Ischemic Heart Disease, Atherosclerosis, and Longevity

By John W. Gofman, M.D., Ph.D., Wei Young, Ph.D., and Robert Tandy

In the late 1940's Duff and McMillan made the remarkable observation that alloxan-diabetic rabbits developed equal or higher blood cholesterol levels, but markedly less atherosclerosis, than did nondiabetic rabbits fed an equivalent high-cholesterol diet. From the excessive visible lipemia characteristic of the alloxan-diabetic rabbits in this experiment, Duff and McMillan surmised that the physical state of blood cholesterol might be altered in the alloxanized animals and that this alteration might account for their lower degree of atherosclerosis.

During those same years, the difficulties attending the study of serum macromolecules in the ultracentrifuge were understood and resolved. It was shown that in humans and in several other mammalian species a spectrum of lipoproteins, bearing cholesterol, triglycerides, and phospholipids, existed spontaneously or could be induced by a variety of experimental means. In the rabbit it was demonstrated early that aortic atherogenesis, at least, was strongly related to the serum level of lipoproteins of a rather narrow size-range, the level of lipoproteins larger or smaller in size being unrelated to the rate of development of the atherosclerotic lesion. The Duff observations were explained when it was demonstrated that the alloxanized, cholesterol-fed rabbit transported its massive concentrations of cholesterol in lipoproteins of $S_r$ values greater than 80, with almost no transport in the form of atherosclerosis-associated $S_r$ 12-40 lipoproteins.

The obvious and exciting question presented itself, "Could a similar phenomenon be operative in the human population developing atherosclerosis of such critical arterial sites as the coronary or cerebral beds?" It was evident that such a question had to be studied in the human, for valid concern existed that rabbit atherosclerosis might bear little or no relationship to the stenotic arterial disease responsible for ischemic heart or brain disease in the human.

Two potential avenues of investigation were evident: (1) a study of the relationship of various serum lipoproteins to the occurrence of overt clinical ischemic disease, such as ischemic coronary heart disease; and (2) a study of the relationship of various serum lipoproteins to the degree of intimal arterial narrowing (a key feature of human atherosclerosis). Both avenues had much to commend them; both faced formidable obstacles and extensive requirements on the path to successful execution.

To a large extent, studies of both types have, by now, been completed. Certain apparent paradoxes seem to attend the results. Our purpose herein is to present all the evidence together with a framework which allows for at least a first-order, paradox-free understanding of how the various facets of evidence fit together.

The Relationship of Serum Lipids and Lipoproteins to Overt Clinical Ischemic Heart Disease

The early premise in this approach was that persons manifesting overt clinical ischemic heart disease at a given point in life must have been developing stenotic coronary artery disease at a greater rate than cohorts not manifesting clinical disease at that same point in life. Ideally, such information must be sought in a prospective study, that is, one in which

From the University of California, Bio-Medical Research Division, Lawrence Radiation Laboratory, Livermore, California.

This communication was presented as the Lyman Duff Memorial Lecture, entitled "Atherosclerosis, 1965," at the meeting of the Council on Arteriosclerosis, American Heart Association, Bal Harbour, Florida, October 13, 1965.
the “cases” of clinically overt heart disease arise out of an ostensibly healthy substrate sample of the population. Only in this way can it be assured that the “cohorts” truly are such. A study of this type that included measurement of serum cholesterol had been initiated by the United States Public Health Service at Framingham, Massachusetts. In 1950, through the participation of the Donner Laboratory, studies of the low-density lipoproteins in serum were added to the Framingham program. In 1953, a similar study, including serum cholesterol, low-density lipoproteins, and high-density lipoproteins in industrial employees of the Lawrence Radiation Laboratory at Livermore, California, was initiated. The results of 12 years of follow-up in the Framingham study and 10 years in the Livermore study will be presented here.

Retrospective Studies of Clinical Ischemic Heart Disease

Pending the anticipated long period for completion of the prospective studies, it was felt that preliminary insight might be obtained through the study of blood lipoproteins in cases of already established clinical ischemic heart disease, such as survivors of myocardial infarction. The prime advantage was that such cases were immediately available and in reasonably large numbers. But major disadvantages were also present: (1) The possibility that blood lipoprotein status might be non-representative in the postmyocardial infarction period was not readily to be ruled out in an unequivocal manner. (2) Even more distressing, was the inordinate difficulty in assuring a proper choice of cohorts without overt ischemic heart disease. The cases of clinically overt ischemic heart disease came from hospital sources, from physicians’ practices, or from the affected individuals still at work in industrial populations under study. Establishment of true “cohorts,” including such variables as weight status, lipid status, and blood pressure status, was painful at best, and never really successful. Nevertheless, highly suggestive information did emerge from those early studies, but always with the reservation that the prospective study might alter at least some quantitative aspects of the conclusions. For example, the mean levels of four serum lipoprotein classes, \( S_f^* \, 0-12 \), \( S_f^* \, 12-20 \), \( S_f^* \, 20-100 \), and \( S_f^* \, 100-400 \), and of the serum cholesterol were significantly elevated in the clinical ischemic heart disease cases contrasted with “ostensible cohorts,” matched by age and sex.\(^8\,10\)

A major objective of all such studies was to determine whether, for the human coronary arteries, any particular segment of the entire lipoprotein spectrum was the atherogenic segment or was more atherogenic than bordering segments, as had already been clearly demonstrated for aortic atherogenesis in the rabbit. It became clear that the weighting factors, expressing the relative importance to atherogenesis of individual segments of the lipoprotein spectrum, were extraordinarily sensitive both to the source of clinical material and to “ostensible cohort” selection. As a result, a more limited objective was attempted, namely, to assign a relative weighting factor to two broad bands in the lipoprotein spectrum, the \( S_f^* \, 0-12 \) and the \( S_f^* \, 12-400 \) classes. To provide some working basis for ongoing studies, pending completion of the prospective studies, a function was defined as follows:

Atherogenic index, or A.I. =

\[
0.1 \left( S_f^* \, 0-12 \right) + 0.175 \left( S_f^* \, 12-400 \right).
\]

The choice of 0.175 was made by the linear discriminant analysis of the then existing clinical cases plus its “ostensible cohort population.” It has been repeatedly stressed\(^11,\,12\) that this relative importance factor was based upon the study of survivors of myocardial infarction, that the prospective study might very well alter it, and further that some part of the spectrum from \( S_f^* \, 0 \) to \( S_f^* \, 400 \) might drop out of consideration with respect to provision of an independent contribution to development of disease.\(^13\)

Still another difficulty arose early in the study of already established clinical ischemic heart disease. Both for the serum cholesterol measure and for the low-density lipoprotein measures, the difference between overt disease and “ostensible cohorts” decrease markedly
with increasing age of the subjects.\textsuperscript{11, 14} This extremely important feature was itself sorely bedeviled by the "appropriate cohort" problem. Here again, only the prospective studies could be expected to provide resolution and understanding. There were some who inferred from the age-dependent difference that several different diseases were involved, one or several for young subjects, another, or several others, for older subjects.\textsuperscript{15} Others suggested that the wrong lipid parameters were being measured, and that the proper parameter would not show such an age-dependent relation.\textsuperscript{16} Neither of these suggestions has ever appeared reasonable or attractive to the present authors. Indeed, the considerations below will lead to a single unifying concept to explain this age-related phenomenon, the existence of which has been amply confirmed in the prospective studies.

