Hyperlipidemia in Coronary Heart Disease

I. LIPID LEVELS IN 500 SURVIVORS OF MYOCARDIAL INFARCTION

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A B S T R A C T   Plasma cholesterol and triglyceride levels were measured after an overnight fast in 500 consecutively studied 3-mo survivors of myocardial infarction. Virtually all patients under 60 yr of age (95% ascertainment) and a randomly chosen group of older survivors admitted to 13 Seattle hospitals during an 11 mo period were included. A comparison of their lipid values with those of 950 controls demonstrated that 31% had hyperlipidemia. These lipid abnormalities were most commonly found in males under 40 yr of age (60% frequency) and in females under 50 yr of age (60% frequency). Elevation in triglyceride levels with (7.8%) or without (15.6%) an associated elevation in cholesterol levels was three times more common in survivors than a high cholesterol level alone (7.6%). These results raise the possibility that hypertriglyceridemia may be as an important a risk factor for coronary atherosclerosis as hypercholesterolemia. The identification of hyper-lipidemic survivors of myocardial infarction provided a unique source of probands for family studies designed to disclose the genetic origin of hyperlipidemia in coronary heart disease.

INTRODUCTION

It is generally recognized that coronary heart disease shows a tendency to aggregate in certain families (2–4). In his monograph on angina pectoris published in 1897, Osler emphasized the importance of genetic factors in the pathogenesis of this disorder (5). Yet despite early recognition of the influence of heredity on atherosclerosis, the nature of the underlying genetic mechanisms has remained obscure. The observed familial aggregation may reflect genetically determined risk factors such as hyperlipidemia, diabetes mellitus, and hypertension (6, 7). Hypercholesterolemia and hypertriglyceridemia, as predisposing factors to atherosclerosis, have received the most recent attention (7, 8). Hence, genetic analysis of families with elevations in these plasma lipids should contribute to an understanding of the inheritance of coronary atherosclerosis and ultimately provide clues for determining the underlying biochemical lesions. Certain forms of hypercholesterolemia and hypertriglyceridemia are known to be inherited (9–11). However, it is not known whether hereditary hyperlipidemia is usually determined by simply inherited (monogenic) factors or by more complex (polygenic) mechanisms, and whether classification of hyperlipidemia by lipoprotein phenotyping provides genetically useful information.

The present study was undertaken to answer these questions by carrying out a detailed genetic analysis of the fasting plasma cholesterol and triglyceride levels in

the families of probands selected for hyperlipidemia from 500 consecutively studied survivors of myocardial infarction. The results are reported in three parts. This first paper discusses the criteria for diagnosis of hyperlipidemia, compares its frequency in survivors of myocardial infarction with that in controls, examines the effect of age and sex on its occurrence, and relates the presence of hypercholesterolemia and hypertriglyceridemia to other risk factors. The second paper (12) reports the analysis of family members, presents evidence for a newly recognized inherited disorder (combined hyperlipidemia), and suggests an approach to classifying hyperlipidemia on the basis of plasma lipid levels in relatives. The third paper (13) examines the genetic significance of lipoprotein phenotyping by determining the lipoprotein characteristics of survivors with different genetically defined lipid disorders.

METHODS

Ascertainment of hospital admissions for myocardial infarction. Two of us (J. L. G. and H. G. S.) examined the records of virtually all patients admitted to the coronary care units of 13 metropolitan Seattle hospitals from 1 November 1970, to 1 October 1971. The 13 hospitals involved are known to admit about 95% of all local patients with acute myocardial infarction (14, 15). The diagnosis of myocardial infarction was accepted when two of these three criteria were met: (a) compatible clinical history; (b) serial electrocardiograms showing development of a diagnostic Q wave or S–T segment elevation followed by T wave inversion (16); and (c) characteristic changes in activity of glutamic-oxalacetic transaminase, lactic dehydrogenase, and/or creatine phosphokinase (17) in serially drawn blood samples. Of the 2793 patients admitted to the 13 coronary care units during the period of the study, 1166 (41.8%) satisfied two of the above criteria. (Of these 1166 survivors, 1049 [90%] fulfilled all three criteria.) For each case, information about coronary heart disease, diabetes mellitus, thyroid disease, peripheral and cerebrovascular disease, hyperlipidemia, hypertension, smoking and drinking habits, weight change, dietary restrictions, and drug therapy was recorded on a
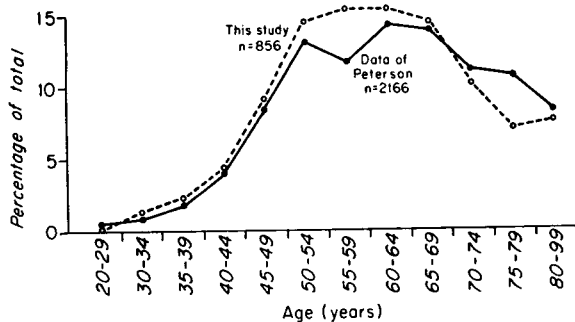

