Serum Cholesterol, Lipoproteins, and the Risk of Coronary Heart Disease

The Framingham Study

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Risk of coronary heart disease over 14 years was examined prospectively in 2,282 men and 2,845 women according to their antecedent cholesterol and lipoprotein status. An increased risk proportional to antecedent serum cholesterol was found whether or not it was associated with elevated S,20-400 prebeta lipoprotein. When adjustment was made for the concomitant prebeta lipoprotein concentration and other factors related both to coronary heart disease risk and to blood lipids, a residual gradient of coronary heart disease risk proportional to the serum cholesterol was still evident. On the other hand, when risk of coronary heart disease was examined according to prebeta lipoprotein concentration, adjusting for cholesterol, no residual risk gradient remained in men. In women over 50, however, prebeta lipoprotein was superior to cholesterol in discriminating potential coronary heart disease cases. Risk of coronary heart disease in men can be estimated using any of the lipids evaluated; however, none proved more useful than an accurate total serum cholesterol.

Virtually every lipid and lipid-bearing substance encountered in the blood has been incriminated in atherogenesis, but none has been more substantially implicated than cholesterol. As a result of a considerable research into the details of lipid metabolism in relation to atherosclerosis, the pathogenetic mechanisms involved are being clarified. A series of presumably genetic lipoprotein disorders that are associated with precocious atherosclerosis have lately been identified (1). There is evidence that the common type of modest “hypercholesterolemia” encountered in the general population may not be a homogeneous entity (1-5).
Neither cholesterol nor any other lipid occurs in the blood in a free state but is linked with protein for transport. Each major lipoprotein fraction carries cholesterol. This report examines prospectively the risk of coronary heart disease in a general population over 14 years, according to antecedent serum cholesterol and lipoprotein status.

Methods

At the time of the initial examination in Framingham 2,282 men and 2,845 women aged 30 to 62, examined and found free of coronary heart disease, were classified into subgroups according to the level of a variety of serum lipids at the time of the first 2 biennial examinations. The rate of development of initial clinical manifestation of coronary heart disease over 14 years of follow-up in the population so classified was determined. This allowed an estimate of the risk in relation to antecedent serum lipid content.

The Framingham Study has been in continuous operation since 1949, following a reasonably representative sample of the adult population of the town for the development of coronary heart disease. The derivation and composition of the population sample under study has been described in detail previously (6-9). After exclusion of those persons with any evidence of coronary heart disease on the initial examination, a study was undertaken to identify factors related to the onset of first events of clinical coronary heart disease. At the time of the initial examinations a variety of lipid determinations were made in the Framingham Study laboratory, including serum cholesterol (by the method of Kendall-Abell) and phospholipids (by the method of Youngberg), and the various lipoprotein fractions were determined by ultracentrifugal analysis at the Donner Laboratory, courtesy of Dr. John Gofman (2, 6, 10). Cholesterol values were determined at each biennial examination. Beta (Sf0-20) and prebeta (Sf20-400) lipoprotein fractions were determined only on the first two biennial examinations owing to the technical complexity of the analyses. All specimens were casual and obtained on subjects initially free of coronary heart disease. The cholesterol and S,0-20 beta lipoprotein concentrations are not materially affected by recent meals. The average S,20-400 prebeta lipoprotein level is higher postprandially than fasting, and this should be taken into account when considering casual S,20-400 values. For men in this population, however, it has been determined that the casual S,20-400 lipoproteins and a fasting triglyceride done 18 to 20 years later were positively correlated. Men and women generally came in for examination as spouse pairs at the same time of day, so there is little likelihood of systematic sampling differences to explain differences between men and women with respect to S,20-400 lipoprotein determinations.

A casual blood sugar was determined by the method of Somogyi-Nelson. Blood pressure determination, vital capacity, weight relative to the median for specified heights, uric acid, and history of cigarette smoking were also obtained.

