Studies of Male Survivors of Myocardial Infarction

IV. Serum Lipids and Five-Year Survival

By J. Alick Little, M.D., Henry M. Shanoff, M.D., Robert D. Roe, M.D., Adele Csima, M.A., and Ruth Yano

It is well established that patients with atherosclerotic coronary heart disease have significantly elevated serum lipids. This is illustrated in figure 1 by the serum cholesterol concentrations of the subjects of the present study. Figure 1 also shows that there is a significant decrease in serum cholesterol from decade to decade in the coronary group (regression coefficient, $-15.4 \pm 3.9$ S.E.). This together with the data of others suggests that the higher the serum cholesterol level the younger is the age of onset of clinical coronary heart disease. Prospective studies also have shown that in healthy men, those who later incur coronary heart disease have significantly elevated serum lipids.

The question now arises whether, in patients who have survived myocardial infarction, there is any relationship between serum lipid levels and prognosis. Certainly, the belief that lowering serum lipids may improve prognosis in patients with atherosclerotic disease is implicit in the use of hypolipidemic regimens such as diet, drugs, and now even surgery. Yet there is still no convincing evidence to support this assumption.

The present study examines the relation between survival and serum lipid levels during a 5- to 7-year follow-up in patients surviving myocardial infarction who received no therapy to alter their serum lipids.

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Material and Methods

The coronary heart disease group consisted of 120 men, age 31 to 83, with unequivocal evidence of myocardial infarction. None had valvular disease, syphilis, anemia, polycythemia, thromboangiitis obliterans, or polyarteritis nodosa, so that the cause was almost certainly atherosclerosis. Healthy men from the same Veteran population were matched by age to serve as controls. The designation into decades was according to age at the first visit. All men over 70 were considered in the “eighth” decade. The numbers and ages in the two groups are presented in table 1.

The selection of the participants attempted to eliminate variables other than coronary disease and serum lipids that might influence survival. The serum lipids were only determined after selection. Both groups were free from hypertension (pressure persistently above 150/90), conditions commonly associated with secondary
hypercholesteremia (diabetes, nephrosis, hypothyroidism), and any serious intercurrent disease. All subjects were ambulatory at home and not on anticoagulant or dietary treatment. In both groups, the total fat consumption was 38 per cent of calories but the controls tended to eat more calories and more milk fat.8

At the initial visit, comprehensive clinical and laboratory examinations were carried out as previously described.9 Periodic follow-up examinations were done seven times in 12, six times in 10, five times in 22, four times in 33, three times in 15, twice in 12, and once in 16 coronary patients. Each control was seen on two occasions with an interval of approximately 5 years. No subject in either group was lost to follow-up.

Serum lipid determinations were performed on fasting blood specimens at each visit. The coronary patients were seen at least 3 months after infarction to avoid its lowering effect on serum lipids.10 Serum cholesterol was estimated by the method of Sperry and Webb,11 the Std. S7 lipoprotein fractionation by the technic of de Lalla and Gofman.12 The standard technical errors have been given previously.13 Free cholesterol and phospholipid were also measured. Since both were highly correlated with total cholesterol (r = 0.9 and 0.8, respectively), it was necessary to relate survival to total cholesterol only.

Survival was estimated by the actuarial or life table method.14 The significance of the differences of the survival rates between two groups was determined by the normal deviate test. Because survival was being related to serum lipid levels, the starting point for part of this study was the date of the initial examination and serum lipid determination in each subject in 1952-1954; the end of the follow-up was October 15, 1959.

Causes of Death

Table 2 lists the causes of death in the coronary group. In the fourth to sixth decades, all deaths were due to coronary heart disease and its immediate complications. Of the 22 deaths in the seventh and eighth decades, seven were not due to cardiovascular disease. Thus, survival rates in the older decades are affected by the intrusion of noncoronary deaths.

