ATHEROSCLEROSIS AND THE DIET*

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In the middle of the twentieth century all the world extols the marvels of the science and practice of medicine. Our steady progress is measured by the increasing expectation of life. In some of our most highly civilized communities the new-born baby has an average expectation of almost the biblical allotment of three score and ten years. In contrast are the estimates of half that life span for many populations in Asia, Africa, South America and the Near East. These are not racial differences for we too had similar poor expectations not so long ago. But, we say, our superior mode of life, industry and medical knowledge have made all the difference.

Actually, our triumphant progress towards better health and lower mortality has been uneven. We have made tremendous gains in the fight against infant and maternal mortality; tuberculosis and other communicable diseases are rapidly disappearing; the antibiotics have given us remarkable control over all manner of infections; and the surgeons are doing an amazing job repairing our mechanical defects and injuries. But our improved life expectation turns out to be very largely accounted for by a great reduction of deaths in infancy and youth. The gain for adults, particularly men, proves to be small.

If we make allowance for the lives saved by modern medicine and public health, we come to a startling conclusion. It is difficult to escape the suggestion that adult men in our so-called most advanced communities are little if any healthier than their grandfathers. They are certainly much less healthy than their wives if we measure the outcome in mortality. How can we explain this? Heart disease is the trouble.

DEGENERATIVE HEART DISEASE

The rise of heart disease to the dominant position it holds today is not merely a reflection of the increased average age of the population. The picture is much the same if we examine mortality rates at given ages. For example, I have just received the latest analysis of life insurance experience in the United States. I will give you the findings on white men aged 50-65, with the distribution of ages standardized to average 55 years. The total death rate from all causes in 1925 was 21·8 and in 1950 19·4. This nice little gain is more than accounted for by improvements in tuberculosis and influenza alone. But heart deaths rose from 4·5 in 1925 to 8·6 in 1950. Moreover, the death rate from heart diseases of infectious origin—rheumatic and syphilitic—decreased by 20% over this period. In other words, our age-specific mortality from the degenerative heart diseases, mainly coronary heart disease, has more than doubled. In the United States coronary heart disease is now our leading cause of death. Other countries with a high standard of living are showing the same trend. Our women are not immune but they apparently preserve their youth a little longer than the men; they also show up in the column of coronary deaths a few years later.

It has been suggested that our high adult mortality rate is a result of our success in preventing infant mortality. The weaklings, we might say, are preserved for death in early adult life. But I find it impossible to believe that infantile diarrhea and diphtheria can be a 'kill or cure' vaccination against atherosclerosis and coronary disease 50 years later. Or that, given a chance, tuberculosis kills the very men who are otherwise destined to die of a coronary occlusion. And I want to know why over half of the hearts of American soldiers killed in action in Korea show atherosclerosis definitely developing. The average age of these boys was 22.

Our exasperation with the coronary problem is increased by the fact that it is certainly not merely the result of age. At the same time, however, in this fact is our greatest hope. Men and women are not doomed to coronary heart disease merely because of the passing of years. This is the fact that has led us to study people in England as well as in America, in Spain, in Sweden and in several parts of Italy. This is the reason Mrs. Keys and I are in Cape Town, taking advantage of the co-operation of Professor Brock, Dr. Bronte Stewart and their colleagues.

In South Africa, and in many other places in the world, there are large populations who seem to be singularly free of atherosclerosis, even at advanced age. We want to study such people in the hope of learning how we too may eventually present the pathologist with aortas and coronaries to be proud of. My own generation, perhaps, is beyond redemption, but I firmly believe that the answer, its application and the reward in the next generation, can be assured by *research in the next few years.* It is even possible to hope that some of the atheromata many of us now hide can regress. The main clue, I think, is in the diet, but I do not deny other factors.

ATHEROSCLEROSIS AND BLOOD CHOLESTEROL

Now it is time to discuss the facts. It is agreed that coronary and related degenerative heart disease seldom develops except on the basis of atherosclerosis. I exclude, of course, syphilis and other infections that are now preventable and are, in fact, already becoming excessively rare as causes in many regions. And atherosclerosis is, by definition, the condition where the intima of the artery is invaded by deposits of cholesterol. It has

* An address delivered at the University of Cape Town on 11 March 1955. Professor Keys illustrated the address by many statistical tables, which are only briefly summarized in the paper as printed.

been argued that some fault in the arterial wall invites such deposits but whether this is true or not, the crucial facts are two: First, this cholesterol undoubtedly comes from the blood. Second, statistically, the tendency to form atheromata is related to the blood concentration of cholesterol and cholesterol-bearing lipoproteins.

