Atherosclerotic Lesions in Diabetes

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Since arteriosclerosis accounted for 69.4 per cent of deaths in a series of diabetic subjects in the five-year period from 1944 to 1949,[1] it seems appropriate to reassess our knowledge of this serious complication of diabetes in the last trimester of 1954.

"Atherosclerotic lesions" I have interpreted as meaning those lesions, primarily intimal, which occur in the large and medium-size arteries of the body. Within the limitations of this paper the term "atherosclerosis" will be considered to be synonymous with arteriosclerosis of the intimal type. I propose to discuss atherosclerosis from the pathologist's point of view, to consider the relationship between this disease and diabetes, and to summarize some of the problems that confront investigators in the field of arteriosclerosis.

DEVELOPMENT OF THE LESION

Almost all pathologists are of the opinion that the earliest visible lesions of atherosclerosis are the minute, slightly elevated yellow flecks seen in the aortas of children. Holman and Strong[2] in a series of 120 patients ranging from one to seventeen years of age found no child over the age of three years who was exempt from these lesions; Zinserling[3] saw them in 95.4 per cent of 302 children under sixteen years. The flecks tend to coalesce, forming longitudinal streaks along the long axis of the posterior wall of the aorta and small elevations at the orifices of the intercostal arteries. Although the disease involves the thoracic portion of the aorta predominantly before the age of twenty, the lesions encountered in children up to six years are more abundant in the ascending portion of the arch.[3] After the age of twenty the abdominal aorta is the most severely involved area. Thus it appears that the lesions progress distally in the aorta, increasing in size, severity, and incidence.

The fatty flecks and streaks in the aortas of children are not limited to the juvenile type of atherosclerosis but represent the fundamental pattern of atherosclerosis seen in the lesions of adults. The development of lesions in other arteries is identical, although the structure of the wall of those arteries differs in the thickness of the intima and the composition of the media.

On anatomic grounds there is presumptive evidence that the lipid in the lesions is not static.[4] The flecks and streaks may regress to a point where they are no longer visible, or they may remain as fibrotic areas devoid of sudanophilic material. In the majority, however, lipid continues to accumulate and is covered by connective tissue. The thickness of this covering determines the appearance of the plaque, which may vary from bright yellow to pearly gray. It is unusual to observe these so-called pearly plaques before the age of thirty-five. Lipid in the central portions of the lesion undergoes necrosis and forms the "mush" from which the name atheroma is derived. From this stage the lesion may enlarge until it coalesces with neighboring plaques, or the thickened intima may become so distended that it ruptures and the grumous material is then discharged into the blood stream, leaving behind an ulcerated surface to which thrombi become attached. The plaque may also destroy the underlying muscle and elastic tissue so that the wall is weakened and dilatation occurs.

Microscopic examination of the juvenile lesions shows a swelling of the ground substance of the intima with metachromasia and minute lipid droplets scattered throughout it. These droplets are predominantly in the deeper layers of the intima and are rarely intracellular. Later foam cells laden with fat and mesenchymal cells accumulate. As the fibrous tissue proliferates the foam cells are compressed, and many disintegrate, leaving a collection of debris in which pyknotic nuclei, cholesterol crystals, and large amounts of sudanophilic material can be identified. Foam cells and a few lymphocytes are seen at the margins of the lesion. Changes are not confined to the intima, even in the early lesions, for there is abundant lipid present in the upper layers of the media and along the elastic lamellae. This is present even though the elastic membrane remains intact, but it would appear that the elastica does act as a more or

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less effective barrier against the accumulation of lipid in the media.

As the lesion progresses, it exhibits the pleomorphism which is well-known. The thickened fibrous tissue may undergo hyalinization, still retaining droplets of lipid, or it may ulcerate. Hemorrhage may occur in the plaques due to the rupture of newly formed or pre-existing vasa vasorum. Calcium may be precipitated; the elastic tissue becomes frayed and reduplicated. As lipid penetrates the media, the muscle cells atrophy and become separated. The adventitia, as though to strengthen the damaged wall, acquires additional layers of fibrous tissue, which may become hyalinized.

