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THE PATHOGENESIS OF ATHEROSCLEROSIS*

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"ATHEROSCLEROSIS" is a term that is coming more and more into fashion to replace that venerable term "arteriosclerosis", which was coined in 1833 by Lobstein, who was then Professor of Pathological Anatomy at the University of Strasbourg. He defined arteriosclerosis as meaning any hardening or thickening of the walls of arteries. Thus defined, the word served a useful purpose, until it eventually became evident that several quite different diseases of arteries were included in this all-embracing term.

It is obvious that Lobstein's definition included a number of inflammatory diseases of arteries, such as syphilitic aortitis and arteritis, thromboangiitis obliterans and even periarteritis nodosa. We have become accustomed to think of these disease entities each under its own specific name and not under the general term "arteriosclerosis", but confusion has persisted in relation to Mönckeberg's medial calcification of arteries and atherosclerosis by reason of the inclusion of both of them under the term arteriosclerosis and the general lack of appreciation that they are two separate and distinct disease processes. It is true that both conditions affect arteries in the older age groups and that they frequently occur together in the same artery for this very reason, but there is no essential connection between them, and either disease can reach an advanced stage in a particular patient or a particular artery without the other being present to any significant degree.

Mönckeberg's sclerosis, as it is sometimes called, occurs particularly in the arteries of the extremities, especially the lower extremities, and consists of deposits of calcium salts in the middle of the medial coat in areas of degeneration of the muscle. These deposits frequently become massive enough in persons above middle age to be easily seen in x-ray pictures and to render the artery palpably hard or even rigid or "pipe-stem" in character. Such findings give no information whatever as to the patency of the lumen of the affected vessels which in the absence of atherosclerosis will be widely patent. Nor does the presence of Mönckeberg's medial calcification in the peripheral arteries permit any inferences to be drawn regarding the state of other important groups of vessels, such as the coronary or cerebral arteries. Mönckeberg's sclerosis, in fact, has practically no functional significance, and it is important only because it so frequently misleads the clinician if he is not thoroughly aware that there is no close correlation between this disease and atherosclerosis of the intima.

In contrast to this lesion of the media, atherosclerosis of the intima of arteries is a disease of the highest importance. This is what is generally meant nowadays by the term arteriosclerosis, but it seems better to leave no doubt in the matter by employing the term "atherosclerosis" to indicate what appears to be one disease, and one disease only.

For the purposes of this discussion, I propose to define the term "atherosclerosis" as a disease of the arteries affecting primarily the intimal coat and characterized in general by increasing accumulations of cholesterol, cholesterol esters and other lipids in localized areas in the intima associated with fibrous thickening of the intima. The frequent occurrence of coalescence of individual lesions and of further degenerative changes in them is well recognized, but these are not essential to the definition. The further degenerative changes associated with

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progression of the disease include necrosis of the centres of the atherosclerotic lesions with the formation of atheromatous cavities filled with lipid-rich debris, the extension of the process to involve the media, necrosis and disintegration of the intimal lining over atheromata (erosion) and calcification of the lesions.

Through extension of the atherosclerotic process into the media over any significant area of the arterial wall, the medial coat may be sufficiently weakened to permit aneurysmal dilatation of the artery, ending sometimes with rupture. Examples of these complications are seen occasionally in the abdominal aorta, splenic artery, popliteal artery and basilar artery, but rarely elsewhere. The exact cause of the rupture of small intracerebral arteries leading to cerebral hæmorrhage is not known. A much more frequent and important consequence of atherosclerosis is the progressive narrowing of the lumina of arteries by thickening of the intima which may advance even to the point of producing complete occlusion of the lumen. Moreover, complete occlusion may be produced suddenly at any stage in the development of atherosclerosis by the occurrence of thrombosis in the arterial lumen to which atherosclerosis is the principal predisposing factor. Narrowing or occlusion of coronary, cerebral or peripheral arteries brought about by atherosclerosis with or without thrombosis accounts in preponderant measure for the morbidity and mortality associated with the disease.

