High Density Lipoprotein As a Protective Factor Against Coronary Heart Disease

The Framingham Study

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Lipid and lipoprotein values, including fasting triglycerides and high density lipoproteins (HDL), low density lipoproteins (LDL) and total cholesterol levels, were obtained on 2,815 men and women aged 49 to 82 years chiefly between 1969 and 1971 at Framingham. In the approximately four years following the characterization of lipids, coronary heart disease developed in 79 of the 1,025 men and 63 of the 1,445 women free of coronary heart diseases. At these older ages the major potent lipid risk factor was HDL cholesterol, which had an inverse association with the incidence of coronary heart disease ($p < 0.001$) in either men or women. This lipid was associated with each major manifestation of coronary heart disease. These associations were equally significant even when other lipids and other standard risk factors for coronary heart disease were taken into consideration. A weaker association with the incidence of coronary heart disease ($p < 0.05$) was observed for LDL cholesterol. Triglycerides were associated with the incidence of coronary heart disease only in women and then only when the level of other lipids was not taken into account. At these ages total cholesterol was not associated with the risk of coronary heart disease.

Lipid and lipoprotein studies in the past have generally emphasized the positive relationship of total cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and triglyceride to the risk of coronary heart disease [1–4]. The higher the concentration of any one of these blood lipids, the greater the risk of coronary heart disease. On the other hand, the high density lipoproteins (HDL) or alpha lipoproteins appeared to have an inverse relation to the risk of coronary heart disease; the lower their concentration the greater the risk of coronary heart disease. This anomalous relationship, where high levels appear to be protective, may be one reason that HDL has received little attention from investigators.

Beginning in 1968, but chiefly between 1969 and 1971, lipoproteins were measured after an overnight fast on a cohort of the Framingham Study population aged 49 to 82 years. Since that time 142 new cases of coronary heart disease have developed in this group, allowing a detailed analysis of the relationship of antecedent lipoproteins to subsequent risk of coronary heart disease. In this paper we deal with the fact that there was a striking inverse correlation of HDL cholesterol to the incidence of coronary heart disease, and that of all the lipoproteins and lipids measured, HDL had the largest impact on risk in the age group studied. We also consider the value of using measures

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TABLE I Incidence of Coronary Heart Disease by HDL Cholesterol Level—Framingham Study, Exam 11

HDL Cholesterol Level (mg/dl)	Men			Women		
	Incidence of Coronary Heart Disease	Population at Risk	Rate/1,000	Incidence of Coronary Heart Disease	Population at Risk	Rate/1,000
All levels	79	1,025	77.1	63	1,445	43.6
<25	3	17	176.5	0	4	0.0
25–34	17	170	100.0	11	67	164.2
35–44	35	335	104.5	12	220	54.5
45–54	15	294	51.0	19	386	49.2
55–64	8	134	59.7	14	353	39.7
65–74	1	40	25.0	3	216	13.9
75+	0	35	0	4	199	20.1

NOTE: The majority of persons were followed for four years. However, a small number may have been followed for as few as two years or as many as eight years.

of several lipids for the purposes of assessing the risk of coronary heart disease rather than relying on the measure of a single lipid.

METHODS

The details of the delineation of the Framingham Heart Study cohort are described elsewhere [5,6]. Beginning in 1949 a group of 5,209 men and women, then aged 30 to 59 years, were enlisted into a longitudinal study. Since then, they have been followed by means of routine biennial medical examinations and by obtaining information on morbidity and mortality from hospitals and other sources. Starting in 1968, 2,815 men and women, aged 49 to 82 years, had their lipids and lipoproteins characterized after an overnight fast of 12 to 14 hours. In the roughly four years since that characterization, coronary heart disease has developed in 79 of the 1,025 men and in 63 of the 1,445 women free of coronary heart disease by the standard criteria for this diagnosis used in Framingham [5,6].

Blood specimens were collected in an aqueous solution of disodium EDTA, providing 1.275 mg/ml of blood, and the plasma was separated. Lipoprotein separation was accomplished by a protocol developed by the Laboratory for Molécular Disease of the National Heart, Lung, and Blood Institute under the tutelage of Mrs. Betty Masket and Dr. Robert Levy [7,8]. HDL was separated by precipitating the other lipoproteins with heparin-manganese chloride, using a modification of the technic described by Burstein et al. [9]. Cholesterol concentrations were determined by the Abell-Kendall method [10]. Triglycerides were determined by a modification of the Kessler-Lederer method [11]. The criteria and measurement procedures for other characteristics are described in previous reports [5,6].

