Serum Lipid Levels and the Severity of Coronary and Cerebral Atherosclerosis in Adequately Nourished Men, 60 to 69 Years of Age

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ALMOST 10 years have passed since we initiated a long-term project to determine the relationship, if any, between the levels of the serum lipids, estimated serially during life in ambulatory patients who were permanently confined to hospital, and the severity of atherosclerosis found at death and autopsy in the same patients. Several interim reports on our findings have been published,[1-5] each of them failing to show any impressive relationships between the serum lipid levels and the severity of disease. However, none of these interim reports satisfied completely the requirements laid down originally by us for a proper evaluation of the problem. In our first report, for example, because such a small number of fatalities was available at the time, no allowance could be made for the factor of age in the progression of the disease.[1] Later reports took the age factor and other variables into consideration. The number of fatalities that have been autopsied is now sufficiently large that it is feasible to exclude from the series all individuals who died from diseases that involved wasting. This correction has been made because many research workers on this continent believe that the human atherosclerotic process is reversible to a degree, that in emaciated individuals the arterial lipid accumulations may be resorbed in exactly the same fashion as are the fat depots in other parts of the body.

The present report, which we expect will be the last one in this particular series, gives a comparison of the antemortem levels of serum cholesterol, cholesterol-phospholipid ratio, and Gofman's "Atherogenic Index," with the severity of coronary and cerebral atherosclerosis in 42 male patients, aged 60 to 69 years, whose terminal body weights did not fall below the minimum desirable weights for men of stated heights as laid down by the Metropolitan Life Insurance Company.[6]

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Material and Method

Detailed accounts of the materials and methods used throughout this investigation have been given previously, particularly in our first report dated 1956.[1, 2, 4] Only those parts will be repeated that pertain to the clinical material, the methods of determination of the serum lipid levels, the criteria for measuring the severity of coronary and cerebral atherosclerosis, and the manner in which those persons in the series who were not adequately nourished were excluded.

The clinical material consisted of approximately 800 male patients who were permanently confined to Westminster Hospital, London, Canada, either because of intractable psychosis or for domiciliary care. At the initiation of the project, there were approximately 550 World War I veterans over 50 years of age, and approximately 250 World War II veterans of younger ages. Most of the psychotic patients, particularly those who were veterans of World War I, suffered from stages of psychosis that did not affect appreciably their physical health. The majority were burnt-out schizophrenics. They did, of course, suffer occasionally from intercurrent disease, and in this regard we made it a rule never to estimate the antemortem serum lipids at a time when any patient was not in reasonably good physical health. The patients were offered 2,500 to 3,000 calories in their daily diet, of which 25 to 35 per cent was derived from fat.

The first survey of the serum lipid levels was made on the 800 patients early in 1953. A second survey was carried out 6 months later and thereafter surveys were made annually. To date, the largest number of estimations made on any one patient was 11. At each survey, approximately 50 ml. of venous blood were withdrawn from each patient, from 1 to 1½ hours after breakfast.

Table 1

Age Distribution of the Series

Age	No. of cases
Under 40 years	1
40-49 years	5
50-59 years	16
60-69 years	78
70-79 years	85
80 years and over	55

After maximum clot retraction the blood was centrifuged and the serum drawn off. A 10-ml. aliquot was placed in a serum bottle and shipped in wet ice by air mail to Montreal where estimations of Sf 0-12, 12-20, 20-100, 100-400 classes of lipoproteins were carried out at the Department of Chemistry, McGill University. The elapsed time between the taking of blood and its arrival at Montreal was always less than 24 hours. From this latter data the "Atherogenic Index" (Gofman) was calculated,[2] but the results were not sent to us until the patient died and the postmortem findings had been completed.

