12 third-degree relatives. The distribution is divided into increments of 10 mg/100 ml. The smooth stippled curve represents a non-parametric density estimate of the control distribution.

FIGURE 12



Composite showing the pedigrees of 23 families with familial hypertriglyceridemia.

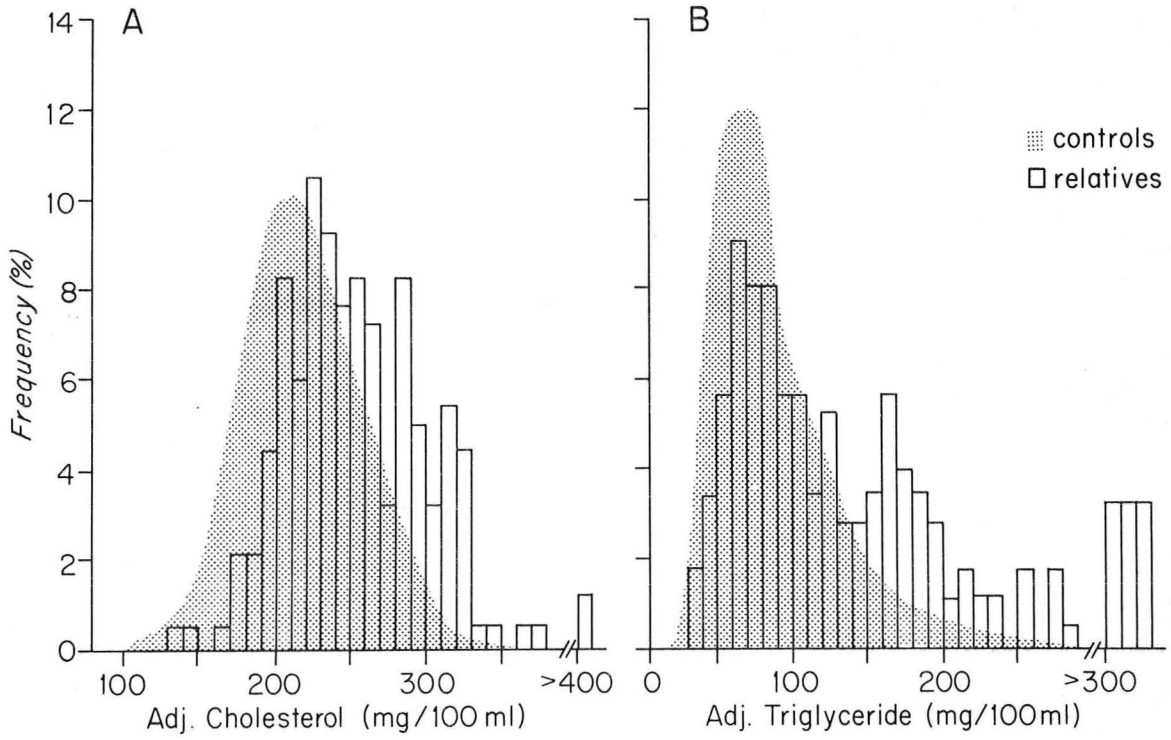
FIGURE 13



Pedigree of a typical family with familial combined hyperlipidemia. The lipid levels shown represent unadjusted (i.e., actual) values.