Results

In the 14 years of follow-up 323 men and 169 women between the ages of 30 and 62 years at initial examination developed for the first time some clinical manifestation of coronary heart disease. The incidence increased with age in both sexes with a striking male predominance in younger victims but a closing gap in incidence with advancing age. The mean level of angina pectoris was higher at the initial examination in those who went on to develop coronary heart disease than in their cohorts, who remained free of clinical manifestations of the disease over the 14-year period of ob-
observation. The levels of cholesterol observed in this population were generally high compared with those reported from other areas in the world, where low coronary heart disease rates have been reported (11, 12). The distributions of all the lipids examined, comparing subjects who did and did not develop the disease, overlapped to such an extent that no concentration of any lipid was characteristic of either group (6).

Reexamination of the relation of the level of each of the major blood lipids and lipoproteins under consideration after 14 years of biennial follow-up continues to show a distinct and striking increment in risk proportional to the antecedent lipid concentration. The relationship was generally stronger in younger than in older persons. It might be expected that the biochemical substance closest to the responsible metabolic defect would show a more striking association with the disease than that secondarily, or less fundamentally, related. Although differences in measurement precision may obscure the comparisons, risk of subsequent coronary heart disease over 14 years was thus studied in the 5,127 men and women participating in the Framingham Study in relation to their antecedent lipoprotein and lipid status, as determined at the time of their first 2 biennial examinations.

Graphing the incidence of coronary heart disease developing in portions of the population grouped by quartiles of the population grouped by quartiles of the distribution of cholesterol and the lipoprotein fractions measured provides a valid visual comparison of the differences in risk between the first and fourth quartile of the antecedent level of each lipid. Risk was proportional to the concentration of each lipid (Figure 1). The gradients of risk so demonstrated were not identical, but the differences observed were not great enough to suggest one particular lipid as most basic to the development of this atherothrombotic disease.

Designating values in the fourth quartile of each lipid and lipoprotein under consideration as "abnormal," each lipid appears to be contributing to risk of coronary heart disease, with the incidence proportional to the number of lipid "abnormalities" so defined (Figure 2). Whether this is a fact or a statistical artifact cannot, however, be discerned from these data. Since these lipids are positively correlated, the mean level of each particular lipid also rises with the number of lipid abnormalities present (Table 1).

Hence, a more detailed examination of the relation of serum cholesterol to risk of coronary heart disease, using a more sophisticated type of analysis, is required. First, the relationships of serum lipids to coronary heart disease do not vary with the type of coronary heart disease so far as can be judged from the available data. The net contribution of cholesterol and $S_{20-400}$ prebeta lipoprotein is about the same for uncomplicated angina as it is for other coronary heart disease. Cholesterol, as indicated by the size of the coefficient in Table 2, carries most of the weight as a contributor to coronary heart disease in men, whether manifested as angina or some more serious form of the disease. For women, numbers allow an examination of the net effect of the lipids only for angina.

Risk of each particular clinical manifestation of coronary heart disease (including angina, myocardial infarction, and sudden death) proved proportional to the antecedent serum cholesterol level in men of all ages studied. The net effect appears to decline with age in both sexes, and in women beyond 50 little relationship can be shown. In men and younger women

![Figure 1. Risk of myocardial infarction (14 years) according to serum lipid content: men, age 30 to 62 at entry. Framingham Heart Study.](image-url)
the risk simply rose in proportion to the antecedent serum cholesterol concentration from the lowest to highest values recorded in this population sample (Figure 3). There was nothing to suggest that some particular level was "critical." Hence, it does not appear logical to examine the relation of cholesterol to risk of coronary heart disease in terms of "hypercholesterolemia" but rather in terms of the actual concentration of cholesterol in the plasma.