In the control group, four subjects died of coronary disease, one in the fifth, one in the seventh, and two in the eighth decade. Six died of noncoronary causes, one in the fifth, one in the seventh, and four in the eighth decade.

Results

Serum Lipids and Lipoproteins

The levels of the serum lipids and lipopro-

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Table 1

Composition of the Groups: Number and Age

<table>
<thead>
<tr>
<th>Decade</th>
<th>Control N</th>
<th>Control Mean age</th>
<th>S</th>
<th>Coronary N</th>
<th>Coronary Mean age</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th</td>
<td>25</td>
<td>34.4</td>
<td>2.9</td>
<td>27</td>
<td>36.2</td>
<td>2.6</td>
</tr>
<tr>
<td>5th</td>
<td>24</td>
<td>43.6</td>
<td>2.8</td>
<td>27</td>
<td>44.5</td>
<td>3.0</td>
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<tr>
<td>6th</td>
<td>27</td>
<td>56.0</td>
<td>2.4</td>
<td>29</td>
<td>55.9</td>
<td>2.6</td>
</tr>
<tr>
<td>7th</td>
<td>23</td>
<td>64.1</td>
<td>2.8</td>
<td>22</td>
<td>64.5</td>
<td>2.6</td>
</tr>
<tr>
<td>8th</td>
<td>21</td>
<td>73.0</td>
<td>2.9</td>
<td>15</td>
<td>74.7</td>
<td>4.3</td>
</tr>
</tbody>
</table>

N-number; S-standard deviation.

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Table 2

Causes of Death in the Coronary Group

<table>
<thead>
<tr>
<th>Decade</th>
<th>(a) Acute myocardial infarct</th>
<th>(b) Sudden death, presumed coronary heart disease</th>
<th>(c) Peripheral atherosclerosis</th>
<th>(d) Non-cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5th</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<td>6th</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
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<tr>
<td>7th</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>8th</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

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Circulation, Volume XXXI, June 1965
The cumulative survival over 5 years in the control and coronary groups.

Teins have been reported in detail previously.\textsuperscript{4, 13}

Survival from Date of Initial Examination

Cumulative Survival

The data for the cumulative survival in the entire coronary group, calculated by a month-to-month survey of the number living and the number deceased, are seen in table 3. After the first 12 months, only yearly data are given for the sake of brevity. Figure 2 contrasts the survival curves of the coronary and control groups. The 5-year survival from the initial visit is 59.9 per cent $\pm$ 4.6 (S.E.) for the coronary group and 91.5 per cent $\pm$2.6 (S.E.) for the control.

Figure 3 shows the cumulative survival for each decade in the coronary group and, where significant, the probability levels for the differences. The survival rates are surprisingly similar. In the eighth decade beyond 45 months, there was an accelerated death rate, which is not unexpected at this advanced age.\textsuperscript{15} Here the survival rate was significantly less than that of the fifth and sixth decades. The only other significant difference occurred between the fourth and sixth decades during the 27- to 45-month interval. Otherwise the differences in survival rate were insignificant.

Survival and Initial Total Serum Cholesterol

To study the relationship between serum cholesterol levels obtained at the initial examination and survival, the patients were first divided into those above and those below the mean cholesterol for their decades as in table 4. The survival curves for the two divisions are compared in figure 4, and have no significant differences at any point. It might appear that those patients with the lower serum cholesterol had a significantly longer sur-
SURVIVORS OF MYOCARDIAL INFARCTION