The remainder of the serum sample was fast-frozen at −30 C. and stored at −18 C. until the patient died and the postmortem examination had been completed. (Control studies have shown that no significant deterioration of serum cholesterol or serum phospholipid occurs up to 64 months after fast-freezing and frozen storage.) The serum was then removed from frozen storage and quickly thawed. The serum lipids were estimated as follows: the serum cholesterol was determined by the method of Schoenheimer and Sperry as revised by Hawk and associates;[7] the phospholipid by the method of Fiske and Subba Row, a modification of the Youngberg method as given by Hawk and associates.[7] If two or more serum lipid estimations were made on a patient during life, the levels were averaged.

The postmortem severity of atherosclerosis was evaluated in the coronary and cerebral arteries by means of the following indices: morphologic grading, measuring the thickness of the largest plaque, determining the total amount and concentration of lipid and calcium in the vessels.

In estimating the severity of disease in the coronary arteries, the entire epicardial portions were removed, opened longitudinally with scissors, and the outer medial and adventitial coats stripped from the intima to remove contaminating fat. Although the normal intima was sometimes too thin to strip, areas of disease were readily obtained, thus ensuring that all lipid- and calcium-containing lesions in the major coronary circulation were available for study. A slightly different procedure was followed for the cerebral arteries. The specimen consisted of the basilar artery and the circle of Willis, and approximately half an inch of each of the major vessels arising therefrom. The cerebral arteries were not stripped, since they do not possess adventitial fat.

Morphologic grading was done in a rough manner. The severity of disease was estimated as slight, moderate, or severe, depending upon the degree of stenosis produced by the largest plaque in any part of the coronary or cerebral circulation.[8] Once the crude morphologic index had been declared, a small segment of the largest plaque was removed, fixed in formalin, sectioned and stained, and the thickness of the intima measured with a micrometer eyepiece. The remainder of the specimen was then sent to the chemical laboratory for tissue analysis.

In the chemical laboratory, the fresh tissues were weighed immediately, digested with alkali by the method of Haven and associates,[9] and stored. The total lipid content was determined by the method of Haven and associates.[9] An aliquot of the alkaline digest was subjected to acid digestion by the method of Ma and Zuazaga,[10] and the calcium content of the digestion estimated by the Clarke and Collip modification[7] of the Kramer-Tisdal method. Calcium was determined for both coronary and cerebral arteries, but the data for the cerebral arteries were not used, since the amount of calcium in these vessels was too small to be of any use for grading purposes.

The final step in the procedure was to compare directly the mean antemortem levels of serum cholesterol, cholesterol-phospholipid ratio and "Atherogenic Index" with the severity of atherosclerosis in each individual as measured in the ways described above. The results were assessed statistically by evaluating the significance of the difference between sample means and the significance of the correlation coefficients, in the usual manner. P values of less than 0.05 were considered significant; those equal to 0.05, of borderline significance.

At the conclusion of the ninth year of the project, there were 240 autopsied fatalities in the original series of 800 patients. Of these, 78 were in the age decade 60 to 69 years. However, included in this group of 78 cases were many persons who had died from wasting disease states (such as cancer), and who had obviously lost a good deal of weight during their terminal illnesses. Each of these emaciated individuals was excluded from the series, leaving only those whose body weights did not fall below the minimum desirable weights for men of stated heights, as published by the Metropolitan Life Insurance Company.[6] Slight adjustments had to be made in these minimum desirable weights, since the insurance com-

Table 2

Correlations between Antemortem Serum Lipid Levels and Postmortem Severity of Coronary Atherosclerosis in Adequately Nourished Patients, 60 to 69 Years of Age

