Blood Lipids and Human Atherosclerosis

By John W. Gofman, M.D., Ph.D., Hardin B. Jones, Ph.D., Thomas P. Lyon, M.D., Frank Lindgren, B.S., Beverly Strisower, B.S., David Colman, B.S., and Virgil Herring, B.S.

Previously evidence has been presented relating certain serum lipoproteins to the development of atherosclerosis in man. Further studies now enable us to make quantitative estimations of the relationship of certain aspects of lipid transport via lipoproteins with atherosclerogenesis, including follow-up studies. There are several points of evidence which have led us to an understanding of this derangement of blood lipoproteins from the "normal" pattern. The first observation of derangement of the lipid transport mechanism was made on serum lipoproteins of rabbits subsequent to their development of hypercholesteremia by cholesterol feeding.

In the course of cholesterol feeding, molecules of high $S_f$ classes, $S_f$ 10-30, 30-100, and higher (of higher molecular weight, lower density, higher lipid content and lower protein content than the normally occurring lipoproteins) appear in the serum, in contrast to the normal lipoproteins which are in the class of $S_f$ 10 and below. There is differential significance to the presence of these several lipoproteins which appear in the serum under several types of experimental conditions inducing hypercholesteremia. For the rabbit there is no relation between the serum levels of $S_f$ 10 and lower and atherosclerosis until active atherosclerosis. A lack of positive relationship between $S_f$ 10 and lower molecules and atherosclerosis has been significantly demonstrated ($r \approx -0.32$).

Some of these observations were on rabbits which received potassium iodide in addition to cholesterol feeding. Under this condition the increase in serum cholesterol and serum lipids is primarily in the $S_f$ 10 and lower fraction, which is elevated as high as or higher than in the cholesterol-fed rabbit that develops atherosclerosis. In fact, severe atherosclerosis often develops with low levels of this class of lipoproteins, whereas no atherosclerosis develops in spite of several fold increase in concentration of such lipoproteins. However, there is a high relationship (correlation coefficient $\approx +0.8$) between estimated degree of atherosclerosis as measured at autopsy and the concentration of lipoproteins of the $S_f$ 10-30 class when it develops regardless of the experimental condition. This observation is drawn from rabbits which were rendered hypercholesteremic by: (a) cholesterol feeding, (b) cholesterol and oil feeding, (c) cholesterol and potassium iodide feeding, and (d) cholesterol and oil feeding in the alloxanized rabbit. (Each of these experimental types has a differential alteration of the serum lipoproteins). Under certain uniform conditions such as cholesterol or cholesterol and oil feeding there is an excellent quantitative relationship between degree of atherosclerosis and the total blood cholesterol. However, this is only due to the fact that the $S_f$ 10-30 molecules account in this case for the main proportion of the increase in total serum cholesterol. That the total blood cholesterol itself is not the important feature has been clearly demonstrated by Pierce in our laboratory, studying the Duff type of alloxanized rabbit. Duff has previously shown that feeding cholesterol to alloxan diabetic rabbits results in elevation of serum cholesterol to levels over 2000 mg. per 100 cc. with a much less severe atherosclerosis developing than in the normal cholesterol-fed rabbit at comparable and much lower total cholesterol levels. Pierce has shown that in the Duff type rabbit the cholesterol is transported primarily in the

From the Donner Laboratory of Medical Physics and the Radiation Laboratory, University of California, Berkeley, Calif.

This work was supported in part by the United States Public Health Service, the Atomic Energy Commission, the General Mills Corporation and the Lederle Laboratories Division of the American Cyanamid Corporation.
form of molecules of the Sf 10 and higher classes. Some of the Duff type rabbits develop atherosclerosis, but they are the ones which also develop large amounts of Sf 10–30 molecules as well as the Sf 30 and higher molecules. Recently Graham and co-workers\textsuperscript{6} in this laboratory maintained cholesterol- and oil-fed rabbits on daily injections of heparin (10 mg. per kilogram per day). Heparin minimizes a rise in the concentration in the Sf 10–30 class of molecules by facilitating the formation of lower Sf classes of lipoproteins. These rabbits are markedly protected from atherosclerosis even though they are exposed to a metabolic burden of fat (3 Gm. per day) and cholesterol (1 Gm. per day) which ordinarily produces atherosclerosis.

It appears therefore that high levels of Sf 10–30 lipoproteins are consistently associated with atherosclerosis in the rabbit, whereas no association can be established for the Sf 100 and higher and the Sf 10 and lower classes. Serum cholesterol can be used as a partial guide only under the special conditions where the Sf 10–30 molecules are relatively greatly increased. If cholesteremia in the Duff-alloxan type rabbit and the Anitschkow-cholesterole-fed rabbit is compared with atherosclerosis, a significant negative relationship will actually be found between atherosclerosis and serum cholesterol. As will be discussed later, each of the different types of rabbit hypercholesteremia, (1) the Duff-alloxan type with its increment of increased cholesterol primarily in the lipoproteins greater than Sf 100; (2) the Anitschkow-cholesterole-fed type with its increase first in the Sf 10 and lower; and (3) the later stage of cholesterol or cholesterol and oil feeding (with the bulk of cholesterol carried in the Sf 10–30 class of lipoproteins), has its counterpart in types of human sera which are probably of similar differential significance (see fig. 1).

Preliminary studies (with the cooperation of Kendall\textsuperscript{7} and Chaikoff\textsuperscript{8}) on hypercholesteremic-atherosclerotic dogs and chickens indicate that there is a similar shift in both species of the serum lipids to higher Sf lipoproteins than exist normally. It must still be determined, through a more extensive study, which special class may be involved in these species, although it is known that the Sf 10–30 class becomes elevated in both dog and chicken.