Examination of the risk of developing coronary heart disease according to the actual serum cholesterol concentration of each subject grouped into quartiles showed an increase in risk proportional to the antecedent cholesterol concentration, not only in the general population but in persons free of factors believed associated both with hypercholesterolemia and with coronary heart disease (Figure 4). Even after excluding persons with hypertension, diabetes, ECG abnormalities, and the cigarette habit, a distinct gradient of risk proportional to the cholesterol concentration can be demonstrated. This tends to brand the lipid, not associated variables, as the culprit. This is also shown in discriminant analysis accounting for the presence and the values of some of these associated variables in the entire population. As shown in an earlier analysis, a net effect of cholesterol is clearly apparent in men of all ages (13).

A discriminant analysis was also made of the relation of various lipids measured in the study to incidence of coronary heart disease after 8 years. The net effect of each of the lipids, including cholesterol, phospholipid, and the lipoprotein fractions (S<sub>0-12</sub>, 12-20, 20-100, and 100-400), was assessed. According to this analysis the dominant effect was assigned to serum cholesterol, with an insignificant contribution of the other lipids (6). In multivariate discrimi-
Table 2. Risk of Specified Manifestations of Coronary Heart Disease According to Serum Cholesterol and S,20-400 Prebeta Lipoprotein: Men 30 to 62 Years Old at Entry

<table>
<thead>
<tr>
<th>Lipid Variable</th>
<th>Coronary Heart Disease Other Than Angina Pectoris</th>
<th>Uncomplicated Angina Pectoris</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Coefficient</td>
</tr>
<tr>
<td>Age 30 to 39</td>
<td>42</td>
<td>0.01377</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td>0.00086</td>
</tr>
<tr>
<td>S,20-400 lipoprotein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 40 to 49</td>
<td>83</td>
<td>0.00920*</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td>0.00029</td>
</tr>
<tr>
<td>S,20-400 lipoprotein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 50+</td>
<td>108</td>
<td>0.00864*</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td>0.00026*</td>
</tr>
<tr>
<td>S,20-400 lipoprotein</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant at 5% level.

A nation involving a number of highly correlated variables, however, a slight statistical advantage in one of these variables will lead to a marked depression of the discriminant weights assigned to the other variables. It would be incorrect to dismiss this effect as a mere statistical artifact; rather it indicates that the analytical question cannot be satisfactorily explored with the data in hand and that either the question should be reformulated or other kinds of data should be collected.

Since it was not feasible to retrospectively collect other data, a reduced question was put to the data—namely, does the S,20-400 lipoprotein fraction tell us something about the risk of coronary heart disease over and above what is already shown by the serum cholesterol level? These two determinations are not highly correlated since the bulk of serum cholesterol is ordinarily carried in other lipoprotein fractions, whereas the S,20-400 fraction carries a sizable amount of triglyceride as well as cholesterol.

For the purposes of this analysis persons free of disease at examinations 2, 4, or 6 were assigned to coronary heart disease or noncoronary heart disease categories as they did or did not develop disease in the ensuing 4 years. Although a person may appear in a specified age group only once, he may appear as a noncase in three different age groups, provided he came in for the second, fourth, or sixth biennial examination and was free of disease at the beginning of these three examination periods. Although levels of characterization according to serum lipids and other related variables differed somewhat from one examination to another, both subsequent cases and noncases were measured in the same way and are therefore always directly comparable. For the computation of mean differences all cases and all noncases were pooled without any weighting, it being assumed that age-specific incidence after each of the examinations was the same. Variances and covariances, however, were computed separately for each of the cohorts; and then the within-cohort variances and covariances were combined, thus achieving a slight gain in sensitivity. It is apparent that in men cholesterol accounts for more of the total distance between those who developed and those who remained free of the disease than does S,20-400 prebeta lipoprotein in all but the oldest subjects. The use of both was little better than cholesterol alone in discriminating potential coronary heart disease cases (Table 3). The standardized mean deviations were in general substantially larger for cholesterol than S,20-400 prebeta lipoprotein, and all were positive in the men.

Among younger women the same appeared to hold. In older women, however, S,20-400 prebeta lipoprotein appears to discriminate distinctly better than cholesterol. Beyond age 55 the standardized mean deviations were larger, and the S,20-400 prebeta lipoprotein also accounted for most of the generalized distance between those with and those free of coronary heart disease (Table 3). Again, both do little better than the appropriate lipid alone in discriminating future coronary heart disease.