FIGURE 1 Frequency distribution of the number of hospital admissions for acute myocardial infarction in men of different ages, comparing the results of two different methods of ascertainment. The data of Peterson were collected from the same hospitals as our 11 mo study, but over a more extended period of time (31 December 1967 to 31 December 1969).
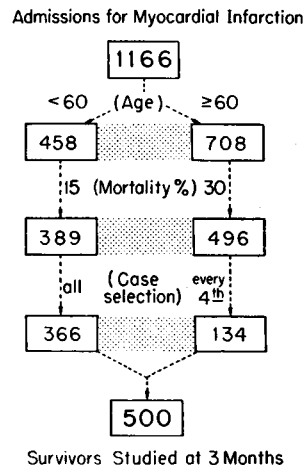

FIGURE 2 Method of selection of 500 survivors of acute myocardial infarction for lipid studies. Details are described in the Methods.

standardized medical history form. The age distribution of all male cases identified during the 11 mo of our study was compared with that of a 24 mo epidemiologic study in this area, covering all hospital admissions for myocardial infarction (14, 15).[1] The close agreement between the two sets of data (Fig. 1) indicated that our ascertainment was valid.

Selection of survivors for lipid study. Of the 1166 patients with acute myocardial infarction, 885 were still alive at 3 mo after hospital admission,[2] and 500 were selected for study, as shown in Fig. 2. An attempt was made to study all survivors under 60 yr of age. Of the 389 survivors under 60 yr of age, 366 (95%) were included. The remaining 23 survivors in this age group were not studied either because they could not be located (9 patients), were psychiatrically unstable (3 patients), or were unwilling to cooperate (11 patients). No attempt was made to study all 496 3-mo survivors 60 yr of age and older. Random selection of 134 of this latter group was made by choosing every fourth consecutively admitted survivor. Whenever a survivor in this older age group either refused to participate (15 patients) or could not be located (5 patients), an alternate was selected on the basis of a similar time of hospital admission.

Survivors. Informed constant was obtained from each patient and his private physician. Survivors were seen 3–4 mo after the acute episode of myocardial infarction by one of two public health nurses (M. J. L. and E. D. C.). They determined the patient's weight and height, recorded a medical history on a standardized form, and collected 30 ml of blood after 12–14 h overnight fast. Before the interview, each survivor had been contacted four times: first by letter, explaining the general nature of the study; second by telephone, fixing the date and place of the interview; third by letter, confirming the date of the interview; and fourth by

[1] These data were made available by Donald R. Peterson, M.D., Professor of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Wash.

[2] The mortality rate for 3-mo survivors of acute myocardial infarction was strikingly dependent on age. The highest mortality (30%) occurred in survivors age 60 and above, while only 15% of the survivors below age 60 expired within 3 mo. Below age 45 the mortality rate was 8%.

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telephone, on the day before the interview. Participants were instructed to remain on their usual diet, and the importance of obtaining a *fasting* blood specimen (no food after 6 p.m.) was repeatedly emphasized. Interviews were conducted between 8 and 10 a.m. either in the patient's home (70%) or in the clinics of the University Hospital or the Veterans Administration Hospital (30%).

None of the 500 survivors selected was excluded from the study. However, at the time of sampling, 11 were taking clofibrate because hyperlipidemia had been previously diagnosed; of these 11, 5 had normal lipid levels when tested by us. No survivors were taking cholestyramine, nicotinic acid, *d*-thyroxine, or other hypolipidemic agents. Medications taken by the 99 female survivors included estrogens (14%), thyroid (11%), oral contraceptives (2%), and estrogens and thyroid (1%). 8 of the 500 survivors had disorders known to cause secondary elevations in blood lipids: 5 with uncontrolled diabetes mellitus (fasting plasma glucose level greater than 200 mg/100 ml) and 1 each with idiopathic nephrotic syndrome, chronic glomerulonephritis and uremia, and parenteral hyperalimentation after a small bowel resection. Three additional survivors had a previous diagnosis of primary hypothyroidism; all were receiving thyroid replacement therapy at the time of the study and were euthyroid on the basis of thyroid function tests. 44% of the 500 survivors said they were conscientiously following a diet low in content of cholesterol and fat, but there was no apparent correlation between dietary intake and levels of plasma lipids. The mean ±SD for adjusted cholesterol and triglyceride levels, respectively, was 233±56 and 143±114 mg/100 ml in those on a low fat diet, as compared with 239±51 and 129±74 mg/100 ml in those on an unrestricted diet. To determine weight stability, 129 hyperlipidemic and 27 normolipidemic survivors were weighed on two occasions averaging 3 mo apart. The mean change in weight was less than 0.4 kg for both groups (13).