**Prospective Studies of Clinical Ischemic Heart Disease**

Sufficient numbers of de novo cases of ischemic heart disease have now arisen both in the Framingham and the Livermore studies to warrant examination of the results. However, even from some 357 new events in the two studies combined, certain questions are still difficult to answer with high confidence.

The first set of results is that for the Framingham study, including the serum lipoprotein and cholesterol data determined at Donner Laboratory (records of which have been on file at the National Heart Institute for over 10 years). Through the generosity of Dr. Thomas R. Dawber, the director of the Framingham study, a listing of de novo cases arising during 12 follow-up years has been made available for this evaluation. Included in this group are an appreciable number of subjects for whom serum lipoprotein and cholesterol measurements are available for two examinations, 1 to 3 years apart, before the occurrence of de novo ischemic heart disease. For such a group, errors due to technical and biological variation are minimized, and hence the results for this group are presented separately.

The second set of results is for 1,961 male subjects employed at Livermore and studied initially between 1954 and 1957. The follow-up period is approximately 10 years. The records of the cases of de novo ischemic heart disease have been made available for this study through the cooperation of Dr. Max Biggs, Medical Director at Lawrence Radiation Laboratory, Livermore, and his staff, and through the diligent efforts of Mrs. Margaret Soderberg of the Bio-Medical Research Division there. This second, independent study allows examination of the possibility, always considered remote, that some special or non-representative feature might be present in the Framingham population sample. It also allows examination of the high-density lipoproteins in relation to the prospective occurrence of ischemic heart disease.\textsuperscript{*}

Test of the Hypothesis That Levels of Certain Serum Lipoproteins and Serum Cholesterol Are Elevated in Advance of de novo Ischemic Heart Disease

**The Framingham Study.** All subjects for whom lipoprotein measurements are available are included in this analysis with the following exceptions: (1) subjects with definite heart disease at entry to the study, and (2) diabetics known to be such at entry. New cases of heart disease arising in Framingham are provided (in nonduplicative manner) in five categories of ischemic heart disease: (1) myocardial infarction, (2) coronary heart disease (death, but not sudden), (3) coronary insufficiency, (4) sudden death, and (5) angina pectoris. The basis for this reporting system has been described in publications of the broader aspects of the Framingham study.\textsuperscript{17–19} While for certain purposes it might be important to use only the group with the apparently strongest manifestation of ischemic heart disease, there is a distinct overriding rationale for combining all cases into one group, labeled "de novo ischemic heart disease" (I.H.D.). The rationale is that the true problem to which we address ourselves is the stated "epidemic of our time—ischemic coronary heart disease," rather than any

\textsuperscript{*}In all the tables the data are for the Framingham population sample except where specifically labeled as Livermore.
subsegment thereof. No significant differences exist either for serum lipoproteins or serum cholesterol between the strongest diagnostic category of de novo ischemic heart disease, that is, myocardial infarction, and the other four categories combined.

The findings in 221 cases of de novo ischemic heart disease in men and in 98 cases of such disease in women are presented in tables 1 and 2, respectively. The mean ages noted in those tables are the means for the group of de novo cases at the time of entry into this study. In both tabulations the de novo cases are compared with the substrate population out of which they arose, with all parameters adjusted to match the de novo cases upon the variable of age. Age-matching was achieved in the following manner. Since the de novo cases include cases from the 30-39, 40-49, and 50-69 year age groups, the mean parameter values for the substrate age groups were weighted in the same proportion as the distribution of de novo cases. A similar procedure was adopted to provide a weighted standard deviation in the base population values. Failure to make such an age-matching can lead to deceptive results.

For men, it can be stated, at or beyond the $P=0.001$ level of confidence, that $S_t^0$ 0-12, $S_{t}^0$ 12-20, $S_{t}^0$ 20-100, $S_{t}^0$ 100-400 lipoproteins, the atherogenic-index (A.I.) function, the serum cholesterol level, the systolic and diastolic blood pressures, and the relative weight are all elevated in those destined to develop ischemic heart disease during a 12-year period following initial study. However, as a result of correlation, imperfect but definite, between several of the measured variables, it is not possible to translate the positive findings into any statement of independent contribution of each variable to the predictive association with ischemic heart disease. Even this series of 221 cases of de novo ischemic heart disease suffers from sufficiently large standard errors of the difference in means (I.H.D. vs. base population) for several measures to preclude a reliable assessment of weighting factors, and, in turn, strength of independent contribution. The analogous data for women show similar trends, but for all the measures of lipid and lipoprotein, the differences between I.H.D. and base population are much smaller than they are for men. Also the overall group of women with de novo ischemic heart disease is 5 years older at entry than the corresponding overall group of men.

### Table 1

<table>
<thead>
<tr>
<th>Measure</th>
<th>Donovo I.H.D.</th>
<th>Base Population</th>
<th>Difference</th>
<th>Significance Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donovo</td>
<td>De novo Cases</td>
<td>(221 Subjects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td>386.3</td>
<td>359.2</td>
<td>27.3</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>12-20</td>
<td>76.4</td>
<td>67.0</td>
<td>9.4</td>
<td>$p=0.001$</td>
</tr>
<tr>
<td>20-100</td>
<td>120.9</td>
<td>108.2</td>
<td>12.7</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>100-400</td>
<td>94.0</td>
<td>76.7</td>
<td>17.3</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>A.I.</td>
<td>89.2</td>
<td>80.0</td>
<td>9.2</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>249.0</td>
<td>230.7</td>
<td>18.3</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Systolic B.P</td>
<td>143.8</td>
<td>136.3</td>
<td>7.5</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Diastolic B.P</td>
<td>91.8</td>
<td>88.5</td>
<td>3.3</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Relative Wt</td>
<td>116.3</td>
<td>113.2</td>
<td>3.1</td>
<td>$p&lt;0.001$</td>
</tr>
</tbody>
</table>