A detailed account of the chemical composition and physical nature of the lipoproteins composing the lipid transport system has appeared.\textsuperscript{9, 10} Each of the lipoproteins (at least nine discrete components up to Sf 17 and a host of unresolved components above Sf 20 have been observed) contains cholesterol, phospholipid and protein, but in different amounts. Those lipoproteins above Sf 13 contain neutral fat also. Since each lipoprotein can vary in concentration in a semi-independent way, there is no assured relationship between total serum cholesterol or phospholipid or fat and the concentration of any particular lipoprotein species. We have seen no higher correlation than $r \cong 0.4$ to 0.5 between serum cholesterol and any one of these lipoprotein components or between the individual lipoprotein classes. It is the purpose of this paper to evaluate quantitatively the relationship that does exist between total serum cholesterol and the certain classes of lipoproteins in the human and the relation of each to atherosclerosis. We have previously indicated that elevation of the Sf 12–20 lipoproteins\textsuperscript{9, 11} is part of a lipid metabolic defect which is often associated with elevations in level of the Sf 20–100 class of lipoproteins. Further, there are many individuals who have inordinately high Sf 20–100 levels at a modest Sf 12–20 level. (See later section concerning Sf 12–20 intercorrelation with lipoproteins above Sf 20.) In humans with less severe degrees of the metabolic error, Sf 20–100 levels fluctuate acutely with reference to ingestion of fat. However, in those with severe degrees of the metabolic error the Sf 20–100 class is elevated even postabsorptively.\textsuperscript{11} Until now we have refrained from using the lipoproteins higher than Sf 20 as a correlative guide because of the greater fluctuations in concentrations of these lipoproteins than occurs in the Sf 12–20 class. In spite of the variability in levels of molecules from Sf 20–100, it has now become evident, as will be explained below, that these molecules are strongly related to atherosclerosis and represent an independent
contribution to accountability for atherosclerosis, in addition to the already established association of the $S_f$ 12–20 class of lipoproteins with atherosclerosis. It should be pointed out that the intercorrelation between the $S_f$ 12–20 and the $S_f$ 20–100 classes of lipoproteins is relatively low, and it is common to see severe disproportion in the concentration of $S_f$ 12–20 and $S_f$ 20–100 classes. Atherosclerosis is associated with elevated levels of either class of lipoproteins, and since the intercorrelation of the two classes is low, a significant improvement in identification of atherosclerogenic states results from consideration of the entire $S_f$ 12–100 class of lipoproteins (that is, the sum $S_f$ 12–20 and $S_f$ 20–100).

The entire $S_f$ 12–100 class of lipoproteins represents only about 10 to 15 per cent of all the serum lipoproteins and contains approximately 10 to 15 per cent of the total serum cholesterol. As will be shown in analysis of the data below, it is the cholesterol within the $S_f$ 12–100 lipoproteins that represents the entirety of the association of cholesterol with atherosclerosis. Since this amount is such a small fraction of the total cholesterol, and is so poorly related to the remaining 85 to 90 per cent of the cholesterol, it is largely masked in the routine determination of total serum cholesterol, even if the latter measurement is done with great accuracy.

In this report we have studied two groups:

---

**Fig. 1. Ultracentrifugal flotation patterns, showing the increase in the lipid metabolic defect in the human and the experimental rabbit. In all these figures the $S_f$ rates can be read off the $S_f$ scale placed on all frames; concentrations of various lipoprotein fractions are proportional to the shaded areas.**

A shows the flotation pattern of a normal child and a normal rabbit, both having low concentrations of lipoproteins below $S_f$ 10 and trivial concentrations above $S_f$ 10. B shows the patterns for a normal human and for a rabbit with elevation of the concentrations of lipoproteins below $S_f$ 10 but without appreciable elevations of lipoproteins of higher $S_f$ classes. C shows corresponding patterns for human and rabbit with moderate concentrations of lipoproteins of $S_f$ 10 and less, but with great elevations in the $S_f$ 12–20 and 20–40 classes in the human and $S_f$ 10–30 class in the rabbit. This rabbit developed marked atherosclerosis. D shows analogous patterns for human and rabbit with marked elevation of $S_f$ 12–20 class in human and $S_f$ 10–30 class in rabbit, but with depression of the concentration of lipoproteins of $S_f$ 10 and less. This rabbit also developed marked atherosclerosis. E shows the manifestation of severe lipid metabolic error in human and rabbit. Note the low concentration of lipoproteins below $S_f$ 10, moderate concentration of lipoproteins of $S_f$ 12–20 class in the human and $S_f$ 10–30 class in the rabbit, and high concentration of lipoproteins from $S_f$ 20–100 in both human and rabbit.
(1) patients with coronary artery disease manifested by either myocardial infarction or classic angina pectoris, and (2) individuals who are presumably normal in that they show no clinical sign of atherosclerosis and are in active physical condition normal to their mode of living. While other diseases with atherosclerotic complications are discussed, particular use is made of coronary artery disease, for it can be diagnosed with a high degree of reliability. This criterion group is manifesting a complication of atherosclerosis of the coronary arteries in an estimated 90 to 95 per cent of cases. Among normal persons, atherosclerosis is consistently reported with high occurrence rate from autopsy reports. Presumably, for many years of evolution of the atherosclerotic state, there was no external sign of the disease. It is estimated that in any group of supposedly normal, adult men, 30 to 50 per cent may be actively developing arterial atheroma. Statistical comparisons made between presumed normals and atherosclerotics are, in their crude form, of limited quantitative interpretation, since they contrast a population about 95 per cent atherosclerotic to a population 50 to 80 per cent “true normal” admixed with 50 to 30 per cent atherosclerotic normal. However, it is possible to estimate a correction for the impurity of the latter criterion group, as will be described in a later section.

We have studied 253 normal men and 93 men with coronary artery disease, all between the ages of 41 and 50 years. Of the coronary group, 75 were men studied at least six weeks after a myocardial infarction and 18 were men manifesting typical angina pectoris. In another group of men between the ages of 51 and 60 years 149 were normal and 126 had coronary disease; in this coronary group there were 110 survivors of myocardial infarction and 16 patients with typical angina pectoris. There were no significant differences in lipoprotein or cholesterol levels between the cases with angina and those with myocardial infarction, so in each age group both types were combined as “patients with coronary artery disease” for purposes of analysis.

Several approaches were made to the analysis of the data in an effort to assess the relationship $S_f$ 12–20 and $S_f$ 20–100 lipoproteins and of total serum cholesterol to atherosclerosis. Over-all relationships and the relationship of each measure independent of the others were evaluated previously; it was demonstrated that the $S_f$ 12–20 lipoprotein levels were consistently two to four times as effective as the serum cholesterol level in segregating atherosclerotics from normals. It became apparent in those data that there was a slight residual association of serum cholesterol levels with atherosclerosis in the 41 to 50 year age group, even when the relationship of $S_f$ 12–20 lipoprotein levels with atherosclerosis was taken into account. This suggested the probable existence of certain additional lipoprotein classes independently associated with atherosclerosis. The current analysis confirms the association of certain lipoproteins (the $S_f$ 12–20 and $S_f$ 20–100 classes) with atherosclerosis and the exclusion of other lipoproteins from such association. The analysis shows further that the total serum cholesterol level is associated with atherosclerosis only through its weak relationship with the important $S_f$ 12–20 and $S_f$ 20–100 classes of lipoproteins. When individuals are evaluated at the same combined level of lipoproteins of the $S_f$ 12–100 class ($S_f$ 12–20 plus $S_f$ 20–100), there is no residual relationship of the remaining bulk (≈ 85 to 90 per cent) of the serum cholesterol with atherosclerosis, even in individuals with marked hypercholesteremia. Serum cholesterol measurements permit only a slight segregation of atherosclerotics from normals in the age group under 50 years, and permits no segregation of the atherosclerotic group from the normal group above the age of 50 years. Overall, a serum cholesterol determination tends more to obscure than to clarify the status of an individual with respect to atherosclerosis. By contrast, the $S_f$ 12–100 lipoprotein determination offers a continuous scale of positive association with atherosclerotic activity, no matter whether the serum cholesterol is low, moderate, or high.
ANALYSIS OF THE RELATIONSHIP OF $S_f$ 12-20 AND $S_f$ 20-100 LIPOPROTEINS AND OF SERUM CHOLESTEROL TO Atherosclerosis

The literature concerning serum lipids is marked by great differences which are the result both of nonuniformity of populations sampled and of technical differences in laboratory procedures of analysis. It is ridiculous to contrast serum lipid analyses between groups without rigorous control of both of these sources of variation in reported lipid concentration. For this study it has been an absolute requirement to determine both lipoproteins and total serum cholesterol on the same serum sample under controlled laboratory conditions. This approach permits a direct comparison between these two types of lipid analysis as to their association with atherosclerotic tendency.