FIGURE 14

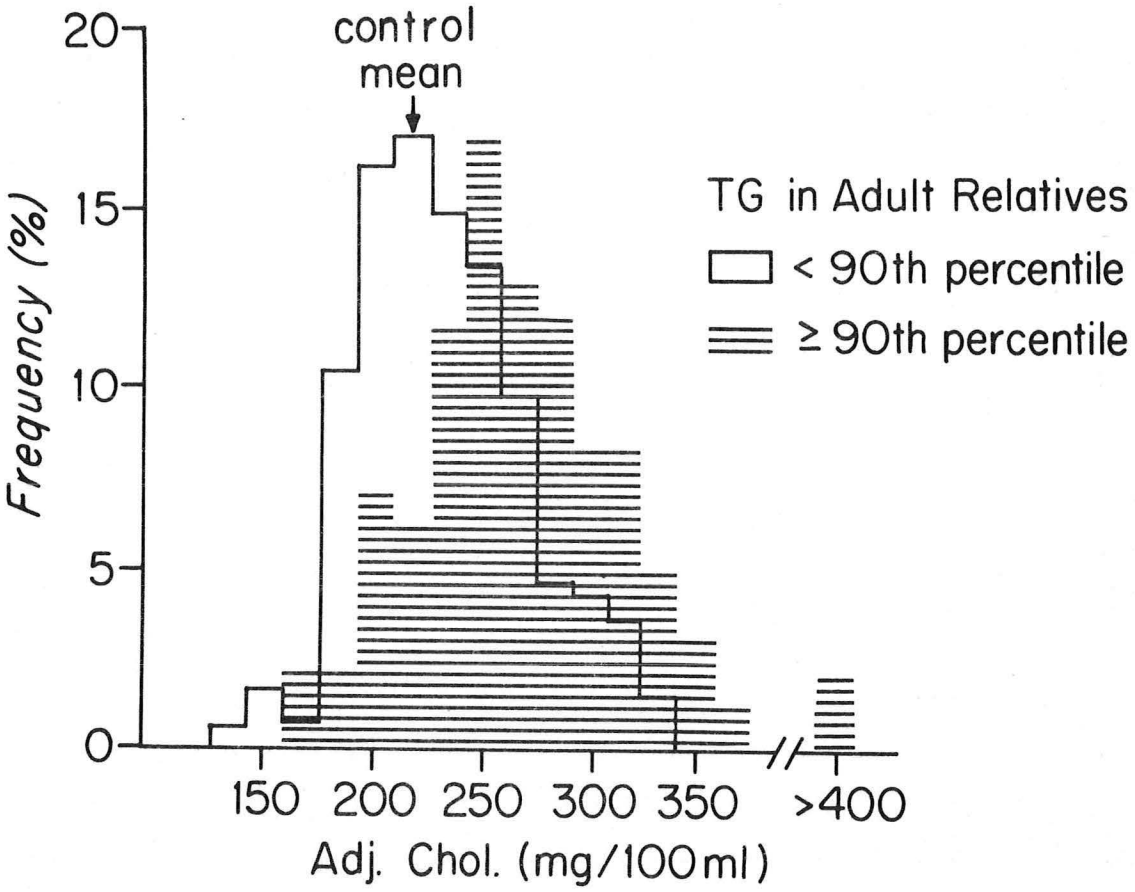
Familial Combined Hyperlipidemia



Frequency distributions of adjusted lipid levels in 234 first-degree adult (≥ 20 years of age) relatives of 47 survivors with familial combined hyperlipidemia. The distribution is divided into increments of 10 mg/100 ml. The smooth stippled curve represents a non-parametric density estimate of the control distribution.

