Age, Serum Cholesterol and Coronary Artery Disease

By Menard M. Gertler, M.D., Stanley Marion Garn, M.D. and E. F. Bland, M.D.

The question of an age-associated rise in serum cholesterol has been undecided. This communication presents evidence in favor of a rise in serum cholesterol with increasing age between the third and the fifth decades. In a control group of 146 individuals and a coronary disease group of 97 individuals, there was a positive correlation between age and serum cholesterol. In the coronary disease group, there was a rise in serum cholesterol superimposed upon an initially higher level of serum cholesterol. The concept of "cholesterol age" is presented on the basis that a patient with coronary heart disease at 25 has a serum cholesterol similar to a "normal" male at the age of 45. The role of serum phospholipids is considered in the age-associated rise in serum cholesterol.

Several studies have concluded that there is probably a rise in the serum cholesterol level after puberty in the male, while other reports have claimed no such relationship. Before puberty, however, the serum cholesterol level seems to be lower than in adult life, and the evidence appears to support Sperry who asserts that the cholesterol level is lowest during the neonatal period in (full term) infants and approximates adult levels in late prepuberty or early puberty. Page and his co-workers have concluded that no comparable rise exists postpubertally, although our calculation from their data did not entirely confirm this conclusion.

Sampling errors may account for some of the discrepancies, negative results and differences in opinion; several studies were conducted on groups too small to yield statistically significant results. Also, individuals hospitalized for disorders presumed not to be related to cholesterol metabolism were included with the so-called "normals" though no evidence has yet been offered that systematic errors do not appear in such procedures. Furthermore, the influences of race, diet, occupation and socio-economic status, though discussed in theory, have in general not been considered in previous studies.

There is, at present, no unanimity on the possible relationship between serum cholesterol and age. It is not definitely known whether the cholesterol level is constant with advancing years or whether there are continuous changes with age and, if the latter is true, when the greatest changes occur. The increase in severity and frequency of arteriosclerosis with age and the possible relationships of arteriosclerosis and cholesterol make such a study of age changes of serum cholesterol worthwhile. Accordingly, this study was undertaken to determine the influence of age on serum cholesterol in both the normal individual and the patient with coronary artery disease.

Method and Materials

The blood for cholesterol determination was obtained in the manner described in a previous paper in this series. The Bloor technic was employed for these determinations. Two groups are considered in this study: a coronary disease group and a healthy control group. The healthy control group consisted of 146 men who were working in a large industrial plant in Cambridge, Massachusetts. They were considered healthy by ordinary clinical standards and in addition showed no pathologic abnormalities in the electrocardiograms. Furthermore, they were rejected if they showed frequent absenteeism from work. In contrast, 97 males who had experienced myocardial infarction prior to the age of 40 comprised the coronary series. Two blood samples from the coronary disease group are not included because the patients were over 50 years of age at the time of examination. Both groups were comparable in age, occupation and race (predominantly northwest European). Each member of the coronary disease group was referred for study by private physicians, clinics, or the Veterans' Administration. Eighty-two per cent of the coronary disease group came from New England and the Atlantic states, and were similar to the control.
group in diet and general mode of life. The detailed analysis of the national and racial origins of the two groups is considered elsewhere. 14 Sufficient it to say that the two groups were comparable with two exceptions; the normal group had 23 per cent Irish as compared to 1 per cent in the coronary group, and the latter group had 26 per cent Jews as compared to 1 per cent in the control group. The occupations likewise are examined elsewhere in detail, 15 and may be considered entirely comparable on the professional, semi-professional and craftsman levels with a negligible difference in the manual labor category.

Results

In the first paper of this series 16 it was reported that the average serum cholesterol in the coronary disease group was 286.5 mg per cent with a standard error of 7.14, and the comparable mean value of the normal group was 225.3 mg per cent with a standard error of 3.59, the critical ratio of the difference being 7.91. This means that the difference in serum cholesterol is statistically highly significant.*

No attempt was made in the first paper to associate or correlate a possible serum cholesterol change with increasing age in either group. When such a calculation in the normal group was made, the level of serum cholesterol was shown to rise with age as is evident from table 1. Thus, there is a constant progression from decade to decade, though the rise is not always statistically significant. The greatest rise is from the third to the fourth decade (ages 20-29 to 30-39). In order to express the strength of this association between age and cholesterol over the entire age range, a suitable measure is necessary.