| Base Population (2022 Subjects) |

### Table 2

<table>
<thead>
<tr>
<th>Measure</th>
<th>Donovo I.H.D.</th>
<th>Base Population</th>
<th>Difference</th>
<th>Significance Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donovo</td>
<td>De novo Cases</td>
<td>(98 Subjects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12</td>
<td>385.4</td>
<td>364.7</td>
<td>18.7</td>
<td>$p=0.002$</td>
</tr>
<tr>
<td>12-20</td>
<td>94.4</td>
<td>90.2</td>
<td>4.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>20-100</td>
<td>109.8</td>
<td>96.1</td>
<td>13.7</td>
<td>$p=0.002$</td>
</tr>
<tr>
<td>100-400</td>
<td>57.7</td>
<td>50.3</td>
<td>7.4</td>
<td>N.S.</td>
</tr>
<tr>
<td>A.I.</td>
<td>84.2</td>
<td>76.2</td>
<td>8.0</td>
<td>$p=0.001$</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>267.2</td>
<td>253.5</td>
<td>13.7</td>
<td>$p=0.005$</td>
</tr>
<tr>
<td>Systolic B.P</td>
<td>161.6</td>
<td>149.0</td>
<td>12.6</td>
<td>$p=0.001$</td>
</tr>
<tr>
<td>Diastolic B.P</td>
<td>94.8</td>
<td>90.5</td>
<td>4.3</td>
<td>$p=0.001$</td>
</tr>
<tr>
<td>Relative Wt</td>
<td>126.0</td>
<td>121.0</td>
<td>5.0</td>
<td>$p&lt;0.002$</td>
</tr>
</tbody>
</table>

| Base Population (1689 Subjects) |

The data for men are subdivided into four categories in tables 3 to 6, utilizing age groups 30-39 years, 40-49 years, 50-55 years, and 56-69 years. For all lipid and lipoprotein parameters the differences (I.H.D. vs. base population) are much greater for the 30-39 year group than for those above 40 years. As for the overall group, the standard errors of differences in means for I.H.D. versus base population do not allow accurate assessment of independent weighting factors for the age subcategories. Overall, it appears clear that
these prospective studies do not support a weighting factor of 1.75 for the S<sub>1</sub> 12-400 lipoprotein classes in comparison with 1.00 for the S<sub>1</sub> 0-12 lipoprotein class.

The similar breakdown for women is available in tables 7 to 9. In both men and women the segregation of de novo ischemic heart disease from the base population by any of the lipid or lipoprotein parameters is weak indeed in the older age groups. It will be recalled that the early retrospective studies of the 1950's suggested this age-related phenomenon; the prospective studies prove it beyond doubt. Kagan and associates have already called attention to the loss in segregation power of the serum cholesterol measure in women over 50 years of age.

It should be asked whether some feature
of this study itself accounts for the decreasing power of segregation of ischemic heart disease through blood lipid parameters with increasing age. The possibility that a 12-year follow-up period might have washed out segregation was checked by dividing the entire study into two 6-year follow-up periods. No appreciable difference in segregation upon any lipid or lipoprotein parameter was apparent for the first 6 years versus the second 6 years. The possibility that combined biological plus technical error might result in loss of segregation power was evaluated by consideration of individuals who had been studied twice prior to the occurrence of de novo ischemic heart disease. The mean value of each parameter was used in this evaluation. While the base population available for this evaluation was much smaller than the overall group, it is clear that the multiply sampled group does not demonstrate appreciably improved segregation of de novo ischemic heart disease from the base population.

Lastly, could the loss of segregation power of blood lipid parameters with increasing age be accounted for by some characteristic(s) peculiar to the Framingham population sample? Here the follow-up results of the Livermore study are pertinent. The comparison of de novo ischemic heart disease and base population is presented in table 10. The overall lipid differences, in men, for I.H.D. versus base population appear larger for the Livermore sample than for the Framingham group. However, the mean age at entry to study is 43.7 years for the I.H.D. group at Livermore versus 49.2 years at Framingham, so that the larger differences in the Livermore group are consistent with the general trends observed within the Framingham study. Thus, the Livermore results are entirely consistent with the Framingham results. This similarity speaks against any peculiarity of either sample being responsible for the age trend in segregation by blood lipid parameters. Presented in tables 11 to 13 are the strengths of the lipid parameter segregation as a function of age for three variables, S° 0-12, A.I., and serum cholesterol for the Framingham and Livermore studies. The similarities are striking, both with respect to absolute values and changes in relation to age. Beyond age 55 years, none of the data demonstrate any significant segregation power for blood lipid parameters.

$S^{°} 20-100$, $S^{°} 100-400$, High-Density Lipoproteins, Pre-A-I-Lipoprotein, and Triglycerides in Relation to Segregation of Ischemic Heart Disease

As mentioned earlier, a major objective of all such endeavors is to determine for the human lipoprotein spectrum the lower and upper limits with respect to association with ischemic heart disease. Ultimately, it is not enough to prove association of a particular lipoprotein class with the disease; rather, it is necessary to know whether an independent contribution to the association is made by that particular lipoprotein class. In the Framingham data, the S° 100-400 class is significantly elevated in the 30-39 year old group with de novo ischemic heart disease versus the base population. In no other age category studied could this class be shown to be
Table 11

**MEN**

AGE vs. Lipid Parameter Segregation Of DeNovo Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>A.I.</th>
<th>Cholesterol</th>
<th>Sf° O-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>35.7</td>
<td>102.1</td>
<td>-4.1</td>
</tr>
<tr>
<td>40-49</td>
<td>45.3</td>
<td>89.8</td>
<td>8.9</td>
</tr>
<tr>
<td>50-55</td>
<td>52.7</td>
<td>88.9</td>
<td>-8.9</td>
</tr>
<tr>
<td>55-69</td>
<td>58.2</td>
<td>82.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Mean Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>267.7</td>
<td>249.5</td>
<td>238.2</td>
</tr>
<tr>
<td>Base Population</td>
<td>76.6</td>
<td>82.3</td>
<td>80.9</td>
</tr>
<tr>
<td>I.H.D.-Base</td>
<td>25.5</td>
<td>7.5</td>
<td>8.0</td>
</tr>
</tbody>
</table>

**BASED UPON:**
- DeNovo I.H.D.
  - □ = 32 CASES ARISING IN 687 SUBJECTS
  - ◆ = 76 CASES ARISING IN 678 SUBJECTS
  - ▲ = 51 CASES ARISING IN 353 SUBJECTS
  - ⬣ = 62 CASES ARISING IN 304 SUBJECTS