The meaning of this analysis may be a little clearer.
from an examination of Figures 5 and 6. These show the relative risk of coronary heart disease according to the concentration of each of these lipid values after adjustment for the level of the other lipid and the values of the other associated variables. An expected number of coronary heart disease events was obtained from a computed "risk function" derived from the values of each of the other variables for each subgroup of the lipid under consideration. This was compared with the number of cases actually observed in each lipid subgroup. The ratio of the observed to the expected number of cases times 100 (morbidity ratio) gives an expression of the relative

risk with the standard risk set at 100. For cholesterol in men a strong residual effect remains after accounting for the level of $S_{20-400}$ lipoprotein and the other factors (Figure 5). This independent effect, however, is much more modest than noted without such adjustment. In younger, but not older, women distinctly higher cholesterol values may also contribute independently to risk (Figure 6).

On the other hand, when risk of coronary heart disease is examined according to $S_{20-400}$ prebeta lipoprotein level, adjusting for cholesterol and the other factors, it is difficult to discern any residual risk gradient in men (Figure 5). In older women there

Table 3. Discriminant Analysis Relation of Serum Cholesterol and $S_{20-400}$ Lipoprotein to Subsequent Coronary Heart Disease: Men and Women 38 to 69 Years Old

<table>
<thead>
<tr>
<th>Age</th>
<th>Standardized Mean Deviation</th>
<th>Generalized Distance</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholesterol</td>
<td>$S_{20-400}$</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38-41</td>
<td>1.17</td>
<td>0.74</td>
<td>16.26*</td>
</tr>
<tr>
<td>42-45</td>
<td>0.54</td>
<td>0.20</td>
<td>7.59*</td>
</tr>
<tr>
<td>46-49</td>
<td>0.87</td>
<td>0.72</td>
<td>18.26*</td>
</tr>
<tr>
<td>50-53</td>
<td>0.65</td>
<td>0.21</td>
<td>17.68*</td>
</tr>
<tr>
<td>54-57</td>
<td>0.25</td>
<td>0.05</td>
<td>3.28</td>
</tr>
<tr>
<td>58-61</td>
<td>0.27</td>
<td>0.32</td>
<td>3.29</td>
</tr>
<tr>
<td>62-65</td>
<td>0.22</td>
<td>0.08</td>
<td>1.19</td>
</tr>
<tr>
<td>66-69</td>
<td>0.06</td>
<td>0.33</td>
<td>0.04</td>
</tr>
<tr>
<td>Average</td>
<td>0.45</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38-41</td>
<td>0.73</td>
<td>-0.30</td>
<td>4.21†</td>
</tr>
<tr>
<td>42-45</td>
<td>1.10</td>
<td>0.06</td>
<td>8.49*</td>
</tr>
<tr>
<td>46-49</td>
<td>0.84</td>
<td>0.10</td>
<td>7.65*</td>
</tr>
<tr>
<td>50-53</td>
<td>0.06</td>
<td>0.23</td>
<td>0.07</td>
</tr>
<tr>
<td>54-57</td>
<td>0.17</td>
<td>0.29</td>
<td>1.03</td>
</tr>
<tr>
<td>58-61</td>
<td>-0.04</td>
<td>0.43</td>
<td>0.03</td>
</tr>
<tr>
<td>62-65</td>
<td>-0.53</td>
<td>0.77</td>
<td>5.60†</td>
</tr>
<tr>
<td>Average</td>
<td>0.32</td>
<td>0.32</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant at 1% level (14-year follow-up).
† Statistically significant at 5% level (14-year follow-up).
may be an independent residual effect of Sf20-400 prebeta lipoprotein, although an inverse relationship, if anything, appeared to exist in younger women (Figure 6). If one puts a further question to the data and asks if by adjusting the Sf20-400 by Sf0-20 lipoproteins the risk gradient is also made to disappear, the answer is yes, suggesting that in the general population the people with high Sf20-400 often tend to have high Sf0-20 or cholesterol levels that may well explain their subsequent higher risk of coronary heart disease.

