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CONSTITUTIONAL AND ENVIRONMENTAL FACTORS RELATED TO SERUM LIPID AND LIPOPROTEIN LEVELS*

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SUMMARY PAGE

THE PROBLEM

Serum lipids are significant risk factors in the development of coronary heart disease, but the information is meager about factors determining levels of serum lipids.

FINDINGS

Serum lipoproteins and lipids were measured in 657 men (age 48) and were correlated with multiple constitutional and environmental variables. The two lipoprotein groups, Sf 0-12 and Sf 20-400, had a low intercorrelation and each correlated with different factors. The Sf 0-12 lipoproteins were related to constitutional obesity, cigarette smoking, and family history of vascular disease. The Sf 20-100 and Sf 100-400 lipoproteins were related to acquired obesity, carbohydrate tolerance, and "aggressiveness" and "sociability" as determined by personality survey. Carbohydrate tolerance, obesity, and personality were apparently independent variables. Serum triglyceride levels correlated with the same variables as the Sf 20-400 lipoproteins; serum cholesterol levels were related to factors that correlated with both lipoprotein groups. High levels (above 90th percentile) of each lipoprotein fraction and each lipid were associated with significantly greater quantities of the variables found to be correlated with each lipid fraction. The prevalence of familial hyperlipidemias was low (approximately 3-4%), but 18 per cent of individuals with elevated cholesterol and a high risk of coronary heart disease could be tentatively classified as having a type of familial hyperlipidemia.

ACKNOWLEDGMENTS

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INTRODUCTION

Despite the important association between elevated plasma lipids and the development of coronary heart disease, there is a surprising lack of information relating plasma lipid levels to specific genetic and environmental factors. The striking differerences in plasma lipids between populations with environments that are widely divergent are readily explained by dietary and other ecological differences. However, these factors are relatively homogenous within population groups, particularly in this country, and individual differences in lipid levels cannot be accounted for by ecological differences. Constitutional and environmental factors are primarily responsible for these differences (1-3), but few of these have been identified and quantified in the general population. The majority of studies have focused on the influence of one factor or studied a single lipid measurement, usually cholesterol. Moreover, these studies were usually confined to special segments of the population, often those with disease, or hospitalized patients. The present investigation examines the relationships between serum lipids and a variety of factors, both hereditary and environmental, in a group of men who have been studied extensively for 24 years.

These men, former naval aviation cadets, have been examined periodically since age 24, and during the last two examinations in 1958 and 1964, serum lipids and lipoproteins were measured. Their average age in 1964 was 48 years (±2.1 years), and although not a cross-sectional sample of the general population, they are generally characteristic of middle-class, middle-aged American men who are particularly susceptible to coronary heart disease. Data acquired in these examinations were used to determine the frequency of various lipid patterns, and these lipid patterns were correlated in turn with other parameters, including family history, somatotype, personality assessment, obesity, exercise, carbohydrate tolerance, and smoking. This is the first comprehensive study in which all of the factors suspected of influencing lipids have been evaluated in each member of a population unselected for a particular characteristic and the only study to relate these factors to a complete lipid profile.

Particular emphasis was directed to relationships between these variables and lipoproteins; though serum lipids were assessed, lipoproteins represent the physiologic form in which plasma lipid is transported. Two lipoprotein groups are of particular importance in atherogensis: the Sf 0-12 (beta) lipoproteins which contain cholesterol and phospholipid, and the Sf 20-100, Sf 100-400 (pre-beta) lipoproteins which contain primarily triglyceride, but also contain significant amounts of cholesterol and phospholipid. These lipoprotein groups are related to different metabolic processes, have a low intercorrelation ($r = .09$), and thus may be treated as independent variables. On the other hand, serum cholesterol and triglyceride are closely related ($r = 0.44$, $p < .001$) and cannot be considered as independent variables. Furthermore, the familial hyperlipidemias, which may be particularly important in coronary heart disease, are best defined by lipoprotein analysis (4). The present report also presents a preliminary evaluation of the variability of serum lipids and of their relationship to coronary artery disease.

PROCEDURE

COMPOSITION OF THE GROUP

The study group is composed of survivors of a group of 1056 men who were physically qualified for naval flight training in 1940. They were examined in 1940 (mean age 24 years), 1952 (36 years), 1958 (42 years), and 1964 (48 years). A history, physical examination, chest x-ray, and electrocardiogram were obtained on each examination. General aspects of these examinations and studies of electrocardiograms and blood pressure have been reported (5-8). Ninety-six per cent of the survivors were reexamined in 1958, and 84 per cent in 1964. Of those not examined in 1964, medical histories were available on all but four who are considered lost to follow-up. Eighty per cent of the group were scored between 24 and 37 on the social scale described by McGuire and White (9); this indicates that the majority correspond to middle-class American men. Slightly less than half have continued a career in the military or in flying.

PERTINENT ASPECTS OF HISTORY AND PHYSICAL EXAMINATION

Complete information on testing procedures, analysis of results, and frequency distribution of variables are available (8, 10), and only aspects pertinent to the present analysis are described here.

Special attention was directed toward obtaining an accurate family history, especially of cardiovascular disease. A "pseudovariable" was constructed by ranking these data in the following manner: death from cardiovascular disease, history of cardiovascular disease, death from cancer or other causes, healthy. The histories of mother, father, and siblings were evaluated separately. Cigarette smoking was evaluated during the 1964 examination both as to amount and to duration; there was a close correlation of these items. The amount of cigarette smoking was categorized in the following way: nonsmokers and pipe or cigar smokers, 1-19 cigarettes/day, 20/day, 21-39/day, 40 or more/day. The consumption of alcohol was coded similarly: never drink, rarely drink, drink once or twice/week, one drink/day, two or three drinks/day, more than three drinks/day, and problem with alcohol. Physical activity was quantified using a questionnaire designed to evaluate activity during work hours and leisure hours (8). Weight was recorded to the nearest pound and height to the nearest tenth of an inch. Several blood pressure measurements were obtained, but "casual" supine blood pressures recorded during the 1964 examination were utilized for these present analyses.

PHYSIOLOGICAL AND PSYCHOLOGICAL MEASUREMENTS

During the examinations in 1940 and 1964, nude photographs were taken of each subject for determination of somatotype (11). Photographs from both examinations were scored by Dr. Albert Damon. The scores from the examination in 1940 were utilized for the present analysis because all subjects were at ideal weight and structural features were less likely to be obscured by obesity or by changes due to aging. The subject was

rated on the following components: endomorphy (visceral structure and body roundness), mesomorphy (dominance of muscle and bone), and ectomorphy (linearity and delicacy of structure). Skinfold thickness (12) was measured in 1964 with Lange calipers in four areas: 1) midway between the acromial process and the olecaranon ("skinfolds-arm"), 2) inferior tip of scapula ("skinfolds-back"), 3) midaxillary line at the level of the xiphoid ("skinfolds-chest"), and 4) midaxillary line at level of umbilicus ("skinfolds-abdomen"). The calipers were read to the nearest 0.5 millimeter, and the mean of three determinations was recorded. Anthropometric measurements were made in 1964 and calculations of lean body mass (13) and body fat were made.