This is to say that the composition of the blood plasma is a major determinant, though not necessarily the sole cause of atherosclerosis development, and that the cholesterol-bearing moiety of the plasma is the responsible factor. I do not propose to discuss here the relative merits of various measurements as indices of the atherogenic potential of the blood. These include the total cholesterol, the cholesterol-phospholipid ratio, the amounts of cholesterol, of amino nitrogen and of lipid in the beta lipoproteins, and the total amount of beta lipoproteins of given density estimated by flotation in the ultracentrifuge. All of these measures, statistically, have highly significant and similar value in distinguishing between coronary patients and clinically healthy controls and, I believe, in predicting, statistically, the likelihood of eventual coronary disease in groups of people. But it is quite clear that all of them fail, and to rather similar degree, to yield reliable predictions for individuals. In my own laboratory we currently measure total cholesterol and the cholesterol in the beta lipoprotein fraction as separated both by paper electrophoresis and by cold ethanol precipitation. For several years we also measured phospholipids and carried out the ultracentrifugal analysis so stridently advocated by Gofman. We have now abandoned these as laborious and costly elaborations that contribute little or no additional information for our purposes.

In the present lecture the discussion is concentrated on total cholesterol because most of the relevant data concern this factor. And the first problem is, *what controls the cholesterol concentration in the blood?*

Forty-five years ago it was shown that the blood cholesterol concentration in the rabbit is readily altered by adding large amounts of cholesterol to the diet. The chick, but not the adult chicken, is equally sensitive. The dog with thyroid function destroyed and fed colossal amounts of pure cholesterol sometimes responds similarly. The importance of the animal experiments is to show that in all species tried, if the blood cholesterol can be increased enough and maintained that way, atheroma will develop. These animal experiments also show that there are tremendous differences in cholesterol metabolism between species and that if we are to discover the effect of the diet on man, we must study man himself.

Dietary Cholesterol. First, let us consider dietary cholesterol. Cholesterol is contained only in foods of animal origin; the chief sources are egg yolks, milk and milk products, and meats. On the average, the man who eats eggs for breakfast ingests twice as much cholesterol as the man who eats a European diet but takes kippers or porridge instead of eggs. Hence it is easy to make an approximate estimate of the cholesterol in the diet.

In 5 years of diet surveys in Minnesota—all on upper-middle-class business and professional men of ages 45-60—there was no sign whatever of any relation between the quantity of cholesterol in the diet and the serum level of cholesterol. This was the case even in experiments with controlled diets with daily doses of cholesterol varying from zero to 30,000 and 60,000 mg.—20 to 40 times the maximum in any natural diet.

DIETARY FAT AND BLOOD CHOLESTEROL

But diet apart from cholesterol content *can* affect the blood cholesterol. In an early experiment in 2 brothers with abnormally high blood cholesterol (idio-hypercholaemia) and cholesterol deposits in the body, a diet of rice and fruit immediately brought the blood cholesterol down—it appeared that the blood cholesterol does respond to the removal of the *last scrap* of cholesterol from the diet. But when vegetable oils were added to the zero-cholesterol diet, in 2 weeks the blood cholesterol was back almost to its old 'high'.

This observation was followed by systematic studies all of which showed a big and fast fall in the blood cholesterol on zero-cholesterol and low-fat diets; but when fat (even vegetable fat) was added to the diet (replacing carbohydrate) the blood cholesterol rose in spite of the absence of dietary cholesterol. Next, men were given a constant controlled mixed diet containing 110 g. of fat per day, and it was always found that the blood cholesterol responded to a change in the amount of fat in the diet but never to the amount of dietary cholesterol. These results continued up to the maximum duration of the experiments—6 months. But we then wanted to know the very-long-range effect in men leading normal lives.

These questions could not be answered by laboratory experiments, and we therefore turned to the experiments of nature. We estimated in certain national population diet averages the percentage of the total calories in diet that was supplied by fat. It varied from 8% in Japan and 15% in the South African Bantu to 39 in Australia, 41 in U.S.A. and 45 in the U.S. Army. (In U.S.A. the fat in the diet is contained in the following articles of diet: fats and oils other than butter (43%), meat, fish etc. (21·9%), milk and dairy produce other than butter (18·5%), eggs (6·2%), butter (4·8%), other sources (5·5%)—total 99·9%.) In studies on population samples in England, Italy, Sweden and the United States a close correlation was found to exist between these diet-fat percentages and the average blood-cholesterol level in the different populations—both at the age of 25 years and the age of 50 years.