Table 1 provides a summary of the pertinent data for the various lipoprotein classes measured and for the total serum cholesterol in the 41 to 50 and 51 to 60 year age groups considered. These data are requisite to a further evaluation of the association of any of the measures with atherosclerosis. It is evident that for the 41 to 50 year age group, all three measures, the $S_f$ 12-20 level, the $S_f$ 12-20 level, and the total serum cholesterol level, are significantly higher in patients with coronary artery disease than in normal persons. The first crude assessment of the association of each measure with atherosclerosis can be made by comparing the difference in mean levels (between the normal and coronary group) with reference to the standard deviation of the distribution of values for each measure. Thus it is seen that the greatest relative difference established for normal subjects and coronary patients 41 to 50 years old is in the combined $S_f$ 12-20 and $S_f$ 35-100 lipoprotein measure. Next is the separation achieved by the $S_f$ 35-100 lipoprotein measure.

Table 1.—Lipoprotein and Cholesterol Measurements in Normal Subjects and Patients with Coronary Artery Disease

<table>
<thead>
<tr>
<th></th>
<th>41-50 Year Age Group (Males)</th>
<th>51-60 Year Age Group (Males)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Subjects</td>
<td>Coronary Disease Patients</td>
</tr>
<tr>
<td>No. Cases</td>
<td>253</td>
<td>93</td>
</tr>
<tr>
<td>Mean $S_f$ 12-20 Lipoprotein Level</td>
<td>45 ± 27</td>
<td>71 ± 32</td>
</tr>
<tr>
<td>Mean $S_f$ 35-100 Lipoprotein Level</td>
<td>64 ± 49</td>
<td>120 ± 74</td>
</tr>
<tr>
<td>Mean Combined $S_f$ 12-20 + $S_f$ 35-100 Lipoprotein Level</td>
<td>109 ± 65</td>
<td>191 ± 93</td>
</tr>
<tr>
<td>Mean Serum Cholesterol Level</td>
<td>200 ± 63</td>
<td>297 ± 68</td>
</tr>
<tr>
<td>Intercorrelations*</td>
<td>0.40</td>
<td>0.39</td>
</tr>
<tr>
<td>$S_f$ 12-20 vs. Chol...</td>
<td>0.3</td>
<td>0.13</td>
</tr>
<tr>
<td>$S_f$ 35-100 vs. Chol...</td>
<td>0.41</td>
<td>0.54</td>
</tr>
</tbody>
</table>

All values are given plus or minus the standard deviation of the distribution.

* Coefficients of correlation are expressed as Pearson r.

An almost equivalent separation exists for the $S_f$ 12-20 lipoprotein measure. The poorest separation exists for the serum cholesterol measure. The actual values of the quotient of difference in means by the $\sigma$ for each measure is given in table 2.

Consideration of the ratios in table 2 reveals that for the 41 to 50 year age group measurement of either $S_f$ 12-20 or $S_f$ 35-100 lipoprotein segregates patients with coronary disease from normal subjects with high efficiency. The best segregation of coronary disease patients from normal subjects is achieved by combining the $S_f$ 12-20 and $S_f$ 35-100 lipoprotein values. Since the contribution of the $S_f$ 12-20 and $S_f$ 35-100 measures are in large part independent of each other, it is under-

* $S_f$ 20-100 class equals $S_f$ 20-35 plus $S_f$ 35-100. As discussed in the text, the independent contribution of $S_f$ 20-35 is small; it is omitted from this analysis.
standable that the combination is superior to either alone. Individually and combined the lipoprotein measurements are highly superior to serum cholesterol measurement in segregating coronary disease patients from normals. In fact, in the 51 to 60 year age group the serum cholesterol measurement cannot be shown to produce any significant segregation of the coronary disease group from the normal group.

Table 2.—Crude Segregation of Patients with Coronary Disease and Normals by the Lipoprotein and Cholesterol Measures

<table>
<thead>
<tr>
<th></th>
<th>Difference in Means (Coronary Disease – Normals)</th>
<th>Standard Deviation of Normal Distribution</th>
<th>Ratio, Difference in Means: Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg. per 100 cc.</td>
<td>mg. per 100 cc.</td>
<td></td>
</tr>
<tr>
<td><strong>41–50 Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined S,f 12–20 + S_f</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–100</td>
<td>82</td>
<td>65</td>
<td>1.3</td>
</tr>
<tr>
<td>S_f 35–100</td>
<td>56</td>
<td>49</td>
<td>1.1</td>
</tr>
<tr>
<td>S_f 12–20</td>
<td>25</td>
<td>27</td>
<td>0.9</td>
</tr>
<tr>
<td>Serum Cholesterol</td>
<td>37</td>
<td>53</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>51–60 Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined S,f 12–20 + S_f</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–100</td>
<td>55</td>
<td>57</td>
<td>1.0</td>
</tr>
<tr>
<td>S_f 35–100</td>
<td>31</td>
<td>45</td>
<td>0.7</td>
</tr>
<tr>
<td>S_f 12–20</td>
<td>24</td>
<td>21</td>
<td>1.1</td>
</tr>
<tr>
<td>Serum Cholesterol</td>
<td>12</td>
<td>65</td>
<td>0.19</td>
</tr>
</tbody>
</table>

A simple method of measuring the association of each factor (that is, S_f 12–20 level, S_f 35–100 level, or serum cholesterol level) independently with atherosclerosis is achieved by comparing the lipoprotein segregating ability at any particular serum cholesterol level, and conversely the serum cholesterol segregating ability at any particular lipoprotein level. Thus, there are given in figure 2 A, B, C the average values of S_f 12–20 and S_f 35–100 lipoprotein levels for every part of the serum cholesterol range, for both normals and patients with coronary artery disease. It is evident that the patients with coronary artery disease show essentially the same elevation of S_f 12–20 and S_f 35–100 lipoproteins above normal levels when compared at the same cholesterol level throughout the entire cholesterol range. This is equivalent to matching each patient with coronary disease with a normal who has the same cholesterol level. Conversely, the data of figure 2C can be used to compare the serum cholesterol level in patients with coronary disease with the level in normal persons at the same lipoprotein level. It is seen that when individuals in the coronary group are matched with normals having the same lipoprotein levels there is no significant difference in cholesterol level, indicating that cholesterol level of itself does not segregate coronary and normal populations independently of its weak association with the lipoprotein classes (S_f 12–20 and S_f 35–100) which are truly associated with atherosclerosis. For the two age groups studied, the actual data obtained in such comparisons are given below.