Each subject completed the Guilford-Zimmerman Temperament Survey (14) which is a self-administered paper and pencil test consisting of 300 questions and assessing the following personality characteristics: general activity, energy, restraint, seriousness, emotional stability, ascendance sociality, objectivity, friendliness, thoughtfulness, personal relations, and masculinity. There is minimal intercorrelation between the traits assessed by this test (14).

LABORATORY DETERMINATIONS

During examinations in 1964, blood was obtained following an overnight fast. In 1958 some subjects were not fasting, but no record was kept of the dietary status because it was not believed to influence the concentration of lipoproteins. Therefore, the present analysis is based on data from the study in 1964 when the subjects were post-absorptive. "Standard" serum lipoproteins were determined in 1958 and 1964 at the Institute of Medical Physics using the method of de Lalla and Gofman (15). Serum cholesterol was measured by the method of Abell et al. (16) during both examinations. Serum triglyceride was measured in 1964 using the method of Carlson and Waldström (17). Because of methodological difficulties (probably involving inadequate activation of silica), only the last 252 determinations of triglyceride were considered to be sufficiently accurate for analysis. The laboratory performing the triglyceride and cholesterol determinations participated in the standardization program of the Public Health Service.

Blood for determination of sugar (18) was obtained in the fasting state and two hours after a 100 g-glucose meal. Although this blood was placed in tubes containing sodium fluoride, comparison of data from the first 384 subjects and from the subsequent 253 subjects indicated that the blood sugars averaged 12mg/100 ml less in the first group. Initially, these two "series" of blood sugars were analyzed separately and compared. The distribution curves of values from both were identical in configuration, and there were no apparent differences between the two groups. The correlations between blood sugar and other variables were the same in both groups. To make the data comparable, the blood sugars from both series were separated into 13 percentiles and the corresponding percentiles combined for analysis. Blood from fasting subjects were also analyzed for protein bound iodine (19) and for uric acid (20).

ANALYSIS OF DATA

Data were coded and analyzed on an IBM 1620 computer using standard statistical procedures. When distributions of a variable were found to be skewed (e.g., Sf 20-100 and Sf 100-400 lipoproteins), these variables were converted to the natural logarithm: $f(x) = \log_e (x + 1)$; this procedure yielded a standard distribution. Correlation coefficients (Pearson product-moment) were determined between each lipid measurement and 94 other variables. Parameters having significant correlations ($p < .01$) were analyzed further. Multiple correlation coefficients, corrected for shrinkage in the correlation, were calculated using each lipid measurement as the criterion variable and relating nonlipid parameters to each, using the technique and formulation described by Wherry (21). This is an iterative technique that selects at each iteration the variable making the largest addition (or explanation of variance) until the level of significance of this addition drops below 0.3. When two variables are interrelated, this program selects the variable most closely related to the criterion variable and selects the remaining variable only if it makes a significant contribution that is independent of its association with the first selected variable.

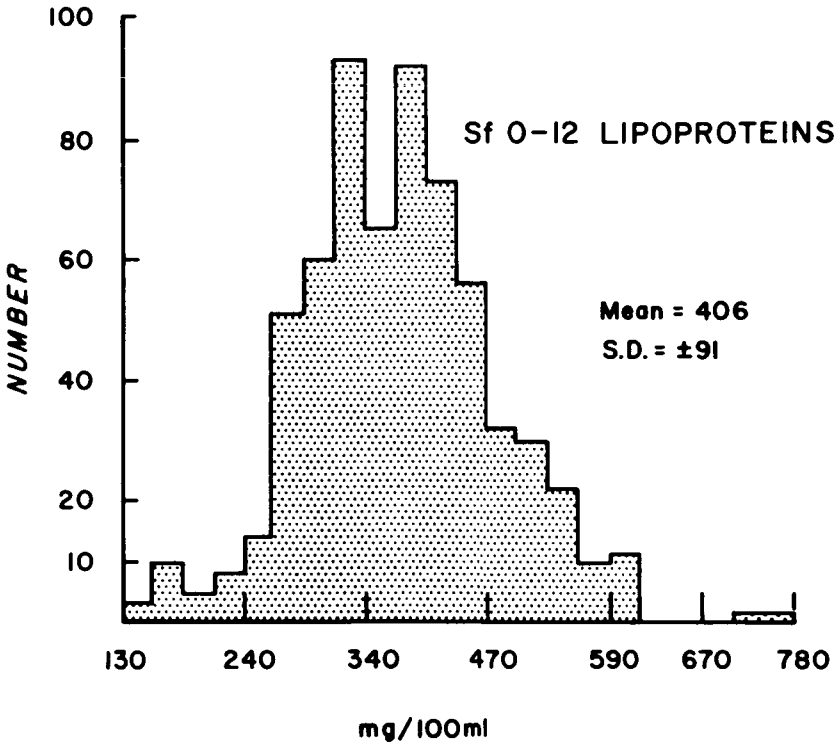
RESULTS

CORRELATIONS BETWEEN LIPIDS AND NONLIPID PARAMETERS

Frequency distributions of values for each lipid fraction and the multiple correlations of nonlipid variables with each fraction are presented in Figures 1-5. Data from 657 individuals comprise the frequency distributions; the multiple correlations are based on data from 441 individuals on whom all data were available. Variables with multiple correlation coefficients significant at the 5 per cent level or less appear in large lettering on the Figures and variables making contributions with less statistical significance (up to 30% level) appear in small lettering. Where the Z-score is negative, a (-) follows the variable.

The Sf 0-12 lipoproteins (β- lipoprotein), which are composed predominantly of cholesterol (51%) and phospholipid (24%) but little triglyceride (5%), were related to cigarette smoking, skinfold thickness of the chest, uric acid, and had a negative relationship to weight gained from age 24 to age 48. Although the number of cigarettes was selected by this analysis, the duration of cigarette smoking also had a significant correlation, these variables being highly interrelated. Similarly, skinfold thickness of the chest and back were closely related, and selection of the chest measurement excluded that of the back. However, skinfold thickness in other areas was not related to these lipoproteins. The minor contribution of protein bound iodine (PBI) to the multiple correlation is of interest, considering the close relationship between pathological levels of PBI and serum cholesterol.