PROBLEMS IN PATHOGENESIS

All stages in the progression of atherosclerosis can be accounted for on the basis of accepted pathological principles by assuming the continued operation of the same causal factors that initially set the disease process in motion. Unfortunately, however, these causal factors are largely unknown. The factors that have been recognized as having importance in the etiology and pathogenesis of the disease have probably been overemphasized in the past through ignorance of all the others. In fact, many published articles in this field give the impression that the problem of atherosclerosis has been practically solved by modern research, and that only a few details of pathogenesis remain to be determined. On the contrary, only a relatively few points of real importance have been established with certainty, and the rest is largely intelligent speculation. Since it is impossible to present a solution to the problem, I propose instead to give in outline a survey of the many problems that present themselves in connection with the pathogenesis of atherosclerosis.

The fact that atherosclerotic lesions contain lipid material was recognized at an early date. Chemical analysis of this material eventually proved that its principal constituent is cholesterol and cholesterol esters. Other lipids consisting of neutral fats, phospholipids and other sterols are present in smaller proportions. Chemical quantitation of the content of cholesterol in the aorta has shown in several studies a close positive correlation between the cholesterol content and the subjective appraisal of the degree of atherosclerosis present in the aorta. Accordingly, it would appear that the accumulation of cholesterol in the intima is a process of prime importance in the pathogenesis of the disease. The quantities of cholesterol that are found in the atherosclerotic lesions are much too large to have originated from local breakdown of tissue and it is, therefore, evident that cholesterol must be derived from another source, brought into the intima and deposited there.

It is commonly taken for granted that the primary event in the development of atherosclerosis is the deposit of lipids in the intimal layer, and that fibrous proliferation leading to fibrous thickening of the intima is secondary to this. The microscopic appearance of very early lesions is not entirely consistent with this view, and it is entirely possible that subtle changes in the endothelium, the ground substance, or other constituents of the intima may antedate the appearance of lipids. Indeed, it is difficult to account for the localization of atherosclerotic lesions except by assuming that this is so. Certainly it is true that pre-existing fibrous thickening of the intima predisposes to the deposit of cholesterol and the development of atherosclerosis. This phenomenon may be observed in the aortic scar of the obliterated ductus arteriosus, and is particularly conspicuous in areas of the aorta previously involved by syphilis.

THE RÔLE OF CHOLESTEROL

The rich content of lipids in atherosclerotic lesions and the accompanying fibrosis of the

intima were the central features that led Marchand to coin the term "atherosclerosis" in 1904 to indicate this type of arterial disease, but the early recognition that cholesterol forms a large part of the lipid content had little effect on current thought relative to the etiology and pathogenesis of atherosclerosis. The present preoccupation with the rôle of cholesterol in the pathogenesis of this disease had its origin with the experiments of Anitschkow and of Wacker and Hueck, who demonstrated almost simultaneously in 1913 that the daily feeding of cholesterol to rabbits over a period of several months led to the development of lesions of the aorta closely comparable with those of atherosclerosis in man. Wacker and Hueck also showed that the feeding regimen induced a marked elevation of the cholesterol content of the blood, which was due in greater part to the elevation of cholesterol esters.

This experimental disease of the arteries has since come to be generally known as "experimental cholesterol atherosclerosis", and the study of this condition in rabbits and certain other animal species through the intervening years has had a tremendous influence on the development of present ideas regarding the etiology and pathogenesis of atherosclerosis. Indeed, there has been a tendency to accept altogether too readily the implications of the experimental findings as translated into terms of the human animal, often in the complete absence of evidence that conditions truly comparable with those observed in the experimental animal actually occur in man. Nevertheless, experimental work along these lines has been of great value in indicating directions of search for etiologic and pathogenetic factors in the human subject. The experimental studies have contributed a good deal and may yet contribute much more toward a clear understanding of the factors that govern the process of deposition of cholesterol in the intima of arteries.