Controls. The controls consisted of 550 adult women and 400 adult men selected from the nonblood relatives of the survivors. 125 were the spouses of the survivors and 825 were spouses of their relatives. All but 1% were white. None of these subjects was excluded as a control, but 4% had a history of previous myocardial infarction or were being treated with nitroglycerin for angina pectoris. 7.8% of controls indicated on a standardized medical history form that they had been diagnosed previously as having hyperlipidemia; only one of these individuals was on hypolipidemic drug therapy. 2.4% of controls claimed that they were conscientiously following a diet low in content of cholesterol and fat. One male control without known hyperlipidemia was taking clofibrate as part of another study. Drug therapy among the 550 female controls included estrogens (18.4%), thyroid (7.8%), oral contraceptives (9.2%), and both estrogens and thyroid (5.3%).

Collection of blood specimens. Fasting blood specimens from controls were obtained in one of two ways: (*a*) If the individual lived in the greater Seattle area, he was contacted and interviewed as described for survivors (see above) with the exception that each person filled out his own standardized medical history form. (*b*) Subjects living outside the Seattle area were initially contacted by telephone by J. L. G. or H. G. S., who explained the study, after which they were sent by mail the following items: (*a*) two tubes each containing 10 mg of ethylenediaminetetraacetic acid (EDTA) and one tube without EDTA; (*b*) a set of instructions addressed to a physician or technician collecting the blood sample; and (*c*) a standardized medical history form to be filled out by the individual. The instructions stated that 10 ml of blood was to be collected into each of the two tubes after a 12–14 h overnight fast and that the two EDTA tubes were to be centrifuged and the plasma placed in the empty tube for return to Seattle at ambient temperature by air mail, special delivery, in the stamped mailing container provided. The physician or technician was asked not to return specimens obtained on nonfasting subjects. Out-of-town specimens usually arrived at the Seattle laboratory within 24–36 h of collection and immediately refrigerated at 4°C until further processed.

The validity of this method of collection for out-of-town samples was established in a pilot study in which the distribution of fasting plasma cholesterol and triglyceride levels of 100 consecutively studied out-of-town controls was compared with that of 100 consecutively studied Seattle controls. Mean ±SD for age and sex-adjusted cholesterol values was 223±41 and 225±46 mg/100 ml for out-of-town and Seattle controls, respectively. Mean ±SD for age and sex-adjusted triglyceride values was 94±64 and 94±59 mg/100 ml for out-of-town and Seattle controls, respectively.

Analyses of plasma lipids, glucose, and uric acid. All analyses were performed on fasting venous blood samples collected in tubes containing EDTA (10 mg/10 ml blood). Samples obtained in Seattle were centrifuged at 3000 rpm for 15 min within 2 h of collection. Out-of-town plasma samples were recentrifuged in a similar fashion. All plasma samples were kept frozen at −20°C until analysis.

All lipid analyses were performed in the laboratory of the Division of Metabolism and Gerontology under the supervision of W. R. H. and E. L. B. Plasma cholesterol and triglyceride concentrations were measured from separate portions of a single chloroform:methanol (2:1 vol:vol) extract. Cholesterol was measured by AutoAnalyzer method N-24a (18) and triglyceride by a semiautomated method modified from the procedure of Carlson (19, 20). This laboratory had previously passed phase I of the triglyceride standardization program of the U. S. Center for Disease Control (Atlanta, Ga.) with a coefficient of variation of 5% and accuracy within 10% of the true value. Reproducibility of these methods was determined periodically throughout the 15 mo of analyses by repeated checking (n = 128) of portions from a frozen standard plasma pool. Results (mean ±SD) for this standard were: cholesterol, 244±9.5 mg/100 ml and triglyceride, 90±3.7 mg/100 ml. Coefficients of variation were 3.9 and 4.3%, respectively. Similar results were also obtained by using a lower standard cholesterol plasma (level of 164 mg/100 ml) and a higher standard triglyceride plasma (level of 234 mg/100 ml). Samples from controls and survivors were analyzed simultaneously throughout the study.

The glucose and uric acid levels, measured on the fasting plasma samples of survivors, were determined by Auto-Analyzer methods N-2b and N-13b respectively (21) at the Pathology Central Laboratory, Seattle, Wash. Reproducibility of these methods was checked periodically throughout the 2 wk of analyses by examining a frozen plasma standard. Results (mean ±SD) for these standards were 109±0.84 mg/100 ml for glucose (n = 50) and 5.4±0.1 mg/100 ml for uric acid (n = 50). Coefficients of variation were 0.8 and 1.8%, respectively.

Processing, transformation, and analysis of data. Data processing was performed on the CDC 6400 computer at the University of Washington Computer Center. Initial input was by key punched cards with permanent storage of the raw and transformed data on magnetic tape.