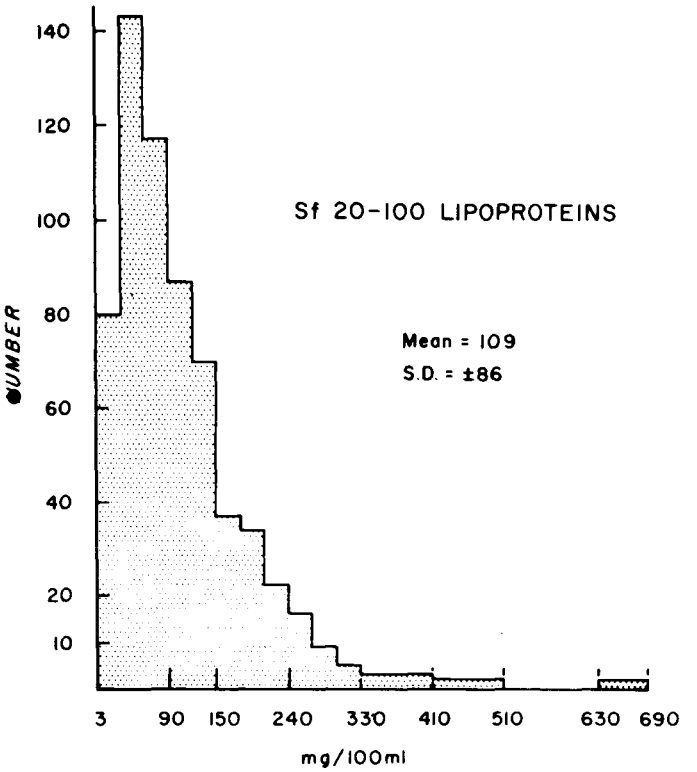
The Sf 20-100 and Sf 100-400 lipoproteins are frequently combined and considered as a single fraction, the Sf 20-400 lipoproteins, but each was evaluated separately to determine whether each might have different correlations. The correlates were similar



Variable	Cumulative Multiple r
SMOKING - AMOUNT	0.144
SKINFOLDS - CHEST	.198
URIC ACID	.221
WEIGHT GAIN 24 - 48 yr. (-)	.241
Fasting glucose	.252
Family history - father	.260
Mesomorphy	.267
Family history - mother	.274
PBI (-)	.278

Figure 1

Frequency distribution of values for Sf 0-12 (beta) lipoproteins and factors correlated with levels of these lipoproteins. Factors having correlations significant at 5 per cent level or greater are listed in bold type. Skinfolds are a measurement of subcutaneous adipose tissue at the site noted. See text for other abbreviations and description of analytical methods.

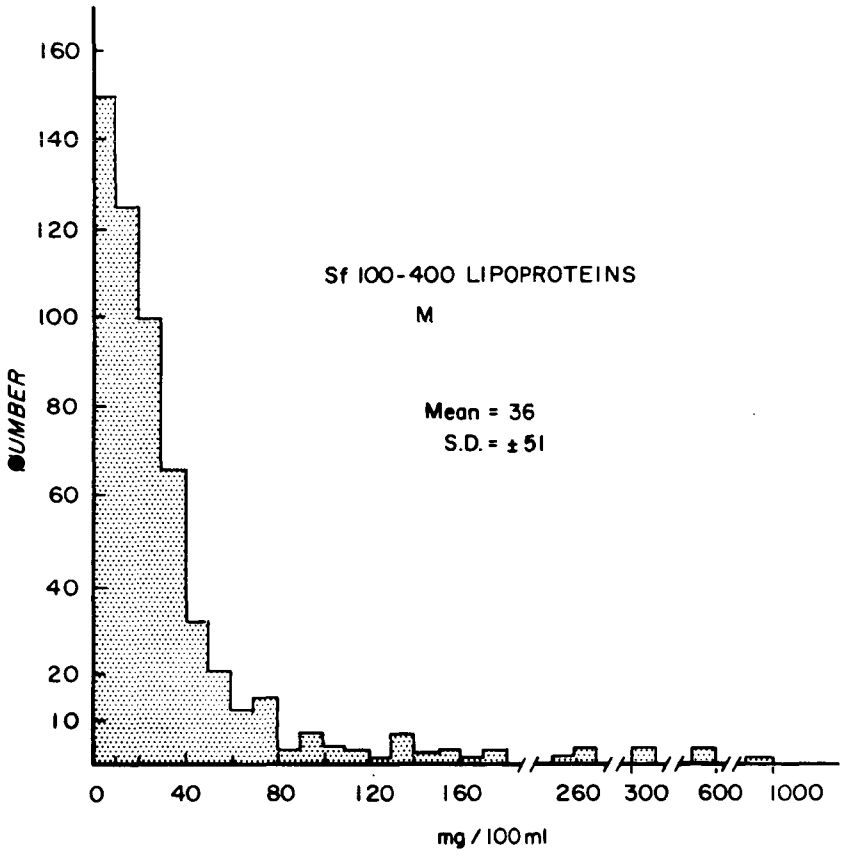


Variable	Cumulative Multiple r
WEIGHT GAIN 24 - 48 yr.	0.215
G - Z, R SCALE (-)	.248
GLUCOSE - 2h pc	.267
SKINFOLDS - ARM (-)	.279
SKINFOLDS - CHEST	.312
MESOMORPHY (-)	.324
FAMILY HISTORY - MOTHER	.334
G - Z, S Scale	.340
Uric acid	.345
Fasting glucose	.349
Family history - father	.353
Smoking - amount	.356

Figure 2

Frequency distribution of values for Sf 20-100 (pre-beta) lipoproteins and factors correlated with levels of these lipoproteins. G-Z refers to Guilford-Zimmerman personality test; the R scale measures restraint; the S scale measures sociability.

for each of these fractions but differed from factors correlating with the Sf 0-12 lipoproteins (Figures 2 and 3). Two measurements of adiposity, weight gain and skinfold



Variable	Cumulative Multiple r
URIC ACID	0.186
GLUCOSE - 2h pc	.247
G - Z, R SCALE (-)	.270
WEIGHT GAIN 24 - 48 yr.	.286
Skinfolds - Arm (-)	.296
Alcohol intake	.303
Family history - father	.309
Mesomorphy (-)	.315
G - Z, S Scale	.320

Figure 3

Frequency distribution of values for serum triglyceride and factors correlated with levels of these lipoproteins. Abbreviations as noted for Figures 1 and 2.

thickness (chest), correlated independently with these lipoproteins. The negative Z-score (-) noted for arm skinfold probably indicates that this was acting as a suppressor variable to remove variance from the more important variable, skinfold thickness of the chest. The relationship was, therefore, primarily to truncal adiposity, and elimination of individuals with peripheral adiposity strengthened this relationship. Similarly, mesomorphy, a measure of muscular development, had a negative Z-score and perhaps removed muscularity from the estimate of truncal mass. This suggests that central adiposity and particularly that developing in middle-life is the variable having the greatest

influence on these lipoproteins. Physical activity correlated poorly with the Sf 100-400 lipoproteins ($r = 0.09$, $p < .05$) and did not correlate significantly with other lipid measurements. On further analysis, the relationship of exercise to these lipoproteins appeared to be due to the decreased activity of the more obese subjects, rather than the effect of exercise per se. Blood sugar two hours after a 100 g-glucose meal was highly related to these lipoproteins, but the fasting blood sugar had an insignificant correlation.