Although there has been in the past some dispute on the question, it is now generally conceded that the earliest lesions of atherosclerosis in man are the "fatty flecks" or "fatty streaks" seen in the aorta and sometimes in other arteries in early adult life, adolescence or even on occasion in early childhood or infancy. These occur in the intima of the arch of the aorta as yellow flecks and in the thoracic part of the descending aorta as yellow streaks, longitudinally disposed and slightly elevated above the surrounding intimal surface. The earliest of these lesions are generally thought to be completely reversible although there is no sure evidence to support this belief. Histological examination of the earliest lesions readily visible to the naked eye shows that there is already swelling of the ground substance and some increase of fibrous connective tissue cells in the intima. Lipid material stainable with Sudan III is found in the intima in the spindle shaped fibroblastic cells, in globular phagocytic cells or "foam cells" and also diffusely strewn through the swollen intercellular ground substance. The lining endothelial cells seldom contain any more than traces of stainable lipid.

The supposition that these lesions are reversible assumes that there is a stage at which there is no increase of connective tissue in the intima and further assumes the possibility of the complete removal of the accumulated lipids through the metabolic activity of the cells containing them. These assumptions seem reasonable, and while not proved by evidence from human material, they are supported by the study of the earliest lesions of experimental cholesterol atherosclerosis, which consist simply of subendothelial aggregations of "foam cells" filled with lipids. Here, too, there is a small amount of extracellular lipid material in the ground substance of the intima, but there may be a complete absence of fibroblastic proliferation. It seems highly probable that such lesions are capable of complete resolution under suitable conditions.

In the fatty flecks and streaks of the human aorta where slight fibrous proliferation has occurred, there is the possibility of complete removal of the lipids, leaving only a slight fibrous thickening of the intima to mark the sites of the lesions. I have been convinced that this may occur by the observation of children's aortas in which gray flecks and streaks of the intima were seen having the typical distribution of fatty flecks and streaks, and yet showing microscopically only slight fibrous thickening of the intima without a trace of lipid content. There is abundant evidence of the same kind to indicate the possibility of more or less complete removal of lipids from the more advanced lesions of athero-

sclerosis. Leary has brought forward evidence that this removal of lipids from atherosclerotic lesions occurs more readily in youth and more sluggishly with increasing age. He explains this phenomenon on the assumption that cholesterol and its esters are more rapidly metabolized in youth than in old age by the cells of the intima. From other evidence already mentioned, it may be inferred that the fibrous thickenings of the intima remaining after the removal of lipids has been accomplished would be more susceptible than the normal parts of the intima to a renewed deposit of lipids, if favourable conditions for the occurrence of this process should again arise.

THE INFLUENCE OF HYPERCHOLESTEROLÆMIA

Among the conditions that might be conceived as favouring the deposit of cholesterol in the intima only one, namely hypercholesterolæmia, has received more than casual attention in the past. Indeed, the concentration of attention on the absolute levels of cholesterol in the blood has undoubtedly led to the neglect of other factors that are probably much more important. The observation that the development of experimental cholesterol atherosclerosis in rabbits fed cholesterol does not occur in the absence of a significant elevation of cholesterol in the blood was responsible for the idea that hypercholesterolæmia in man must be a factor of the first importance in the pathogenesis of human atherosclerosis. It was even suggested that the eating of foods rich in cholesterol might be dangerous for this reason, in spite of the absence of any evidence to show that the ingestion of cholesterol causes hypercholesterolæmia in man and, indeed, in the face of evidence to the contrary. Not only does the ingestion of quantities of cholesterol fail to produce significant elevation of the cholesterol in the blood in normal persons, but recent studies by Ancel Keys have shown that there is no correlation in normal adults between the differing cholesterol contents of the diets habitually selected by different individuals in accordance with their tastes and the cholesterol content of their blood. Drastic reduction of the cholesterol content of the diet has no significant effect on the blood cholesterol levels in normal persons. Only diets completely free of cholesterol and of fat as well are capable of reducing the blood cholesterol to any significant degree.

