EDITORIALS

SERUM LIPIDS AND ATHEROSCLEROSIS

That hyperlipemia may be responsible for atherosclerosis has long been hypothecated on the grounds of what might be termed circumstantial evidence. The first experimental proof of this concept was provided by Anitschkow's[1] demonstration in 1913 that atheroma can be produced in rabbits by feeding cholesterol. In recent years similar lesions have been induced by similar methods in five other species: the dog[2] (when fed thiouacil in addition to cholesterol), the chicken[3], the rat[4], the hamster[4a], and the guinea pig[4a].

The use of these observations, however, to defend the argument that atherosclerosis in man originates from excessive levels of circulating lipids is open to several objections. First, it has not been conclusively shown that the experimental lesions are identical with those seen in human arteries, although they are similar. Second, the levels of serum cholesterol which are necessary to produce the disease in animals are far higher than those encountered in most patients. An exception is the finding of Katz[5], in chickens, that feeding small amounts of cholesterol, with resultant blood levels which are only slightly above normal, still leads to moderately severe atheromatosis of the aorta. Third, the causal relationship between hypercholesterolemia and atherosclerosis which has been so clearly established in other species has not been, and probably cannot be, equally well shown in human beings. For the present, at least, clinical investigators, hampered by the limitations of man as an experimental animal, must be content to determine whether, and how frequently, *an association* between serum lipids and arterial disease exists, and in so doing must recognize that, while such an association, if sufficiently close, may suggest cause and effect, it does not constitute proof.

Attempts to demonstrate this sort of relationship have taken four lines of approach. It is our purpose critically to review a few of the most significant and representative of recent investigations which have been reported in each of these areas.

a. Comparison of Lipid Levels in Living Individuals with and without Arterial Disease

The best indicator of atherosclerosis during life seems to be coronary occlusion. It is generally agreed that nearly all patients dying of myocardial infarction show atheroma of the coronary arteries. Using this criterion, Steiner[6] made frequent determinations of the serum cholesterol over periods up to two years in fifteen patients with coronary disease proven by clinical and electrocardiographic evidence, and compared these values with those similarly obtained in fifteen normal individuals. A total of 914 determinations of serum cholesterol were made. Values for the former group averaged 355, and for the latter, 254 mg. of cholesterol per 100 ml. The significance of this study lies in the fact that multiple determinations for each subject over many months of time have given it an unusual degree of statistical validity.

Gertler, Garn and Lerman[7] investigated various lipid fractions of the blood in three groups of men: (a) patients with proven myocardial infarction occurring before the age of 40, (b) miscellaneous normal persons of the same age group as the cardiac patients, and (c) a group of "matched controls," each of whom was selected as being free of coronary disease but closely resembling, with respect to age, weight, body build, national origin and occupation, one of the patients with heart disease. The results (Table 1) show that values for all fractions are highest in the patients, lowest in the miscellaneous controls and intermediate in the "matched controls." It is to be hoped that a careful following of the members of the "matched control" group for evidence of frank coronary disease is being carried out.

It is evident from these and other reports that there is a general trend toward hypercholesterolemia in patients with coronary sclerosis. There are, however, numerous individual exceptions to which insufficient attention has been paid. This is illustrated by the study of Morrison, Hall and Chaney[8], who determined the serum cholesterol concentration in 200 cases within two days of admission to the hospital for acute myocardial infarction. Of the 75 patients who were under 60 years of age, 68 per cent had concentrations greater than 260 mg. per 100 ml. of blood. Of the 125 patients over 60 years of age, only 48 per cent had abnormally high values. Thus, about one-third of the first group and one-half of the second had normal cholesterol values in the face of clear cut coronary accidents presumably due to atherosclerosis. It must be concluded that at least this kind of vascular disease occurs often in the absence of hypercholesterolemia.