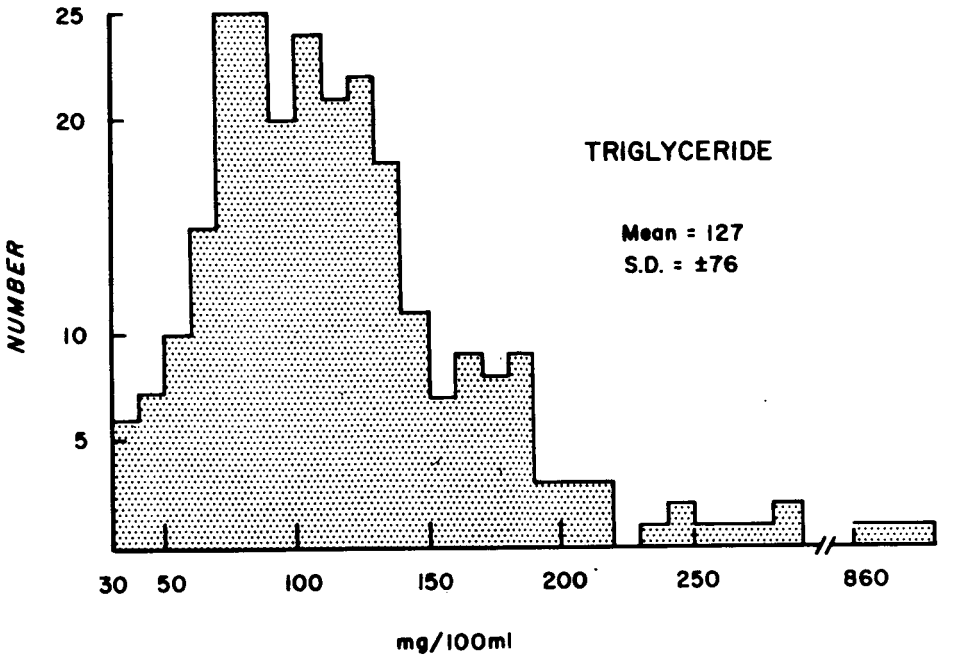
The R scale ("restraint") of the Guilford-Zimmerman personality assessment correlated significantly with these lipoproteins. This relationship, however, was inverse, indicating unrestrained or aggressive personality features are directly related to lipoprotein levels. Increased "sociability" (S scale) was also associated with increased levels. Convivial habits, smoking, and alcohol consumption correlated to a lesser degree, and the correlation with sociability could not be explained on this basis alone. Systolic and diastolic blood pressure correlated significantly with these lipoproteins, but these correlations were due to the relationship of obesity to both blood pressure and Sf 20-400 lipoproteins. When the variance due to obesity was removed, there was no significant correlation between blood presure and lipoproteins.

In the postabsorptive state, most of the plasma triglyceride is transported in the Sf 20-100 and Sf 100-400 lipoproteins, and thus, it is not surprising that factors correlated with these lipoproteins also related to triglyceride (Figure 4). The correlation between triglyceride and Sf 20-400 lipoproteins was 0.88. Adiposity, carbohydrate tolerance, personality, and family history correlated with triglyceride as well as Sf 20-400 lipoproteins.

Serum cholesterol concentration correlated with factors associated with both lipoprotein groups (Figure 5); this would be anticipated since cholesterol is transported in both the Sf 0-12 and the Sf 20-400 lipoproteins. The greater correlation between cholesterol and fasting blood sugar as compared to the correlation with two-hour blood sugar is probably explained by the fact that fasting sugar was related to both lipoprotein fractions while two-hour blood sugar levels were related only to Sf 20-400 lipoproteins.

PATTERNS OF LIPOPROTEIN ELEVATION

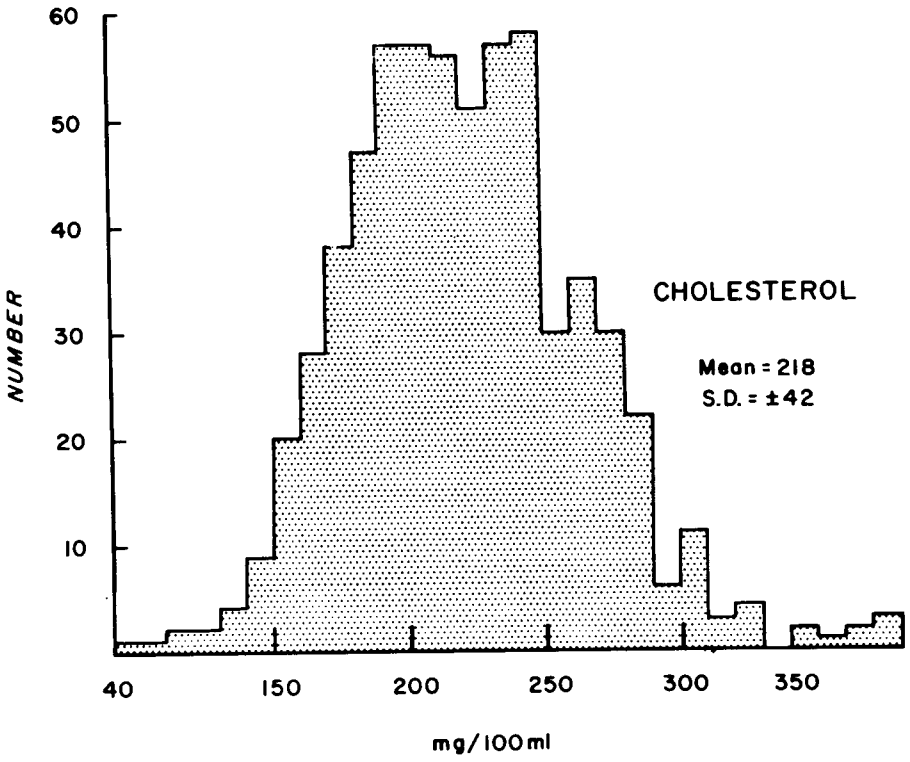
The frequency distributions of each lipoprotein and lipid were skewed toward high values, and there was a cluster of values at the extreme upper ranges of each distribution. The individuals with values clustered at the extreme upper end can be classified as having familial hyperlipidemia, the type being dependent upon the specific lipoprotein elevated. Since the metabolic defects are unknown and only limited quantitative criteria are available to diagnose these disorders, the categorization of these subjects is tentative, particularly in the absence of lipid analyses on direct relatives. Based on diagnostic criteria described for familial hypercholesterolemia (serum cholesterol > 310 mg/100 ml, predominant elevation of Sf 0-12, and normal Sf 20-400) (22), the prevalence of familial hypercholesterolemia was 1.4 per cent (9 of 649). The true prevalance may be somewhat greater because three subjects with serum cholesterol over