Table 12

**WOMEN**

AGE vs. Lipid Parameter Segregation Of DeNovo Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>A.I.</th>
<th>Cholesterol</th>
<th>Sf° O-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-49</td>
<td>44.4</td>
<td>66.3</td>
<td>-11.9</td>
</tr>
<tr>
<td>50-55</td>
<td>52.7</td>
<td>87.7</td>
<td>86.6</td>
</tr>
<tr>
<td>56-69</td>
<td>58.7</td>
<td>86.6</td>
<td>260.4</td>
</tr>
<tr>
<td>Mean Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>274.0</td>
<td>259.1</td>
<td>367.1</td>
</tr>
<tr>
<td>Base Population</td>
<td>67.1</td>
<td>78.6</td>
<td>83.2</td>
</tr>
<tr>
<td>I.H.D.-Base</td>
<td>-0.8</td>
<td>9.1</td>
<td>3.4</td>
</tr>
</tbody>
</table>

**BASED UPON:**
- DeNovo I.H.D.
  - □ = 19 CASES ARISING OUT OF 1635 SUBJECTS
  - ◆ = 39 CASES ARISING OUT OF 468 SUBJECTS
  - ▲ = 43 CASES ARISING OUT OF 384 SUBJECTS

significantly elevated. The data for the 30-39 year old Framingham group are not good enough to resolve the issue of independent contribution from Sf° 100-400 lipoproteins. The observed elevation could be due in part, or even in whole, to interclass correlations. The weakness of segregation power for Sf° 100-400 in all other groups suggests that
the contribution must be lower than that for the other classes. Precise establishment of the upper limit of the lipoprotein spectrum for association with ischemic heart disease is not possible. While segregation power appears to drop above $S_f^0 100$, some importance cannot be ruled out for lipoproteins of $S_f^0 > 400$.

On the other side of the lipoprotein spectrum are the high-density lipoproteins HDL$_2$ and HDL$_3$ and a class known as HDL$_1$, lying between the low- and high-density lipoproteins. No measurements of these classes were available for the Framingham population sample. In the Livermore study, all three

### Table 13

**MEN**
(Livermore)
10 yr. Followup

**AGE vs. Lipid Parameter Segregation Of DeNovo Ischemic Heart Disease**

<table>
<thead>
<tr>
<th></th>
<th>A.I.</th>
<th>Cholesterol</th>
<th>$S_f^0$ 0-12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic Heart Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LESS THAN 45 YRS.</td>
<td>96.7</td>
<td>280.5</td>
<td>451.0</td>
</tr>
<tr>
<td>45 + YRS.</td>
<td>81.6</td>
<td>249.6</td>
<td>402.5</td>
</tr>
<tr>
<td><strong>Base Population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LESS THAN 45 YRS.</td>
<td>73.0</td>
<td>231.7</td>
<td>365.0</td>
</tr>
<tr>
<td>45 YRS. OR OLDER</td>
<td>76.8</td>
<td>239.4</td>
<td>381.7</td>
</tr>
<tr>
<td><strong>I.H.D.-Base</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LESS THAN 45 YRS.</td>
<td>23.7</td>
<td>48.8</td>
<td>86.0</td>
</tr>
<tr>
<td>45 + YRS.</td>
<td>4.8</td>
<td>10.2</td>
<td>20.8</td>
</tr>
</tbody>
</table>

21 CASES LESS THAN 45 YRS. (MEAN AGE = 38.0 YRS.)
17 CASES 45 YRS. OR OLDER (MEAN AGE = 50.8 YRS.)

### Table 14

**MEN**
Age Group 20-66 yrs.
Mean Age = 43.7 yrs.
10 yr. Followup
LIVERMORE

**DeNovo Ischemic Heart Disease (38 Cases)**

**VS.**

**Base Population (1961 Subjects)**

(HIGH DENSITY LIPOPROTEINS)

<table>
<thead>
<tr>
<th>Measure</th>
<th>DeNovo I.H.D.</th>
<th>Base Population</th>
<th>Difference</th>
<th>Significance Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. D. L$_1$</td>
<td>25.6</td>
<td>25.0 ± 16.8</td>
<td>0.6</td>
<td>N. S.</td>
</tr>
<tr>
<td>H. D. L$_2$</td>
<td>25.8</td>
<td>38.0 ± 29.1</td>
<td>-12.2</td>
<td>$p=0.01$</td>
</tr>
<tr>
<td>H. D. L$_3$</td>
<td>204.8</td>
<td>223.6 ± 47.8</td>
<td>-18.8</td>
<td>$p=0.02$</td>
</tr>
</tbody>
</table>

* MEAN ± STANDARD DEVIATION OF DISTRIBUTION
classes, HDL1, HDL2, and HDL3 were measured for all subjects. The results for de novo ischemic heart disease and base population sample are presented in Table 14. It is evident that no segregation of ischemic heart disease can be proved for HDL1 lipoproteins. Both HDL2 and HDL3 classes are significantly lower in the cases of de novo ischemic heart disease than in the base population. It is known that levels of both HDL2 and HDL3 are inversely correlated with levels of the low-density lipoproteins, Sf0 0-400.11, 20 From these data it is not observed lowering of HDL0 and HDL3 in ischemic heart disease are in excess of those anticipated from the inverse correlations. This, again, would ultimately be desirable information, since if there is any lowering beyond that expected from interclass correlations, the possibility of a protective role of high-density lipoproteins would require consideration. The lowering of HDL2 and HDL3 lipoprotein classes is consistent with reports from Barr’s group21, 22 concerning chemically measured α-lipoproteins in retrospective studies of myocardial infarction.

Recently Albrink and associates16 published data on serum triglyceride in a small series of 50-59 year old male survivors of myocardial infarction. They concluded that serum triglyceride level shows powerful segregation of ischemic heart disease vs. base population for the age group above 50 years and suggest further that poor segregation in this age group is the result of measurement of less consequential blood lipid parameters. Their study of myocardial infarction survivors is fraught with all the difficulties described above for the choice of an appropriate base population for comparison with the infarction survivors. They speculated that the triglyceride elevation is probably due to elevation in the very low-density, glyceride-rich Sf0 20-400 lipoproteins. Our data are clearly at variance with the conclusions of Albrink and associates, since the segregation power beyond 50 years of age, while poor in general for all blood lipid parameters, seems especially poor for the triglyceride-rich Sf0 20-400 lipoproteins. Carlson,23 who also studied myocardial infarction survivors, concluded that serum triglyceride segregation is poor in patients beyond 50 years of age. Fredrickson and Lees,24 quoting Besterman’s data25 on infarction survivors, remarked on the powerful segregation of myocardial infarction survivors measured electrophoretically by pre-β-lipoproteins, which are known to be essentially equivalent to Sf0 20-400 lipoproteins.