Table 3

Cumulative Survival for 120 Survivors of Myocardial Infarction

<table>
<thead>
<tr>
<th>Months after initial examination</th>
<th>Died during interval</th>
<th>Withdrawn alive during interval</th>
<th>Cumulative survival</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>99.2</td>
<td>0.8</td>
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<tr>
<td>2</td>
<td>2</td>
<td>0</td>
<td>97.5</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
<td>95.8</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0</td>
<td>93.3</td>
<td>2.3</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
<td>92.5</td>
<td>2.4</td>
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<tr>
<td>8</td>
<td>2</td>
<td>0</td>
<td>90.9</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0</td>
<td>89.2</td>
<td>2.8</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>0</td>
<td>87.5</td>
<td>3.0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>0</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>0</td>
<td>82.4</td>
<td>3.5</td>
</tr>
<tr>
<td>36</td>
<td>11</td>
<td>0</td>
<td>73.0</td>
<td>4.1</td>
</tr>
<tr>
<td>48</td>
<td>12</td>
<td>15</td>
<td>62.1</td>
<td>4.5</td>
</tr>
<tr>
<td>60</td>
<td>2</td>
<td>31</td>
<td>59.9</td>
<td>4.6</td>
</tr>
<tr>
<td>72</td>
<td>5</td>
<td>6</td>
<td>53.5</td>
<td>4.9</td>
</tr>
<tr>
<td>74</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Method of Cutler and Ederer.14 The calculations throughout were done for month-to-month intervals. After the first 12 months only yearly data are given. The 5-year survival rate is in heavy type.

Table 4

Coronary Patients Divided above and below the Mean Serum Cholesterol Level for Each Decade

<table>
<thead>
<tr>
<th>Decade</th>
<th>No.</th>
<th>Mean</th>
<th>S.D.</th>
<th>No. above the mean</th>
<th>No. below the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th</td>
<td>27</td>
<td>277.4</td>
<td>55.6</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>5th</td>
<td>27</td>
<td>261.7</td>
<td>39.1</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>6th</td>
<td>29</td>
<td>252.1</td>
<td>47.0</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>7th</td>
<td>22</td>
<td>234.7</td>
<td>36.5</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>8th</td>
<td>15</td>
<td>230.0</td>
<td>53.8</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Survival because their curve was consistently above the other. After the tenth month, however, the curves were generally parallel, with no tendency to diverge. Further, it cannot be held that the consistently longer survival of one group over the other, at comparable times, is of additive significance, since it is obvious that the vertical position of each point on a curve is already affected by the preceding points of that curve.

The 120 patients were also divided into the 40 with the lowest cholesterol values, the 40 with the highest, and the 40 between. The survival curves of these three divisions, as shown in figure 5, are also similar.

Finally, the five patients with the highest cholesterol values from each decade were grouped together and compared to the group composed of the five with the lowest values from each decade. Again, there were no important differences in survival.

Survival and Average Total Serum Cholesterol of the Individual

Blood cholesterol readings in an individual are variable. To make most efficient use of the data, the average of all available cholesterol readings in each coronary patient was calculated. Before this mean figure for each patient could be related to survival, it was considered necessary to define within the individual, the relationship of cholesterol to age. Regression coefficients of cholesterol on age were calculated, and an analysis of covari-

Circulation, Volume XXXI, June 1965
Survival curves from initial examination for the 40 coronary patients with the highest serum cholesterol levels, the 40 with the lowest levels and the 40 between. There were no significant (N.S.) differences at any point.

Examination of the data showed that no bias was introduced by the age trend in cholesterol because the period of follow-up was similar for the groups above and below the mean cholesterol value in each decade.

Therefore, the average of all available cholesterol determinations in each individual was obtained. The mean of these averages was determined in each decade and was designated the "mean of means." The survival of those patients whose average cholesterol was above the mean of means for their decade was compared to that of patients below the mean of means. There was no difference.

Survival from Date of First Diagnosis
Cumulative Survival

Instead of calculating survival from the date of the initial examination as above, it was calculated from the date of first diagnosis of myocardial infarction. This could be determined accurately in 118 patients. By this method, the 5-year cumulative survival was 79.2 per cent.

Survival and Total Serum Cholesterol

These patients were divided into those above and those below the mean cholesterol of each decade. The survival rates for the two divisions were similar, as shown in figure 6.