Variable	Cumulative Multiple r
SKINFOLDS - CHEST	0.231
FAMILY HISTORY - SIB.	.311
GLUCOSE - 2h pc	.366
Diastolic BP	.384
G - Z, R scale (-)	.399
G - Z, S scale	.406

Figure 4

Frequency distribution of values for serum triglyceride and factors correlated with this serum lipid. Only the 252 measurements considered to be reliable were analyzed.



Variable	Cumulative Multiple r
FASTING GLUCOSE	0.193
SKINFOLDS - CHEST	.229
SMOKING - AMOUNT	.264
FAMILY HISTORY - MOTHER	.278
URIC ACID	.289
G - Z, R Scale (-)	.299
Family history - father	.305
Weight gain 24 - 48 yr. (-)	.311
Systolic BP	.317
Ectomorphy	.321
Family history - Sib.	.324

Figure 5

Frequency distribution of values for serum cholesterol and factors correlated with this serum lipid. Factors influencing both Sf 0-12 (beta) and Sf 20-400 (pre-beta) lipoproteins were found to influence cholesterol as might be anticipated since cholesterol is transported in both of these lipoprotein fractions.

310 mg/100 died before the last two examinations. However, lack of complete lipid data precludes exact classification of these men. Two of the subjects with familial hypercholesterolemia had borderline or abnormal glucose tolerance tests; this is the incidence in the entire group. There are no quantitative criteria for diagnosis of familial endogenous hyperglyceridemia, and subjects were arbitrarily classified as having this disorder if the Sf 20-400 lipoprotein concentration was greater than 500 mg/100 ml and the Sf 0-12 lipoprotein concentration was less than 450 mg/100 ml. There were eleven subjects (1.7%) so classified using these criteria, and seven of these eleven subjects had borderline or abnormal glucose tolerance. Three subjects (0.5%) had elevation of Sf 0-12 and Sf 20-400 fractions and could be classified as having intermediate hyperlipidemia; all of these subjects had abnormal glucose tolerance. Eighteen subjects had serum cholesterol levels greater than 300 mg/100 ml; eleven of these had familial hypercholesterolemia, three had intermediate hyperlipidemia, and four had endogenous hyperglyceridemia. One subject could not be classified since the cholesterol was elevated without elevation of the measured lipoproteins.

Individuals with elevated lipoproteins were investigated to determine whether the factors correlating throughout the entire range were also related to high levels since individuals with elevated lipids are of greatest clinical interest. The Sf 0-12 and Sf 20-400 lipoproteins were handled as independent variables because of their low correlation ($r = 0.09$). The Sf 12-20 fraction correlated highly with the Sf 0-12 ($r = .41$) and the Sf 20-400 ($r = .53$) lipoproteins and was not considered further. Elevation of each fraction was arbitrarily defined as the 90th percentile and above. Four groups were determined by this separation: both fractions "normal" (Group A), elevation of Sf 0-12 only (Group B), elevation of Sf 20-400 only (Group C), and elevation of both (Group D). The number of subjects in each group and the values for associated variables and their statistical significance are shown in Table I. Approximately 10 per cent had elevation of either the Sf 0-12 or Sf 20-400 lipoproteins and approximately 1 per cent had elevation of both fractions. This prevalence pattern suggests that elevation of both fractions may result from the coincidence of factors causing elevation of each, rather than being caused by a third, unique, set of factors. Further confirmation for this interpretation is provided by the finding that the characteristics of Group D were similar to those of Groups B and C.

The variables correlated with lipoprotein levels were also significantly related to high levels of the corresponding lipoproteins. Thus, elevated Sf 20-400 lipoproteins were associated with significantly greater truncal adiposity (skinfold thickness of chest) and higher postprandial blood sugar; these factors were previously found to correlate at all levels. This was also true for the relationship between cigarette smoking and the Sf 0-12 lipoproteins. For these analyses, individuals tentatively designated as having familial hyperlipidemia were not removed from these groups.

Serum cholesterol was high when either or both lipoprotein fractions were elevated, but significant elevation of triglyceride was present only when the Sf 20-400 fractions were increased (Group C and D). This is consistent with the lipid compositions of these

Table I

Patterns of Serum Lipoproteins and Their Relationship

Lipoprotein Patterns	Number Classified	Cholesterol (mg/100 ml)	Triglyceride (mg/100 ml)	Skinfold Thickness-Chest	Smoking Amt.*	Blood sugar 2 hr pc (mg/100 ml)	Serum uric acid (mg/100 ml)
A. Normal Sf 0-12 (< 520) Normal Sf 20-400 (< 273)	493	208 ±36	109 ±38	14.7 ±6.1	2.4 ±1.3	94 ±23	5.9 ±1.4
B. Elevated Sf 0-12 (> 519) Normal Sf 20-400 (< 273)	65	272 ±38	112 ±40	16.1 ±6.7	2.7 ±1.3	97 ±19	6.0 ±1.4
C. Normal Sf 0-12 (< 520) Elevated Sf 20-400 (> 272)	69	236 ±44	243 ±130	17.5 ±5.8	2.8 ±1.3	102 ±33	6.3 ±1.7
D. Elevated Sf 0-12 (> 519) Elevated Sf 20-400 (> 272)	10	278 ±34	196 ±34	14.2 ±4.6	3.5 ±1.0	95 ±40	6.4 ±1.2
Significant differences $p < .05$ or less		A vs B,C,D, B vs C C vs D	A vs C B vs C,D	A vs C C vs D	A vs B,D B vs D C vs D	A vs C	--

*Coded as given in text

fractions. The Sf 0-12 lipoproteins contain primarily cholesterol while the Sf 20-400 lipoprotein contain both triglyceride (52%) and significant amounts of cholesterol (22%).