To allow comparison of cholesterol and triglyceride levels of controls and survivors of different age and sex, lipid levels were transformed by using control means derived by linear regression analysis. This transformation was based on the following principle (22): For each individual the deviation of his lipid level from that of the control mean for his or her age and sex was given a positive or negative sign according to whether it was above or below the mean value. This deviation was then adjusted to a reference age at which the mean and standard deviation was the same for the two sexes; in this way the lipid values were adjusted also for sex. The formula used was as follows: adjusted lipid value = (observed lipid value − control mean lipid value of appropriate age and sex) + mean lipid value at age 45 yr of appropriate sex. Control mean lipids values for men and women at different ages were derived from the regression equations for the appropriate sex: $y = ax + b$, where y = mean cholesterol concentration or mean log_{10} triglyceride concentration; x = age in years; a = average annual change of cholesterol or log_{10} triglyceride concentration; and b = cholesterol or log_{10} triglyceride concentration when $x = 0$. The constants for a (coefficient of linear regression) and b (y intercept) used in the calculation of the adjusted lipid values are summarized in Table I.[3] Under these conditions of the regression equations, mean lipid values for both men and women were nearly equivalent at age 45 yr. Since the logarithms of triglyceride levels in controls were found to be distributed more normally than the corresponding skewed, untransformed values, the log scale was used for age and sex adjustments of triglyceride with subsequent reconversion to the arithmetic scale.

Data were analyzed by the following procedures: (a) Estimates of various population parameters, such as means, standard deviations, and correlation coefficients, were made with standard statistical package programs such as XTAB (Computer Programs for Biomedical Data Processing)[4] and BMD (Biomedical Computer Programs).[5] (b) Frequency distributions of plasma cholesterol and triglyceride concentrations were plotted on relative frequency histograms with interval widths of 10 mg/100 ml. Smooth distribution curves for both the adjusted cholesterol and adjusted triglyceride values of the control group were drawn with a CalComp Plotter.[6] The plotted values were calculated by a method developed by Tarter and Kronmal, which uses the or-

thogonal polynomial to derive nonparametric density estimates for the distributions (23). (c) Upper percentile lipid values (i.e., 90th, 95th, and 99th percentile cut-off points) in the controls were computed from the adjusted mean and standard deviation values of their respective normal distributions (Fig. 4) in conjunction with a table of cumulative standardized normal values (24). The actual mean and standard deviation values used were 219 and 40 for cholesterol and 1.922 and 0.202 for log_{10} triglyceride. Since the logarithms of the triglyceride of controls were more normally distributed than the corresponding untransformed, skewed values, percentile values for triglyceride were derived from the sex and age-adjusted log_{10} values. For clarity of presentation, all log percentile values were reconverted to the arithmetic scale. Therefore, our computed upper percentile cut-off values for triglyceride (Table II) are not directly applicable to untransformed triglyceride data. However, they can be used as approximate guidelines for "upper limits of normal" if the untransformed values are increased by 10-15 mg/100 ml.[7] In other words, the 95th percentile cut-off point for the untransformed triglyceride level of a 45-yr old man or women would be about 175 mg/100 ml (165 + 10) and the corresponding 99th percentile value would be about 215 mg/100 ml (200 + 15) (Table II).

RESULTS

Plasma lipid levels in controls. The age and sex composition of the 950 controls and their unadjusted and untransformed lipid values grouped by decade are shown in Table III. These figures were remarkably similar to those reported in other studies (25, 26).

A plot of unadjusted control cholesterol levels against age (Fig. 3 A) showed that in both sexes cholesterol concentration increased with age up to about 60 yr, that the rate of increase with age (coefficient of linear regression) was higher in women than in men (Table I), and that the standard deviations of cholesterol at different ages were nearly identical. Above age 60 the cholesterol level in men fell sharply, suggesting the possibility that hypercholesterolemic men die prematurely. A comparable fall in female levels was not seen until after age 70. At age 45 the mean cholesterol values for men and women, as determined from the regression equations, were equal (220 mg/100 ml).

Triglyceride levels in controls also increased with age (Fig. 3 B and Table I), especially in women (Table I). Unlike the constant variation pattern seen for cholesterol, the standard deviations of triglyceride differed markedly at different ages, especially above age 40. However, when the triglyceride data were converted to the logarithmic scale (Fig. 3 C), this age variation was much less apparent. At age 45, the mean log_{10} value for triglyceride levels in both sexes was nearly equal (1.921 and 1.937, respectively). In contrast to the cholesterol data, no

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[3] Although the relationship between age and cholesterol for men fit a quadratic function better than a linear function (Fig. 3), age and sex-adjustments were carried out on the linear scale for the following reasons: (a) assuming that the fall that is observed in cholesterol levels in men above age 60 (and to some extent in triglyceride levels in men above 60) occurs because older hyperlipidemic men die prematurely, the adjustment on a fitted curvilinear regression line would result in a false elevation of the values of the surviving older individuals; and (b) as compared with adjustment on a fitted curvilinear line, adjustment by linear regression had the overall effect of underestimating, rather than overestimating the absolute levels of cholesterol or triglyceride in older men and hence the data were not biased in favor of high values. Patterson and Slack also found linear regression to be a satisfactory method for age and sex adjustment of lipid levels (26).