Serum lipid fractions	Pairs of variables	n*	r†	P value
Total serum cholesterol	Total arterial lipid vs. cholesterol	42	−0.02	>0.10
	Arterial lipid conc. vs. cholesterol	42	0.03	>0.10
	Total arterial calcium vs. cholesterol	42	−0.03	>0.10
	Arterial calcium conc. vs. cholesterol	42	0.01	>0.10
	Arterial plaque thickness vs. cholesterol	38	−0.24	>0.10
Cholesterol-phospholipid ratio	Total arterial lipid vs. C/P ratio	42	−0.12	>0.10
	Arterial lipid conc. vs. C/P ratio	42	−0.03	>0.10
	Total arterial calcium vs. C/P ratio	42	0.00	>0.10
	Arterial calcium conc. vs. C/P ratio	42	0.02	>0.10
	Arterial plaque thickness vs. C/P ratio	38	0.00	>0.10
Atherogenic Index (Gofman)	Total arterial lipid vs. atherogenic index	40	0.02	>0.10
	Arterial lipid conc. vs. atherogenic index	40	−0.07	>0.10
	Total arterial calcium vs. atherogenic index	40	−0.07	>0.10
	Arterial calcium conc. vs. atherogenic index	40	−0.11	>0.10
	Arterial plaque thickness vs. atherogenic index	37	0.20	>0.10

*Indicates number of cases.

†Correlation coefficient (for perfect correlation, r = 1.00).

pany table gave them for men wearing shoes and ordinary clothing. One inch was therefore subtracted to compensate for shoes, and 3 pounds for clothing. It was also noted that the insurance company table gave different ranges of desirable weights for men, depending upon their body builds. We were unable to correct for this factor, since descriptions of body build were not given in our autopsy reports. Accordingly, the minimum desirable weights for men of *slight* body build were chosen as the lowest acceptable figures.

Observations

To make the story complete we show in table 1 the age distribution of the entire series of 240 fatalities. It will be seen that adequate numbers of cases for statistical study are present only in the seventh, eighth, and ninth decades. We have chosen to report the data from the 60 to 69-year-old group, mostly because criticisms have been voiced in the past that our investigation has been concerned only with very old people. We do not concede, of course, that a man in his sixties is very old. The number of cases listed in this decade was reduced by excluding all those who lost weight excessively in the days or months before death —thus leaving us with 42 cases for the present analysis. The data on each of these acceptable cases are given in detail in the Appendix,* and are summarized below.

Coronary Arteries

The data pertaining to these vessels have been analyzed in three different ways. First, the mean level of each of the three serum lipid fractions has been compared with each of the quantitative measurements of severity of disease. The correlation coefficients for these 15 individual comparisons are reported in table 2, and none was significant. Furthermore, no trends toward a relationship are apparent except perhaps in the comparison between the atherogenic index and the thickness of the largest plaque in the coronary arteries ($r = 0.20$). In all of the other comparisons the values for r were either extremely low or were negative.

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Table 3

Relationships between Serum Lipid Levels and Morphologic Grade of Coronary Atherosclerosis in Adequately Nourished Patients, 60 to 69 Years of Age

Serum lipid fraction	Serum lipid levels with different morphologic grades of disease: Slight	Moderate	Severe	P value Slight vs. severe
Total cholesterol in mg. %	235 ± 23.9*(5)†	253 ± 17.5 (10)	245 ± 9.5 (27)	>0.10
Cholesterol-phospholipid ratio	0.96 ± 0.08 (5)	1.03 ± 0.13 (10)	0.97 ± 0.07 (27)	>0.10
Atherogenic Index (Gofman)	69 ± 10.2 (5)	66 ± 3.2 (10)	70 ± 4.2 (25)	>0.10

*Mean ± S.E.M.
†Number of cases.

The comparisons between the serum lipid fractions and the severity of disease as measured by crude morphologic grading had to be made in a different way. The series was divided into three groups of morphologic severity—severe, moderate, and slight; the intermediate (or moderate group) was eliminated, and the mean antemortem serum lipid levels of the two remaining groups were compared statistically by the method of Fisher.[11] The results are summarized in table 3, and it will be seen that there were no significant relationships between any of the serum lipid levels and the morphologic severity of disease in the coronary arteries. Nor were any particular trends apparent in these comparisons, nothing like the one that occurred in our analysis 2 years ago, which did not exclude individuals with poor body nutrition (see table 3 in our 1960 report).[4]