RELATIONSHIPS TO WEIGHT AND CARBOHYDRATE TOLERANCE

Since adiposity and carbohydrate tolerance are related to each other, it was important to separate these factors and determine the relation of each to lipoprotein elevation. These factors were separated by comparison of groups with comparable weight gain and carbohydrate tolerance (Table II). The Sf 20-100 and Sf 100-400 lipoproteins were significantly higher in groups B and D which had abnormal carbohydrate tolerance (2 hr. blood sugar > 120 mg/100 ml) than in Groups A and C, respectively, which had comparable weight gains but normal carbohydrate tolerance. In addition, groups with comparable glucose tolerance had significantly higher lipoproteins of the Sf 20-100 and Sf 100-400 groups when the weight gain was 20 pounds or more. Thus, both weight and carbohydrate tolerance were independently related to elevations of the very low density (Sf 20-100 and Sf 100-400) lipoproteins, and the influence of each factor was present in both lipoprotein fractions. Serum uric acid was significantly related to increase in weight but not to abnormalities in glucose tolerance. Serum cholesterol and Sf 0-12 lipoproteins were not significantly affected by weight change or carbohydrate tolerance.

The temporal relationship between weight change and lipoprotein levels was determined by separating the 24 years of follow-up into two periods, age 24-42 (first 18 years) and age 42-48 (last 6 years) (Table III). No significant differences were found between subjects maintaining constant weight during both periods (Group B) and subjects having initial weight gain followed by a decrease in weight (Group D) although Group D gained 10 pounds more during the entire period. Group C ("constant-gain") and Group D ("gain-decrease") had comparable total increments in weight and degrees of truncal adiposity, and the lipoproteins were not significantly different, although the Sf 20-400 lipoproteins were slightly less in the group with recent weight loss. Postprandial blood sugar was not significantly related to the pattern of weight change. We conclude that the total weight gained (or adiposity) is a more important factor than recent alterations in weight, but the latter has some influence on lipoprotein concentration.

RELATIONSHIP OF LIPOPROTEINS TO CORONARY ARTERY DISEASE

The study population was separated by electrocardiographic and clinical criteria into a group with coronary artery disease and a "healthy" group (Table IV). Serum cholesterol and Sf 0-12 lipoproteins were significantly higher in the group with coronary disease, but serum triglyceride and Sf 20-400 lipoproteins were not significantly different from those in the "normal" group. Three patients dying with myocardial infarction prior to the time when complete lipid analysis was performed had serum cholesterol values above 320 mg/100 ml and a fourth patient had a serum cholesterol of 238 mg/100 ml. Blood sugar two hours after a 100 g-glucose meal tended to be higher in the coronary group but the difference was not statistically significant.

Table II

Relationships Among Weight Gain, Glucose Tolerance, Serum Lipids, and Uric Acid

Weight gain age 24-48 2 hr blood sugar	Cholesterol mg/100 ml	Lipoproteins (mg/100 ml) Sf 0-12	 Sf 20-100	 Sf 100-400	Uric Acid mg/100 ml
Weight gain 19 lbs. or less					
A. Normal blood sugar N = 305	215 ±41	403 ±72	96 ±78	26 ±34	5.7 ±1.4
B. Sugar > 120 mg/100 ml N = 45	225 ±46	407 ±97	122 ±107	46 ±74	5.9 ±1.4
Weight gain 20 lbs. or more					
C. Normal blood sugar N = 234	220 ±44	407 ±95	116 ±80	38 ±65	6.2 ±1.5
D. Sugar > 120 mg/100 ml N = 52	224 ±47	399 ±92	169 ±160	103 ±80	6.6 ±1.7
Significant differences $p < .05$ or less	-	-	A vs B,C,D B vs D C vs D	A vs B,C,D B vs D C vs D	A vs C,D B vs D

Table III

Pattern of Weight Change and Its Relationship to Serum Lipids and Glucose Tolerance

Change in Weight Age 24-42	Change in Weight Age 42-48	N	Lipoproteins (mg/100 ml) Sf 0-12	Sf 20-400	Blood Sugar 2 hr pc (mg/100 ml)	Skinfold Thickness-Chest	Total Change in weight Age 24-48
Constant (± 10 lbs)	A. Decrease (-4 to -48 lbs)	44	388	110	91	10.2	-6.3
	B. Constant (-3 to +6 lbs)	83	402	132	96	12.9	+5.5
	C. Gain (+ 7 to +46 lbs)	64	403	147	93	16.1	+16.3
Gain (+11 to +60 lbs)	D. Decrease (-4 to -48 lbs)	142	401	133	92	14.5	+15.2
	E. Constant (-3 to +6 lbs)	148	403	168	99	16.5	+25.2
	F. Gain (+ 7 to +46 lbs)	94	413	171	97	20.6	+35.1
Significant differences	$p < .05$ or less	-		A vs E, F D vs F	-		-

Table IV

Relation of Serum Lipids to Development of Coronary Heart Disease

Condition	Cholesterol mg/100 ml	Triglyceride mg/100 ml	Lipoproteins (mg/100 ml) Sf 0-12	Sf 12-20	Sf 20-400	Blood Sugar 2 hr mg/100 ml	Uric Acid mg/100 ml
"Healthy Group" N = 597	217 ±42	124 ±73	400 ±92	51 ±22	161 ±90	95 ±12	5.9 ±1.5
Coronary Heart Disease N = 42	242 ±51	124 ±66	474 ±86	62 ±29	170 ±102	100 ±13	6.1 ±1.6
Significance	$p < .01$	N.S.	$p < .01$	$p < .01$	N.S.*	$p < .1 > .05$	$p < .05$

*N.S. - Not significant

Although the limited number of individuals with coronary disease precludes extensive analysis, the patterns of lipid elevation are interesting in this group. Fourteen individuals (33%) had only elevation of the Sf 0-12 lipoproteins (and cholesterol); four (10%) had elevation of the Sf 20-400 lipoproteins (and triglyceride); and four (10%) had elevation of both lipoprotein fractions. The last group with elevation of both fractions was found in the coronary group in considerably greater prevalence than this pattern was found in the general population. Abnormal glucose tolerance was not associated with a particular lipid pattern in these subjects and appeared to operate as an independent variable.

VARIABILITY OF SERUM LIPIDS

Repeat determinations of cholesterol and lipoproteins were available on 381 subjects who had these analyses in 1958 and 1964. Correlations between the two determinations were high: cholesterol, $r = .78$; Sf 0-12, $r = .72$; Sf 20-400, $r = .42$. Of greater importance, however, is the intraindividual variability between examinations since this indicates the reliability of a single determination. For the Sf 0-12 lipoproteins, 80 per cent of the values on the second examination were within -12 per cent and +20 per cent of the first examination. For cholesterol, 80 per cent of the values were within -18 per cent and -21 per cent of the first examination. For each, 90 per cent of the group had values within ± 30 per cent of the first determination. The variability was not related to the absolute levels. The variability of the Sf 20-100 or Sf 100-400 lipoproteins could not be determined because not all subjects were postabsorptive during the 1958 examination.