It is true in experimental cholesterol atherosclerosis in the rabbit that the degree of atherosclerosis produced can be correlated roughly with the quantities of cholesterol fed, the height of the resulting hypercholesterolæmia and the duration of this latter condition. Modifications of the experiment, such as thyroidectomy, that tend to increase the height of the induced hypercholesterolæmia, tend also to increase the severity of the resulting atherosclerosis, while modifications that tend to decrease the degree of hypercholesterolæmia produced by cholesterol feeding, such as the concomitant administration of thyroid extract, tend to reduce the severity of the resulting atherosclerosis. It is true also in man that metabolic disturbances known to be characterized by hypercholesterolæmia are associated in many cases with the development of a degree of atherosclerosis greater than that found in persons of the same age groups who have not suffered such metabolic disturbances. The commonly quoted examples of diseases showing this association are diabetes mellitus, hypothyroidism, lipoid nephrosis and essential hypercholesterolæmic xanthomatosis. However, even in these conditions it remains to be demonstrated that hypercholesterolæmia is always followed by an excessive development of atherosclerosis and there are outstanding exceptions in our own autopsy experience, particularly among cases of myxœdema and lipoid nephrosis.

It may be admitted from experimental and clinical observations of the kinds outlined in the preceding paragraph that elevation of the blood cholesterol content above its normal level is one of the conditions that favour instability of the colloidal suspension of cholesterol in the plasma (dyscholesterolæmia), and hence promotes the deposit of cholesterol in the intima of the arteries. Hypercholesterolæmia happens to be the only factor thus far recognized as being capable of affecting the stability of the blood cholesterol in this way and accordingly great emphasis has been placed upon it as a factor in the pathogenesis of atherosclerosis. However, numerous studies of the blood cholesterol levels in human subjects have failed to establish the thesis that hypercholesterolæmia is the cause of atherosclerosis in the generality of mankind.

The normal level of cholesterol in the blood of the rabbit is low relative to that in man. The exact degree to which it must be increased by cholesterol feeding in order to bring about the development of experimental cholesterol atherosclerosis has not been determined. How-

ever, an increase to the level that normally exists in man appears to be sufficient. Accordingly, it is quite conceivable that atherosclerosis may develop in man without any elevation of the blood cholesterol level above the normal limits. It is entirely reasonable to believe from the evidence available that a decrease in the stability of cholesterol in the blood will usually result when there is hypercholesterolæmia, but it is quite evident that the process of deposition of cholesterol in the intima of arteries would be enhanced by any change, not necessarily associated with hypercholesterolæmia, that decreases the stability of cholesterol in the plasma.

STABILITY OF CHOLESTEROL IN SOLUTION

Practically nothing is known of factors that may operate *in vivo* to decrease the stability of cholesterol in the blood. Recently, however, Dr. McMillan and I have demonstrated that the stability of the blood cholesterol can be greatly increased, by an appropriate experimental technique, to the point that very marked hypercholesterolæmia in cholesterol-fed rabbits is quite ineffective in producing any change in the arteries. In later studies, Dr. Payne and I have shown that this unusual stability is associated with an excessive elevation of the neutral fat and phospholipid fractions, of which the latter is probably the more important factor. It is probably true in general that the relation of cholesterol to the other lipids in the plasma and to the plasma proteins is much more important in the maintenance of its stability than is the absolute level of cholesterol itself.

There is some experimental evidence to indicate that choline feeding renders the solution of cholesterol in the blood more stable and it has even been reported that the addition of choline to the diet facilitates the removal of cholesterol already deposited in the vessel walls. The observations on these points are conflicting and our own studies of this question seem to offer an explanation for some of the discrepancies. Dr. Meissner and I have found in experiments not yet published that the addition of choline to the diet, even in large amounts, has no discernible influence on the development of experimental cholesterol atherosclerosis in rabbits if the daily dose of cholesterol is moderately high. However, when the dose of cholesterol is reduced to one gram given three times a week and choline is administered in the highest daily dose that the animals will tolerate, there is a slight but definite retardation of the development of atherosclerosis. We were unable to discover significant differences between the control and experimental animals, either in the degree of hypercholesterolæmia or in the plasma lipid patterns, to account for this rather minor effect. In retrogression experiments, we found that the addition of choline to the diet in large amounts has no effect in promoting the resolution of established atherosclerotic lesions.