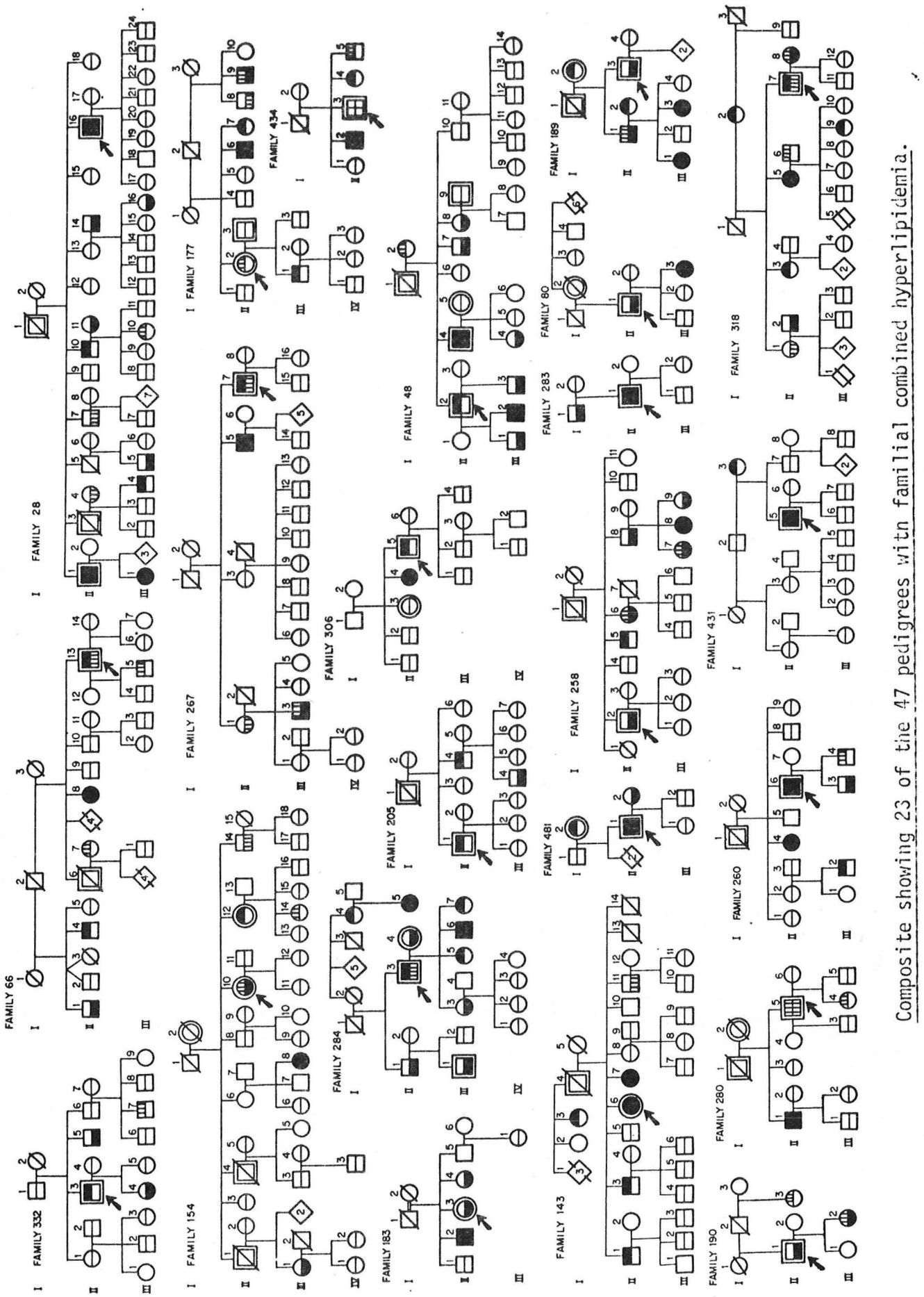
FIGURE 15

Familial Combined Hyperlipidemia



Relation between the level of cholesterol and triglyceride in 234 first-degree adult (≥ 20 years of age) relatives of 47 survivors with familial combined hyperlipidemia. The 234 relatives were divided into two groups depending on whether their triglyceride level fell above (n = 98) or below (n = 136) the 90th percentile of controls. The mean value for adjusted cholesterol levels in controls (218 mg/100 ml) is indicated by the arrow at the top of the figure.

FIGURE 16



Composite showing 23 of the 47 pedigrees with familial combined hyperlipidemia.

TABLE 8

Analysis of Sibships of 47 Survivors with Familial Combined Hyperlipidemia

	Sibs (No.)					Proportion Affected (No.)	
		Dead					
	Total	By All Causes	By M.I.*	Living	Tested	Observed‡	Expected§
Brothers	95	24	9	71	60	30 (9,7,14)¶	30
Sisters	89	14	1	75	66	31 (7,11,13)¶	33
Total	184	38Π	10	146	126	61	63

* Deaths by myocardial infarction (M.I.) were documented by death certificates.

‡ A relative was considered affected if either his cholesterol or his triglyceride level or both equaled or exceeded the 95th percentile values for cholesterol and triglyceride.

§ Expected proportion of affected relatives by the hypothesis of autosomal dominant inheritance, assuming no effect of the gene on mortality at the ages tested.

Π 14 of these 38 deaths occurred prior to age 35 years.

¶ Distribution (no.) of phenotypes of affected relatives are indicated in parenthesis in the following order: hypercholesterolemia alone, hypertriglyceridemia alone, and both hypercholesterolemia and hypertriglyceridemia.