Traditionally, it has been held that a high concentration of cholesterol is more serious when not accompanied by a commensurate elevation of phospholipid. The cholesterol to phospholipid ratio has long been advocated as an index of atherogenesis. Prospective examination of this hypothesis among persons with modest “hypercholesterolemia” as it occurs in the general population showed no clear trend of increased risk proportional to the cholesterol to phospholipid ratio (Figure 7).

As regards risk of coronary heart disease in relation to serum cholesterol concentration, the concomitant blood pressure had a more pronounced effect than either the lipoprotein pattern or the phospholipid content of the serum. Elevated serum lipid content, whether it be the cholesterol or the Sf20-400 pre-beta lipoprotein value, is considerably more
ominous in hypertensive than in normotensive individuals. The risk at any lipid level varies over a wide range, depending on the associated blood pressure. The converse was also true, and at any level of blood pressure risk was markedly influenced by the associated lipid value (Figure 8).

Discussion

Multiple interrelated factors, both host and environmental, have been shown to play a role in the evolution of this disease in various general population samples (14-19). Of all the identified host factors associated with increased susceptibility to coronary heart disease, the blood lipids are among the strongest. The accumulated evidence from epidemiologic studies, clinical observations, laboratory research, and animal experiments permits the logical conclusion that lipids must play at least a contributory role in atherogenesis. If there is in fact a single common denominator through which the multiple interrelated predisposing factors in coronary heart disease operate, an abnormal accumulation or handling of blood lipids would appear the most likely candidate.

Since the discovery over a century ago that cholesterol was a prominent constituent of the atherosclerotic plaque (20) and that this same substance was also present in the blood, a huge volume of research has been directed toward obtaining a better understanding of the precise nature of the relationship of cholesterol to atherogenesis. Subsequent research has shown that cholesterol from the blood does actually enter into intimal atheromas (21-24) and that inducing a high blood cholesterol content in a variety of ways has resulted in an accelerated development of

Figure 7. Risk of coronary heart disease (14 years) in hypercholesterolemic subjects according to cholesterol to phospholipid ratio: men, age 30 to 62 at entry. Framingham Study.

Figure 8. Risk of coronary heart disease (14 years) according to serum lipid and blood pressure status: men, age 30 to 49 at entry. Framingham Study.
atherosclerotic lesions in a number of animal species (25-28). Reduction of the concentration of cholesterol in the blood in some animal experiments appears to reverse the process (29, 30). In addition, populations with a high average level of serum cholesterol tend to have a high reported mortality from coronary heart disease. Conversely, lower death rates and less extensive atherosclerosis at postmortem have been reported from areas where substantially lower indigenous cholesterol levels are found (12). That this is not simply a racial difference has been demonstrated in migrants of the same race from a low to a high cholesterol area who appear to correspondingly change their cholesterol levels and propensity to coronary heart disease mortality (11).

More direct epidemiologic evidence has been provided by prospective studies that have repeatedly demonstrated, in a variety of population samples, that risk of subsequent disease is directly related to the antecedent serum cholesterol values of individuals within the population (31, 14-18).

Depending on the age group studied, clinicians have often (32-34), but not always (35-37), found a higher concentration of cholesterol in the blood of coronary patients than in suitable controls. Based on a comparison of serum lipids in persons already afflicted with coronary heart disease with some group labeled a “control,” it has been claimed that one or another lipid or lipoprotein vehicle is more specific for the disease than is cholesterol. These investigators have found significant differences in the blood content of a variety of lipids and have implicated the total fasting triglyceride, beta and prebeta lipoprotein, alpha to beta cholesterol ratio, cholesterol to phospholipid ratio, and fatty acids (1, 2, 32, 37-42). These findings have generated a vast amount of research into the details of lipid metabolism in general and its relation to atherosclerosis in particular. It has been pointed out that lipids other than cholesterol are also present in the atherosclerotic plaque (43, 44) and that none of the major blood lipids, including cholesterol, phospholipid, triglyceride, or nonesterified fatty acid, circulate in the blood in a simple state. They are transported as part of various lipoprotein complexes or in association with albumin. It has been suggested that faulty lipid transport may be more fundamental in atherogenesis and that the lipoproteins more accurately mirror the underlying metabolic defect.