Great interest has recently been aroused by the work of Gofman and his associates who have demonstrated in the serum of certain persons, though not in that of others, the presence of giant cholesterol-bearing molecules of low protein content and of low specific gravity. They have brought forward evidence to indicate that the occurrence of these giant cholesterol-containing complexes may be correlated with the development of atherosclerosis in human beings and also in cholesterol-fed rabbits. It is interesting to note that these giant molecules are not found by any means exclusively in persons with hypercholesterolæmia. There is a tendency for their occurrence to be more frequent in sera that have a cholesterol content exceeding 200 mgm. per 100 c.c. However, they also occur in sera with normal or low cholesterol values and are absent in some cases in spite of definite hypercholesterolæmia. While it is possible that these giant molecules may actually enter the arterial intima with their load of cholesterol and other lipids, there is no evidence as yet to show that they do and it is entirely possible that their presence may merely reflect a state of general instability of the solution of cholesterol in the blood.

In summary, it may be stated that it has not been demonstrated that hypercholesterolæmia is a factor essential to the development of atherosclerosis in man. It may be that the effective periods of elevation of blood cholesterol are of short or irregular duration, and for this reason have not been detected and correlated with the development of atherosclerosis. However, it seems evident that there must be many factors other than simple elevation of the cholesterol content of the blood that could disturb its stability or physico-chemical state. It would appear that more intelligible informa-

tion would be gained if the state of suspension of cholesterol in the plasma were studied as it affects the stability of the cholesterol solution rather than merely the quantity of cholesterol present in the blood.

THE RÔLE OF LOCAL FACTORS

Although it is generally agreed that fatty flecks and streaks of the human aorta represent the earliest atherosclerotic lesions, and that the deposit of cholesterol and cholesterol esters in them is an essential feature, there is no general agreement on many fundamental points concerning the development of these earliest lipid deposits. The same is true of the pathogenesis of experimental cholesterol atherosclerosis. This lack of agreement is clearly due to the lack of adequate evidence. Here, indeed, is a field for fruitful research on questions that penetrate to the very root of the problem of atherosclerosis.

Our abysmal ignorance in this field may be emphasized by a recitation of some of the important points of information that still lie beyond our ken. It is not known, for example, in what form cholesterol enters the intima, whether as free or ester cholesterol, or both together, whether in colloidal suspension alone or in association with neutral fats or phospholipids or as a lipoprotein complex, or whether contained in fatty droplets, the so-called chylomicrons.

Moreover, it is not known how cholesterol, in whatever form it is carried, enters the intima. It is commonly supposed that cholesterol in colloidal suspension permeates the intima with the nutritive fluid derived from the plasma that normally seeps through from the lumen to provide nutrition for the inner layers of the arterial wall that are not reached by the vasa vasorum. It is not known whether the normal endothelial lining of the arteries is permeable to colloidal cholesterol. If it is not, then the deposit of cholesterol in the intima may be due solely to an increase of endothelial permeability sufficient to permit cholesterol to enter the intima, where it might be supposed that conditions suitable for the aggregation and accumulation of cholesterol always exist. Atherosclerosis might thus be looked upon as a disease dependent on primary changes in endothelial permeability. If, on the other hand, the arterial endothelium is normally permeable to colloidal cholesterol, it follows that its deposit in the intima must depend upon local changes in the subendothelial layer of the intima that favour the deposit of cholesterol as well as on qualitative or quantitative changes in the cholesterol content of the infiltrating nutritive fluid that flows through the intima. On the latter question there is a growing body of illuminating evidence, but there is practically no information as to the character of the local changes in the intima that favour the deposit of cholesterol, and which might well account for the localization of individual atherosclerotic lesions.

Among those investigators who believe that cholesterol enters the intima in colloidal suspension, there is no agreement as to where the cholesterol is initially deposited, whether in the subendothelial ground substance from which it is taken up by phagocytic cells, or whether primarily in the phagocytic cells themselves, or whether in both. Certain it is that in experimental cholesterol atherosclerosis in the rabbit large globular phagocytic cells filled with lipids ("foam cells") are present in very early lesions, but at the same time there is also present extracellular lipid material in the ground substance between them. The same is true of the earliest atherosclerotic lesions in man.