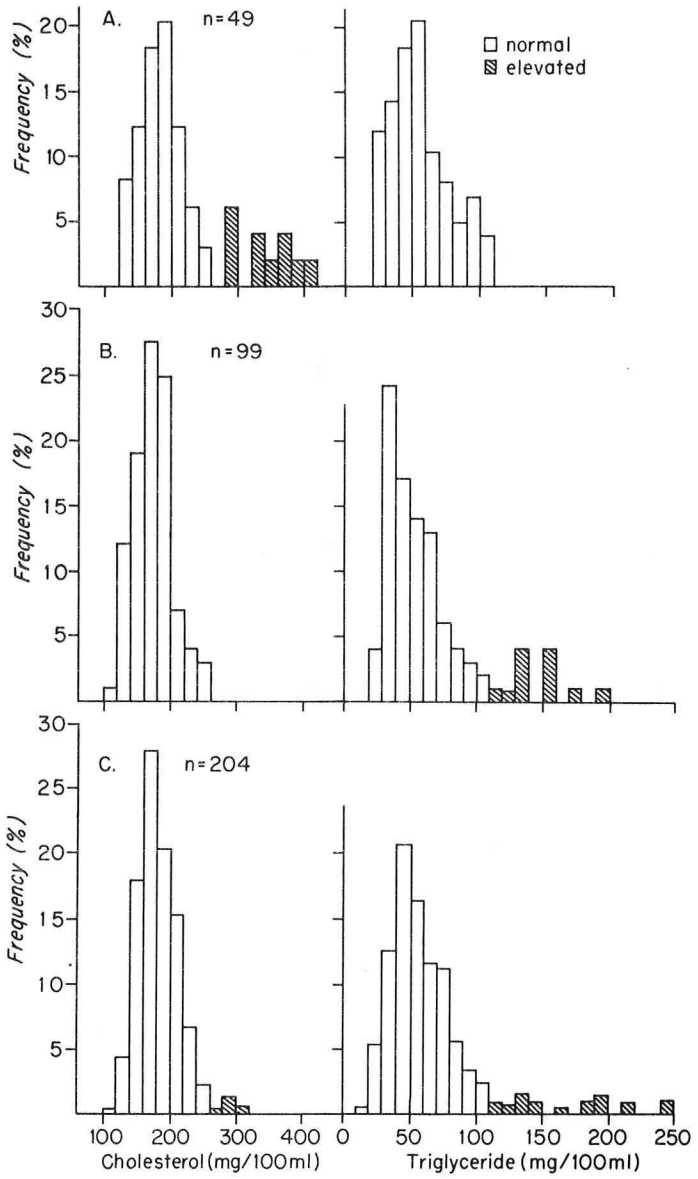
TABLE 9

Analysis of 22 Informative Matings from 20 Families with Familial Combined Hyperlipidemia*

Mating Type (no.)	Distribution of Phenotypes in Offspring (no.)			
	Normal	↑Cholesterol	↑Triglyceride	↑Both
↑Cholesterol x Normal (6)	4	1	3	2
↑Triglyceride x Normal (9)	10	1	6	5
↑Both x Normal (7)	10	0	8	3

* Parents and offspring were considered affected if the indicated lipid level equaled or exceeded the 95th percentile of controls. This analysis includes all matings from families with combined hyperlipidemia which met both of these criteria: 1) the parental mating type was affected x normal and 2) at least one offspring was affected.