Gofman[9] has presented data (Table 2) purporting to show that there is a greater difference between normal subjects and patients with coronary disease with respect to the "atherogenic" lipoproteins than with respect to the serum cholesterol. He has reported also that, among patients who have already experienced myocardial infarction, the recurrence rate is 20 per cent per year for those whose S_f 12-20 lipoprotein levels are of the order of 100 mg. per 100 ml., while the recurrence rate is only 6 per cent per year for those whose S_f 12-20 levels are of the order of 50 mg. per 100 ml. That these studies demonstrate some positive relationship between coronary disease and levels of certain serum lipoproteins cannot be denied. Examination of Table 2, however, reveals standard deviations of such magnitude as to suggest that some of the individuals without coronary disease must have had lipoprotein concentrations as high as, or higher than, some of the subjects with coronary disease, and that some of the coronary patients had levels as low as some of the normal persons. As in the case of cholesterol, there appears to be a tendency toward abnormally high levels of the "atherogenic" lipoproteins in patients who have experienced coronary occlusion, but the correlation is by no means complete.

TABLE 1* Serum lipids in myocardial infarction cases, controls and "matched controls"

	Total cholest.	Cholest. esters	Cholest. phosph. lipid
97 Coronary	286.5±6.6	176.7±5.5	89.4±2.0
146 Control	224.4±3.5	124.6±2.6	71.4± .9
97 Matched	241.9±5.5	141.0±3.9	77.6±1.3

*From Gertler et al[7].

TABLE 2* Comparison of serum lipoproteins and cholesterol in coronary disease

	Number of cases	S_f 12-20—S_f 35-100	Mean total serum cholesterol
Normals 41-50 yrs.	253	109±65	260±63
Coronaries 41-50 yrs.	93	191±93	297±68
Normals 51-60 yrs.	149	107±57	274±65
Coronaries 51-60 yrs.	126	162±79	286±69

*From Gofman et al[9].

TABLE 3* Relation between cholesterol in vessel wall (coronary) and in serum compared with degree of sclerosis

Deaths	No.	Mg. cholest. per gm. of dried coronary (av.)	Blood cholest. mg.% (av.)	Gross degree of coronary sclerosis (av.)
Coronary	11	20.4	303	3.5
Other	14	5.1	186	1.5

*From Morrison and Johnson[10].

b. Post Mortem Studies of Blood Vessels in Relation to Levels of Serum Lipids

Morrison and Johnson[10] determined the cholesterol content of the first 6 cm. of the anterior descending coronary artery in 11 cases of fatal myocardial infarction and in 14 patients of comparable age who had died of other causes. The cholesterol content of the vessels was compared with the degree of atherosclerosis as estimated grossly and with the levels of serum cholesterol. As indicated in Table 3, all *average* values were considerably higher for the patients with infarction than for those without. The individual data, however, show that two of the patients not dying of infarction had Grade 3, and six Grade 2, coronary sclerosis in the presence of normal amounts of cholesterol in the arterial wall and normal concentrations in the serum.

Faber[11] measured the cholesterol of the aorta in 26 subjects (all but two were men) ranging in age from 18 to 73 years and attempted to relate these values both to age and to serum cholesterol. The cholesterol content of the aorta was found to rise progressively with age, but it failed to correlate with cholesterol concentrations in the blood. In Figure 1, Faber's data derived from analyses of the aortas have been recalculated and plotted as mg. of cholesterol per gm. of aorta. In the same figure are plotted, not Faber's data on serum cholesterol, which are not numerous enough to be statistically valid, but the average values for serum cholesterol obtained by Keys[12] in a study of 2056 normal subjects, chiefly men, in various age groups.