In most instances the base line lipid and lipoprotein determinations were made between 1969 and 1971. A relatively small number of determinations made outside that time span are also available. At the time of the lipid determinations most of the cohort was in the age range 50 to 79 years. For convenience the 13 persons aged 49 and the 20 persons aged 80 to 82 are included with those aged 50 to 59 and 70 to 79, respectively. Follow-up was essentially complete through 1974.

In evaluating the relationship between base line characteristics and the subsequent development of coronary heart disease, use was made of the logistic function. Parameters of this function were estimated by the method of Walker-Duncan [12]. These were standardized by multiplying them by the standard deviation of the characteristic. Such standardized coefficients may be used for a rough comparison of the strength of the independent variables as risk factors for coronary heart disease, a larger standardized coefficient representing a stronger risk factor. Likelihood ratios of the logistic functions indicate how well the various risk functions fit the actual data. These likelihood ratios follow a chi-square distribution, the number of degrees of freedom being equal to the number of variables. Roughly speaking, the larger the likelihood ratio for a given number of variables the better the set of variables fits the data.

RESULTS

In both men and women there is a clear gradient of the risk of coronary heart disease by HDL level, persons with low HDL cholesterol levels being at higher risk than persons with high levels (Table I). On the sample data, in persons with HDL cholesterol levels below 35 mg/dl the incidence rate is more than eight times that in persons with HDL levels 65 mg/dl or above. The incidence rate for women was significantly lower than that for men.

This finding is also manifest in the logistic regression coefficients of incidence of coronary heart disease on HDL cholesterol level (Table II). The standardized coefficient for "all coronary heart disease" is slightly greater for women than men, but it is statistically significant ($p < 0.001$) for both sexes. As judged by the

TABLE II Univariate Logistic Regression Coefficients for Coronary Heart Disease on HDL Cholesterol by Type of Coronary Heart Disease—Framingham Study, Exam 11

	Men	Women
All coronary heart disease	−0.506* (79)	−0.682* (63)
Coronary attacks	−0.410† (58)	−0.742* (38)
Angina (uncomplicated)	−0.711† (24)	−0.561† (25)
Coronary heart disease death	−0.244 (24)	−0.852† (18)

NOTE: Parenthetical entries are the number of cases. Coefficients are estimated by the method of Walker-Duncan and standardized.
*p <0.001.
†p <0.01.

TABLE IV Relation of HDL Cholesterol with Other Variables—Framingham Study, Exam 11

Variable	Men	Women
Correlation Coefficient of HDL Cholesterol with. . .		
Total cholesterol	0.10*	0.07†
LDL cholesterol	−0.04	−0.16‡
Triglycerides	−0.35‡	−0.43‡
Blood glucose	−0.07	−0.14‡
Relative weight	−0.28‡	−0.24‡
Systolic blood pressure	0.04	−0.11‡
Diastolic blood pressure	0.05	−0.06*
Cigarettes/day	0.01	−0.07*
Mean Levels of HDL Cholesterol (mg/dl)		
Diabetes		
No	45.6	57.6‡
Yes	44.2	51.8
Urine glucose		
No	45.5†	56.9
Yes	36.7	47.5
LVH-ECG		
No	45.9	57.5
Yes	42.9	52.6
Cigarette smoking		
No	45.5	57.5
Yes	45.6	55.6

NOTE: Except for cigarette smoking and measures of glucose intolerance, data are available for 1,025 men and 1,445 women free of coronary heart disease. LVH = left ventricular hypertrophy; ECG = electrocardiogram.
*p <0.01.
†p <0.05.
‡p <0.001.

TABLE III Mean Levels of HDL and LDL Cholesterol and Triglycerides—Framingham Study, Exam 11

Age (yr)	Mean Levels (mg/dl)	
	Men	Women
	HDL Cholesterol	
50–59	45.2	58.9
60–69	46.4	56.9
70–79	46.7	54.9
	LDL Cholesterol	
50–59	143.6	151.1
60–69	143.0	159.3
70–79	137.0	157.1
	Triglyceride (triolene)	
50–59	143.5	111.2
60–69	133.4	117.3
70–79	117.2	126.1

TABLE V Univariate and Multivariate Logistic Regression Coefficients for Coronary Heart Disease on HDL Cholesterol—Framingham Study, Exam 11