Finally, we have compared the mean levels of the serum lipids in each subject with the presence or absence of those sequelae of coronary atherosclerosis that can be demonstrated at autopsy: coronary thrombi, massive hematomas of the occlusive type, recent or old cardiac infarcts, and sudden and unexpected death from coronary insufficiency in individuals with severe grades of coronary sclerosis and no other apparent cause for sudden death. The results are given in table 4, and again it will be seen that no significant elevation of any of the three serum lipid fractions occurred in individuals with those sequelae of coronary atherosclerosis that can be demonstrated at autopsy. Indeed, each of the lipid fractions was higher in persons without sequelae than in those with sequelae.

The data on one patient in the series (case 31 in the Appendix) were so unusual that they deserve special mention. Over a 9-year period, this man consistently showed a serum cholesterol level of less than 145 mg. per cent. The mean level was 111 mg. per cent. In our experience this is an extraordinarily low value; nevertheless, a severe grade of coronary sclerosis was demonstrated at autopsy, there were large amounts of lipid in his arteries (the third highest recovery in the series) and a heavy deposit of calcium (the third greatest in the series). He also had a cardiac infarct. Although this man was obviously not hyperlipemic during the last 9 years of his life, it is important to note that he was hypertensive as well as having controlled diabetes.

Cerebral Arteries

The data for these vessels were handled in a similar way to those given above for the coronary arteries. It should be noted, however, that the indices of total calcium and of calcium concentration were not determined, since the quantity of this material is so small

Table 4

Serum Lipid Levels in Adequately Nourished Patients, Age 60 to 69 Years, with and without the Sequelae of Coronary Atherosclerosis

Serum lipid fraction	Serum lipid levels: With sequelae	Without sequelae	P value
Total cholesterol in mg. %	236 ± 9.8* (24)†	258 ± 12.2 (18)	>0.10
Cholesterol-phospholipid ratio	0.96 ± 0.02 (24)	1.02 ± 0.04 (18)	>0.10
Atherogenic Index (Gofman)	67 ± 4.4 (22)	72 ± 3.7 (18)	>0.10

*Mean ± S.E.M.
†Number of cases.

Table 5

Correlations between Antemortem Serum Lipid Levels and Postmortem Severity of Cerebral Atherosclerosis in Adequately Nourished Patients, 60 to 69 Years of Age

Serum lipid fractions	Pairs of variables	n*	r†	P value
Total serum cholesterol	Total arterial lipid vs. cholesterol	42	0.00	>0.10
	Arterial lipid conc. vs. cholesterol	42	−0.19	>0.10
	Arterial plaque thickness vs. cholesterol	42	0.35	<0.05
Cholesterol-phospholipid ratio	Total arterial lipid vs. C/P ratio	42	0.07	>0.10
	Arterial lipid conc. vs. C/P ratio	42	−0.21	>0.10
	Arterial plaque thickness vs. C/P ratio	42	0.43	<0.01
Atherogenic Index (Gofman)	Total arterial lipid vs. atherogenic index	40	0.01	>0.10
	Arterial lipid conc. vs. atherogenic index	40	−0.09	>0.10
	Arterial plaque thickness vs. atherogenic index	40	0.18	>0.10

*Indicates number of cases.
†Correlation coefficient (for perfect correlation, r = 1.00).

in the cerebral arteries. The results of the various comparisons are given in tables 5, 6, and 7. A much closer relationship exists between the serum lipid levels and the severity of atherosclerosis than was demonstrated in the coronary vessels: there were significant relationships in four of the 15 individual analyses. However, these were encountered only with the serum cholesterol and the cholesterol-phospholipid ratio, not with Gofman's "Atherogenic Index." Furthermore, none of the significant relationships was found in connection with the total amount or concentration of lipid in the arterial intima (see table 5). In fact, the coefficients of correlation for the lipid accumulations were either extremely low or negative. Finally, no trend toward a relationship was apparent between the three serum lipid fractions and the presence or absence of those sequelae of cerebral atherosclerosis that can be identified at autopsy (see table 7).