Certain investigators believe that cholesterol does not enter the intima by passing through the endothelial lining, but rather that it is taken up initially by the endothelial cells themselves from the plasma that bathes their surface and is then either passed on to the subendothelial layer or else carried into it by inward migration of the lining endothelial cells which then appear as "foam cells" in the subendothelial layer of the intima. While these ideas are perfectly plausible, they are rendered somewhat precarious by the usual absence of more than traces of stainable lipids from the lining endothelial cells covering the developing lesions of atherosclerosis, either in the human subject or in animals fed cholesterol.

One further idea, proposed by Leary, still remains as to the manner in which cholesterol is carried into the arterial intima to initiate the atherosclerotic lesions. In his studies of experimental cholesterol atherosclerosis in rabbits, he was impressed by the accumulation of cholesterol in reticuloendothelial cells, including the Kupffer cells of the liver, at a stage in the regimen of cholesterol feeding antedating the appearance of any lesions in the arteries. Lipid-filled cells also appeared in the circulating

blood, which he supposed represented Kupffer cells that had been swept into the passing blood stream. Leary postulated that these cells filled with lipid become adherent to the endothelial lining of the arteries wherever they happen to come into contact and then migrate into the subendothelial layer of the intima to accumulate there as the familiar foam cells. This theory is not generally accepted because there is no positive evidence to support it and Dr. Payne and I have recently obtained very good experimental evidence against it. Moreover, it seems at present to be quite inapplicable to the pathogenesis of human atherosclerosis, since the accumulation of lipids in reticuloendothelial cells has never been shown to be a characteristic accompaniment of the development of the disease in man, nor have lipophages been found in the circulating blood.

A factor of importance in both the pathogenesis and localization of atherosclerotic lesions is the intracellular metabolism of cholesterol and other lipids by the cells of the normal and atherosclerotic intima. It is one thing for cholesterol to be deposited, but it is another to have it remain where it is deposited. It is apparent that if cholesterol were removed from an area as rapidly as it is deposited, then this area would be considered to be immune. Conversely, if cholesterol were removed at a slower rate than usual, the area concerned would be considered to demonstrate the effects of localizing factors. At the present time there is but little information concerning the metabolic activity of the cells of the intima with reference to lipids or other substances. Mention of phagocytosis of lipids by endothelial cells and by foam cells has already been made. These latter cells are known to undergo mitotic division in the atheromas, to be capable of phagocytosis *in situ,* and to be capable of esterifying and de-esterifying cholesterol. Presumably, they are also capable of migration. Fibroblastic cells appearing a little later in the development of the lesions possess similar metabolic activity. Aside from these few primitive observations we are ignorant of whatever other intracellular lipid metabolic processes may exist, and we are ignorant of the mechanisms controlling those already mentioned.

LOCALIZATION OF ATHEROSCLEROSIS

The problem of the localization of atherosclerotic lesions has always been a vexed one. From the existing observations it is apparent that there are two chief ways in which localization of the deposition of cholesterol in the vessel wall is affected. The first of these depends upon variations in the structure or composition of the vessel wall itself, and the second depends upon mechanical or hydrodynamic forces acting at a particular point of the blood vessel. There is no evidence that the chemical composition of the blood changes while flowing within the vascular tree to a degree capable of influencing the site of deposition of cholesterol.

Mention has already been made of the influence of such lesions as syphilitic aortitis as factors promoting atherosclerosis. It is noted that this effect occurs only in the areas damaged by syphilis. Similar localizing phenomena dependent upon damage and cicatrization of the vessel wall have been demonstrated in a wide variety of experiments. These have all served to show that local injury is able to increase the local susceptibility of arterial walls to the deposition of cholesterol from hypercholesterolæmic serum. It has been suggested that the changes induced in the vessel wall increase endothelial or intimal permeability and hence afford a greater opportunity for the development of atherosclerosis. Nevertheless, it must be admitted that the mechanism of this type of localization has not been seriously investigated and we are ignorant of its processes. Attempts have also been made to demonstrate that normal differences in anatomical structure affect the localization of atherosclerotic lesions. Differences in the morphology and function of endothelium in the sites prone to atherosclerosis and in sites resistant to the lesions have been sought without success. Attempts to implicate the normal variability in vasa vasorum have also been made. If normal morphological variations in the walls of blood vessels are important to the localization of deposits of cholesterol, and there is every reason to think that they may be, then it must be confessed that there is no appreciation of what the essential anatomical differences are or of the mechanisms through which they act to promote or inhibit atherosclerosis.