Age (yr)	Cases (no.)	Univariate	Multivariate	
			Lipids Only	Lipids and Other Factors
		Men		
50–59	25	−0.496*	−0.543*	−0.582*
60–69	32	−0.606†	−0.664†	−0.709*
70–79	22	−0.495	−0.495*	−0.547
All ages	79	−0.506‡	−0.557‡	−0.610‡
		Women		
50–59	27	−0.680†	−0.640†	−1.028‡
60–69	19	−1.318‡	−1.019†	−0.667
70–79	17	−0.087	−0.132	−0.337
All ages	63	−0.682‡	−0.582‡	−0.650‡

NOTE: Coefficients are estimated by the method of Walker-Duncan and standardized. Lipids include LDL cholesterol and triglyceride. Other factors refer to systolic blood pressure, left ventricular hypertrophy by electrocardiogram, relative weight and diabetes.
*p < 0.05.
†p < 0.01.
‡p < 0.001.

regression coefficients, the relationship appears to hold for each major category of coronary heart disease and, so far as can be judged from the available data, the relationship is about as strong for each. What differences appear in the coefficients are indistinguishable from random variation.

Correlated Variables. Relationships as strong as those seen in Tables I and II are unlikely to be entirely secondary to other correlated variables such as sex, other lipids and some established risk factors. It is, nonetheless, important to consider such variables since they may account for at least part of the relationship of HDL cholesterol levels to the incidence of coronary heart disease.

The HDL cholesterol level is substantially higher in women than in men (Table III). There is hardly any age trend discernible for men, but for women there is a slight decrease in the level from age 50 to age 80.

TABLE VI Univariate and Multivariate Logistic Regression Coefficients for Coronary Heart Disease on LDL Cholesterol—Framingham Study, Exam 11

Age (yr)	Cases (no.)	Univariate	Multivariate: Lipids Only	Multivariate: Lipids and Other Factors
		Men		
50–59	25	0.212	0.222	0.288
60–69	32	0.234	0.241	0.321*
70–79	22	0.378*	0.356	0.471*
All ages	79	0.241*	0.242*	0.333†
		Women		
50–59	27	0.211	0.134	0.288
60–69	19	0.743‡	0.518*	0.666†
70–79	17	−0.232	−0.233	−0.159
All ages	63	0.266*	0.188	0.260*

NOTE: Coefficients are estimated by the method of Walker-Duncan and standardized. Lipids include HDL cholesterol and triglyceride. Other factors refer to systolic blood pressure, left ventricular hypertrophy by electrocardiogram, relative weight and diabletes.
*p <0.05.
†p <0.01.
‡p <0.001.

TABLE VII Univariate and Multivariate Logistic Regression Coefficients for Coronary Heart Disease on Triglycerides—Framingham Study, Exam 11

Age (yr)	Cases (no.)	Univariate	Multivariate: Lipids Only	Multivariate: Lipids and Other Factors
		Men		
50–59	25	0.059	−0.067	−0.076
60–69	32	0.118	−0.033	−0.136
70–79	22	0.175	−0.010	0.046
All ages	79	0.075	−0.065	−0.092
		Women		
50–59	27	0.255*	0.036	−0.485*
60–69	19	0.600†	0.307	0.285
70–79	17	−0.025	−0.073	−0.293
All ages	63	0.312†	0.118	−0.106

NOTE: Coefficients are estimated by the method of Walker-Duncan and standardized. Lipids include HDL and LDL cholesterol. Other factors refer to systolic blood pressure, left ventricular hypertrophy by electrocardiogram, relative weight and diabetes.
*p <0.05
†p <0.001.

TABLE VIII Likelihood Ratios for Various Lipid Profiles of Coronary Heart Disease—Framingham Study, Exam 11

Lipid	Men	Women
HDL cholesterol	14.03*	21.21*
LDL cholesterol	4.39†	4.53†
Triglyceride	0.51	9.52‡
Total cholesterol	1.98	2.26
HDL cholesterol:total cholesterol	17.11*	20.41*
LDL and total cholesterol, triglyceride	8.26†	19.69*
HDL and total cholesterol, triglyceride	19.19*	24.21*
HDL and LDL cholesterol, triglyceride	18.90*	24.73*
HDL and LDL cholesterol	18.66*	23.70*
HDL cholesterol:total cholesterol, LDL cholesterol	17.16*	20.77*

*p <0.001.
†p <0.05
‡p <0.01.