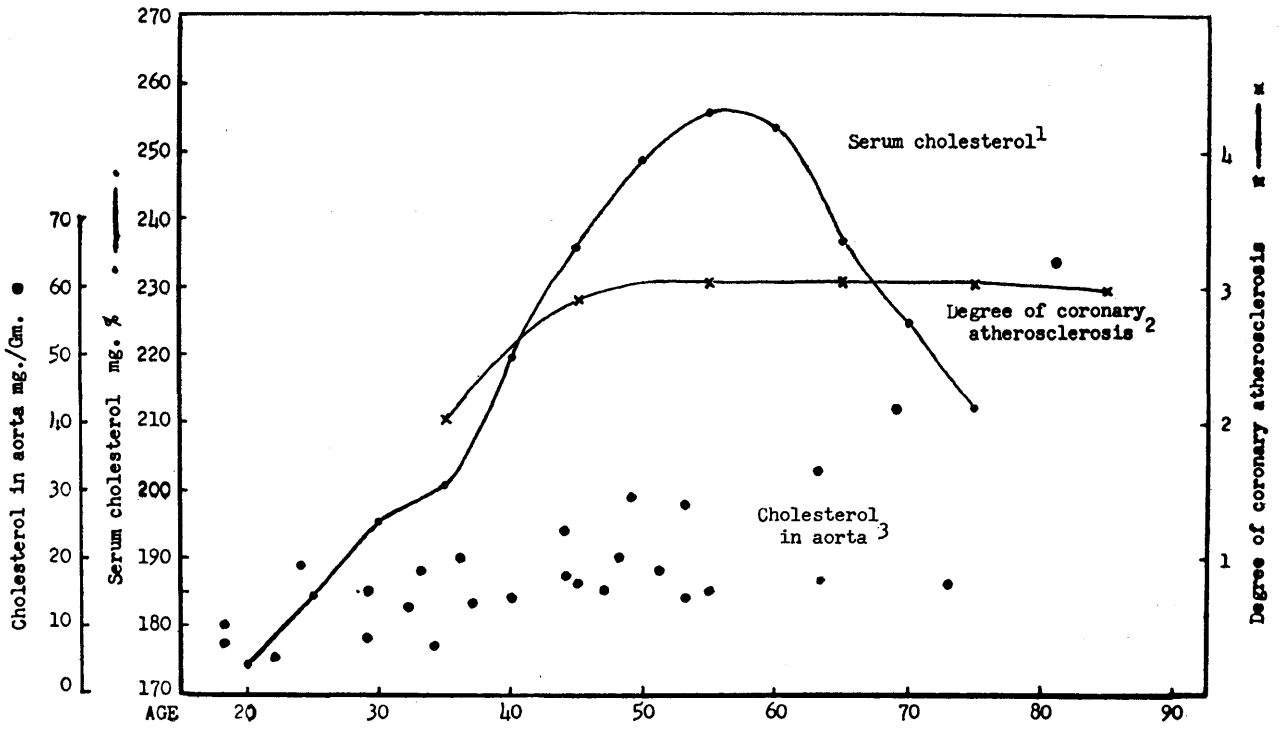
These data confirm Faber's own in showing a lack of correlation between serum and aortic cholesterol for, although both increase up to the sixth decade, thereafter aortic cholesterol continues to rise while serum cholesterol reaches a peak and then falls with advancing age.

Also in Figure 1 are plotted the results of a study by White, Edwards and Dry[13] on the relationship of the degree of coronary atherosclerosis with age in men. These investigators made multiple sections of the coronary system of the hearts of one hundred unselected cases in each decade from age 30 through age 89 (six hundred hearts in all) and graded the degree of atherosclerosis on the basis of 1 to 4. As shown in the figure, the severity of coronary sclerosis increases rapidly, along with serum cholesterol, through the fourth and fifth decades and reaches a maximum in the sixth, after which it levels off despite still rising, and later declining, levels of serum cholesterol. It seems likely that coronary atherosclerosis is not entirely a function either of serum cholesterol concentration or of age, whereas aortic sclerosis, as measured by cholesterol content, is related to the latter but not the former. The reasons for the rise and fall of serum cholesterol with increasing age are not clear.

c. Comparisons of the Dietary Habits of Populations Which Are More Prone, as Opposed to Those Which Are Less Prone to Atherosclerosis

These have generally led to the conclusion that a high fat intake favors, and a low fat intake minimizes, this form of arterial disease. By and large, such investigations have not been sufficiently well documented to provide convincing proof. Furthermore, there has been a dearth of chemical evidence to show that the higher incidence of atherosclerosis reported in peoples subsisting on large amounts of fat is accompanied by increased concentrations of lipids in the blood. Recently Keys[14] and his associates have presented a more complete study of food habits in relation to both the incidence of atherosclerosis, as manifested by coronary heart disease, and levels of serum cholesterol in different European populations. In England, where the incidence of the disease is roughly the same as in the United States, fat constitutes from 35 to 40 per cent

FIGURE 1. Serum cholesterol, cholesterol content of aorta and degree of coronary sclerosis in relation to age