In our description of results for the coronary arteries, we cited a single patient (case 31) for whom the complete data are given in the Appendix. The point was made that he showed an extremely low serum cholesterol level during life but had severe coronary atherosclerosis and myocardial infarction at autopsy. However, if one examines the data for the cerebral vessels in this same individual, they are found to be not nearly so damaging to the lipid theory of atherosclerosis as they were for the coronary arteries.

Discussion

If one takes these results at their face value, it would seem that the levels of the three serum lipid fractions studied are completely

Table 6

Relationships between Antemortem Serum Lipid Levels and Morphologic Grade of Cerebral Atherosclerosis in Adequately Nourished Patients, 60 to 69 Years of Age

Serum lipid fraction	Serum lipid levels with different grades of disease: Slight	Moderate	Severe	P value Slight vs. severe
Total cholesterol in mg. %	227 ± 10.6*(19)†	248 ± 15.6 (11)	273 ± 13.2 (12)	<0.02
Cholesterol-phospholipid ratio	0.94 ± 0.03 (19)	0.98 ± 0.04 (11)	1.06 ± 0.04 (12)	<0.05
Atherogenic Idex (Gofman)	64 ± 3.9 (18)	73 ± 7.5 (11)	73 ± 3.9 (11)	>0.10

*Mean ± S.E.M.
†Number of cases.

Table 7

Serum Lipid Levels in Adequately Nourished Patients, Age 60 to 69 Years, with and without the Sequelae of Cerebral Atherosclerosis

Serum lipid fraction	Serum lipid levels: With sequelae	Without sequelae	P value
Total cholesterol in mg. %	248 ± 10.7*(10)†	245 ± 9.7 (32)	>0.10
Cholesterol-phospholipid ratio	0.96 ± 0.03 (10)	0.99 ± 0.03 (32)	>0.10
Atherogenic Index (Gofman)	74 ± 7.0 (9)	67 ± 3.2 (31)	>0.10

*Mean ± S.E.M.
†Number of cases.

unrelated to the severity of *coronary* atherosclerosis and to its pathologic sequelae in men in the age group 60 to 69 years. No significant relationships were obtained in 21 comparisons, nor were any definite trends toward such relationships apparent. As far as the coronary arteries are concerned we must therefore conclude that the lipid (or filtration) theory of atherosclerosis remains unproved. The results for the *cerebral* arteries in the same patients, however, were not nearly so clear-cut: in four of the 15 individual comparisons, significant relationships between either the serum cholesterol level or the cholesterol-phospholipid ratio (but not the "Atherogenic Index") were obtained. These inconsistencies in the data for the two types of arteries deserve some comment.

We note, first, that the present findings in the cerebral vessels are not unlike those obtained in our previous analysis, carried out and reported in 1960,[4] in which poorly nourished subjects were *not* excluded from the series. The serum cholesterol was the only lipid fraction studied at that time; and it was found that, of five comparisons, there was one significant relationship and one distinct trend toward a relationship—a result much like that in the present series in which emaciated persons were excluded. The results for the coronary arteries reported here are also similar to those given in the 1960 paper.[4] All of this makes us suspect that the influence of body nutrition on the severity of atherosclerosis is of less importance than many research workers today would have us believe. To be specific, we are not convinced that the lipid component of plaques can be resorbed. Direct

evidence is now available that this conviction is probably correct: for example, Field and associates,[12] on giving cholesterol-4-C^{14} to patients with limited life expectancies, found only traces of this material in the free-lying lipids of far advanced atherosclerotic plaques, indicating that the plaque lipids are relatively inert.

