

Human Atherosclerosis and the Diet

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DISCUSSIONS about the possible effects of the diet on the development of human atherosclerosis center on five items: (1) calorie excess and the resulting obesity, (2) cholesterol in the diet, (3) animal fats in the diet, (4) total fats in the diet, (5) the dietary supply of substances which may have a "lipotropic" action, for example, lecithin, choline, inositol. Since the data on the possible action in man of the lipotropic substances pertain to pharmacologic rather than dietary levels and, moreover, are either questionable or negative in regard to an effect on atherosclerosis, the present discussion will not make further mention of these substances.

There are abundant actuarial data which show there is an elevated incidence of fatal atherosclerosis in obese or overweight people. Routine necropsy studies indicate a direct relationship between atherosclerotic changes in the arteries, including the deposition of cholesterol and lipids, and relative fatness of the whole body. Experiments on the production of atherosclerosis in animals likewise show that the relative calorie intake is important.³ But atherosclerosis occurs in many persons who are neither fat nor overweight. Our first real conclusion, then, is that the development of the atherosclerotic process is abetted, at least in some persons, by an excessive calorie intake and/or the resulting obesity. The calorie level of the diet is an influential but not a controlling factor.

At present the greatest concern about the diet in regard to atherosclerosis has to do with the consumption of foods which contain cholesterol. In some animals, notably the rabbit and the chicken, the addition of large amounts of cholesterol to the diet can lead to high serum cholesterol concentrations and to arterial lesions which resemble human atherosclerosis in many respects.

Unfortunately, these animal experiments do not necessarily have any relevance to the ques-

tion of the role of the diet in human atherosclerosis. No animal species close to man in metabolic habitus has been shown to be susceptible to the induction of atherosclerosis by cholesterol feeding. The nearest approach to metabolic comparability is the dog which requires extensive thyroid damage as well as tremendous amounts of dietary cholesterol before positive effects can be elicited. Moreover, even in the favorite species for such experimentation, the herbivorous rabbit, the necessary concentration of cholesterol in the diet is fantastically high in comparison with actual human diets. The actual range of daily intakes of cholesterol provided by real human diets is from zero to perhaps 1000 mg., but the vast majority of human diets seldom average as much as 700 mg. The cholesterol levels in the diets used to induce atherosclerosis in animals range from 0.5 to 5 per cent by weight of the dry food, the most popular level being 2 per cent. This means something like 1000 to 10,000 mg. of cholesterol per 1000 Calories of food, the 2 per cent cholesterol level being equivalent to about 4000 mg. per 1000 Calories if 30 per cent of the calories are derived from fats. We should have to provide some 10,000 to 15,000 mg. of cholesterol daily to a man to be comparable. Moreover, there is reason to believe that man has a greater power of cholesterol regulation than does the rabbit or the chicken. From the animal experiments alone the most reasonable conclusion would be that the cholesterol content of human diets is unimportant in human atherosclerosis.

Direct evidence on man in this connection is unimpressive. Arguments about the incidence of atherosclerosis and the customary intake of cholesterol in the Far East are based on no real data on either atherosclerosis incidence or the character of the diet. The recent analysis of mortality data in Scandinavia¹⁰ is more acceptable but still suffers from the inherent weakness of attempting to discover causation from a parallelism between crude estimates of national averages for two variables. Besides

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the dubious point of attributing war-time changes in vital statistics to actual changes in atherosclerosis, the analysis glosses over the fact that the presumed variations in cholesterol intake were parallel to similar variations in total dietary fat and, at least to some extent, to changes in calories intake and physical activity (see also¹³).

Such, in substance, is the actual evidence on human atherosclerosis itself. But significant inferences can be made from indirect evidence if we admit that there is an important relationship between atherosclerosis and the concentration of cholesterol in the serum. There is overwhelming evidence for such a relationship:

(1) On the average, wherever the serum cholesterol tends to be high—as in diabetes, nephrosis, hypothyroidism, and idiopathic hypercholesterolemia—there is a tendency toward early and severe atherosclerosis.

(2) Persons with definite evidence for disease of the coronary arteries tend to have elevated serum cholesterol values⁴ especially when they are compared with properly matched “normals.”⁵ Good confirmation can be obtained from recent raw data.^{6, figs. 14, 15}

(3) There is at least some parallelism between the age trend of cholesterol concentration in the serum and the age trend in atherosclerosis development.^{7, 9}

(4) In animal experiments there is a close parallelism between the serum cholesterol level and the development of experimental “atherosclerosis.”