Survival and Interval Between First Diagnosis and Initial Examination

At the time of entry into the study, 100 of

Figure 5
Survival curves from date of initial examination for patients with a first infarct less than and more than 6 months before the initial examination. There were no significant (N.S.) differences at any point.
Survivors of Myocardial Infarction

Discussion

Because of the criteria of selection for this study, the coronary patients could be considered relatively good risks. The 5-year survival of 79 per cent, calculated from date of first infarct, is similar to that of other good-risk groups in the literature and confirms a recent editorial opinion. The indifference of survival to the age of the patient, as shown in figure 3, is similar to the experience of Honey and Truelove. However, in comparison to life expectancy of healthy insured Canadian men, the ratio of actual to expected deaths was much greater for the younger than for the older coronary patients, as shown in table 5. Similar comparisons have been made in previous publications. Of course this does not indicate more “malignant” disease in the younger patients with coronary heart disease.

The evidence outlined in the introduction suggests that the higher the serum lipid level, the younger is the age of onset of clinical

Survival and Serum Lipoproteins

The relationship between survival and Std. SF 0-12, 12-20, 20-100, and 100-400 lipoproteins was studied in the same way as survival and serum cholesterol. Survival rate was calculated both from the date of the initial visit (fig. 9) and from the initial myocardial infarction. There were no important differences between the curves above and below the arithmetical mean of any of these lipoprotein fractions.

Figure 8
Survival curves from date of first infarct for patients with a first infarct less than and more than 6 months before initial examination. The significance of the differences between the curves are indicated by the p values.

Figure 9
Survival curves from the initial examination for patients divided by the mean serum lipoprotein values for their respective decade. The differences between the curves of each pair are not significant.
coronary disease. Unexpectedly, the results of the present study indicate that once clinical coronary disease is manifest, the serum lipid levels no longer influence prognosis.

This apparent paradox may be resolved by a concept that considers atherosclerosis to occur in two stages: preclinical and clinical. In the long, silent preclinical stage, during the first four or five decades of life, higher levels of serum lipids in some way accelerate atherogenesis with progressive narrowing of arterial lumens. The level of the serum lipids is to some extent an individual, life-long, inherited characteristic. From personal observations, essential familial hypercholesteremia is frequently evident in childhood. In one example, serum cholesterol, which had been 123 mg. per cent at birth, was 386 mg. per cent by 6 months of age.

The clinical stage of atherosclerosis begins with some complication such as coronary occlusion and myocardial infarction. On the average, it is much shorter, lasting from minutes to several years. The influence of the serum lipid levels on survival becomes insignificant compared to more critical, nonatherogenic factors that come into operation, such as collateral circulation, electrical excitability of the myocardium, and hemorrhage into an atheroma. Also in a stenosed atheromatous artery, slowing and eddying of the blood stream may be a more potent influence on thrombus formation than that postulated for elevated serum lipids.

The literature contains no compelling evidence that serum lipid levels influence prognosis in survivors of myocardial infarction. In a 1-year follow-up of 359 such patients, Jones et al. found that those with higher levels of Sf 12-20 lipoproteins suffered a higher recurrence rate. In the same group of patients, it was later reported that those who lived beyond 5 years had significantly lower Std. Sf 0-400 lipoproteins than those who died of recurrent infarction. However, deaths from other causes and over-all survival figures were not given. Marmorston et al. found no relation between serum lipid levels and survival in patients with coronary heart disease who were treated with estrogens.

Since the present study examined survivors at least 3 months after infarction, the relation of the serum lipid levels to the immediate mortality could not be studied. In this regard, Jones et al. reported that in 49 patients studied within 1 week of an acute infarct, those dying in hospital had significantly higher serum Sf 0-12 lipoprotein levels.