DISCUSSION

Individual differences in circulating lipids result from the interaction between genetic and environmental factors. In this study group, as in the majority of Americans with similar socioeconomic and dietary backgrounds, constitutional factors probably have the greatest influence on lipid levels, although environment may modify expression of these hereditary differences. Genetic differences may be expressed in two ways. A single mutant gene, altering a particular metabolic pathway, can cause extreme elevations of lipids. These familial hyperlipidemias are affected by environment to a relatively minor degree (22). Similarly, very low levels due to absence of a particular lipoprotein species may result from monogentic inheritance. However, in the majority of the population, multiple hereditary factors, each of which is insufficient to produce major changes, determine lipid levels and environment plays a more important role. It is important to determine the frequency of each of these mechanisms and to identify and quantify the factors involved in the multifactorial determination of lipid concentrations.

The frequency distributions of lipids and lipoproteins in this group were continuous but skewed toward higher values, and there was a cluster of subjects at the extreme upper end. These individuals, comprising approximately 3 or 4 per cent, were categorized as having familial hyperlipidemia, although without precise biochemical criteria this definition must be tentative. The type of familial hyperlipidemia can be classified by

the elevated lipoprotein fraction, the Sf 0-12 in familial hypercholesterolemia, the Sf 20-400 in familial hyperglyceridemia (endogenous), and both in intermediate hyperlipidemia (4, 22). The diagnosis of familial hypercholesterolemia is more secure due to the more compact distribution of values for cholesterol and Sf 0-12 lipoproteins and the availability of quantitative criteria (22). This disorder, affecting approximately 1.4 per cent of this population is associated with elevated cholesterol, normal triglyceride, and the same frequency of abnormal glucose tolerance observed in the remainder of this group. The skewness of values for triglyceride and Sf 20-400 lipoproteins makes exact classification of familial hyperglyceridemia more difficult. This disorder, comprising perhaps 1.7 per cent of this group, is associated with high triglyceride levels, an increased prevalence of abnormal glucose tolerance, and high serum cholesterol. Elevation of both groups of lipoproteins was present in only 0.5 per cent, and all of these patients had abnormal glucose tolerance.

The relatively low prevalence of familial hyperlipidemia belies its potential importance in arteriosclerotic disease. The incidence of coronary heart disease is increased in individuals with serum cholesterol above 274 mg/100 ml (23), and in the present study, 18 per cent of these "high risk" individuals could be classified as having familial hyperlipidemia. Similar data relating triglyceride levels to risk of disease are not available, but a relatively high prevalence of familial hyperlipidemia would also be expected in the group having high triglyceride levels.

The majority of the population, including individuals with values skewed to higher levels, had lipid levels determined by multiple factors. Different factors correlated with the major group of lipoproteins, the Sf 0-12 and the Sf 20-100 and Sf 100-400 fractions, as might be expected since these lipoprotein groups have different metabolism. The Sf 0-12 lipoproteins correlated with a variety of factors, including family history of vascular disease, body habitus, cigarette smoking, and serum uric acid. The relationship of these lipoproteins to adiposity and body habitus deserves clarification because of the contradiction between the direct relationship to truncal adiposity (expressed by skinfold thickness of chest) and the inverse relationship to weight gain. This apparent paradox was resolved by the demonstration that Sf 0-12 lipoproteins and cholesterol correlated ($r = 0.18$, $p < .001$) with endomorphic habitus at age 24, but not with endormorphy at age 48. This suggested that adiposity at different phases of life has different physiologic implications. Thus, constitutional obesity (manifest by endomorphic habitus while at "ideal weight") rather than acquired obesity, expressed by weight gain in middle life, was the more important determinant of levels of these lipids. This formulation is compatible with observations that serum cholesterol correlates with skinfold thickness in younger men (20 to 24 years) but not in older men (24) and with the studies of others (25, 26) that body weight and weight gain are not related to serum cholesterol or Sf 0-12 lipoproteins after the subjects reach maturity.

The association between cigarette smoking and Sf 0-12 lipoproteins has been reported (27) in smaller numbers of subjects as has the relationship between serum cholesterol and smoking (28), but the mechanism of this relationship remains unknown. The absence of correlations with other variables related to these lipids suggests that smoking

may not be dependent on other factors for its relationship to lipid levels. Unfortunately, it has been difficult to induce individuals to stop smoking, thus making it difficult to determine whether the relationship to lipids is a causal one. The direct correlation between smoking and serum cholesterol does suggest a mechanism to explain partially the observations relating cigarette smoking to the degree of coronary arteriolsclerosis (29) and to the development of myocardial infarction (30). Of additional interest is the relatively minor relationship between Sf 0-12 lipoproteins and protein-bound iodine (PBI) because serum cholesterol and Sf 0-12 lipoproteins are dramatically altered by pathological levels of PBI. However, as reported by Tucker and Keys (31), the relationship is relatively minor within the physiologic range.

In contrast to the Sf 0-12 lipoproteins, the Sf 20-100 and Sf 100-400 lipoproteins reflected the environmental influence of increasing weight. Numerous variables related to adiposity were measured, but skinfold thickness, a measurement of subcutaneous adipose tissue, and the amount of weight gained were as informative as more complex measurements. The relationship was stronger with central or truncal adiposity than with peripheral adiposity (skinfold thickness of arms), and this association with truncal obesity was improved when variance due to peripheral adiposity and muscular build (mesomorphy) were removed. Albrink and Meigs (32) also found that weight gain after age 25 and increased central adiposity were associated with higher levels of triglyceride. Since the Sf 20-400 lipoproteins transport most of the triglyceride in the postabsorptive state, these results are in general agreement. These observations suggest that higher triglyceride (and Sf 20-400 lipoprotein) levels are associated with caloric excess and acquired truncal adiposity, whereas constitutional obesity, present early in life and having a fairly uniform distribution, is related to serum cholesterol and Sf 0-12 lipoproteins.

Obesity and abnormal carbohydrate tolerance occur together frequently and both have been reported in association with high plasma triglyceride levels (33, 34). In spite of their frequent coincidence, these characteristics correlate independently with the Sf 20-400 lipoproteins. Significantly higher levels of Sf 20-400 lipoproteins were found in subjects with excessive weight gain (over 20 pounds) but normal carbohydrate tolerance; conversely, subjects with abnormal glucose tolerance without excessive weight gain also had significantly higher levels. Recent changes in weight appeared to influence these lipoproteins as well, although not so much as the total weight gained. However, physical activity, when separated from inactivity associated with obesity, did not have a significant relationship to lipid levels.