The best single measure of concomitant variation between two variables in the coefficient of correlation, usually designated as r. Values of r vary from 0 (complete independence) to +1.0 (perfect positive correlation) and −1.0 (perfect negative correlation). The coefficient of correlation for the whole healthy control series is +0.30 with a standard error of ±0.08. While not high in terms of predictability, this r is highly significant statistically (p < 0.01) and indicates a positive association between age and serum cholesterol.

Computations on the coronary disease group likewise show a steady rise with age as shown in table 2.

The serum cholesterol in the coronary disease group is higher at any corresponding decade level than it is in the healthy control group. In addition to this initially high serum cholesterol is the normal "physiologic" rise of serum cholesterol with age, particularly between the third and fifth decades. The rise is apparent between the third and fourth decades, but does not quite reach significance (p = .06, and for significance p = .05). The correlation coefficient between cholesterol and age in the coronary group is +.16 ± .10, not significantly different from zero (p = .10). This correlation is probably not significant since it does not exceed twice its probable error. However, it cannot be said that the association between age and cholesterol in the coronary group (+.16) is significantly less than in the normal group, for the difference between the two (.14) is not a significant one. Therefore, the apparently lower r in this case may have arisen as a sampling variation.

When the differences between the two groups are subjected to tests of significance, decade

TABLE 1.—Serum Cholesterol Values of Normal Individuals by Decades

<table>
<thead>
<tr>
<th>Decades</th>
<th>Number</th>
<th>Range</th>
<th>Mean ± Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>20</td>
<td>149-297</td>
<td>195 ± 9.2</td>
</tr>
<tr>
<td>30-39</td>
<td>74</td>
<td>148-332</td>
<td>224 ± 4.8</td>
</tr>
<tr>
<td>40-49</td>
<td>46</td>
<td>175-331</td>
<td>236 ± 6.0</td>
</tr>
<tr>
<td>50-59</td>
<td>6</td>
<td>214-284</td>
<td>254 ± 13.5</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>148-332</td>
<td>225 ± 3.6</td>
</tr>
</tbody>
</table>

* Small sample formula employed.

TABLE 2.—Serum Cholesterol Values of Male Coronary Disease Patients by Decades

<table>
<thead>
<tr>
<th>Decades</th>
<th>Number</th>
<th>Range</th>
<th>Mean ± Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>7*</td>
<td>194-400</td>
<td>245 ± 27</td>
</tr>
<tr>
<td>30-39</td>
<td>53</td>
<td>167-490</td>
<td>286 ± 9</td>
</tr>
<tr>
<td>40-49</td>
<td>35</td>
<td>208-490</td>
<td>301 ± 11</td>
</tr>
<tr>
<td>Totals</td>
<td>95</td>
<td>167-490</td>
<td>288 ± 6.7</td>
</tr>
</tbody>
</table>

* Small sample formula employed.
by decade as in table 3, both means and standard deviations (a measure of variability or dispersion around the mean) are markedly higher in coronary patients than among normal subjects.

Since there is a rise in cholesterol with age in both groups (see fig. 1) and since there is a significant correlation in one and a possibly significant correlation in the other, it seems

Table 3.—Comparison of Serum Cholesterol Means and Standard Deviations at Various Decades between Normal Group (N) and Coronary Disease Group (C)

<table>
<thead>
<tr>
<th>Decade</th>
<th>Number</th>
<th>Mean Cholesterol</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>20-29</td>
<td>7</td>
<td>20</td>
<td>245</td>
</tr>
<tr>
<td>30-39</td>
<td>53</td>
<td>74</td>
<td>285</td>
</tr>
<tr>
<td>40-49</td>
<td>35</td>
<td>46</td>
<td>301</td>
</tr>
<tr>
<td>Totals</td>
<td>95</td>
<td>140†</td>
<td>288</td>
</tr>
</tbody>
</table>

* Significant.
† Highly significant
‡ Six individuals between 50–59 are not considered in this paper.

As shown, there is no evidence of a dramatic rise in cholesterol with age, but there is a suggestion that lower ages were associated with lower cholesterol values and vice versa. Therefore, a coefficient of correlation was calculated in order to see whether serum cholesterol and age were co-variant in the study by Page and associates. Employing their data for individuals between 21 and 79 (eliminating the 12 eldest individuals in order to straighten the regression curve), a correlation of +.26 ± .13 was obtained. This is statistically significant on the 1 in 20 (i.e., .05) level, and the association is said to be moderately significant.