The correlation of HDL cholesterol with either total cholesterol or LDL cholesterol is rather weak (Table IV). On the other hand, there is a sizeable negative correlation with triglyceride, indicating that special attention must be paid to segregating the respective roles of these two lipids.

Of the other risk factors for coronary heart disease considered, several have moderately strong associations with HDL cholesterol (Table IV). There is a strong inverse correlation with relative weight. There are somewhat weaker negative associations with various measures of glucose intolerance, and with systolic blood pressure, but no significant relation with cigarette smoking or left ventricular hypertrophy by electrocardiogram.

In brief, a person who is obese, has glucose intolerance or a high triglyceride level is more likely to have a low HDL cholesterol level than a high one.

Multivariate Analysis. Age-sex specific univariate logistic regression coefficients for the incidence of coronary heart disease by HDL cholesterol level are all negative and (except for women aged 70 to 79) substantial (Table V). For age groups under 70, they are all statistically significant.

When the previously mentioned covariates are included in multivariate analysis, the relation of HDL cholesterol to the incidence of coronary heart disease evident in univariate analysis is in general either unaltered or actually appears stronger (Table V). This is true whether only other lipids (LDL cholesterol and triglyceride) are considered or whether, in addition to these, the other specified risk factors are included. In fact, when these other factors are taken into account a distinct negative logistic regression coefficient is evident even for women over age 70, noticeably greater than the univariate coefficient, although it does not reach statistical significance.

A comparable analysis for LDL cholesterol indicates that it is a marginal risk factor for people of these age groups (Table VI). For triglyceride, no association is evident, even for women, after allowing for covariates (Table VII). This finding with respect to triglycerides is reinforced by cross-classifying HDL cholesterol level and triglyceride level (Figure 1), since distinct gradients

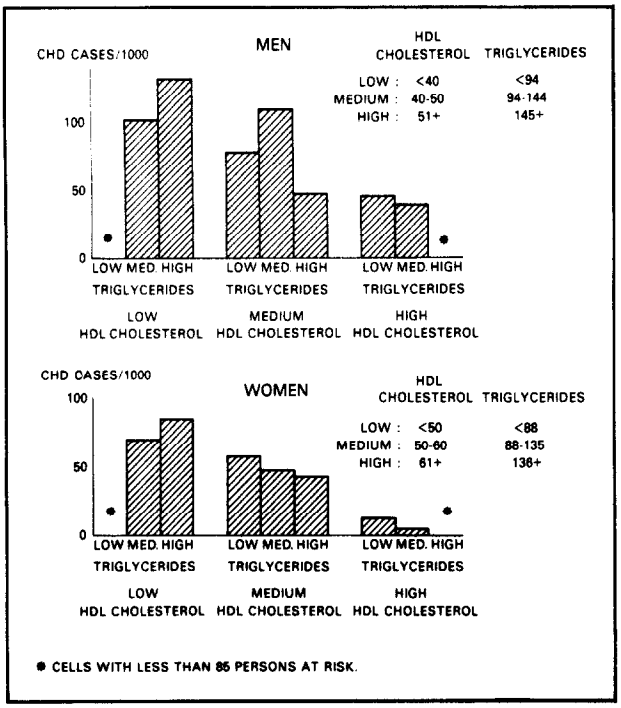

Figure 1. *Incidence of coronary heart disease by level of HDL cholesterol and triglycerides, Framingham Study.*

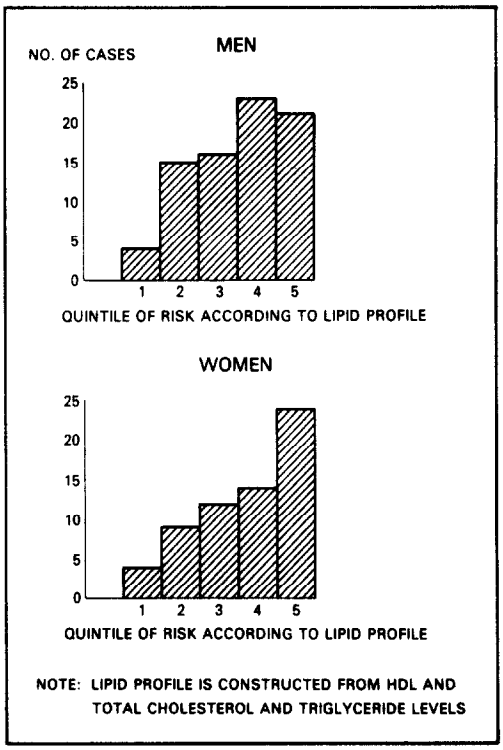

Figure 2. *Number of cases of coronary heart disease by lipid profile, Framingham Study.*

of risk are evident by HDL cholesterol level but not by triglyceride level. (The levels chosen for cutting points divide the groups roughly in thirds.)