[4] University of Washington Computer Center Manual, Seattle, Wash. 1968.

[5] University of California Press, Berkeley, Calif. 1968.

[6] California Computer Products, Inc., Anaheim, Calif.

[7] For a skewed distribution in which the sample mean is greater than the median, the antilog of the geometric mean (i.e., the mean of the log values comprising the sample) is always lower than the arithmetic mean of the corresponding antilog values.

Plasma lipid	Correlation with age	Coefficient of linear regression	Y intercept‡	Mean lipid level at age 45	Standard deviation about regression line
	r	mg/100 ml per yr	mg/100 ml	mg/100 ml	
Cholesterol					
Women, n = 550	+0.41*	1.450	155	220	44.6
Men, n = 400	+0.21*	0.610	193	220	43.6
Triglyceride					
Women	+0.32*	1.294	35	94	52.0
Men	+0.23*	0.759	63	97	50.5
Log$_{10}$ triglyceride					
Women	+0.33*	0.0057	1.66	1.921	0.205
Men	+0.27*	0.0037	1.77	1.937	0.207

* Denotes statistical level of significance at <0.001 using t test.

‡ See Fig. 3.

significant decrease in triglyceride levels was noted in older individuals. Carlson and Lindstedt have reported that the mean triglyceride levels in "healthy" individuals (i.e., those without obesity, coronary heart disease, and hypertension) decrease markedly after age 60 (27). The difference in our data may be related to the fact that all of our spouse controls would not be considered "healthy," since no spouses were excluded because of obesity, hypertension, coronary artery disease, diabetes mellitus, or because they were taking medications known to raise triglyceride levels (e.g., estrogens [28]).

A summary of the data derived from the regression analyses of plasma lipids with age in the 950 controls is presented in Table I. As noted in the previous section, both the cholesterol and triglyceride regression lines of male and female controls crossed each other at age 45 yr, so that adjustment of all values to this age avoided the need for correction for sex. Furthermore, since the standard deviations about the cholesterol and log$_{10}$ tri-

glyceride regression lines were the same in both sexes at different ages, no additional corrections were necessary.

The frequency distribution of the adjusted lipid values in the 950 controls is shown in Fig. 4. The adjusted cholesterol levels appeared normally and unimodally distributed (Fig. 4 A), so that transformation of the data was not necessary for calculation of percentile values. The 90th, 95th, and 99th percentile values were 270, 285,

TABLE II

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

	Upper percentiles		
Plasma lipid	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 as described in the Methods.

TABLE III

Unadjusted Plasma Lipid Levels in Controls

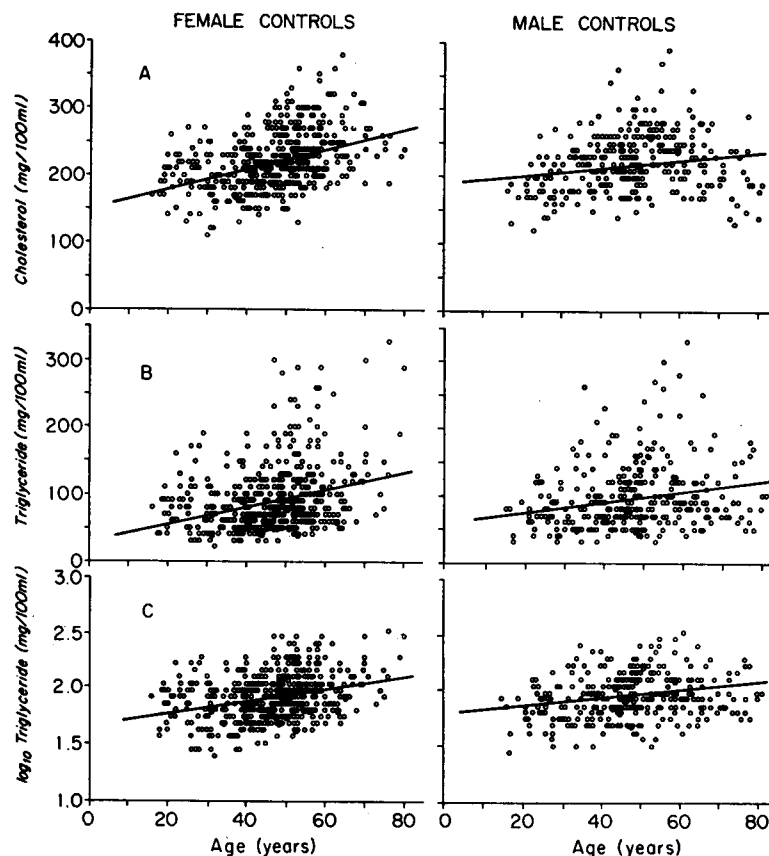| Age range	No.	950 Spouse controls	
		Cholesterol Mean±SD	Triglyceride Mean±SD
yr		mg/100 ml	mg/100 ml
Men			
15–19	13	168±27	53±22
20–29	43	192±33	76±37
30–39	62	212±34	92±56
40–49	116	226±43	101±47
50–59	85	239±42	109±58
60–69	51	226±39	103±58
70–79	24	200±39	98±43
80–89	6	169±21	98±19
Total	400		
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		