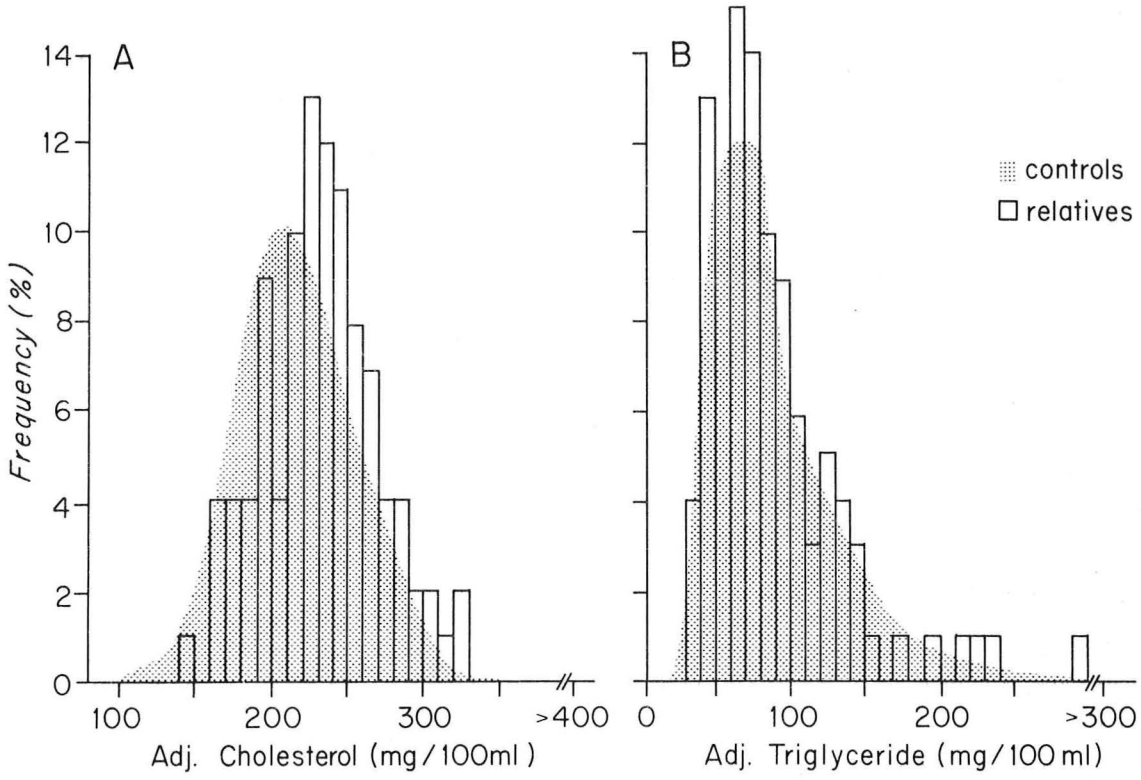
FIGURE 17



Frequency distributions of unadjusted lipid levels in near and distant relatives, age 6-20, of 16 probands with familial hypercholesterolemia (A), 23 probands with familial hypertriglyceridemia (B), and 47 probands with familial combined hyperlipidemia (C). The number of relatives tested for each disorder is indicated in the appropriate panel. No age and sex-adjustments were applied to these data since no significant correlation with age was observed in values from 110 controls, ages 6-20. The arbitrary designation of normal and elevated was made from a consideration of the lipid levels in the 110 controls, ages 6-20, whose values were collected as part of the family studies of the 27 normolipidemic survivors. Since the highest unadjusted cholesterol and triglyceride values observed in these controls were 250 and 115 mg/100 ml, respectively, these values were arbitrarily considered as maximum upper limits of normal for the age range.