Comparison of S_f 12–20 and S_f 35–100 Lipoproteins in Coronary Disease Patients and in Normal Subjects at Identical Cholesterol Levels

From the data shown in figure 2 A, B, C it can be seen that 41 to 50 year old patients with coronary disease average higher than normal in (S_f 12–20 plus S_f 35–100) lipoproteins by 69 mg. per 100 cc., higher in S_f 35–100 lipoproteins by 51 mg. per 100 cc., higher in S_f 12–20 lipoproteins by 18.0 mg. per 100 cc.; all comparisons are with normal subjects at equal cholesterol levels. Patients 51 to 60 years old with coronary artery disease also show equivalent elevations, namely 22 mg. per 100 cc. higher in S_f 12–20 lipoproteins than equivalent normals for the same cholesterol level.

Comparison of Cholesterol Levels at Corresponding Serum Lipoprotein Concentrations

In the 41 to 50 year old group of patients with coronary artery disease, cholesterol is only 17 mg. per 100 cc. higher than in normals compared at the same S_f 12–20 level. This small residual elevation is completely lost when coronary and normal populations are contrasted at the same (S_f 12–20 plus S_f 35–100)
levels; the coronary population is 1 mg. per 100 cc. of cholesterol lower than normals of the same \( S_f 12-20 \) plus \( S_f 35-100 \) levels.

In the 51 to 60 year old group, patients with coronary artery disease are likewise unsegregated from normal subjects by cholesterol when cholesterol levels are compared at the same \( S_f 12-20 \) level.
Thus it is apparent that lipoproteins of the Sf 12-100 class are highly associated with the atherosclerotic state and that total serum cholesterol is only related to the extent that the small fraction of cholesterol (contained in these particular lipoproteins) can influence the bulk of total serum cholesterol. Inasmuch as approximately 90 per cent of total serum cholesterol is unassociated with atherosclerosis, gross deception is usually to be expected in attempting to evaluate atherosclerosis from the serum cholesterol level on the individual basis. A patient with high atherosclerotic activity will frequently be completely misdiagnosed because his serum cholesterol is moderate or low; conversely, there are many hypercholesteremic individuals who are falsely evaluated as having high atherosclerotic activity. Both of these errors will in general be avoided if the truly atherosclerogenic lipoproteins are used as a clinical guide, rather than the serum cholesterol level.

Figure 2D shows clearly the independent association of the molecules of the Sf 35-100 lipoproteins with atherosclerosis. Even though the Sf 35-100 lipoprotein level is partly related to the Sf 12-20 level, the Sf 35-100 level is higher in patients with coronary artery disease when both normal and atherosclerotic persons are compared at the same Sf 12-20 level. Conversely, the Sf 12-20 level is associated with atherosclerosis independently of its partial relation to Sf 35-100 levels.

The Sf 20-35 class of lipoproteins is also somewhat independently associated with atherosclerosis; however, it is related to both the Sf 12-20 class and the Sf 35-100 class. Hence very little additional gain in assessing atherosclerotic potentialities can be made by including this fraction. A more extensive analysis of our data will be necessary to establish the most effective means of assigning relative weights to the various lipoproteins within the Sf 12-100 class. For the present, due to the larger fluctuation of the Sf 35-100 class, it is advisable to regard the Sf 12-20 and Sf 35-100 classes separately and combined. This does not imply that the Sf 35-100 is of less significance, but rather that its variability may be obscuring an even stronger relationship.

Hypercholesteremic States and Atherosclerotic Activity

Hypercholesteremia (levels over 300 mg. per 100 cc.) has long been considered to be associated with atherosclerosis. However, there is reason to believe that there are differences in atherosclerotic activity even among the hypercholesteremics. To study this question we have compared all the normal subjects (134 cases) having serum cholesterol levels over 300 mg. per 100 cc. with all the patients with myocardial infarction (90 cases) of corresponding age and sex. A slight adjustment between the two groups, correcting to the same serum cholesterol level, was made using the regression equation. (Actual serum cholesterol mean for coronaries was 355; for normals, 347.) When patients with infarcts are compared with normals, both at the same mean cholesterol level (355 mg. per 100 cc.), the Sf 12-20 level in the myocardial infarct group is 89.5 mg. per 100 cc., while that of the normal group is 64.5 mg. per 100 cc. The difference of 25 mg. per 100 cc. is highly significant (p < 1 per cent).

If the data for the normals are corrected by the regression equation so that the Sf 12-20 levels are equal in the myocardial infarct and normal groups, the mean cholesterol is not higher in those with infarcts than in the normals.

Of special interest, because of its exceptionally high atherosclerotic activity, is the group manifesting the syndrome xanthoma tuberosum. These patients are quite uniformly hypercholesteremic, but appear to have manifestations of atherosclerosis in excess of what might be anticipated for their degree of hypercholesteremia. Twelve cases of xanthoma tuberosum were matched with hypercholesteremic normals.

The serum cholesterol of the 12 cases of xanthoma ranged from 275 mg. to 640 mg. per 100 cc., averaging 489 mg. per 100 cc. The Sf 12-20 lipoproteins in these cases ranged from 76 mg. per 100 cc. to 520 mg. per 100 cc., averaging 250 mg. per 100 cc. The closest matched group of hypercholesteremic normals that was possible showed a range of 423 to 492...
mg. per 100 cc. serum cholesterol, averaging 447 mg. per 100 cc. The \( S_f \) 12–20 lipoproteins ranged from 48 mg. per 100 cc. to 99 mg. per 100 cc., except for one case at 300 mg. per 100 cc., and averaged 85 mg. per 100 cc. A slight correction of the normal group to serum cholesterol level identical with the xanthoma patients was made by use of the regression equation. The equivalent normals at 489 mg. per 100 cc. serum cholesterol would have an \( S_f \) 12–20 level of 96 mg. per 100 cc. Thus, the extraordinary atherosclerotic tendency of patients with xanthoma tuberosum is explainable because their level of \( S_f \) 12–20 lipoproteins is about two and one-half times higher than even equivalently hypercholesteremic normals.