FIGURE 3   Relation between age and the levels of plasma cholesterol (A), triglyceride (B), and log₁₀ 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. The triglyceride values of four controls (301, 450, 680, 850 mg/100 ml), although included in the calculation of the regression equations, are not shown in panels B and C.
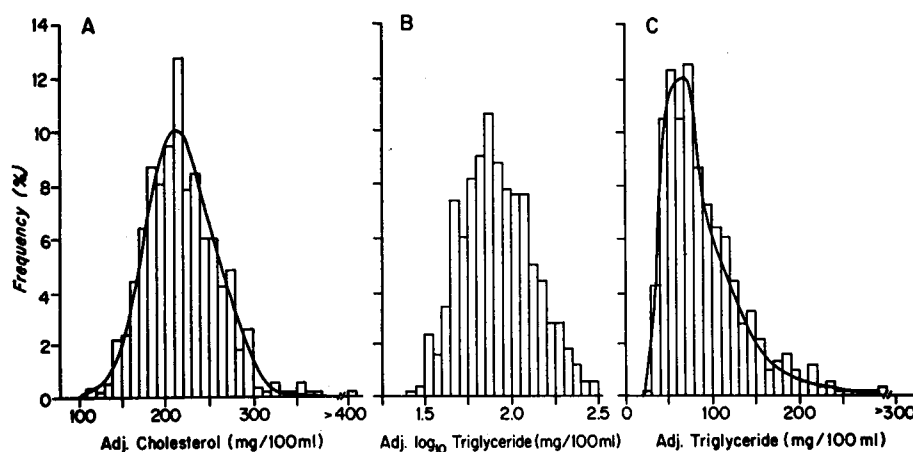

FIGURE 4   Frequency distributions of adjusted cholesterol (A), log₁₀ triglyceride (B), and adjusted triglyceride (C) levels in 950 controls. The smooth curve represents a nonparametric density estimate of the distribution and was plotted as described in the Methods.

TABLE IV

Age and Sex Composition of 500 Survivors of
Myocardial Infarction

| Age range | 500 Survivors | |
	No. of men	No. of women
yr		
30–39*	23	2
40–49*	88	19
50–59*	199	35
60–69‡	57	18
70–79‡	24	19
80–89‡	10	6
Total	401	99

* Represents virtually complete ascertainment of 3-mo survivors of myocardial infarction.

‡ Represents a randomly chosen group of 3-mo survivors of myocardial infarction (one out of four selected).

and 314 mg/100 ml, respectively (Table II). Since the adjusted log₁₀ triglyceride levels appeared normally and unimodally distributed (Fig. 4 B), estimations of percentile values for this lipid class were carried out in logarithms, and the values were reconverted to their antilogs and expressed as adjusted triglyceride values. The 90th, 95th and 99th percentile values were 147, 165, and 200 mg/100 ml, respectively (Table II). The distribution of the adjusted triglyceride levels was skewed to the higher values (Fig. 4 C).

Plasma lipid levels in survivors. The age and sex composition of the 500 survivors of acute myocardial infarction is shown in Table IV. 92.2% were non-Jewish white, and 5% were Jewish; 1.4% were black; and the remaining 1.4% were either Indian, Filipino, Puerto Rican, Japanese, or Arab.

Figs. 5 and 6 show that distribution of adjusted lipid levels in the survivors of myocardial infarction. In the males the distributions of cholesterol (Fig. 5 A) and triglyceride (Fig. 6 A) appeared unimodal, although both curves showed a deficiency of low values and an excess of high values as compared with those of controls. In the females the lipid distributions appeared more abnormal and were suggestive of bimodality, especially with regard to triglyceride (Figs. 5 B and 6 B).