The only prospective study of this question is that reported herein for Sf0 20-400 lipoproteins in the Framingham and Livermore populations. Since segregation power for such lipoproteins is poor for persons beyond 50 years of age, it is likely that, when serum triglyceride and pre-β-lipoprotein measures are subjected to the careful scrutiny of a prospective study, they also will prove equally poor for such age groups.

Estimation of Ischemic Heart Disease Risk from Blood Lipid Parameters

The broad outlines of what may be expected in predictive power of lipoproteins of any class from Sf0 0 to Sf0 400, for A.I., or for serum cholesterol is evident from the behavior of the differences in means (I.H.D. vs. base population), for the several age groups under consideration. Predictive power for de novo ischemic heart disease should be appreciable in the young age group and should deteriorate with increasing age. Tables 15 and 16, which provide incidence rate of ischemic heart disease for the population ranked in deciles, demonstrate precisely this trend for A.I. and serum cholesterol in men in the Framingham study. It is evident that above 55 years there is essentially no predictive power. The age trend is not clear cut for women within these data, but predictive power for women more than 55 years of age does not exist. Since it appears unlikely that a variation in technique of measurement of blood lipoproteins or lipids will materially alter this situation, it is appropriate to consider certain major implications of these findings.

If, for any blood lipid parameter, the difference in value between I.H.D. and the base
population approaches zero, and if the distribution of values of that parameter about the central value is similar in the de novo I.H.D. group and the base population, then it follows that the risk of future ischemic heart disease in such a population is independent of the blood lipid parameter, even for widely differing values of the parameter. It follows, further, that under such circumstances, there would exist no rationale for the expectation that dietary or pharmacological alteration of such blood lipid parameters might alter the risk of de novo ischemic heart disease in such a population.

Circulation, Volume XXXIV, October 1966
Relationship of Serum Lipids and Lipoproteins to Degree of Arterial Narrowing

The study of atherosclerosis in autopsy material from subjects whose blood lipid and lipoprotein parameters had been determined during life represents the second major avenue of approach. Such a prospective study has been carried out by Paterson and his co-workers.26, 27 Ideally, such studies should cover the same age ranges (30-69 years) as do the prospective studies of the development of de novo clinical ischemic heart disease. The difficulties attendant upon such a study, especially for the younger age groups, are self-evident. Hence, the youngest group available in the Paterson study is the 60-69 year age category. In spite of the limitations in age range, the findings of that study are instructive. Multiple determinations of low-density lipoproteins, A.I. values, and serum cholesterol were performed in a population sample of institutionalized psychotic individuals. The choice of a psychotic population sample for such a study may be questioned. No known factors about psychotic subjects would lead one to expect a distortion of relationship between blood lipid parameters and atherosclerosis. Nevertheless, generalization of results to nonpsychotic population samples is subject to reservations on this issue. For those for which autopsy was available, the lipid parameters during life were compared with degree of atherosclerosis of coronary arteries measured at autopsy. Since blood lipid parameters were measured on a regular basis during life, the values are, for many of the cases, much more reliable as indices of blood lipid status than a single determination would be. The grading system for degree of atherosclerosis was certainly not of the quantitative type reported by Young and associates.28 However, it is doubtful that this materially perturbed the central findings that emerged from Paterson's study. Essentially it was demonstrated by Paterson and associates, that the degree of coronary artery atherosclerosis was unrelated, or at best very weakly related, to the blood levels during life of serum cholesterol, A.I., or individual lipoprotein classes for the 60-69 year group of subjects. There is no reason to question the validity of the observations. There is excellent reason to question their interpretation of these findings.

Paterson and associates interpreted the absence of relationship between blood lipid parameters and degree of coronary sclerosis as sounding the death knell for the blood lipid theory of atherogenesis. If these were the only existing data relevant to the problem, it would be fair to agree that, at least for 60-69 year old men (assuming his population sample to be representative), blood lipid parameters are unrelated to degree of atherosclerosis in the coronary arteries. Since no studies are available for men in the younger age categories, the Paterson data allow for no conclusions concerning these age groups. The Paterson group has stated27 that this point is not relevant, as follows: "We do not concede, of course, that a man in his sixties is very old." From considerations to be elaborated herewith, it may well be concluded that 60-69 years of age is indeed very old for coronary atherogenesis.

It is of prime importance at this point to consider how the findings of the Paterson group concerning the degree of coronary atherosclerosis at autopsy compare with the conclusions reached from the study of de novo ischemic heart disease in the Framingham and Livermore population samples. The Paterson data are restricted to the 60-69 year age category, so the appropriate comparative evidence concerning clinical ischemic heart disease is for this same age group.

The basic premise (vide supra) is that blood lipid parameters derive predictive ability for de novo ischemic heart disease indirectly via relationship of blood lipid parameters with coronary atherosclerosis. Since no significant difference could be proved to exist between de novo I.H.D. and base population for subjects over 55 years of age, the conclusion would be drawn that blood lipid parameters are unrelated to coronary atherosclerosis in subjects above 55 years of age. Thus, the Paterson
autopsy findings are precisely those to be expected from the study of de novo ischemic heart disease in the Framingham and Livermore groups. Unfortunately, but for excellent reasons, the Paterson studies provide no evidence concerning the relationship of blood lipid parameters to coronary atherosclerosis in the 30-39 year age group—a group in which risk of de novo ischemic heart disease is strongly related to blood lipid parameters.

Interpretation of the Studies of de novo Ischemic Heart Disease and Coronary Atherosclerosis

None of the observational material presented so far gives any conflicting evidence or real paradoxes. Some integration of all the findings is, however, highly desirable. The central question is, "Why should blood lipid parameters be related to risk of ischemic heart disease (and presumably with coronary atherosclerosis) at approximately 35 years of age, and lose such relationship beyond 55 years of age?" At the outset it can be stated that there is no a priori reason to expect that a relationship between blood lipid parameters and coronary atherosclerosis should be equally strong at all ages or that it should change in any prescribed manner. An understanding of the age-dependence of such relationship depends upon an insight into the process of atherogenesis. There are ancillary items of evidence concerning atherosclerosis that are relevant to such insight. Several years ago Young and associates28-31 conducted an extensive quantitative study of human coronary and cerebral intimal sclerosis. In those studies histological cross-sections of arteries were quantitatively described with respect to degree of sclerosis. The area (in cross-section) of tissue internal to the internal elastic lamella was determined by planimetry and designated as I. The total arterial cross-section area was designated as E. Intimal sclerosis was defined as I/E, the area of intimal tissue per unit cross-section of artery. No differentiation was made between lipids and any other space-occupying material in the intima. While some observers may debate assignment of all intimal material as sclerotic material, there is a reasonable basis for regarding the quantity of intimal material in a "normal" artery to be negligible. In any event, this particular issue can be bypassed, since the operational definition of I/E is clear.