**The Accountability for the Atherosclerotic State from Lipoprotein Measurement**

In a previous paper, by the technic of biserial correlation, we have estimated roughly the extent of accountability for the atherosclerotic state that can be drawn from the measurement of these serum lipoproteins. These correlation technics are not being used to establish the independent significance of the lipoproteins in atherosclerosis, but rather in an attempt to assess how closely these lipoproteins account for the totality of factors which lead to atherosclerosis. An estimation has been made of the biserial correlation coefficient for the combined \( S_f \) 12–20 and the \( S_f \) 35–100 measurement with atherosclerosis for the 41 to 50 year age group reported in this paper. This biserial \( r \) is 0.57. Ideally one may square such a correlation coefficient to obtain the fraction of the total variance (which is unity) that has been accounted for directly. In this case the total \( S_f \) 12–20 and \( S_f \) 35–100 have accounted for about four-tenths of factors associated with atherosclerosis. The serum cholesterol measurement contributes nothing further to this estimate. There are limitations to the general use of the biserial technic in an absolute sense in situations of this type; these have been discussed fully in an earlier paper. For, whatever quantitative methods are used to establish relationship between these serum lipoproteins and atherosclerosis, certain factors will always preclude complete accountability of the true relationship that exists. Among these factors are the following:

1. Accumulated Atherosclerosis vs. Atherosclerotic Activity

   Measurement of derangement of lipid metabolism by \( S_f \) 12–20 lipoprotein molecules is thought to indicate active atherosclerogenesis. Is myocardial infarction caused by active or accumulated atherosclerosis? If it is primarily a disturbance of accumulated atheroma, then angina or myocardial infarction is not a pure criterion of active atherosclerosis and is of value only through the relationship of degree of atherosclerosis to rate of accumulation of atherosclerosis. This error has not been estimated and cannot be estimated at this time.

2. The Impurity of the “Normal” Population

   The normal population is composed of a group of true normals whose atherosclerotic activity is insufficient to produce significant atherosclerosis, and normals whose atherosclerosis has not yet advanced to clinically detectable levels or to manifest complications of atherosclerosis. It is variously estimated that 30 to 50 per cent of normals are moderately to severely atherosclerotic.

3. Focal Factors in Atherosclerosis

   The focal character of atherosclerosis, especially when of mild degree, is indisputable, but this is consistent with the role of lipids in its pathogenesis. It is entirely reasonable that, given the necessary lipid metabolic abnormality, certain susceptible sites will be earlier and more extensively involved. It may well be the case that if such lipid metabolic abnormality is not present, even susceptible focal sites will not show appreciable disease. In this factor alone there can be great individual variation, even though we feel it is justifiable to say that atherosclerosis of the coronary arteries (and its rate of development) will on the average be more pronounced in patients with myocardial infarction than in normals. The exact degree to which this factor prevents accounting for the total variance between atherosclerotic and normal subjects cannot be estimated at this
time. This factor is of importance and it is hoped that follow-up autopsy will enable an assessment of its magnitude.

(4) Reliability, Errors and Consistency of Measurements

Any measured relationships between such factors as total serum cholesterol or $S_t$ 12–20 lipoproteins with atherosclerosis are influenced by errors of measurement and biologic variation with time. Such errors and biologic variation have the effect of reducing the measured relationships, as they have been calculated in this discussion from single measurements on all subjects, normal or atherosclerotic. We have previously made an effort to assess these factors in order that the observed $S_t$ 12–20 or cholesterol relationship to atherosclerosis may be corrected for this attenuation.\(^{11}\)

The over-all reproducibility from determination to determination on the same individual has a coefficient of reliability of 0.67 ± 0.05 for $S_t$ 12–20 determination and 0.75 ± 0.07 for total serum cholesterol determination. (These figures represent the reliabilities over the one-year period during which the data reported in this paper were collected). During the same interval the technical reproducibility of the two measurements showed coefficients of reliability of 0.80 ± 0.04 for $S_t$ 12–20 measurement and 0.91 ± 0.001 for serum cholesterol measurement. Therefore it is estimated that the biologic variation during this period is expressed by a coefficient of reliability of $r = 0.84$ ± 0.06 for $S_t$ 12–20 measurement and $r = 0.82$ ± 0.07 for total serum cholesterol measurement.

This may be translated into terms of observed biologic variation for the average "normal" (41 to 50 years) whose $S_t$ 12–20 level is 45 mg. per 100 cc. From the standard deviation of the distribution of levels ($s = 27$ mg. per 100 cc.) and the reliability coefficient $r = 0.84$, we calculate a standard error of the obtained value of 25 mg. per 100 cc. cholesterol. Thus, a single measurement places the average individual within ± 10 mg. per 100 cc. $S_t$ 12–20 and ± 25 mg. per 100 cc. serum cholesterol of his "true" value for that particular year period two-thirds of the time.

For over-all variation, including biologic variation and technical errors of measurement, a single determination has a standard error of the obtained value of 15 mg. per 100 cc. $S_t$ 12–20 and 29 mg. per 100 cc. serum cholesterol. Thus a single measurement places an individual (including both biologic variation and technical error) within ± 15 mg. per 100 cc. $S_t$ 12–20 and ± 29 mg. per 100 cc. cholesterol of the "true" values two-thirds of the time.

The crude biserial $r$ found for the $S_t$ 12–20 plus $S_t$ 35–100 lipoproteins gives a correlation with atherosclerosis of approximately ± 0.57. When corrected for (1) the fact that the populations of "normals" and coronary disease patients are only impurely identified, and (2) technical errors that separate a single determination of serum lipoproteins from its true value, the true biserial $r$ may be much greater than the 0.57 measured and may be sufficiently close to unity to account for all the etiologic factors in this disease.

**Significance of $S_t$ 12–20 Lipoprotein Levels in the Prognosis and Management of Atherosclerosis**

In the preceding section quantitative evidence has been presented for the relationship of $S_t$ 12–20 lipoprotein levels to atherosclerotic activity. It follows therefore that the $S_t$ 12–20 levels might be of prognostic value in patients with established atherosclerosis, in assessing their present potential of atheroma production, as well as in normals, in predicting their likelihood of developing a clinical manifestation of atherosclerosis. We have sufficient follow-up data now to evaluate both of these possibilities.

**Prediction of Occurrence of Myocardial Infarction in the Normal Population**

A follow-up study has been in progress for the past one and one-half years to obtain
information on the occurrence of clinical manifestations of atherosclerosis in individuals previously classified as normal and measured for their Sf 12-20 lipoprotein level. At this time we have complete follow-up information from a block of 1500 normal subjects studied. There have been four occurrences of myocardial infarction documented in males previously normal. These occurred at ages 38, 42, 45 and 53 with Sf 12-20 levels of 100, 68, 55, and 52, respectively. At the same ages in the normal group there are 1000 cases, of whom 340 were above 50 mg. per 100 cc. at the time of study and 660 were below 50 mg. per 100 cc. While the number of cases of occurrence of myocardial infarction is small, the chance that the relationship between Sf 12-20 levels greater than 50 mg. per 100 cc. and occurrence of infarction is not significant is only 1 in 50.