Lipid Profiles. If only the blood lipids are used to identify persons at high risk of coronary heart disease, then HDL and LDL cholesterol are statistically significant variables for both men and women (Tables V and VI). For women, triglyceride is also a statistically significant risk factor for coronary heart disease by itself (univariate), even though it is not when other variables, including diabetes, are taken into account (Table VII).

In Table VIII a number of lipid profiles for coronary heart disease are compared in terms of their likelihood ratios. One of the two best profiles is derived from total cholesterol, HDL cholesterol and fasting triglyceride. The incidence of coronary heart disease by quintile of risk according to this lipid profile is shown in Figure 2.

COMMENTS

These data provide evidence of a strong negative association of HDL cholesterol level with the subsequent incidence of coronary heart disease in both men and women over age 50. Among the various lipid risk factors considered, HDL cholesterol appears to have the strongest relationship to coronary heart disease.

The impact of HDL on the subsequent risk of coronary heart disease in this age group cannot, in our opinion, be explained by its negative correlation with triglyceride as Carlson et al. [13] have suggested. Indeed, in men, triglyceride shows no impact on risk even when considered by itself, and the relation of triglyceride to the risk of coronary heart disease in women is no longer evident when relative weight or glucose intolerance is taken into account.

In our data there is no relationship of HDL to cigarette smoking although Goldbourt and Medalie [14] have found HDL cholesterol values to be less with greater cigarette usage in the Israeli Ischemic Heart Disease Study. We did not have data with which to examine the reported link between increased physical activity and high levels of HDL [15,16]. The strong negative correlation with obesity and diabetes reported in other studies [17,18] is confirmed in our data.

Unlike the prevalence data of the Cooperative Lipoprotein Phenotyping Study of the National Heart and Lung Institute [19], in which no lessening of risk was found once levels of 45 mg/100 ml HDL cholesterol were reached, these incidence data show that the risk of coronary heart disease continues to decrease as HDL rises to higher levels. Perhaps a super-resistant group of people can be imagined as suggested by Glueck et al. [20].

Recognition of the impact of HDL on coronary heart disease is not new. Indeed, as far back as 1951 Barr et al. [21] studied protein-lipid relationships in atherosclerosis as evidenced by clinical evidence of coronary

heart disease and concluded "the outstanding fact in our observations is the relative and absolute reduction in alpha lipoprotein in atherosclerosis" [21]. Confirmatory evidence was forthcoming from Finland also at this time in a report by E. Nikkila [22]. Expanding on these findings two years later, Barr drew the analogy that the high proportion of serum cholesterol carried in the high density lipoproteins of human babies was similar to that found in animals who appear to have a high resistance to this disease. It is only in later life as alpha lipoproteins decrease that human beings become susceptible [23].

In a series of case-control studies in the late fifties and early sixties, HDL levels were found to be lower in patients with coronary heart disease than in control subjects [21–29]. On a prospective basis, Gofman et al. [1] reported lower HDL levels in young men aged 20 and above in whom coronary heart disease subsequently developed in the Livermore, California Study in 1966. Medalie et al. [14] have reported lower alpha cholesterol levels in men aged 40 and above in whom coronary heart disease subsequently developed in the Israeli Ischemic Heart Study. These studies make it clear that, at least for men, HDL is a significant risk factor for coronary heart disease even at very young ages. Although LDL is a stronger risk factor for coronary heart disease in men at younger ages than at older ages [1], the evidence respecting triglyceride as a risk factor seems somewhat ambivalent.

Recently the Cooperative Lipoprotein Phenotyping Study reported a case-control study with nearly 900 cases of coronary heart disease and a much larger series of controls, involving men and women, whites, blacks and Japanese, and covering the age range 40 to over 80 years. They presented a remarkably consistent finding of a lower HDL level in persons with coronary heart disease than in those without [19].