Since correlation is not synonymous with causation, a causal relationship cannot be postulated between serum cholesterol and age in the present study and in the data of Page and co-workers. There are many explanations for an association between two variables, such as: (a) an actual causal relationship between the two when all other influential factors are ruled out; (b) a primary correlation of each trait not with the other, but with another or several other intercorrelated traits.

In view of the seeming importance of these relationships, the properties of serum phospholipids and their ratios and age changes were investigated more intensively. Since simple correlations alone did not correct all interfering variables, the technic of partial correlations was employed. Thus, if both A and B affect C, it is possible to see the effect of B on C corrected for the presence of A.
It is apparent from table 5 that the phospholipids are highly correlated with cholesterol and show even higher correlations with age than does cholesterol in both the healthy and the coronary disease groups. Since all three variables are intercorrelated, it was decided to employ the technic of partial correlation which would theoretically determine the primary correlations of any pair of variables with

<table>
<thead>
<tr>
<th>TABLE 5.—Coefficients of Correlation (r): with Serum Cholesterol (1), Serum Phospholipids (2),* and Age (3) in Adult Men in Health and in Coronary Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>r_{14}†</td>
</tr>
<tr>
<td>r_{13}</td>
</tr>
<tr>
<td>r_{23}</td>
</tr>
</tbody>
</table>

* Phospholipids are expressed as lecithin which is considered to be 25 times the blood lipid phosphorus level.
† r_{14} means that coefficient of correlation is between serum cholesterol and serum phospholipids.
‡ Only 61 phospholipids out of 62 were taken simultaneously with serum cholesterol.

The third held constant. The significance of this correlation will be discussed later. These correlations are tabulated in table 6.

<table>
<thead>
<tr>
<th>TABLE 6.—Partial Correlations among Cholesterol (1), Phospholipids (2), and Age (3), in the Serum of Adult Men in Health and with Coronary Artery Disease</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>r_{11,3}</td>
</tr>
<tr>
<td>r_{13,3}</td>
</tr>
<tr>
<td>r_{23,3}</td>
</tr>
</tbody>
</table>

* r_{11,3} means that the partial correlation is between cholesterol and phospholipids with age kept constant (See Lindquist, p. 249).18

The difference between the two partial coefficients of correlation (+.32 ± .07 in health and 0.14 ± .13 in coronary artery disease) does not reach significance (p = 0.20), probably because of the small size of the coronary sample, but there is other evidence that the phospholipids play an altered role in coronary artery disease.

**Discussion**

In the two groups considered here, one a group of healthy men and the other a group of men who had experienced myocardial infarction prior to the age of 40, a significant positive correlation is found between age and total serum cholesterol. This rise is not only reflected in the product-moment correlation r but also in comparing the mean values of the various decade groups and, in data collected by this project, by noting the statistical significance of the difference between decade groups.

The general rise between the third and fifth decade appears to be most marked in these data between the third and fourth decade. While the corrected yearly increase would be small (approximately 2.0 mg. per cent of total cholesterol per year), the decade increase would not be important; but a rise over two or three decades would be important in terms of a normal distribution of serum cholesterol values in man. At the age of 50 only 19.23 per cent of males have the cholesterol values typical of youth; conversely, 14.3 per cent of young individuals have serum cholesterol levels typical of the older male.

Since it was anticipated that individuals showing coronary artery disease might, as a group, show elevated serum cholesterol levels, it was thought possible that the normal or physiologic age changes might be masked in this group. Despite their hypercholesterolemia, however, the coronary disease group still show the physiologic age-rise in cholesterol. The two factors may thus be additive rather than potentitative in so far as coronary artery disease is concerned.

Based on the findings of Boas'2 and these...
data, the level of serum cholesterol may be made up of three independent variables: (a) idiosyncratic, probably genetically determined hypercholesterolemia; (b) individual's basic physique-corrected cholesterol; (c) normal age influenced rise in cholesterol.