In a group of hypertensives (200) that had shown no clinical evidence of atherosclerosis at the time their Sf 12-20 levels were determined, there have now been three occurrences of myocardial infarction at levels of 55, 78, and 145 mg. per 100 cc. These numbers are not significant by themselves, but they further show that the range of 50 mg. per 100 cc. Sf 12-20 and above includes the probable occurrences of myocardial infarction, since 50 mg. per 100 cc. is the 50:50 division of the hypertensive population. There are many uncomplicated hypertensives in the normal Sf 12-20 ranges.

Recurrence of Myocardial Infarction in Patients with Established Coronary Artery Disease

In a group of patients with previously known coronary artery disease, a rate of occurrence of myocardial infarction higher than in a normal population is expected. We have now been able to observe 39 recurrent myocardial infarctions in the over-all coronary disease population (359 cases) for which we have follow-up information over a one year period. Of these recurrences, 36 showed a level of Sf 12-20 lipoproteins at the time of initial study over 50 mg. per 100 cc., and three had levels below 50 mg. per 100 cc. The actual levels in the recurrences were: 210, 156, 136, 136, 125, 116, 114, 114, 109, 101, 100*97, 92, 88, 88, 88, 85, 84, 84, 83, 78, 78, 76, 76, 65, 65, 64, 62, 62, 61, 54, 52, 51, 50, 44, 43, and 38 mg. per 100 cc. Sf 12-20 lipoproteins.

There are no factors of difference between the over-all nonrecurrence coronary population and the recurrence population, at least with regard to age, physical activity, sex, previous clinical history, or drug therapy. Some of both the recurrence and nonrecurrence group had been on low fat-low cholesterol diets. Since there are no significant differences between the two groups in other respects, it is justifiable to compare them on the basis of their initial Sf 12-20 lipoprotein levels. Considering a level of 50 mg. per 100 cc. Sf 12-20 lipoproteins, 36 of the recurrences were above this level and three were below this level, whereas in the nonrecurrence group 202 were above and 118 were below this level. A test of significance of the relationship of levels above 50 mg. per 100 cc. with recurrence of myocardial infarction indicates there is less than 1 chance in 1000 that this point of segregation is not real. An even more striking difference is seen above 80 mg. per 100 cc. when the recurrence and nonrecurrence groups are contrasted. In the recurrence group 22 cases were above 80 mg. per 100 cc. and 17 cases were below; in the nonrecurrence group, 64 cases were above 80 mg. per 100 cc. and 256 cases were below. A test of the relationship of Sf 12-20 levels above 80 mg. per 100 cc. with recurrence of myocardial infarction indicates there is less than 1 chance in 10,000 that this point of segregation is not real. These results may be converted to another form of some practical predictive value. The data are plotted in figure 3 as the per cent chance of recurrence of myocardial infarction in one year as a function of a single measured level of Sf 12-20 lipoproteins (along with the data for occurrence of myocardial infarction in one year for individuals who have not previously manifested coronary artery disease). The plot indicates that for a patient with coronary artery disease the over-all chance of a recurrence within one year is approximately 17 per cent for an Sf 12-20 level of 100 mg. per 100 cc., whereas it is approximately 6 per cent for an Sf 12-20 level of 50 mg. per 100 cc. These
data show that the prognosis for a patient with coronary artery disease is much worse if the \( S_f 12-20 \) lipoprotein level is high than if it is moderate or low.

A study of 49 patients in the acute phase of myocardial infarction shows that the \( S_f 12-20 \) lipoprotein level determined during the first week after occurrence (or from autopsy blood for some of the fatal cases) is of prognostic

![Graph showing the per cent chance of recurrence of myocardial infarction in patients with coronary artery disease as a function of \( S_f 12-20 \) lipoprotein level.](http://circ.ahajournals.org/)

**Fig. 3.** Shows the per cent chance of recurrence of myocardial infarction in patients with coronary artery disease as a function of \( S_f 12-20 \) lipoprotein level. It is based upon 39 recurrent myocardial infarctions in one year follow-up of 359 patients with known coronary artery disease. The class intervals are indicated for each calculation made of the recurrences and the number of patients with myocardial infarction that have been studied. The present best estimate for the position of the similar function for the occurrence of myocardial infarction, de novo, in normals is also shown.

significance here also. The data are presented in table 3.

It is seen that the levels are much higher in those not surviving the episode of myocardial infarction than in those who do survive. A significance test splitting the survivors and nonsurvivors at 80 mg. per 100 cc. gives a probability of 1 in 10,000 that the observed difference is not significant. Since the two groups were comparable in age, sex, and previous history, it is justifiable to regard the only difference as the lipoprotein level difference. It will be noted that among the survivors the average level is lower than for those myocardial infarction survivors studied at least six weeks beyond the acute episode (see fig. 13). We have frequently observed rises in level in a given patient after the acute phase of a myocardial infarct is past. This probably indicates that in infarction survivors there is a lability of lipid metabolism incidental to the acute insult, which in itself may have increased the chance of survival. From studies reported elsewhere, it seems possible that this lipoprotein alteration may be related to increased release of heparin or a heparin-like substance. The higher levels observed in the nonsurvivors suggest the possibility that the more extensive atherosclerogenesis and/or accumulated
ATHEROSCLEROSIS. A SYMPOSIUM

atheroma most likely present in this group has unfavorably influenced the prognosis.

The data on recurrences of myocardial infarction and the prognosis during the acute phase of an infarct indicate that the over-all outlook for the patient above 80 mg. per 100 cc. Sf 12-20 lipoproteins is quite poor when he develops coronary disease. It is therefore of real importance to evaluate the possibility of giving such patients some protection against their intense atherosclerotic activity, which we have considered possible by means of reducing the Sf 12-20 lipoprotein level via a reduction of the burden of dietary fat.

Our previous and continuing studies of controlled experimental groups have shown that it is possible in most humans to reduce the Sf 12-20 and the Sf 20-100 classes of lipoproteins by restricting the total dietary fat and cholesterol intake. We are fully cognizant of the evidence that fat and cholesterol are synthesized in the body, but this is in no way inconsistent with the observed fact that a partial reduction in Sf 12-20 and Sf 20-100 lipoprotein levels is achieved by a reduction of total fat intake. The first analysis of a dietary follow-up among patients with coronary artery disease can now be made. Of especial pertinence is a comparison of those patients with high Sf 12-20 lipoprotein levels who have experienced recurrent infarction during the period of follow-up with a group of patients of comparable levels who have not shown recurrence during the one year of follow-up. The only therapeutic measure directed toward reduction of lipoprotein levels was the advice and directions for a low fat-low cholesterol diet. A diet of less than 50 Gm. of fat and 200 mg. of cholesterol per day was advised, but it is evident that one cannot assess how rigorously a given patient adhered to this regimen. Therefore, the objective criterion of serial lipoprotein determination was used solely as the measure of dietary response.