FIGURE 18

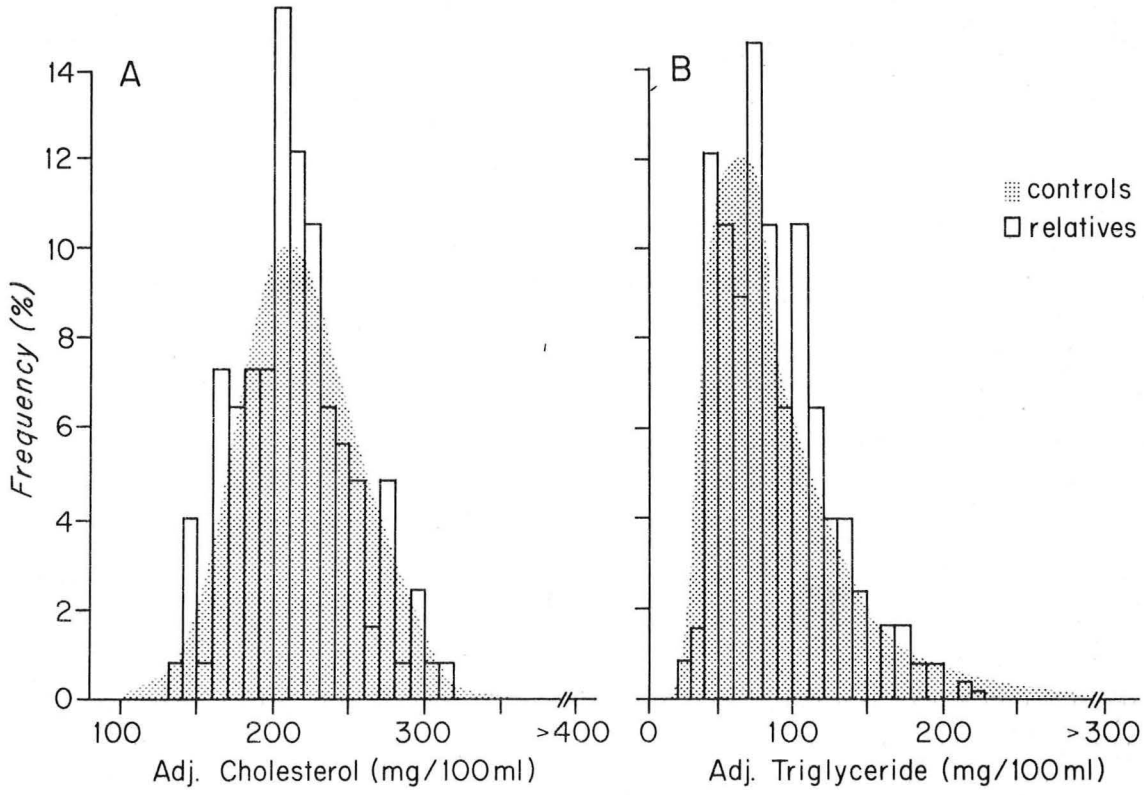
Polygenic Hypercholesterolemia



Frequency distributions of 145 near and distant adult (≥ 20 years of age) relatives of 28 survivors with polygenic hypercholesterolemia. Included in this analysis were 119 first-degree, 20 second-degree, and 6 third-degree relatives. The distribution is divided into increments of 10 mg/100 ml. The smooth stippled curve represents a non-parametric density estimate of the control distribution.

FIGURE 19

Sporadic Hypertriglyceridemia



Frequency distribution of 158 near and distant adult (≥ 20 years of age) relatives of 31 survivors with sporadic hypertriglyceridemia. Included in this analysis were 105 first-degree, 44 second-degree, and 9 third-degree relatives. The distribution is divided into increments of 10 mg/100 ml. The smooth stippled curve represents a non-parametric density estimate of the control distribution.

TABLE 10

Criteria For Lipoprotein Phenotyping

Lipoprotein Phenotype	Plasma Lipid Level		Presence of	
	Whole Plasma Triglyceride $\geq$ 95th percentile*	LDL-cholesterol > upper limit of normal+	Fasting Chylomicrons §	β-migrating VLDL ‖
IIa	-	+	-	-
IIb	+	+	-	-
III¶	+ or -	+ or -	+ or -	+
IV	+	-	-	-
V	+	-	+	-

* Based on age and sex-adjusted data from 950 control subjects.