Several important generalizations emerged from those studies: (1) There was an extremely high degree of correlation of I/E values for any particular cerebral artery with I/E values for all other cerebral arteries (Table 17). This evidence suggests strongly that a general factor is implicated in the pathogenesis of the human cerebral arterial lesion. Blood lipid level could be such a general factor, since the same blood bathes all regions of the cerebral artery bed. (2) There was a moderately high correlation of I/E values between certain parts of the coronary arterial bed and a relatively poor correlation of I/E values between other parts (Table 18). No general factor, such as blood lipid

<table>
<thead>
<tr>
<th>Table 17</th>
<th>Correlations of Degree of Atherosclerosis Within the Cerebral Artery Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient (Pearson r)</td>
</tr>
<tr>
<td>Middle cerebral artery vs. average of all cerebral branches</td>
<td>+ 0.96</td>
</tr>
<tr>
<td>Posterior cerebral artery vs. average of all cerebral branches</td>
<td>+ 0.95</td>
</tr>
<tr>
<td>Carotid and basilar arteries vs. average of all cerebral branches</td>
<td>+ 0.92</td>
</tr>
<tr>
<td>Anterior cerebral artery vs. average of all cerebral branches</td>
<td>+ 0.89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 18</th>
<th>Correlations of Degree of Atherosclerosis Within the Coronary Artery Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient (Pearson r)</td>
</tr>
<tr>
<td>Left circumflex branch vs. average of all coronary branches</td>
<td>+ 0.82</td>
</tr>
<tr>
<td>Anterior descending branch vs. average of all coronary branches</td>
<td>+ 0.80</td>
</tr>
<tr>
<td>Right coronary artery vs. average of all coronary branches</td>
<td>+ 0.74</td>
</tr>
<tr>
<td>Left anterior descending branch vs. average of all coronary branches</td>
<td>+ 0.60</td>
</tr>
<tr>
<td>Left main coronary branch vs. average of all coronary branches</td>
<td>+ 0.44</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXIV, October 1966
level, can explain this finding. Therefore, these latter data bespeak the operation of a strong focal factor in determination of degree of sclerosis, varying appreciably in different regions of the coronary bed of a single individual. (3) Of especial consequence in the present considerations was the demonstration, both in the coronary and cerebral arterial beds, that I/E values are strongly related to arterial radius (see tables 19 and 20). In the cerebral arteries, the I/E value was proportional to arterial radius over the range of radii existing in that bed. In the coronary arteries, where the average degree of sclerosis in I/E units is higher than that for the cerebral arteries at any particular radius, the linear relationship between I/E and arterial radius existed for radii less than 2.0 mm. Above this radius value, the I/E value did not appear to change with radius at least up to 2.5 mm. Certainly no general factor, such as blood lipid level, can explain this radius effect.

At this juncture it is not necessary to understand how arterial radius comes to be related to intimal sclerosis expressed in I/E units. But the existence of the relationship in arteries of 60-89 year old men is not disputable. Young and associates suggested that the radius relation might operate to decelerate the rate of development of new atherosclerosis as the radius of any particular artery is reduced through accumulation of intimal material.

### Construction of a Model of Atherogenesis

Let us now consider a simple model of the development of cerebral and coronary intimal sclerosis utilizing the above findings. (1) Assume that atherosclerosis proceeds by concentric reduction of arterial radius. (Actually eccentricity is more common in advanced disease, but we may reserve this consideration as possibly a second-order correction to the model.) (2) Assume that some blood lipid parameter operates as a general factor in all arteries developing sclerosis. (3) Assume that for each artery segment the focal factor can be expressed as a single value.

Thus,

\[ \text{let } r = \text{radius of lumen of artery at time } t, \]
\[ \text{let } \frac{\text{dr}}{\text{dt}} = \text{accumulation of sclerotic intimal material.} \]

Assume that this can be described in terms of radius reduction, \(-\text{dr},\)

\[ \text{let } k = \text{the focal factor in any particular artery (differing within and between individual subjects), and} \]

\[ \text{let } c = \text{the value of the pertinent blood lipid parameter (in this first approximation the same blood lipid parameter will be assumed to operate for all arterial beds).} \]

Now, explore first the simplest possible dependence of accumulation of sclerosis upon \(k, \ c, \ \text{and } r.\) Such a dependence is written for any particular arterial segment as

\[-\text{dr} = (k)(c)(r)\text{dt} \quad \text{or} \quad \frac{\text{dr}}{r} = (k)(c)\text{dt}. \quad (1)\]

Integrating,

\[ \ln \frac{r}{r_0} = -kct, \text{ assuming } r = r_0 \text{ at some arbitrary time taken as 0 time for the process} \]

or \(r = r_0e^{-kct}.\)

### Table 19

**Table 19**

<table>
<thead>
<tr>
<th>No. of sections</th>
<th>Range of radius (mm)</th>
<th>Mean radius (mm)</th>
<th>(I/E)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>2.1-2.5</td>
<td>2.246</td>
<td>58.5</td>
</tr>
<tr>
<td>151</td>
<td>1.6-2.0</td>
<td>1.700</td>
<td>49.0</td>
</tr>
<tr>
<td>518</td>
<td>1.1-1.5</td>
<td>1.214</td>
<td>32.0</td>
</tr>
<tr>
<td>354</td>
<td>0.6-1.0</td>
<td>0.867</td>
<td>19.8</td>
</tr>
<tr>
<td>2</td>
<td>0.2-0.5</td>
<td>0.470</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Note: \((I/E)b = \text{atherosclerosis of the brain, where } I = \text{intimal material area; } E = \text{total arterial cross-section area; and } b = \text{brain.}\)

### Table 20

**Table 20**

<table>
<thead>
<tr>
<th>No. of sections</th>
<th>Range of radius (mm)</th>
<th>Mean radius (mm)</th>
<th>(I/E)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>2.6-3.0</td>
<td>2.672</td>
<td>58.2</td>
</tr>
<tr>
<td>152</td>
<td>2.1-2.5</td>
<td>2.206</td>
<td>58.5</td>
</tr>
<tr>
<td>212</td>
<td>1.6-2.0</td>
<td>1.737</td>
<td>55.0</td>
</tr>
<tr>
<td>228</td>
<td>1.0-1.5</td>
<td>1.253</td>
<td>43.8</td>
</tr>
<tr>
<td>118</td>
<td>0.5-1.0</td>
<td>0.798</td>
<td>28.1</td>
</tr>
</tbody>
</table>

Note: \((I/E)c = \text{coronary atherosclerosis, where } I = \text{intimal material area; } E = \text{total arterial cross-section area; and } c = \text{coronary artery.}\)
At time t, the degree of sclerosis in \((I/E)\) units is expressed as follows:

\[
(I/E)_t = \frac{\pi r_o^2 - \pi r^2}{\pi r_o^2} = \frac{r_o^2 - r^2}{r_o^2}.
\]

Substituting for \(r\), we have

\[
(I/E)_t = \frac{r_o^2 - r_o^2 e^{-2kct}}{r_o^2}
\]

and

\[
(I/E)_t = 1 - e^{-2kct}.
\]

But this result is clearly at variance with the observation which shows I/E values to be related to initial arterial radius. Therefore, this simple relationship (equation 1) cannot be correct.