Miller and Miller [30] have presented evidence that HDL is inversely related to total body cholesterol. They postulate that the mechanism of action may involve transport of cholesterol back to the liver, the only organ which can catabolize and excrete quantitatively important amounts of cholesterol [31]. In this regard they refer to the work of Glomset [32] who has published data showing that HDL alters the balance of unesterified cholesterol between plasma and cells by increasing its utilization in the lecithin/cholesterol acyltransferase (LCAT) system to form cholesterol-ester which would move less slowly back into cells. Bailey [33] observed that alpha globulins facilitated cholesterol excretion from cells; this was also postulated by Burns and Rothblat [34] using delipidized serum proteins. Using human arterial tissue Bondjers and Bjorkerud [35] showed a potent effect of HDL on elimination of cholesterol from tissue sites into the surrounding medium in which they were bathed. In the human disease in which HDL is nearly absent, Tangier disease, large cholesterol deposits can be found in many tissues throughout the body including arterial tissue [36]. On the other hand, HDL may interfere with cellular uptake of cholesterol as suggested by Kaschinsky, Carew and Steinberg [37].

It must be emphasized that the Framingham data do not speak directly to the no doubt complex involvement of HDL cholesterol in lipid metabolism. On the other hand the data do reiterate the well-demonstrated fact that persons with low HDL levels are at greater than average risk of coronary heart disease. Thus, HDL cholesterol is a reasonable addition to the roster of characteristics that are useful in assessing the chances that coronary heart disease may develop.

It is curious, in retrospect, that the determination of HDL cholesterol concentration has not long since become part of a standard coronary heart disease risk profile. Its negative association with coronary heart disease combined with its very weak correlation with LDL (beta) cholesterol make it clear that a partition of total cholesterol into HDL, LDL and VLDL portions was bound to improve our ability to predict coronary heart disease. This improvement is particularly striking in those in the older age group under consideration. At these ages, total cholesterol per se is not a risk factor for coronary heart disease at all [1], whereas a lipid constellation which includes HDL and LDL cholesterol and triglyceride is a fairly good predictor of the risk of coronary heart disease. From a practical point of view total cholesterol can substitute for LDL cholesterol in this profile with little decrement in the predictability of coronary heart disease, since either lipid in linear combination with HDL cholesterol and triglyceride leads to equivalent statistical functions.

Gofman [1], who was an early advocate of the value of partitioning total cholesterol and who recognized the excess risk of coronary heart disease associated with low HDL levels, never integrated HDL into his atherogenic index. The atherogenic index, as such, was in effect a weighted sum of LDL and VLDL. Because these lipoproteins are highly correlated with total cholesterol, the advantage of the atherogenic index over total cholesterol for assessing the risk of coronary heart disease always remained moot. Had HDL been joined with LDL and VLDL, it would have been immediately obvious that the resulting lipoprotein profile is a better predictor of coronary heart disease than total cholesterol.

In our judgement the literature on these questions has been vexed by a considerable statistical confusion. Absolute values, percentages, ratios and linear sums have marched through the literature and contended with each other. A good deal of this statistical manipulation appears to have been vaguely motivated by an interest in expressing the presumptive process of lipid metabolism in mathematical terms. Since we do not fully

understand that process such an effort is probably premature. Based on our reading of the data presented here, a linear sum of the lipids under consideration, whatever physiologic meaning it may or may not have, is probably the most effective method for the limited practical purpose of constructing a risk profile for coronary heart disease. The common procedure of calculating ratios of HDL to total or LDL cholesterol should probably be avoided since a person may have the same ratio at a low level of HDL and LDL cholesterol or at high levels, and it is difficult to believe that these have the same medical and physiologic significance. Beyond that it appears to be less satisfactory as a risk criterion than a linear combination (Table VIII).

If HDL cholesterol is to become part of a standard risk profile for coronary heart disease, great care must be taken with laboratory precision. A good laboratory can achieve a technical error of 5 mg/dl in measuring this lipid. When it is remembered that an average HDL cholesterol level for men is around 45 mg/dl whereas a significantly high risk of coronary heart disease is evident at 35 mg/dl, it is clear that a technical error of 5 mg/dl is by no means a confortable one. More precise methods would be helpful.

At the same time it remains to be determined whether the HDL cholesterol level is not only a guide to risk but also a guide to therapy. What level of physical activity leads to a rise of the HDL cholesterol level, and does the rise in the HDL cholesterol lead to a diminution in the risk of coronary heart disease? Does weight loss lead to a rise in HDL cholesterol level, and does this have some prophylactic value?

Whatever the answers to such questions it now appears clear that at all ages the HDL cholesterol level is an important index to the risk of coronary heart disease; it should be added to the usual risk profile of coronary heart disease.

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