Fifty-six cases of myocardial infarction with very high levels (above 80 mg. per 100 cc. Sf 12-20) followed with serial lipoprotein determinations for one year are considered. Out of this group there were 16 recurrent myocardial infarctions during the one year follow-up. Since the patient's statement as to adherence to a low fat diet is untrustworthy, we have eliminated such information from the analysis. A segregation of this group is presented on the basis of the reduction or nonreduction of the lipoprotein level for the period of follow-up. In this sample it appears there is a differential favoring nonrecurrence of myocardial infarction at any relatively

<table>
<thead>
<tr>
<th>Level of Sf 12-20 Lipoproteins</th>
<th>Cases Studied during Acute Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survived</td>
</tr>
<tr>
<td>Above 95 mg. per 100 cc........</td>
<td>0</td>
</tr>
<tr>
<td>Above 80 mg. per 100 cc........</td>
<td>0</td>
</tr>
<tr>
<td>Above 60 mg. per 100 cc........</td>
<td>6</td>
</tr>
<tr>
<td>Below 60 mg. per 100 cc.........</td>
<td>17</td>
</tr>
<tr>
<td>Total..........................</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cases starting and maintaining average level above 80 mg. per 100 cc. Sf 12-20........</th>
<th>Recurrence Group</th>
<th>Nonrecurrence Group</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td>Cases starting above 80 mg. per 100 cc. but reducing and maintaining level below 70....</td>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Totals................................</td>
<td>17</td>
<td>40</td>
<td>57</td>
</tr>
</tbody>
</table>

reduced level of Sf 12-20 lipoproteins achieved by diet, but for the purpose of demonstrating a significant effect we have divided the group on the basis of whether the level has been reduced and maintained below 70 mg. per 100 cc. or whether the level has remained above 80 mg. per 100 cc. The following fourfold table (table 4) sharply defines the observed result.

Application of a test of significance has shown a probability of one chance in 100 that
this segregation is not significant. Therefore
the observation that the recurrences have been
in the group that maintained a high level is
highly significant, and we can conclude that
dietary reduction of Sf 12-20 level has given
significant protection against recurrence of
myocardial infarction during this year period
of observation. In table 5 are the initial Sf 12–
20 level and the average level for the period of
follow-up for each of the groups of table 4.

The various groups turn out to be closely
matched for initial Sf 12–20 levels. The only
exception is the nonrecurrence group which
started above 80 mg. per 100 cc. and reduced to
an average level below 70 mg. per 100 cc.

TABLE 5.—Initial Sf 12–20 Level and Average Level
during Period of Follow-up for Two
Groups Shown in Table 4

<table>
<thead>
<tr>
<th>Recurrence Group</th>
<th>Nonrecurrence Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Level</td>
<td>Average Level</td>
</tr>
<tr>
<td>Cases starting and maintaining average level above 80 mg. per 100 cc.</td>
<td>112</td>
</tr>
<tr>
<td>Cases starting above 80 mg. per 100 cc., but reducing and maintaining level below 70</td>
<td>—</td>
</tr>
</tbody>
</table>

Here the slightly lower initial level (by 8 mg.
per 100 cc.) is the result of the lack of a single
matched case at 200 mg. per 100 cc. in this
group, compared with the other two groups.
In the light of our recent findings that the Sf
20–100 class of lipoproteins are highly
associated with atherosclerosis, and that they
are more easily influenced by the restriction of
fat, it is likely that reduction in Sf 20–100 may
also have afforded part of the protection
observed.

**Discussion and Summary**

1. A variety of serum lipid disturbances
experimentally induced in the rabbit, some of
which are associated with the development of
atherosclerosis, have been analyzed. The Sf
10–30 class of lipoproteins, which develops in
the rabbit in certain of these experimental
procedures, is highly associated with and uni-
versally concurrent with the development of
atherosclerosis, independent of the type of
metabolic disturbance experimentally induced.
The normally occurring lipoproteins (Sf 10
and less), even when elevated experimentally,
show no significant positive association with
atherosclerosis. Certain other cholesterol-bear-
ing lipoproteins (Sf 100 and higher) are either
not associated with atherosclerosis or are
inversely associated with atherosclerosis.

2. In the rabbit, total serum cholesterol
levels, considering as a group all the types of
induced lipid metabolic disturbances, are either
unrelated to atherosclerosis, or may be in-
versely associated with atherosclerosis. Only
under the special condition where the major
fraction of the cholesterol is in the Sf 10–30
class of lipoproteins does total serum cholesterol
correlate well, positively, with atherosclerosis.

3. An estimate of the quantitative associa-
tion of the Sf 12–20, Sf 20–35, Sf 35–100 lipopro-
tein classes and of total serum cholesterol
with atheroslerogenesis in the human has
been made, studying each on the same serum
sample from a given individual. Patients with
coronary artery disease have served as a cri-
terion group for the atherosclerotics. Through-
out the entire age range evaluated, from 41 to
60 years, the Sf 12–20 lipoprotein levels show
at least a twofold, and up to a possibly tenfold,
higher relationship with atherosclerosis than
does the total serum cholesterol. The Sf 20–100
lipoproteins (containing the Sf 20–35 class plus
the Sf 35–100 class) also show a correspondingly
higher relationship with atherosclerosis than
does the total serum cholesterol. The Sf 12–20
lipoproteins and the Sf 35–100 lipoproteins are
partially intercorrelated; but each shows, in
addition, strong independent associations with
atherosclerosis. The Sf 20–35 lipoproteins show
a lesser association with atherosclerosis than
either of the other classes, and, further, much
of the association that is present depends upon
partial correlation of the Sf 20–35 lipoprotein
with either Sf 12–20 or Sf 35–100 or with both.

The Sf 12–20 and Sf 35–100 lipoproteins show strong association with atherosclerosis,
regardless of age or total serum cholesterol level. Thus, even for individuals with the same total serum cholesterol, be it low, moderate, or high, there is strong ability of the S₉ 12-20 and S₉ 35-100 lipoproteins to segregate atherosclerotics from normals.

Total serum cholesterol shows a much lower ability to segregate atherosclerotics from normals in the 41 to 50 year age group than the S₉ 12-20 and S₉ 35-100 lipoproteins. In the age group 51 to 60, while the lipoproteins maintain their strong association with atherosclerosis, there is only a borderline ability, if any, of the serum cholesterol to segregate atherosclerotics from normals.

4. What little association total serum cholesterol does have with atherosclerosis is wholly due to its partial correlation with the S₉ 12-20 and S₉ 20-100 lipoproteins, which are strongly associated with atherosclerosis. In essence, this means that approximately 10 per cent of the serum cholesterol is important for atherosclerosis (namely, the fraction in the S₉ 12-20 and S₉ 20-100 lipoproteins), while the remaining bulk, approximately 90 per cent, of the cholesterol is unassociated with atherosclerosis. As a result of the fact that the vast bulk of the serum cholesterol is in nonatherogenic lipoproteins, the measurement of total serum cholesterol in an over-all way, does more to obscure the atherosclerotic potentialities of an individual than to clarify them.