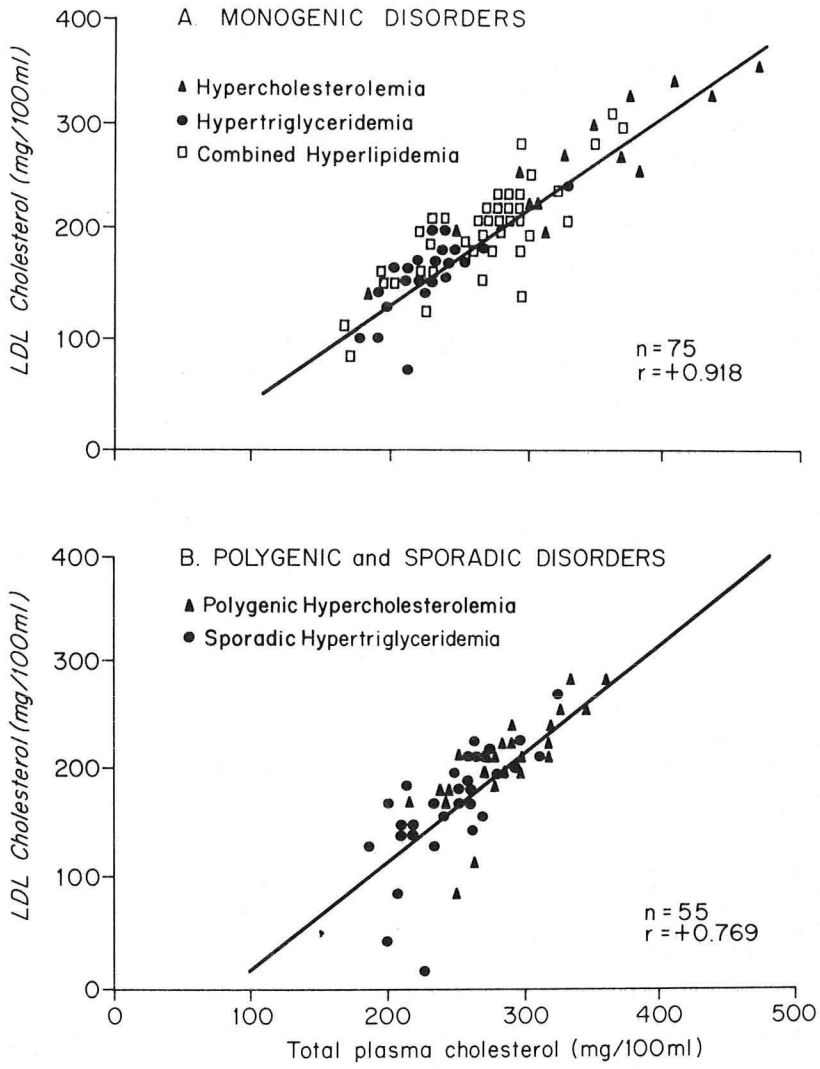
\+ Based on age-related 95th percentile values estimated by Fredrickson.

§ By PVP flocculation and agarose gel electrophoresis.

‖ By agarose gel electrophoresis (see footnote 2).

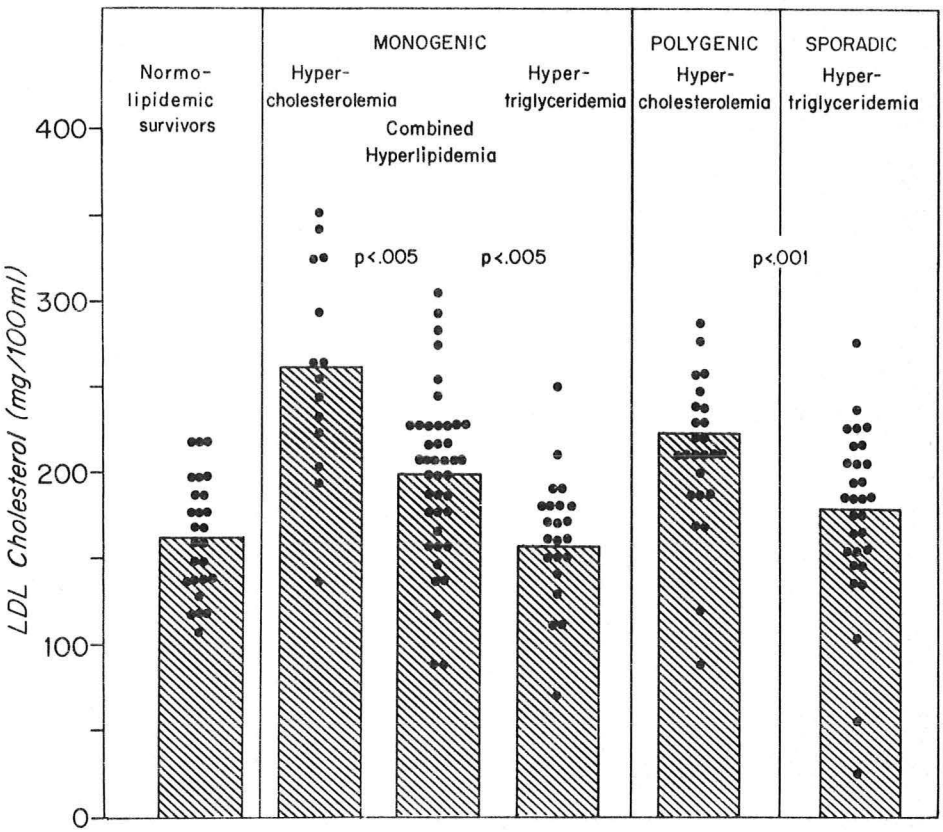
¶ Lipid composition of isolated VLDL (and of fasting chylomicrons, when present) and electrophoretic mobility of lipoproteins in whole plasma were used as confirmatory diagnostic criteria for the type III pattern but by themselves were not considered sufficient for its assignment.