In the present study, no attempt was made to lower serum lipid concentrations and, therefore, it cannot be concluded that lowering serum lipids would not have prolonged survival. Morrison described an 8-year mortality of only 44 per cent in 50 survivors of myocardial infarction who followed a low-fat

Table 5

Ultimate Mortality Experience by Attained Agea

<table>
<thead>
<tr>
<th>Attained age</th>
<th>No. of life years expected</th>
<th>No. of expected deaths</th>
<th>Actual no. of deaths</th>
<th>Ratio of actual to expected</th>
<th>95% Confidence range of the ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>60.1</td>
<td>0.09</td>
<td>6</td>
<td>6390</td>
<td>3781-8999</td>
</tr>
<tr>
<td>40-49</td>
<td>113.1</td>
<td>0.38</td>
<td>9</td>
<td>2337</td>
<td>1558-3116</td>
</tr>
<tr>
<td>50-59</td>
<td>126.6</td>
<td>1.14</td>
<td>11</td>
<td>779</td>
<td>544-1014</td>
</tr>
<tr>
<td>60-69</td>
<td>144.4</td>
<td>5.67</td>
<td>11</td>
<td>299</td>
<td>209-389</td>
</tr>
<tr>
<td>70-79</td>
<td>69.3</td>
<td>1.99</td>
<td>10</td>
<td>257</td>
<td>176-338</td>
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<tr>
<td>80-89</td>
<td>13.7</td>
<td>1.77</td>
<td>4</td>
<td>226</td>
<td>112-340</td>
</tr>
<tr>
<td>Entire group</td>
<td>527.2</td>
<td>11.21</td>
<td>51</td>
<td>454</td>
<td>391-517</td>
</tr>
</tbody>
</table>

*aCalculated by Mr. R. Leckie, Manufacturers' Life Insurance Co., Toronto, from the date of onset of clinical coronary disease, using 1952-56 Canadian Association of Acturaries Ultimate Table, which reflects average mortality of Canadian Policyholders who had had their policies in-force for at least 5 years.
low-cholesterol diet and maintained weight reduction and lower serum lipid levels. In comparison, 50 control patients on unrestricted diet had a 76 per cent mortality. However, uncooperative patients were dropped from the original treatment group and new ones were added, which introduced some bias. Surprisingly, only half the deaths in both groups were due to cardiovascular disease. Lyon et al. \(^\text{26}\) reported a decrease in recurrence rate and death rate of myocardial infarction in patients who adhered to a low-fat, low-cholesterol diet as compared to those who did not. Unfortunately, deaths from other causes and the over-all survival rate in each group were not presented. Hansen, Geill, and Lund \(^\text{29}\) described a significantly decreased incidence of thrombotic disease among elderly persons receiving a diet with vegetable oils replacing dairy and meat fats, as compared to control subjects. They did not mention serum lipid levels or over-all mortality rates. In a 5-year study of 50 coronary patients, Oliver and Boyd \(^\text{30}\) successfully reduced serum cholesterol levels with estrogens but failed to reduce morbidity and mortality. Thus, the available evidence fails to show that lowering serum lipids improves the prognosis of coronary heart disease.

### Summary

This study examined life expectancy and serum lipids in 120 men with atherosclerotic coronary heart disease. Five-year survival from onset of infarction was 79 per cent. No relationship could be demonstrated between survival and the level of the total serum cholesterol, Std. S, 0-12, 12-20, 20-100, and 100-400 lipoproteins. Survival for patients with an infarct less than 6 months before entry into the study was shorter, despite serum lipid levels the same as the remainder of the group.

Although the age of onset of coronary disease is influenced by serum lipid levels, survival subsequent to infarction is not. This paradox suggests that serum lipids affect rate of atherogenesis in the long preclinical stage but in the short clinical stage other factors determine survival.

### Acknowledgment

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Science and the Modern World

I do not think we can maintain our position in the postwar world unless we are an exceptionally well-educated people and unless we can handle easily and with comprehension the problems and inventions of the new scientific age.—Winston Churchill.
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