Each major lipoprotein fraction carries cholesterol. The S0-20 beta lipoprotein fraction is the principal carrier in most normal persons. The S20-400 “pre-beta” lipoprotein fraction also carries a modest amount of cholesterol. On occasion a high serum cholesterol content may result primarily from a pronounced increase in this lipoprotein fraction. The common variety of “hypercholesterolemia” seen in the general population is, however, often associated with a modest elevation of both beta and prebeta lipoprotein fractions. “Elevation” of the prebeta lipoprotein without a concomitant “elevation” (in the fourth quartile of each) of beta lipoprotein is relatively uncommon, occurring in less than 10% of the “hypercholesterolemia” in the Framingham population.

A general population such as encountered in the Framingham Study includes few persons with serum cholesterol levels greater than 400 mg/100 ml and few xanthomatous individuals. There were 6 xanthomatous individuals in the Framingham population sample of 5,127 men and women. All had serum cholesterol values exceeding 400 mg/100 ml and a strong family history of coronary heart disease, and within the follow-up period all six died of coronary heart disease before their fiftieth birthdays.

The distribution of serum cholesterol values that has been reported in such persons clearly belongs to a different universe than that which has been observed in general population samples such as Framingham (Figure 9). Moderate serum cholesterol elevations between 250 and 350 mg/100 ml constitute the bulk of “hypercholesterolemias” that appear to be predisposing to the abundance of coronary heart disease as it occurs in the general population. Such levels constitute the upper quartile of the distribution of cholesterol in this general population sample. Moderate elevations in this range, depending on age and sex, are associated with a risk of coronary heart disease two to five times higher than is noted with values below the average of about 220 mg/100 ml (Table 4). This modest level of “hypercholesterolemia” therefore represents both a potent and a common factor contributing to risk of coronary heart disease.
Current investigations raise the possibility that it may be useful to determine the lipoprotein pattern in order to select more specific corrective therapy in those with marked hypercholesterolemia (1, 45). This information may also be useful in treating the common moderate degrees of hypercholesterolemia encountered in the general population. On the other hand, the observation of the lack of a relation of the cholesterol to phospholipid ratio to risk of coronary heart disease among "hypercholesterolemic" persons suggests that the phospholipids as a group play little role in atherogenesis, either protective or otherwise. This does not preclude a powerful effect of some particular component of the phospholipid group such as the cephalins (40).

One can properly view triglyceride and S,20-400 prebeta lipid determinations obtained in the nonfasted state with skepticism, although this skepticism may be exaggerated in view of the correlation in population samples between fasting and nonfasting specimens. Unfortunately, it is seldom feasible to obtain fasting specimens in large voluntary general population studies where subjects have to be seen in the evening in order to obtain cooperation. The data presented in this study do not necessarily reflect on the issue of a possible association of fasting endogenous triglyceride or fasting prebeta lipoprotein on incidence of coronary heart disease. In medicine these days, however, dynamic tests of function are replacing static ones that are often much less sensitive. Metabolic tests may be normal in the fasted state but distinctly abnormal after a load. Such tests in the fasted state do not necessarily reflect the usual metabolic state of persons in the course of daily living. Despite or because of the fact that these specimens were casual, risk of coronary heart disease was strikingly related to antecedent S,20-400 prebeta values.