Under these circumstances the absolute cholesterol level of an individual can be considered as meaning little to the clinician unless these other factors are known. By extending this reasoning the clinician might employ the concept of "cholesterol age"; since low cholesterol levels are more typical of youth and higher cholesterol levels are more typical of old age, one may simply consider an individual with a low serum cholesterol level as one with a "young cholesterol age." An individual who has an elevated cholesterol may be considered to have an "older cholesterol age." However, to derive the most benefit from such a concept, the magnitude of the difference between the chronologic age and the cholesterol age should be considered. This will become more apparent when one recalls that a patient 25 years of age with coronary artery disease has a serum cholesterol level the same as, or higher than a healthy individual 45 years of age; the values for both individuals average 245 mg. per cent and 236 mg. per cent, respectively.

There is some evidence that beyond the sixth decade of life no further elevation of cholesterol occurs, and that there may even be a drop in cholesterol level after this time (see table 4). While this has been interpreted by some as evidence of "debility" in age, it is more likely that it is a statistical phenomenon due to the differential mortality of low-cholesterol and high-cholesterol individuals. Thus, if elevated cholesterol is associated with decreased longevity, then the longer-lived individuals in an older group would simply be the low-cholesterol surviving population. It is possible, therefore, that such data, though scanty, may point to basic factors in human survival.19,20

The tabular material provided in the preceding section illustrates the need for larger samples in each decade or age group than have been customarily used in previous studies. Thus, the small size of decade samples in the study by Page and associates masked a slight but real correlation between age and cholesterol.

In this study, only a cross section of a population between the third and sixth decades was studied. Obviously, the best method of study to learn the age influence of cholesterol would be the longitudinal study to follow individuals from infancy to old age.

In this discussion, the relationship between cholesterol and age is considered with some suggestions that the cholesterol does not increase infinitely, but that a more stable period appears at some time during middle age. If this is so, why should atherosclerotic disorders increase after this period? The answer appears to lie (on the basis of partial correlation and previous data) not in the absolute cholesterol levels but in the relationship between cholesterol and the other serum lipids. As we have reported in the first paper in this series, there is an important difference in various lipid levels in coronary artery disease and in health. Thus, individuals who have hypercholesterolemia, but who are healthy and well, differ in cholesterol: phospholipid ratios from individuals of comparable cholesterol level who have experienced coronary artery disease. Moreover, individuals who have experienced coronary artery disease but who have low cholesterol levels still differ from normal individuals with identical cholesterol levels: this difference expresses itself in various lipid ratios, especially in the cholesterol: phospholipid ratio.

It is apparent from table 6 that (1) in both health and coronary artery disease the cholesterol-phospholipid correlation is high, independently of age; (2) the correlation of cholesterol and age disappears when the influence of phospholipids is removed; and (3) the phospholipids in the healthy individuals tend to remain correlated with age, but may not keep pace with age in coronary artery disease. The difference between the two partial r's, +.32 in health and +.14 in disease, fails to reach statistical significance (p = .20) because of the small size of the coronary sample. One interpretation of these findings, at this juncture, is to stress again the importance of serum phospholipids in the normal aging process and, particularly, in coronary artery disease.
SUMMARY AND CONCLUSIONS

1. The serum cholesterol levels were determined in 146 healthy, working males and 95 males who had experienced myocardial infarction prior to the age of 40. The control group and the coronary disease group approximated each other in age, ethnic and racial origin, and occupation.

2. A steady and significant rise in the level of serum cholesterol occurs with increasing years between the third and sixth decades in the healthy control (normal) group ($r = +.30 \pm .08$).

3. A steady, but less marked rise in the level of serum cholesterol occurs with increasing years in the coronary disease group between the third and sixth decades. In this group, the normal physiologic rise is superimposed upon the initial pathologic rise ($r = +.16 \pm .10$).

4. At every age level between the third and sixth decade the coronary disease group has markedly higher and more variable serum cholesterol levels than the healthy group.

5. Serum phospholipids are highly correlated with serum cholesterol in both health ($r = +.66 \pm .05$) and disease ($r = +.51 \pm .09$).

6. Serum phospholipid levels rise at least as much as serum cholesterol levels with age in health ($r = +.42 \pm .07$) and probably to a lesser extent in disease ($r = +.20 \pm .12$).

Partial correlations show that serum cholesterol and serum phospholipids remain highly correlated independent of age; the association between age and cholesterol disappears when the effect of phospholipids is removed; and, with the effect of cholesterol removed, phospholipids keep pace with age in health but apparently fail to do so in coronary artery disease.

7. It is hypothesized that the levels of serum cholesterol and serum phospholipids are less important in coronary artery disease than is the ratio of cholesterol and phospholipids.

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