1. Based on data obtained in 2056 normal men (Keys et al[12]).
2. Based on necropsy examination of 600 unselected hearts of normal males (White et al[13]).
3. Based on chemical analyses of aortas from 2 females and 27 males (normal) (Faber[11]).

of the diet and serum cholesterol tends to be relatively high. By contrast, the poorer classes of Italy, whose diets contain only about 20 per cent fat, have lower levels of serum cholesterol and, it is stated, a much lower incidence of all forms of heart disease including, presumably, coronary sclerosis. In the upper classes of southern Europe, on the other hand, fat intake, serum cholesterol and the estimated frequency of vascular disease are all higher. These differences on dietary fat seem to be reflected in serum cholesterol levels only after age 30. While not supported by adequate vital statistics, these studies, bringing to the problem more quantitative answers than have heretofore been available, bear out the generally accepted association between serum lipids and atherosclerosis. There is little doubt, however, that here, as in other investigations, discrepancies would appear in individual cases were detailed information at hand.

d. Experimental Observations

Such observations in human material, for obvious reasons, have been limited. Space permits mention of only one such study. Evans[15] and others have pulsated the oxalated blood of young normal individuals and of patients with coronary disease, some of them diabetics, against strips of normal human aorta at a pressure of 300/0 mm. of mercury and a rate of 80 pulsations per minute for 72 hours. Seventy-five per cent of strips pulsated with patients' blood showed a well marked deposition of birefringent particles in the vessel wall, closely resembling early spontaneous atheroma, while 82 per cent of strips treated with the blood of normal subjects contained no such particles. Although these ingenious experiments were performed under highly artificial conditions, they do demonstrate a difference between the normal and abnormal bloods in respect to the ease with which their lipid constituents, not chemically identified, were taken up by previously normal aortas.

That long standing diabetes predisposes to premature and severe vascular disease is well known. That diabetes is often accompanied by hyperlipemia has also been known for many years. A relationship between these two facts has been commonly assumed. It is pertinent to ask, however, how frequently elevation of the blood lipids actually occurs in diabetes. For our present purposes, we are not interested in the characteristic lipemia of the untreated diabetic or of the diabetic in acidosis. If the lipids have any significance for vascular disease, it must be by virtue of the levels which obtain in the treated diabetic over a long period of years. The literature contains surprisingly few reports on this subject, and those that we have are not only conflicting, but are based on analyses made at only a single point in time.

Chaikoff and others[16] compared serum cholesterol, phospholipids and fatty acids in 23 normal children and 26 children with diabetes under good control with diet and insulin. They found no appreciable difference between the two groups, nor did the duration of diabetes or the daily insulin requirement (10 to 68 units) have any relation to the cholesterol levels.

Man and Peters[17] found the serum cholesterol normal or below in 64 per cent of 79 diabetics not suffering from dehydration or acidosis. Of nineteen patients who showed rather marked hypercholesterolemia, sixteen had complicating conditions such as cirrhosis or nephritis which in themselves might have explained the high cholesterol levels. Among the uncomplicated cases the cholesterol did not exceed 304 mg. per cent—certainly not a striking figure.

Pomeranze and Kunkel[18] recently examined 273 diabetics in various clinics in New York City. Almost exactly half had total serum lipids about 750 mg. per cent (the upper limit of normal) while the other half had levels below this.

These data suggest that in children with well controlled diabetes there is little if any increase in blood lipids but that among adults, with diabetes of varying severity and under varying degrees of control, the lipids are elevated in 35 to 50 per cent of the cases.

Respecting lipoproteins in diabetes, Barach and Lowy[19] report the S_f 12-20 fraction above 50 mg. per cent in 33 per cent of males and 43 per cent of females. Hanig and Lauffer[20] were unable to find any significant difference between normal persons and diabetics. The data of Keiding and associates[21] would justify a similar conclusion, although they do not state it in so many words. Among the diabetics themselves, S_f 12-20 levels tend to be higher in patients under poor control than in those under good control.