It remains to be clarified whether the moderate hypercholesterolemia so prevalent in the general population and so potent a contributor to coronary heart disease morbidity and mortality is principally a hereditary state for one or more inborn errors of lipid metabolism or simply an acquired state caused by overnutrition. It is possible that both play a role. Although it seems likely that the blood lipid content, enhanced by increased blood pressure, is related in a fundamental way to the rate of general deposition of lipid in the intima, local factors appear to determine the site of deposition. These local factors include damage to the intima (46), the caliber of the vessel (47), dynamics of flow (48), factors promoting fibrin deposition (49), and possibly metabolic factors in the vessel wall (24, 44). Factors promoting thrombus formation, so important in determining whether an occlusion occurs, must also play a prominent role in determining whether these atheromatous lesions prove lethal. They may also participate in initiating the lipid-laden atheromatous lesion (49, 50). Also, transient tides in the blood lipid content may enhance blood clotting and sludging (51).

Many questions remain concerning the details of atherogenesis. Promising new analytical techniques developed by Fredrickson, Levy, and Lees (1) are under active investigation. Such investigations may throw a new light on the entire subject. These uncertainties should not be allowed to obscure the firmly established striking association between high blood lipid content in general, and cholesterol in particular, and coronary atherosclerotic disease. Evidence is beginning to accumulate to suggest that effective lowering of the serum cholesterol level may be followed by a corresponding reduction in coronary morbidity and mortality (52-57).

Prospective data concerning the risk of coronary heart disease in relation to antecedent lipoprotein status are quite scarce. Those relating to lipoprotein types (as proposed by Fredrickson and colleagues) are nonexistent since this concept has been too recently introduced. Prospective data relating lipoprotein status to coronary heart disease in women are nonexistent. The data herein reported provide some indication of the contribution of lipids and lipoproteins to risk of coronary heart disease within the scope of contemporary concepts.

In men, knowledge of both the serum lipoprotein levels and the cholesterol concentration appears to provide no better discrimination of potential coronary victims than can be deduced from an accurate serum cholesterol value alone. Any one of the lipids or lipoproteins examined, and, by inference, a triglyceride as well, can be used effectively for assessing vulnerability to coronary heart disease. None, however, would appear superior to the more convenient serum cholesterol determination for this purpose.

Table 4. Factor of Increased Risk of Coronary Heart Disease Over 14 Years According to Antecedent Serum Cholesterol Concentration*: Men and Women 35 to 64 Years Old

<table>
<thead>
<tr>
<th>Age</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>yr</td>
<td>Men</td>
</tr>
<tr>
<td>35 to 44</td>
<td>5.5</td>
</tr>
<tr>
<td>45 to 54</td>
<td>2.4</td>
</tr>
<tr>
<td>55 to 64</td>
<td>1.7</td>
</tr>
<tr>
<td>All ages</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Cholesterol level of 265 mg/100 ml or higher versus cholesterol level of under 220 mg/100 ml.
pose. Specific tables describing the relation of serum cholesterol to coronary heart disease incidence in absolute rather than relative terms appear in other Framingham reports (58).

In women, however, the picture appears to be somewhat different. In women under the age of 50, as in men, high cholesterol values and not S20-400 prebeta lipoprotein appear to be associated with an increased risk. In older women, on the other hand, cholesterol appears to have no predictive value, and S20-400 prebeta lipoprotein actually appears to be superior to cholesterol for estimating risk.

The data presented suggest that in men the moderately elevated cholesterol values commonly encountered in the general population, regardless of the metabolic aberration responsible or how it is transported or partitioned among the lipoproteins, are associated with increased risk of coronary heart disease. Elevated endogenous triglyceride values appear significant in coronary atherogenesis only when accompanied by high cholesterol values. Knowledge of the associated lipoprotein pattern in "hypercholesterolemic" men may be important for determining the nature of the responsible metabolic defect and for selecting the most efficacious therapy, but its contribution to assessing risk of coronary heart disease remains to be determined. In older women, on the other hand, S20-400 prebeta lipoprotein, or by inference a fasting triglyceride, may be the only lipid capable of prognosticating coronary heart disease.

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