5. Even marked hypercholesteremia is not uniformly associated with atherosclerosis. The groups manifesting advanced atherosclerosis (including patients with coronary disease or xanthoma tuberosum) are strikingly segregated from equivalently hypercholesteremic individuals without manifest atherosclerosis by the S₉ 12-20 and S₉ 35-100 lipoprotein measurements.

6. The crude estimate of the factors which segregate atherosclerotics from normals, based upon biserial correlation, indicates that the combined S₉ 12-20 and S₉ 35-100 lipoproteins account for at least 35 per cent of the total etiologic factors. When the impurity of the normal population (i.e., admixture with atherosclerotics), the fallibility of diagnosis in the criterion group with coronary disease, the focal factors in atheroma formation, the difference between accumulated atherosclerosis and atherosclerotic activity, and the biologic and technical variation of measurement are all taken into consideration, the combined S₉ 12-20 and S₉ 35-100 lipoproteins will account for at least 75 to 80 per cent of the total variation between atherosclerotics and normals, and may very well account for the entire difference.

7. Follow-up studies have shown that early recurrence of myocardial infarction in patients with coronary disease is positively and highly related to the S₉ 12-20 lipoprotein levels. The recurrence rate of myocardial infarction is approximately 20 per cent per year for those patients with S₉ 12-20 levels of 100 mg. per 100 cc., whereas the recurrence rate is approximately 6 per cent for those patients with S₉ 12-20 levels of 50 mg. per 100 cc. It may be that when the combined S₉ 12-20 and S₉ 35-100 levels are evaluated, the relationship of recurrence with lipoprotein level may become stronger.

8. The occurrence of myocardial infarction, de novo, in normals is positively related to elevation in S₉ 12-20 lipoprotein levels.

9. The depression of high S₉ 12-20 levels by dietary restriction of fat and cholesterol has been shown to decrease significantly the chance of recurrence of myocardial infarction in patients with established coronary artery disease. At this time a significant statement on the point of dietary protection can be made on a follow-up of high-level patients with coronary disease (above 80 mg. per cent S₉ 12-20) only because their recurrence rate has provided significant data in a short period.

10. The demonstration that the S₉ 35-100 lipoproteins, in addition to the S₉ 12-20 lipoproteins, are associated with atherosclerosis is of especial significance with respect to the ingestion of fat. This class of lipoproteins, the S₉ 35-100 class, may be raised acutely in a high proportion of humans following ingestion of fat. In patients with a severe degree of the lipid metabolic derangement which leads to "abnormal" lipoprotein patterns, this S₉ 35-100 class of molecules is sustained even postabsorptively. It appears, since we have already demonstrated that a dietary lowering of the
Sf 12–20 lipoproteins has an ameliorative effect on coronary disease (based upon atherosclerosis), that dietary fat restriction is equally important, by way of depressing the Sf 35–100 level, in the effort to control atherosclerosis.

11. The rating of a patient with respect to atherosclerogenic potentialsities is best achieved by a measure of the levels of Sf 12–20 lipoprotein and Sf 35–100 lipoproteins. Of the two measures, the Sf 12–20 level is the more stable, not being acutely influenced by diet. The Sf 35–100 level, even though more variable acutely with diet, is nevertheless highly associated with atherosclerosis and provides valuable additional assessment with regard to atherosclerosis. Thus we may regard the Sf 12–100 lipoproteins as the “atherosclerogenic band” of the serum lipoproteins. The exact assessment of relative atherogenicity of each subsegment within this region is not now possible, so that, for the present, classification is made without weighting within this region.

Acknowledgments

As part of a long-term evaluation of the prognostic significance of lipoproteins in atherosclerosis, several groups are participating in the provision and evaluation of clinical subjects, in both normal and disease categories. The results of this follow-up will be published jointly by the cooperating groups. Some of the clinical material reported on in this paper has been furnished by such groups, for whose cooperation the authors are grateful. The groups involved are the Framingham Heart Project of the United States Public Health Service (Thomas Dawber, M.D.), The Los Angeles Civil Service Commission (Edward Phillips, M.D.), The Eastman Kodak Corporation (David Fassett, M.D.), The Pan American Airlines (Frederick Leeds, M.D.), The United Airlines (A. C. Ladd, M.D.), the Permanente Hospital (Morris Collen, M.D., and David DeKruif, M.D.), The Fort Miley Veterans Hospital (Gerald Whipple, M.D., and Gordon Hein, M.D.), The Medical Department of San Quentin Prison (Leo Stanley, M.D., and Justin Fuller, M.D.). Individual physicians furnishing material are Hyman Engelberg, M.D., Francis Chamberlain, M.D., Harry Akesson, M.D., Frank Anker, M.D., Norman Leet, M.D., William Donald, M.D., Alexander Yankley, M.D., Mary Lou Eilert, M.D., Dale Groom, M.D., Henry Kempe, M.D., and John Sampson, M.D.

We wish to acknowledge especially the encouragement and support of Mrs. Albert Lasker.

References

Blood Lipids and Human Atherosclerosis

JOHN W. GOFMAN, HARDIN B. JONES, THOMAS P. LYON, FRANK LINDGREN, BEVERLY STRISOWER, DAVID COLMAN and VIRGIL HERRING

Circulation. 1952;5:119-134
doi: 10.1161/01.CIR.5.1.119

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/5/1/119.citation

An erratum has been published regarding this article. Please see the attached page for:
http://circ.ahajournals.org/content/5/5/797.1.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
ABSTRACTS


The circulatory aspects of pulmonary insufficiency were studied by cardiac catheterization in 18 patients with chronic hypertrophic vesicular emphysema. The pressures found in the right side of the heart in cases of emphysema without heart failure were normal. In the presence of right ventricular failure, there was elevation of the ventricular pressure and of the mean intra-auricular pressure, as well as of the peripheral venous pressure. The right heart pressure was found to be lower in the sitting position than in the supine position, in opposition to the views of Sir Thomas Lewis.

Cardiac output in cases of emphysema without failure is also normal. The findings of McMichael and Sharpey-Schafer on cardiac output, the lack of value of digitalization in right heart failure and of the presence of a “hyperkinetic circulation” in patients with emphysema were not confirmed. They believed the fullness of the neck veins to be mechanical, due to a rise in intrapleural pressures from negative values to those approaching zero. The circulation times were normal.

BERNSTEIN

ERRATA

In the article “Blood Lipids and Human Atherosclerosis,” by Dr. John W. Gofman and associates (5: 119, 1952), the following change should be read in table 1: the Mean Serum Cholesterol Level for normal males in the 41-50 year age group should be 260 ± 53.

In the article “Surgery for Mitral Stenosis. A Review of Progress,” by Dr. Edward F. Bland (5: 290, 1952), the following changes should be read in table 2: the footnote “Operations by Drs. J. G. Scannell and R. Warren” applies to the entry “Author’s series (Boston)” rather than to the “Totals.” Please note that Dr. Warren has no middle initial.