Let us next assume dependence upon \(r^2\) rather than \(r\), writing

\[-dr = (k)(c)(r^2)dt, \text{ or } -\frac{dr}{r^2} = (k)(c)dt.\]  

Integrating,

\[
\frac{1}{r} \frac{1}{r_o} = kct, \text{ with } r = r_o \text{ at some arbitrary time taken as 0 for this process.}
\]

\[
\frac{1}{r} = \frac{1}{r_o} + kct
\]

\[
r = \frac{r_o}{1 + r_o(kct)}
\]

\[
(I/E)_t = \frac{\pi(r_o^2 - r^2)}{\pi r_o^2}, \text{ and substituting for } r,
\]

\[
(I/E)_t = \frac{r_o^2 - r_o^2}{r_o^2}(1 + r_o(kct))^2
\]

\[
(I/E)_t = 1 - \left(\frac{1}{(1 + r_o(kct))^2}\right).
\]

It is evident that in this relationship, \((I/E)_t\) is a function of initial radius \(r_o\), and that for particular values of \(k\), \(c\), and \(t\), the degree of sclerosis, \((I/E)_t\), increases with increase in \(r_o\). Also, the boundary conditions are satisfied, since at \(t = 0\), \((I/E)_o = 0\) and as \(t\) becomes very large, \((I/E)_t\) approaches 1, which expresses complete luminal obliteration by intimal sclerosis. I/E can never become greater than 1.0.

**Validity of the Model of Atherogenesis**

We may now explore whether this simple relationship fits: (1) the de novo ischemic heart disease findings of Framingham and Livermore, (2) the Paterson findings concerning blood lipids and coronary sclerosis in 60-69 year old men, and (3) the observations of Young and associates relating arterial radius to I/E values.

As a first approximation, this test was done with the following simplifications:

Let \(c = 5\) represent the median value of the blood lipid parameter and assume no age dependence for the blood lipid parameter itself.

Let the process start, arbitrarily, at age 25 years. After preliminary trials of appropriate \(k\) values, a value of \(k = 0.01\) was selected, and I/E values were calculated as a function of \(c\), \(t\), and \(r_o\), using the integrated form of equation 2. In figure 1 are presented the calculations for I/E in an artery of \(r_o = 2.0\) mm, as a function of blood lipid parameter and age. In figure 2 are presented the calculations for I/E as a function of initial arterial radius and age, at the median value for the blood lipid parameter, \(c = 5\). Consideration of these figures allows exploration of where this simple model fits reality and where it does not.

1. From figure 1 it is noted that in early years after inception of the process, the degree of sclerosis differs appreciably with change in value of \(c\), the blood lipid parameter. Progressively with age, the degree of sclerosis,
in I/E units, differs less and less over a wide range of c values. At age 30 years, I/E = 0.55 for c = 5, I/E = 0.75 for c = 10. Thus for a twofold increase in blood lipid parameter, I/E increases by 36%. In contrast, at age 60 years, I/E = 0.94 for c = 5, I/E = 0.97 for c = 10. Thus at age 60 years, I/E increases by −3% for a twofold increase in blood lipid parameter. Thus, early in this idealized development of atherosclerosis, degree of atherosclerosis is strongly related to blood lipid parameter. If clinical incidence of ischemic heart disease is related to degree of atherosclerosis, then such incidence should show strong dependence upon blood lipid parameter. This was observed in the Framingham and Livermore studies. Late in the idealized development of atherosclerosis, degree of atherosclerosis is only minimally related to blood lipid parameter. Hence, on the same grounds as above, clinical incidence should show very little relationship with blood lipid parameter, even over a very large range of blood lipid parameter values. This also was observed in the Framingham and Livermore studies.

2. Late in the idealized development of atherosclerosis, such as at age 65 years, the degree of sclerosis is calculated to be trivially different over a wide range of blood lipid parameter values. This is precisely what the Paterson group found—namely, that the degree of coronary atherosclerosis was not significantly related to blood lipid parameters.

3. Lastly, this idealized development of atherosclerosis leads to a prediction of increasing I/E values at any time with increasing initial radius of artery (see figure 2), as observed by Young and associates.

A major disagreement with reality in figure 1 is that the predicted degree of coronary sclerosis (I/E) approaches values of 0.9 to 1.00, which is at variance with the observations of Young and associates. Lowering of the value chosen for k will improve this aspect of the model, but will worsen the agreement of the calculated values both with the data on incidence of ischemic heart disease and with the Paterson studies of degree of sclerosis in relation to blood lipid parameters. However, if k itself is allowed to decrease as appreciable atherosclerosis develops, the only major disagreement with reality is removed. Examination of atherosclerosis in autopsy material reveals in general that new sclerosis is not the rule over the “fibrous cap” commonly described in moderately advanced lesions. This observation would be consistent with a decrease in k as atherosclerosis becomes appreciable, over and above the radius effect itself.

A simple function expressing the decline in k with appreciable development of atherosclerosis is the following:

\[ k = k_0 \ e^{-m(I/E)^2} \]  

(3)

The choice of \( m = 6.93 \) allows k to become 
\( = 0.5 \) \( k_0 \) for \( (I/E)^2 = 0.10 \), that is, where \( (I/E) = 0.32 \).