That the difference was not racial was indicated in various series. For example, in Spain the diet of the upper classes is about as rich in fat as that of U.S.A., whereas the poor working men have a diet poor in fat; the blood-cholesterol figures correspond. Nor is the difference due to different levels of physical activity—at least not in the main (there is some tendency for the blood-cholesterol value to be lower in men on heavy work). There is also evidence that when populations change their diets, the cholesterol follows suit. In Germany there was a great fall in diet fats after the war during 1946-47, and a high fat diet again in 1949. The figures for blood cholesterol in sample groups from different population class in Stuttgart corresponded. In these population surveys similar results were obtained

when beta lipoproteins were measured as well as the total cholesterol.

HEART-DISEASE STATISTICS

National Death Rates. The relationship was then considered between fats as percentage of calories in the diet and degenerative heart disease (angina pectoris, coronary heart, arteriosclerotic heart, chronic myocarditis, myocardial degeneration) as shown in national vital statistics. The comparisons made between Italy and U.S.A. were very complete, and they showed that the excess of U.S.A. over Italy in deaths from these degenerative heart conditions were not accompanied by any corresponding difference in the morbidity rates from cancer, nephritis, cirrhosis of the liver, *intracranial lesions of vascular origin* or *heart disease other than degenerative.* Moreover, an excess of degenerative heart disease in the U.S. accounts for the otherwise surprising fact that the mortality from all causes of men from 40 to 70 is higher in the United States than in Italy.

Life-Insurance Statistics. Last year a prominent life-insurance actuary made a comparison between Italy and U.S.A. based on the number of policy-holders and the deaths amongst them. The same excessive mortality from degenerative heart conditions was found in the U.S.A. as compared with Italy.

To exclude a difference in clinical diagnosis this aspect was carefully investigated by an international team of reliable clinicians, including cardiologists from the U.S.A. and Sweden as well as from Italy. It was found that the doctors of Italy were *not* missing coronary cases in in-patient, out-patient or domiciliary services and, moreover, there was no bias against the admission of coronary cases to hospital.

Hospital Records. Passing from death statistics to hospital records, it was found in Naples, Bologna, South Sweden, Boston and the Twin Cities (Minneapolis and St. Paul) that the cases of coronary disease expressed as a percentage of all hospital cases rose in proportion to the fat content of the diet.

Autopsy records have been similarly examined. The p.m. data from Italy are scanty, but good records are available from Japan. The percentage incidence of high-grade coronary sclerosis in Japanese postmortems (males) is 1 : 10 compared with Minnesota males; it is even 1 : 3 when compared with Minnesota females.

The whole picture of a relation between the percentage of fat in the diet and coronary sclerosis is consistent throughout the world. An interesting feature is that it is not dependent on the presence or absence of *obesity.* The Italians, with their low incidence of coronary disease, are as fat as the Minnesotans, and fatter than the English.

Other Factors than Diet. The question may be asked whether the differences between nations and population groups is concerned not merely with the diet but with the whole complex of genetic factors, mode of life, emotional life, etc. Bearing on this point are the variations in mortality from degenerative heart conditions which accompanied the changes in the amount of fat in the diet during or after the last war. Examination of the death rates shows that in the countries affected there was a fall in this mortality figure proportionate to the decrease in diet-fat, and a rise with the subsequent increase in diet-fat after the war. In Germany the change in organic heart disability was seen in both the *Arbeiter* and *Angestellte* ('white collar') classes but it was greater in the latter. The change was greater in males than females. It is found generally that the percentage difference between heart conditions in the sexes climbs with the proportion of fat in the diet. This fact suggests that the sex ratio of the circulatory-disease death rate might be used as a crucial statistic in this connexion.

CONCLUSIONS

In this short review of a very complicated problem and selections from a great amount of data I have given only samples of the large amount of evidence, all of which is consistent to date, from which the following conclusions emerge.

Atherogenesis is markedly affected by, though not completely dependent on, the concentration of cholesterol or the cholesterol-bearing lipoproteins in the blood plasma. The cholesterol in the beta lipoprotein fraction may be more important than that in the alpha fraction but the great majority of the cholesterol is in the beta fraction anyway, and so the total cholesterol is a good measure for statistical purposes.

We can state confidently that the most potent influence on the blood cholesterol and lipoproteins known is the diet. However, dietary cholesterol itself is unimportant for man in all conceivable natural diets.