There is much new evidence on the effect of the diet on the serum cholesterol level in man. In the first place, the serum cholesterol level of man is independent of large differences in the habitual voluntary intake of cholesterol.^{7, 8} Several important confirmations of this fact have been published recently.^{4, 14} Colossal intakes, however, far beyond those possible in natural diet, may cause a slow rise in the serum cholesterol.¹²

The rice-fruit diet, which is devoid of both fats and cholesterol, produces a prompt fall in the serum of men with normal levels of cholesterol² and a dramatic fall in patients with

severe idiopathic hypercholesteremia.⁸ We have found that the addition of vegetable fat to this cholesterol-free diet is followed by an equally dramatic rise of serum cholesterol to previous levels.

We have been able recently to make systematic studies on these questions with men under full supervision on diets rigidly controlled for some four months. Starting (and ending) with standard diets providing daily intakes of 150 Gm. of fat and 600 to 700 mg. of cholesterol, the following findings emerged:

(1) Change to a diet devoid of cholesterol and providing 15 Gm. of fat daily produced a rapid fall in serum cholesterol to about 80 per cent of the control value.

(2) Almost identical results were obtained with the same diet to which had been added about 500 mg. of cholesterol daily.

(3) Change to a diet devoid of cholesterol but providing about 70 Gm. of fat daily, produced a decline in serum cholesterol about half as great as when the fat level was only 15 Gm. (No. 1, above).

(4) The addition of 500 mg. of cholesterol daily to the diet (No. 3, above) providing 70 Gm. of fat did not change the result.

It should be noted that all of these experimental diets were comparable in calories and proteins, that the differences in fat intake were achieved by changing the amount of vegetable fat in the diet, and that the differences in cholesterol intake were achieved by adding or withholding whole egg yolks (from which cholesterol is readily absorbed). Finally, with each of the diets the major change in serum cholesterol occurred in the first week or so, and there was a tendency to reach a plateau, or at least a much slower rate of change, in subsequent weeks.

Much longer-term experiments on man are desirable but, so far as they go, these data are consistent within themselves and with all other facts known to me. The ensemble points strongly to the conclusion that, other things being equal, the serum cholesterol level in adult man is independent of the cholesterol intake over the range of zero to at least 700 mg. daily. But the fat intake is quite another

matter and appears to have great importance. However, there is not the slightest evidence for a difference between animal and vegetable fat in this regard.¹

It is now well recognized, and should have been clear long ago, that all animals, including man, have a large capacity for synthesizing cholesterol. Our experiments on fat-free diets also show that man has a large capacity to remove the cholesterol already present in the blood serum. On such diets the rate of removal of cholesterol from the serum seems to be proportional to the initial (control) serum level of cholesterol. In one patient with hypercholesteremia (900 mg. per 100 ml. of serum), the rate of disappearance from the blood was about 1500 mg. daily for several weeks on a fat-free diet. But with the same cholesterol-free diet to which were added about 50 gm. of vegetable fat, there was an increase of cholesterol in his total serum amounting to about 1000 mg. a day for a period of several weeks.

Now, clearly the cholesterol level is not the whole story in the development of atherosclerosis; otherwise the patient mentioned above would have been dead long ago. But, in so far as there is an important relationship between serum cholesterol and atherosclerosis, these dietary data have both theoretic and practical implications of some consequence.

A final question may be raised about the significance of all this in view of the studies by Gofman and his colleagues on the materials separated in the ultracentrifuge. From the evidence reported so far we may make two comments and draw a tentative conclusion:

(1) The response to diet of the serum concentration of substances characterized by -10 to -20 Svedberg units of sedimentation (the "G" substances) appears to be similar to our findings with serum cholesterol, and

(2) There is as yet no reason to suggest that the concentration of G substances in the serum is any more closely related to atherosclerosis than is the concentration of total cholesterol.

(3) At present, we may conclude that the implications for atherosclerosis drawn from dietary effects on serum cholesterol would be

similar if the serum criterion were the concentration of the G substances.

In summary, then, we may remark that direct evidence on the effect of the diet on human atherosclerosis is very little and is likely to remain unsatisfactory for a long time. But such evidence as there is, plus valid inferences from indirect evidence, suggests that a substantial measure of control of the development of atherosclerosis in man may be achieved by control of the intake of calories and of all kinds of fats, with no special attention to the cholesterol intake. This means: (1) avoidance of obesity, with restriction of the body weight to about that considered standard for height at age 25; (2) avoidance of periodic gorging and even temporary large calorie excesses; (3) restriction of all fats to the point where the total extractable fats in the diet are not over about 25 to 30 per cent of the total calories; (4) disregard of cholesterol intake except, possibly, for a restriction to an intake less than 1 Gm. per week.

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