The implication that personality and stress may be involved in the pathogenesis of coronary heart disease has intrigued physicians and the public, but documentation of their influence and even reliable measurement of individual differences have been elusive. The Guilford-Zimmerman temperament survey, an objective and reliable test measuring personality characteristics, was used in these studies. Lack of "restraint" ("aggressiveness") correlated directly with the Sf 20-100 and Sf 100-400 lipoproteins and to a lesser degree with serum cholesterol and triglyceride. This characteristic did not correlate with other variables that were associated with these lipoproteins, thus suggesting that this psychological factor or some associated, but unmeasured, characteristic was responsible

for this relationship. The "sociability" index also had a positive correlation, but this relationship may reflect differences in convivial patterns of eating and alcohol consumption rather than a difference in temperament, although no related differences in these patterns were elicited in the medical history. Friedman and Rosenman (35, 36), using a subjective classification based on interviews, found competitive, ambitious individuals (Type A) had significantly higher cholesterol and triglyceride and a greater incidence of coronary heart disease, and further noted that this relationship could not be explained by differences in glucose metabolism. Our observations, however, represent the first demonstration of such relationships using an objective assessment of temperament. The mechanism for this influence is unknown, but may be related to observations that periodic "stress" is associated with increases in cholesterol (37). The apparent influence of stress and personality could be dependent on differences in diet or physical activity, which are also difficult to quantify. Obviously, much more work needs to be done in this area which has been beclouded by a paucity of objective measurements.

The correlative data express relationships between lipids and nonlipid variables throughout the entire range of lipid concentration, but high levels command the greatest clinical interest and deserve some comment. Elevated levels of the Sf 0-12 and Sf 20-400 fractions were found to occur independently, and those variables correlated with each lipoprotein group were found in significantly greater degree in subjects with high levels. Elevation of both lipoprotein groups was encountered with a frequency suggesting that this situation resulted from coincidence of factors responsible for elevation of each fraction. Hyperlipidemia can be examined from another standpoint, that of lipid patterns associated with increased risk of coronary disease. Assuming serum cholesterol above 274 mg/100 ml conveys an increased risk (23), the following lipoprotein patterns were found in this group: elevation of the Sf 0-12 lipoproteins alone in 57 per cent, elevation of Sf 20-400 lipoproteins alone in 33 per cent, and elevation of both fractions in 10 per cent. Thus hypercholesterolemia and increased risk can result from any of these three patterns, but elevation of the Sf 0-12 fraction was most common. Hyperglyceridemia, however, can be present only when the Sf 20-400 lipoproteins are elevated.

Coronary heart disease in this group has not become manifest with sufficient frequency to permit more than a tentative statement regarding the relationship between lipid patterns and heart disease. Serum cholesterol and Sf 0-12 lipoproteins were significantly higher in the group with coronary heart disease, but serum triglyceride and the Sf 20-400 lipoproteins, although higher, were not significantly greater than values in "healthy" subjects. Our findings are comparable to those of Brown, Kinch, and Doyle (38) who found serum cholesterol discriminated between individuals with high and those with low prevalence of disease better than did serum triglyceride. These results contrast with those of others (39, 40) who compared patients with myocardial infarction to control subjects selected in different manner. Rather than belabor these differences, which will be clarified only when data from prospective studies are available, it is perhaps more pertinent to inquire whether measurements of triglyceride or Sf 20-400 lipoproteins define individuals at significant risk who would not be defined by elevated cholesterol levels or by abnormal glucose tolerance. In this study and that of Brown, Kinch, and Doyle (38), individuals with extremely high levels of Sf 20-400 lipoproteins

(and triglyceride) had high levels of cholesterol as well. Therefore, these individuals would be categorized as "high risk" on the basis of serum cholesterol. Serum triglyceride and Sf 20-400 lipoproteins would, consequently, have value only in identifying individuals with moderate elevations of these lipids that are not accompanied by high serum cholesterol. However, this latter group have a greater prevalence of abnormal carbohydrate tolerance, and our experience plus that of others (41) indicates that this is also a significant risk factor. The more appropriate question might be, therefore, whether the circulating triglyceride or the underlying metabolic abnormality, perhaps diabetes mellitus, is the primary factor in the pathogenesis of coronary disease. Further studies in which both carbohydrate tolerance and triglyceride are assessed should permit evaluation of each factor separately, and determine whether triglyceride per se is the important factor or its association with other factors, high serum cholesterol and abnormal carbohydrate tolerance.

These observations must be interpreted in light of the population studied and the reliability of the measurements. The value of observations on a free-living population, unselected for presence of disease, is obvious, but the uniqueness of this group, which was initially selected by rigorous medical criteria, suggests caution in extending these observations to the general population. In fact, the relative homogeneity of the group with the restricted range of most variables probably substantually reduced the size of the correlations obtained. However, it is likely that these observations can be extrapolated to middle-aged American men with some confidence since it is the extremes, or abnormals, that are not studied. In studies of patients selected for abnormality, it is the normal subjects who are missing. Moreover, the results from this comprehensive evaluation agree, in general, with observations by others evaluating a limited number of variables in smaller groups of subjects.

The reliability of a single lipid measurement, subject to laboratory error and biologic variability, has concerned some investigators (42). The intraindividual variation in values over a six-year interval was significant, but less than many other biological measurements, such as blood pressure. Despite this variability, single determinations do permit rough categorization of individuals, and the relationships developed from this categorization did not change between the two examinations.

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13. ABSTRACT

Serum lipoproteins and lipids were measured in 657 men (age 48) and were correlated with multiple constitutional and environmental variables. The two lipoprotein groups, Sf 0-12 and Sf 20-400, had a low intercorrelation and each correlated with different factors. The Sf 0-12 lipoproteins were related to constitutional obesity, cigarette smoking, and family history of vascular disease. The Sf 20-100 and Sf 100-400 lipoproteins were related to acquired obesity, carbohydrate tolerance, and "aggressiveness" and "sociability" as determined by personality survey. Carbohydrate tolerance, obesity, and personality were apparently independent variables. Serum triglyceride levels correlated with the same variables as the Sf 20-400 lipoproteins; serum cholesterol levels were related to factors that correlated with both lipoprotein groups. High levels (above 90th percentile) of each lipoprotein fraction and each lipid were associated with significantly greater quantities of the variables found to be correlated with each lipid fraction. The prevalence of familial hyperlipidemias was low (approximately 3-4%), but 18 per cent of individuals with elevated cholesterol and a high risk of coronary heart disease could be tentatively classified as having a type of familial hyperlipidemia.

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