Though obesity is detrimental to the diseased heart, the total calories in the diet, and their reflection in the resulting relative obesity of the body, are not of more than secondary importance *per se* in the development of atherosclerosis. But outstanding importance must be attached to the fat content of the diet, measured as the percentage of the total calories derived from fats. In populations, when this percentage is less than 20%, atherosclerosis is slight and coronary heart disease is rare. At 30 to 35% fat calories atherosclerosis becomes a major problem and coronary heart disease tends to become the first cause of death for all ages over 40. At 40% or more, coronary heart disease tends to become a veritable plague and to cancel all the other health gains of modern medicine and public health.

There is evidence that the habitual level of physical activity also influences the development of atherosclerosis, though to a smaller extent than the fat in the diet. I have not had time here to discuss this but the effect may be explained, possibly, without conflict with my theory. The greater average speed of the circulation in physical work and the more rapid use of the fat moiety of the lipoproteins for the immediate metabolism of the muscles should be noted.

Role of Cholesterol in Fat Metabolism. Now a last word as to why dietary fat exerts its controlling influence on the plasma-lipoprotein concentration. The key is, I think, in the fact that neutral fats and fatty acids are not soluble in water or in the aqueous medium of the body but lipoproteins are water soluble. The formation of lipoproteins in the body is, in fact, nature's answer

to the problem of how to transport the fats in solution in the watery system which is the animal body. And cholesterol is an essential ingredient of the lipoproteins; so if fat is to be transported cholesterol must be provided from somewhere. Cholesterol is synthesized in the liver, or it is discharged or degraded, according to the load of fat presented for transport. The proof of this is seen in several other situations besides those produced by changing the dietary fat. Complete fasting, for example, demands the mobilization of fat from the fat depots and its transport to all parts of the body where it must take over almost the whole burden of supporting the energy metabolism. And so it is not surprising that we frequently see the serum cholesterol rise in complete fasting. Another excellent illustration of this principle that the blood cholesterol concentration is a response to the load of fat to be transported is provided by the situation in kwashiorkor, which is unfortunately so common here in South Africa. The baby with kwashiorkor is admitted to the hospital with a grossly fatty liver and a low level of serum cholesterol. It is fed on skimmed milk, which contains no fats and very little cholesterol and this results in two things which are interdependent: the liver fat is removed and the serum cholesterol may rise very high during this period. In later recovery the serum cholesterol gets to normal levels, less than in the fat-mobilization period and higher than in the fat-stasis period before treatment.

The Future. There remains a great deal of research to be done and our answers as yet are rough and without adequate detail. But you may share with me the view that the road ahead looks bright and that we are not being unduly sanguine when we hope for the day when, by scientific adjustment of the diet and widespread public health application, we can control our most ominous current problem of health in a prosperous world.

Our current research here in Cape Town, will, I believe, make a definite contribution to this end. The essential pieces in this puzzle are being sought by close collaboration between Professor Brock and Dr. Bronte Stewart here, Malmros and Biörck in Sweden, Fidanza, Poppi and Postelli in Italy, Kimura and Kusukawa in Japan, Morris in England, Paul White in Boston and my team in Minnesota. Other medical scientists are cooperating in Guatemala and in Finland.

Tonight I have emphasized the fats in the diet as a major factor. So far it stands out as the most intriguing and the most hopeful clue. But we are also trying to give full consideration to other possibilities; physical activity (or the lack of it), smoking, and the stress of modern life, whatever that is. We have even given thought to alcohol. In comparing heavy drinkers with teetotallers the blood cholesterol values are found to be in conformity with the findings at post-mortem examinations of severe alcoholics. They may have 'knobs' on their livers, but their coronary arteries are usually an affront to teetotallers. This is one among many mysteries still to be studied.

SUMMARY

1. In spite of the lives saved by modern medicine and public health, it is difficult to escape the conclusion that adult men in America and other 'advanced' communities are little if any healthier than their grandfathers. The chief reason for this is degenerative diseases of the heart.

2. These diseases are the result of atherosclerosis of the coronary arteries, which is primarily dependent on a high blood content of cholesterol. And an important, if not the main, cause of high blood cholesterol is a diet containing a high proportion of fat. Both vegetable and animal fats are effective, though perhaps they are not identical in quantitative effect.

3. The amount of cholesterol in the diet has no bearing on the question. The reason why the amount of fat ingested affects the blood cholesterol is that the fats, which are insoluble in water, are conveyed in the blood in the form of soluble lipoproteins, of which cholesterol is an important constituent. The necessary cholesterol is readily synthesized by the liver.

4. Investigations are referred to—carried out in many countries—which substantiate these views. The answers as yet are rough and without adequate detail but there are good grounds for hope that by scientific adjustment of diet and widespread public health application coronary disease can be controlled.