The next question is whether the diabetics who do have hyperlipemia are the ones who also have vascular disease. Among the cases studied by the New York group[18], 78 per cent of the patients with hyperlipemia had severe atherosclerosis as shown by electrocardiographic evidence of coronary disease, calcified vessels or retinal arteriosclerosis. Twenty-two per cent were classed as having moderate atherosclerosis or none. On the other hand, of the patients who had normal serum

lipids, about forty per cent had severe atherosclerosis and sixty per cent had a moderate amount or none. We are left, then, with the dilemma of what caused the vascular disease in the forty per cent without hyperlipemia.

Referring again to the lipoproteins, Barach[19] found the S_f 12-20 fraction elevated in 45 per cent of 162 diabetics with vascular calcification. This is not significantly different from the incidence of elevated S_f 12-20 levels in the entire group of diabetics. Essentially the same results were reported by Keiding[21], with the additional surprising finding that these lipoproteins were distinctly increased in patients with retinopathy. It is not stated how many of the patients with retinopathy also had the Kimmelstiel-Wilson lesion—a condition in which the S_f 12-20 levels are almost uniformly high[22].

In the diabetic population, just as in the nondiabetic, it seems clear that while there is some general, over-all association between the level of serum lipids and the occurrence of atherosclerosis, this relationship fails in many individual cases, and that abnormalities of the circulating lipids do not provide a wholly satisfactory answer to the problem.

Should dietary fat and cholesterol be restricted in an effort to prevent vascular disease? In the present state of our knowledge, it would be reasonable to take the position that excessive amounts of these substances should be avoided. On the other hand, the extreme restriction necessary to produce a significant reduction in the lipid constituents of the blood would seem to be unjustified and may indeed by harmful.

SUMMARY

There is no doubt that in certain animals, under certain conditions, the induction of chronic hypercholesterolemia leads to atheromatosis. For the most part, the levels of serum cholesterol in such experiments have been far in excess of those found in patients with naturally occurring atherosclerosis. While the disease in man has a tendency to be associated with higher values for serum cholesterol than are present in normal persons of comparable age, this association is loose and decidedly inconstant, and the differences in cholesterol levels are not striking. Even if they were, it would still remain to be proven that the relationship is one of cause and effect. Studies of the serum lipoproteins do not yet warrant final conclusions. The evidence to date would seem to justify the same comments that have been made concerning cholesterol.

The tendency of the treated diabetic to have increased concentrations of serum cholesterol and lipoproteins is neither so frequent nor so marked as has been commonly supposed. Furthermore, early data indicate that these chemical abnormalities are no greater in diabetics with vascular disease than in those without it. An apparent exception is retinopathy. High levels in intercapillary glomerulosclerosis are more likely a result than a cause of the renal disease.

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SPECIALIZATION AND RESEARCH

In delivering the John Phillips Memorial Lecture before the American College of Physicians in Atlantic City on April 15th, Dr. Charles H. Best prefaced his address with the following cogent remarks on the problems of research and specialization. They should be of interest to all workers in specialized fields and particularly to readers of DIABETES.

"We have obviously passed the point of medical development at which an individual physician can truly qualify as a specialist in all branches of internal medicine. The clinical investigator must concentrate even more than the practicing physician if he is to pin-point his target, clearly visualize the problems, and advance knowledge of his special subject. The physiologist is, of course, also witnessing the division of his "country" into scores of "states," the boundaries of which are fixed by knowledge of technics as well as by scientific interest and capacity. I lecture to advanced students only on carbohydrate and fat metabolism, on blood clotting and thrombosis, and on certain aspects of endocrinology and nutrition, but it requires constant application and effort to keep abreast of the advances in these fields. To plan, direct and do good research you *must* frequently think well ahead of existing knowledge. Occasionally it is known to everyone that a great goal has *not* been reached and the literature may be ignored, but the individual who follows this path more often attains oblivion than fame. When a real advance has been made it is a relatively short time before the weight of interest and ability of other laboratory groups force the originators to share or relinquish leadership. This is as it should be and there will always be hosts of glittering new problems for those who can never be completely happy unless they are venturing into some phase of the unknown. It is more exciting to tackle a problem and, if fortunate, to enjoy for even a brief space the thrill of a new trail, than to develop well-established fields—but the latter course may be much more productive. As long as an investigator can continue to attract young minds and to keep his own open to the myriads of opportunities which lie ahead in research, there is scope—and hope—for him."