MODIFYING FACTORS

There is good reason to believe that hypertension, either localized or generalized, promotes the development of atherosclerosis in

man. Atherosclerotic lesions of the pulmonary artery are most common and extensive in association with pulmonary hypertension, while it is common knowledge that hypertensive patients are prone to an excessive development of atherosclerosis. Supporting experimental data are scanty, but consistent with these findings. It has been suggested that this occurs because of anoxia and damage of the vessel wall due to compression, or that it is due to an increase in the rate at which cholesterol-bearing nutrient juices permeate the intima. Neither explanation is more than hypothetical.

Similarly, evidence derived from such lesions as congenital anomalies of the blood vessels or from traumatic arteriovenous aneurysms indicates that a stream of blood which impinges at an open angle and with unusual force on the vessel wall will elicit an atherosclerotic reaction. It has been suggested that at least three hæmodynamic mechanisms are active in the production of such lesions. The rôle of increased pressure is one. In addition, it has been thought that the endothelium may be damaged, or that the unusual swirling and eddying of the blood stream may mechanically disturb the solution of cholesterol in the blood and thus promote the deposition of cholesterol in the intima. The concepts implicit in these observations are also applied to the known tendency for atheromas to occur about the mouths of the large and small branch vessels of the aorta and at the sites at which arteries suddenly change direction or bifurcate.

CONCLUSION

It is evident from what has been said, that our knowledge of atherosclerosis today is largely confined to what is known about the behaviour of cholesterol in the body. The deposition and accumulation of cholesterol in the intima of arteries has come to be regarded as the central feature of the disease. There exists a fairly satisfactory body of knowledge concerning the morphological characteristics of human atherosclerosis and its experimental counterpart, experimental cholesterol atherosclerosis. It is in regard to mechanisms or dynamics of development that we are particularly ignorant.

The recitation that has been given of all that we do not know about the pathogenesis of atherosclerosis must surely throw into sharp relief the fact that all of the results of numerous investigations have fallen far short of a solution of the problem. Research in this field has only scratched the surface. We still lack sure proof of many of the most elementary items of factual information that would be required for a clear understanding of this disease process. The great amount of investigative work that is currently being carried on in this field should accelerate the expansion of our knowledge, but until the pool of well-established scientific information has become a good deal larger, no one can justly claim that the riddle of atherosclerosis is solved or is even near to a solution.

Meanwhile, suggested regimens for the prevention or amelioration of atherosclerosis that purport to be founded on a scientific understanding of the pathogenesis of the disease should be viewed with suspicion. Low fat-low cholesterol diets offer no real hope of lowering the blood cholesterol level significantly, though it is conceivable that they might alter the physicochemical state of cholesterol in the blood without changing its quantity. Such diets might bring about clinical improvement through loss of weight or for other reasons, but there is no sure evidence to indicate that they offer a means of reversing the atherosclerotic process. The use of choline in the treatment of atherosclerosis has as its only basis the experimental studies that indicate a slight effect of choline in retarding the development of experimental cholesterol atherosclerosis under certain conditions. On the other hand, the one report that choline will cause the disappearance of established experimental lesions of the arteries is not confirmed in our own experiments. No clinical studies have been reported that establish convincingly any beneficial effect of choline in cases of atherosclerosis. Indeed, in view of our present ignorance of the pathogenesis of atherosclerosis, any form of treatment directed toward the reversal of the lesions in the arteries, even if such treatment should be conclusively demonstrated by well controlled clinical tests to be of clinical benefit, must be regarded, for the time being at least, as purely empirical.

In carefully controlled studies of 309 patients with head colds there was no significant difference in the proportion of cures reported by patients receiving aureomycin and by those receiving a placebo.—Hoagland, R. J., *et al., Med.*, **243**: 773, 11-16-50.