FIGURE 20



Relation between total plasma cholesterol and low-density lipoprotein (LDL)-cholesterol levels in 75 survivors with monogenic lipid disorders and in 54 survivors with polygenic hypercholesterolemia (n = 25) and sporadic hypertriglyceridemia (n = 29).

FIGURE 21



Comparison of low-density lipoprotein (LDL)-cholesterol levels in survivors of myocardial infarction grouped according to their genetic diagnosis.

TABLE 11

Relationship Between Genetic Classification and Lipoprotein Phenotyping in Hyperlipidemic Survivors of Myocardial Infarction

Genetic Disorder	No. of Subjects	Lipoprotein Phenotype				
		Normal	IIa	IIb	IV	V
Monogenic						
Familial hypercholesterolemia	14	1*	7	4	2+	0
Familial hypertriglyceridemia	22	8§	0	2Π	11	1
Familial combined hyperlipidemia	41	7¶	13**	10	10	1
Polygenic						
Hypercholesterolemia	25	9	9	2	5	0
Sporadic						
Hypertriglyceridemia	31	10	4++	2	14	1

* Taking clofibrate at the time of the repeat sample.

\+ 1 of these subjects was under treatment for acute hyperthyroidism with ^{131}I and prednisone at the time of the repeat sample.

§ 4 were taking clofibrate.

Π 1 was taking clofibrate.

¶ 2 were taking clofibrate.

** 4 were taking clofibrate.

++ 1 was taking clofibrate.

TABLE 12

Frequency of Hyperlipidemia

Disorder	Survivors of Myocardial Infarction			General Population*
	< Age 60 (a)	≥ Age 60 (b)	Ratio a/b	
	%	%		%
A. Monogenic Hyperlipidemia				
Familial Hypercholesterolemia	4.1	0.7	5.9	∿ 0.1 - 0.2
Familial Hypertriglyceridemia	5.2	2.7	1.9	∿ 0.2 - 0.3
Combined Hyperlipidemia	11.3	4.1	2.8	∿ 0.3 - 0.5
Total	20.6	7.5		∿ 0.6 - 1.0
B. Polygenic Hypercholesterolemia	5.5	5.5	1.0	-----
C. Sporadic Hypertriglyceridemia	5.8	6.9	0.8	-----

* These estimates of heterozygote frequency in the general population are minimal since they were made under the following assumptions: 1) that the prevalence rate of coronary heart disease in adults, age 30-59, is 3%; 2) that the frequency of these disorders as observed among unselected three-month survivors of myocardial infarction would be the same among individuals with other manifestations of coronary disease, such as angina pectoris, sudden death, and fatal myocardial infarction; and 3) that all heterozygotes for one of these monogenic lipid disorders manifest clinical evidence of coronary disease before age 60 years.

TABLE 13

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

Disorder	Typical Age	Typical Lipid Level*		Lipoprotein Types	Mode of Inheritance	Penetrance Below Age 25§
		Cholesterol	Triglyceride			
Monogenic		mg/100 ml	mg/100 ml			
Familial Hypercholesterolemia	M 45 F 55	353	126	IIa, IIb	Autosomal Dominant	∿ 0.92
Familial Hypertriglyceridemia	M 50 F 55	241	267	IV, V	Autosomal Dominant	∿ 0.26
Combined Hyperlipidemia	M 50 F 60	300	241	IIa, IIb, IV, V	Autosomal Dominant	∿ 0.18
Polygenic						
Hypercholesterolemia	M 55 F 60	308	187	IIa, IIb	Polygenic	Not Applicable
Sporadic						
Hypertriglyceridemia	M 55 F 60	233	243	IV, V	Nongenetic	Not Applicable

* Unadjusted lipid values which represent mean levels of each group.

§ Penetrance was estimated by determining the ratio of the proportion of individuals expressing with hyperlipidemia to the expected proportion on the dominant hypothesis.