The second point that should be emphasized is that, although elevations in serum cholesterol and of the cholesterol-phospholipid ratio may have an accelerating effect upon the disease process in the cerebral arteries (but not, from our data, in the coronary arteries), this acceleration is not due to an increased accumulation of lipid. No significant relationships occurred in the comparisons concerning the amount or concentration of extractable lipid in the arterial intima; they were found only with those measurements of disease that are purely morphologic (i.e., criteria having to do with the size of plaques, not with their composition). So, if one concedes that an elevation in certain serum lipids may perhaps result in an increased severity of cerebral atherosclerosis, the reason for this acceleration must be sought elsewhere. It is well known, of course, that there is much more to the atherosclerotic process than the accumulation of lipid in arteries. Abnormal deposits of fibrous tissue, blood and blood products, and complex carbohydrates, also occur;[13] and it is quite conceivable that one of these (fibroplasia) might be enhanced by hyperlipemia. To elaborate, it is suspected by some research workers that high serum cholesterol levels induce a state of blood hypercoaguability, that this causes repetitive depositions of mural thrombi on arterial walls, and that fibroplasia from organization of the thrombi eventually takes place.

These matters, however, still lie in the realm of speculation. All we are prepared to say about the results of the present study, and of our previous ones, is that a definite relationship between hyperlipemic states and the severity of *coronary* sclerosis, or of clinical disease arising therefrom, has not been demonstrated. As far as the relationship of the serum lipid levels to *cerebral* atherosclerosis is concerned, the results are too equivocal to allow a final opinion. We note, however, that there is no proof that high serum lipid levels cause more lipid deposition in cerebral arteries than do low levels, even though other components of atherosclerotic plaques are perhaps increased in amounts.

Finally, there was little to choose in the present analyses among the relative atherogenic properties (or lack of such properties) of the three serum lipid fractions examined. Specifically, Gofman's "Atherogenic Index" was no more closely related to the severity of disease in either type of artery than was the total serum cholesterol or the cholesterol-phospholipid ratio. Indeed, there seemed to be even less relationship between this index and the severity of cerebral sclerosis than with the other two fractions. And of course, Gofman's test is quite expensive to perform.

Summary and Conclusions

Comparisons have been made between the antemortem levels of serum cholesterol, cholesterol-phospholipid ratio, and Gofman's "Atherogenic Index" and the postmortem severity of atherosclerosis in the coronary and cerebral arteries of 42 male patients, 60 to 69 years old, all of whom were adequately nourished at the time of death. No significant relationships, nor any trend toward such relationships, were found in 18 individual analyses concerning the coronary arteries. Furthermore, the mean serum lipid levels were consistently (but not significantly) higher in persons who did *not* have demonstrable sequelae of coronary sclerosis at autopsy than in persons who had sequelae. We conclude from these results that the validity of the "lipid theory" of atherosclerosis remains unproved, as far as the coronary arteries are concerned.

Similar comparisons of the data for the cerebral arteries resulted in significant relationships being obtained in four of 15 individual comparisons—findings so equivocal that a final opinion cannot be expressed. Nevertheless, two negative results emerged

that are worth emphasizing: none of the serum lipid levels was related significantly to the amount or concentration of extractable lipid in the cerebral arteries, or to the presence or absence of those sequelae of cerebral sclerosis that can be identified at autopsy.

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The Internal Environment

Considered in the general cosmic environment, the functions of man and of the higher animals seem to us, indeed, free and independent of the physico-chemical conditions of the environment, because its actual stimuli are found in an inner, organic, liquid environment. What we see from the outside is merely the result of physico-chemical stimuli from the inner environment; that is where physiologists must build up the real determinism of vital functions.

Living machines are therefore created and constructed in such a way that, in perfecting themselves, they become freer and freer in the general cosmic environment. But the most absolute determinism still obtains, none the less, in the inner environment which is separated more and more from the outer cosmic environment by reason of the same organic development. A living machine keeps up its movement because the inner mechanism of the organism, by acts and forces ceaselessly renewed, repairs the losses involved in the exercise of its functions.—CLAUDE BERNARD, M.D. *An Introduction to the Study of Experimental Medicine.* New York, The Macmillan Company, 1927, p. 79.

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