Since bimodality could not be unequivocally demonstrated in these lipid distributions, arbitrary cut-off values had to be established for classifying survivors as hyperlipidemic or normal. The proportion of survivors exceeding several upper limits of normal for plasma lipids are shown in Table V. From these comparisons of the distribution of lipids in survivors and controls, a number of points are evident: (*a*) hypertriglyceridemia was more
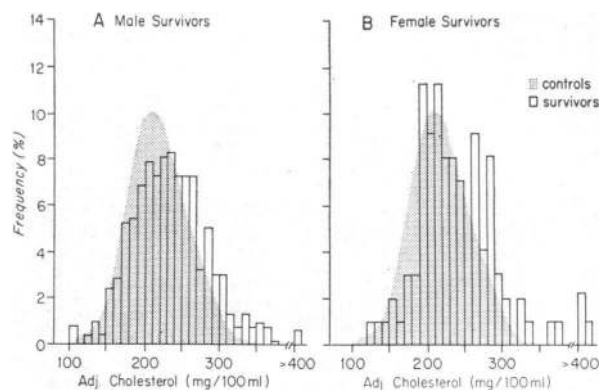

FIGURE 5 Frequency distributions of adjusted cholesterol levels in male (A) and female (B) survivors of myocardial infarction. The distribution is divided into increments of 10 mg/100 ml. The smooth stippled curve represents a nonparametric density estimate of the control distribution.

common among survivors than hypercholesterolemia no matter which upper limits of normal were used to define hyperlipidemia; (*b*) the separation between controls and survivors was greatest at the 99.9th percentile for both cholesterol and triglyceride, there being a 36-fold difference for cholesterol and an 80-fold difference for triglyceride in the observed/expected ratio of the two groups; and (*c*) although the 99.9th percentile value was associated with the highest ratio of survivors/controls for both plasma lipids, a clear-cut excess of survivors/controls was also apparent when the 99th, 95th, and 90th percentile values were used as cut-off levels for hyperlipidemia.

Frequency of hyperlipidemia in survivors. When the 95th percentile was used to separate normals and affected, 157 (31.0%) of the 500 survivors were consid-
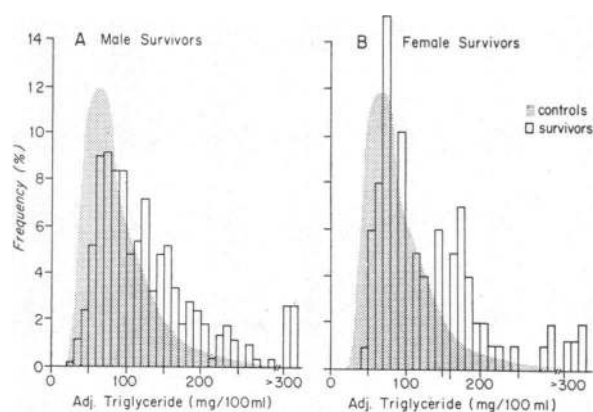

FIGURE 6 Frequency distribution of adjusted triglyceride levels in male (A) and female (B) survivors of myocardial infarction. The distribution is divided into increments of 10 mg/100 ml. The smooth stippled curve represents a nonparametric density estimate of the control distribution.

TABLE V

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‖	0.1	3.8	38.0	0.1	8.0	80.0

* Independent of level of other plasma lipid.

‡ Expected = percent of controls with plasma lipid level equal to or exceeding indicated percentile.

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

‖ 99.9th percentile for adjusted cholesterol = 342 mg/100 ml and for adjusted tryglyceride = 245 mg/100 ml.

ered hyperlipidemic (Table VI). 78 (15.6%) showed hypertriglyceridemia without associated hypercholesterolemia; 41 (7.8%) showed both hypercholesterolemia and hypertriglyceridemia; and 38 (7.6%) showed hypercholesterolemia without associated hypertriglyceridemia.

The relation between the frequency of hyperlipidemia and the age and sex of survivors is shown in Fig. 7. The highest frequency (60%) was found in male survivors below age 40 and female survivors below age 50. With increasing age, the proportion of males with hyperlipidemia decreased markedly and by age 70 was almost zero. However, in the women hyperlipidemia remained at relatively high frequencies in the older ages, and about 30% of women between ages 70 and 79 had elevated levels.

Risk factors in hyperlipidemic and normolipidemic survivors. To determine the relation between hyperlipidemia and other risk factors for coronary heart disease, the frequency of diabetes mellitus, hypertension, obesity, hyperuricemia, and excessive smoking among normolipidemic and hyperlipidemic survivors was compared (Table VII). Obesity was significantly more frequent among hyperlipidemic survivors than among those with normal lipids. This increase in obesity in the hypercholesterolemic g.oup was apparently independent of any associated hypertriglyceridemia, since hypercholesterolemic survivors with triglyceride values below 165 mg/100 ml (n = 38) had a similar proportion of obesity (23.8%). Both diabetes mellitus and hypertension occurred more commonly in the hypertriglyceridemic survivors than in either the hypercholesterolemic or normolipidemic survivors. Hyperuricemia and excessive smoking appeared equally common among hypercholesterolemic, hypertriglyceridemic, and normolipidemic survivors.