Utilizing this variation in k, with \( k_0 = 0.005 \), calculations similar to those described above were carried through with the same integrated form of equation 2 as before for variation in I/E with age, blood lipid parameter, and initial arterial radius. These are presented in figures 3 and 4. By choosing a particular age, the variation of I/E with initial arterial radius can be replotted from the calculations of figure 4. This was done for early, intermediate, and late periods in figure 5, in which the variation in I/E as a function of initial arterial radius alone is presented at early, intermediate, and late periods. Superimposed on this last plot are the observational data.
with risk of de novo ischemic heart disease as a function of age; (2) the lack of relationship between degree of coronary atherosclerosis and blood lipid parameter in the 60-69 year age bracket—as already observed by Paterson; (3) the approximate extent of the coronary (I/E) values to be expected in the 60-89 year age bracket observed by Young and associates, and (4) the positive relationship between I/E and arterial radius observed by Young and co-workers, including the nearly linear relationship with radius for moderate disease, and a flattening out at radii above 2.0 mm with advanced disease.

Implications

A first-approximation description of the development of atherosclerosis has been presented in relationship to a general parameter (blood lipid level), a focal parameter (the value of k), arterial radius, and age. One may legitimately ask what mechanism of atherogenesis underlies the very simple equations employed and what assurance there is that the equations and the description are correct. The mechanism of atherogenesis remains unknown, so it can be unequivocally stated that the description and equations do no violence to well-established mechanism concepts. The correctness of a concept such as we have presented is best tested against reality in the clinical sense. Several major relationships having reality in the clinical sense have been shown herein to be consistent with the concepts and the equations. The crucial additional tests lie in the prediction of additional phenomena concerning atherogenesis and in a comparison of prediction with reality. We may now consider what some of the additional phenomena are that would be predicted. For some, data are already available. For others, as data develop, the validity or lack of validity of the predictions will become evident.

Prediction 1. Blood lipid parameters lose predictive value for de novo ischemic heart disease in the neighborhood of 55 years of age, not because of the improper choice of parameters, but rather because of the nature of the evolution of the atherosclerotic process.
The loss of predictive value for those parameters already measured is evident from the data presented herein. The prediction is that such parameters as serum triglyceride, pre-
\( \beta \)-lipoproteins, or other lipid parameters will do no better if subjected to the rigorous scrutiny of a valid prospective study.

Prediction 2. Blood lipids are intimately related to the pathogenesis of atherosclerosis, but on the basis of the nature of the evolution of the process we can predict: (a) no appreciable relationship between degree of sclerosis and blood lipids when the process is advanced, and (b) an appreciable relationship when the process is early or moderate.

The lack of relationship observed by the Paterson group between coronary atherosclerosis and blood lipids was discussed in detail. It may be noted in observational material of Young and associates that cerebral atherosclerosis is much less advanced than coronary atherosclerosis, even in old subjects (60-89 years of age). Paterson and associates, in their most recent report,\(^27\) reported that even though no relationship existed between coronary atherosclerosis and blood lipids in 60-69 year-old men, a weak but significant relationship did exist between blood lipids and cerebral atherosclerosis.

Further evidence on this prediction must be sought in (a) a study of younger subjects, which is difficult, or (b) animals. If an appropriate experiment were done in animals developing appreciable coronary atherosclerosis, it would be predicted that early in the course of the disease blood lipid levels would be related to degree of coronary sclerosis, but with advancing disease the relationship would weaken progressively.

Prediction 3. Blood lipid parameters are not likely to provide any prognostic information in already established ischemic heart disease in persons above 50 years of age or probably even in younger groups.

Roe and associates\(^32\) have already tested this and found it to be the case for subjects who have experienced myocardial infarction.

Prediction 4. Moderate alteration of blood lipid parameters by dietary or pharmacological means in subjects beyond 50 years of age can hardly be expected to alter the risk of de novo development of ischemic heart disease.

Over a wide range of blood lipid parameters, the data and concepts presented herein indicate no appreciable difference in risk for subjects who are over 50 years of age. Thus, it is hardly likely that alterations of blood lipid parameters within this range can produce measurable alteration in risk.

It is essential to qualify this prediction lest it be misunderstood. A dietary regimen or a pharmaceutical agent may influence the disease by other means than via effects upon blood lipid parameters. Prediction 4 is necessarily silent about effects other than those related to blood lipid parameters.

Prediction 5. If dietary and pharmacological alteration of blood lipid parameters cannot be expected to alter the risk in ostensibly healthy subjects over 50 years old, there is no reason to expect that such measures will alter the risk for persons with established ischemic heart disease.

Two recent controlled studies, one with low fat diets\(^33\) and the other with corn oil supplements,\(^34\) indicate no suggestion that such measures alter prognosis in established ischemic heart disease.

Prediction 6. If moderate reduction in blood lipid parameters does prove to alter the risk of de novo ischemic heart disease in ostensibly healthy subjects of young age groups (well below 55 years of age), the effect will be lost when the subjects reach 55 years of age, even if the regimen prescribed is adhered to faithfully. In essence this is a statement that the life expectancy at 55 years of age and beyond will not be materially altered, so far as coronary disease is concerned, by moderate reductions in blood lipid levels within the range of values characteristic of the U.S. population at present.

Prediction 7. If longevity as limited by coronary atherosclerosis is to be altered through effects upon blood lipid parameters, a drastic rather than moderate reduction in such parameters is required. (Note effect of a value of 1.0 in figure 5.)

Circulation, Volume XXXIV, October 1966
At present, we do not know how to provoke such drastic alteration in blood lipids, nor do we know whether such drastic lowerings are otherwise consistent with health. A small proportion of the U.S. population is spontaneously characterized by extremely low blood lipid levels and appears to enjoy good health. Such individuals deserve intensive study if clinical use is ever to be made of drastic lowering of serum lipoproteins or cholesterol.

**Prediction 8.** The k value, expressing the focal determinant of development of atherosclerosis deserves intensive study. At present we have essentially no information concerning factors that may reduce the value of k or how it comes to have the value it does have. It is clear that k differs within segments of a single artery, between arteries in a single individual, and between individuals in the population for a particular artery. It is not inconceivable that a concerted attack upon understanding k may be more rewarding than efforts to alter blood lipid parameters.

**Prediction 9.** All the findings discussed here-in pertain to blood lipid parameters as they exist in free-living population samples studied in the United States. Specifically, they refer to two samples, at Framingham and at Livermore. It is conceivable that alteration in composition of blood lipoproteins, as suggested by Geer and McGill, might lead to alterations in development of atherosclerosis even though no alteration in absolute lipidprotein levels occurred. A priori, a particular alteration may be possible for better, for worse, or for no change with respect to atherogenesis. Certainly the burden of proof that any alteration in composition is beneficial rests upon those proposing such alteration.

**Prediction 10.** In the absence of significant progress in beneficial alteration of k values or of ability to produce safe widespread drastic lowering of serum lipids, it would appear highly desirable to devote major attention to the acute determinants of myocardial infarction or other clinical manifestations of coronary heart disease rather than to coronary atherogenesis itself.

**References**

Atherosclerosis