TABLE VI

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 ml	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 becomes 162 (32%) if five normolipidemic survivors who were taking clofibrate for previously diagnosed hyperlipidemia had been included.
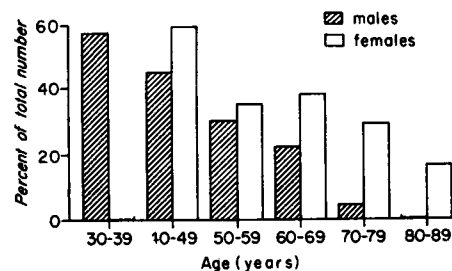

FIGURE 7 Relation between frequency of hyperlipidemia and age and sex of survivors. The number of survivors in each age and sex category is indicated in Table IV.

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%.

DISCUSSION

The extensive epidemiological investigations in the last decade have established an association between coronary heart disease and elevated levels of plasma cholesterol and triglyceride (6–8, 29–32). Less certain, however, is the frequency of lipid abnormalities and the nature of the different types of hyperlipidemia in carefully defined pations with coronary heart disease, such as survivors of myocardial infarction or patients with angiographically proven coronary heart disease. Although in a number of recent investigations the plasma lipids in such patients have been measured (33–47), most of these studies were performed either on small numbers of patients, often without adequate control data, or on biased, nonrandom groups of patients. However, Patterson and Slack's recent investigation was carefully designed and had few biases in patient ascertainment (26). They found that about one-fourth of survivors of myocardial infarction were hyperlipidemic as defined by a cholesterol or triglyceride level exceeding 2 SD of control values. Their study included a total of 193 patients, representing about 50% of all their consecutively ascertained hospital survivors of myocardial infarction (26).

The design of our study differs from all previous investigations. A large control group consisting of 950

spouses was obtained for direct comparisons of plasma lipid levels with survivors and their relatives (12). We studied virtually all 3-mo survivors under age 60 in a large metropolitan area (population estimated at 700,-000) during an 11 mo period. One-fourth of the other survivors who were aged 60 and older were selected at random and also included in the study. This approach permitted a more rigorous and less biased measurement of the frequency and characterization of hyperlipidemia in patients with myocardial infarction.

The results of the present study show that when the 95th percentile of controls was used as a cut-off level, hyperlipidemia was found in 31% of the 500 consecutively studied survivors of myocardial infarction. Moreover, the presence of hyperlipidemia in survivors was critically dependent on both age and sex. The highest frequency of hyperlipidemia (60%) was found in male survivors below age 40 and in female survivors below age 50.

The finding that hypertriglyceridemia with or without associated hypercholesterolemia occurred in survivors at nearly three times the frequency of hypercholesterolemia alone raises the possibility that the level of plasma triglyceride may be as important a risk factor for coronary atherosclerosis as is the level of plasma cholesterol.

In this respect, these data are in close agreement with the studies of Albrink, Meigs, and Man (31) and Carlson (33, 34, 37, 48), who have stressed the importance of triglyceride as a predictor of coronary artery disease. An alternative explanation for the high frequency of triglyceride elevations observed among our survivors may be related to the dietary alterations applied to subjects surviving a myocardial infarction. Since a diet low in content of cholesterol and fat can reduce cholesterol and often elevate triglyceride levels (49), the effect of such a diet may have minimized the prevalence of hypercholesterolemia and maximized the prevalance of hypertriglyceridemia in the survivors as a group. However, this possibility seems unlikely in view of the family data reported in the next paper in this series (12), which demonstrate that as a whole elevations in triglyceride were more common than elevations in cholesterol among the presumably "healthy" relatives of these hyperlipidemic survivors of myocardial infarction.

Another interesting finding emerged from comparing the frequencies of nonlipid risk factors (viz., hypertension, diabetes mellitus, smoking, obesity, and hyperuricemia) among the normolipidemic, hypercholesterolemia, and hypertriglyceridemic survivors. Among hypertriglyceridemic survivors, there was significantly more obesity, hypertension, and diabetes mellitus than in either the hypercholesterolemic or normolipidemic survivors. This unique aggregation of metabolic abnormalities in certain patients with coronary heart disease has been noted previously (50).

The single most important result of this study was the identification of a large number (n = 157) of hyperlipidemic survivors of myocardial infarction who represented unselected patients with coronary heart disease and provided probands for investigating the genetics of hyperlipidemia. As demonstrated in the next paper in this series (12), the genetic approach to hyperlipidemia in coronary heart disease offers a powerful tool for classifying lipid disorders and for clarifying basic mechanisms.

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