Turning from this description of the lesion to arteries other than the aorta, the pathologist can trace a basic pattern of evolution of the disease. The coronary arteries develop similar lesions, but usually later than the aorta. They occur only as small macroscopic flecks or streaks in the first decade. Holman[5] states that he has never seen an arteriosclerotic lesion of the coronary in a child in the absence of an aortic lesion. However, in young adults it is not uncommon to observe a severe segmental sclerosis of the coronary arteries with minimal involvement of the aorta. The coronary plaques are usually situated near the origins of the vessel and extend peripherally toward the small epicardial branches, but are seldom seen in the branches penetrating and covered by the myocardium. The entire histopathologic sequence described above may occur within the coronary plaque. Paterson[6] has emphasized that these lesions tend to vascularize and to be subject to hemorrhage and formation of hematomas. Because of hemorrhage the lumen may be narrowed or the plaque may rupture, thus setting the stage for thrombosis. Various observations[7, 8] on the structure of the coronary arteries in male versus female infants have led some investigators to conclude that the irregular thickening of the intima, which is greater in males, accounts for the increased incidence of coronary disease therein. The high incidence of cardiac infarction in female diabetic subjects casts serious doubt on this concept.

The cerebral arteries develop plaques much later than the coronaries or the aortas. It is rare to find plaques in an individual younger than thirty. The lesions are identical with those seen elsewhere, but Duff[4] has called attention to a peculiarity of the cerebral arteries, where at the point of interruption of the internal elastica lipid can be seen pouring through the gap and destroying the media. A series of post-mortem examinations of 866 diabetic individuals in whom arteriosclerosis was considered the major cause of death revealed that cerebral arteriosclerosis was the lethal factor in only 9.7 per cent.[1] It is noteworthy that the incidence is no greater than in nondiabetics.

The intimal plaques that develop in the arteries of the extremities are predominantly fibrous at the time they are examined, but lesions rich in lipid and identical with those found in other arteries are not unusual. Warren[9] has commented on the frequency of the lipid-rich lesions in the peripheral arteries of diabetic subjects. In the series quoted above, the incidence of death due to gangrene of the lower extremities was 9.4 per cent. This was one-fourth the incidence of an earlier series and probably reflects the influence of antibiotic therapy as well as of education of the diabetic in the care of his feet.[1]

RELATION OF ATHEROSCLEROSIS TO DIABETES

Despite the morphologic identity of the atheromatous lesions in diabetics and in nondiabetics, there are certain variations of the lesion in diabetics. The abundance of lipid in the plaques in the peripheral arteries has been mentioned. Lipid-rich atheromatous lesions often occur in the renal arteries of patients with the Kimmelsteil-Wilson syndrome, whereas they occur rarely in the renal arteries of nondiabetics with other forms of chronic renal disease.

Almost no one will dispute the statement that diabetes accelerates the development of arteriosclerosis. The experience of pathologists who can cite post-mortem examinations of aged patients with diabetes of long standing in which less arteriosclerosis is seen than in nondiabetic subjects indicates that diabetes cannot be a cause of arteriosclerosis. Indeed, in Warren and Le-Compte's[1] series of 816 autopsies of diabetics 66 were described as free of aortic atheromata. The absence of aortic lesions might be questioned, but the statement implies that the lesions were not conspicuous and hence probably less than the number expected. This small group of diabetics who enjoy relative freedom from atherosclerosis warrants intensive study.

Is good control of diabetes in these individuals responsible for their relative freedom from arteriosclerosis? Evidence both for and against this has been submitted. Wilson, Root, and Marble[10] found less *clinical* evidence of vascular disease in young diabetics of long duration under the authors' standards of excellent or good control than those under fair or poor control. In contrast, Bell[11] concluded from post-mortem studies that severe vascular lesions are independent of the severity of the diabetes, although he believed that the severity of the lesions increased with the duration of the diabetes in patients

who died before the age of sixty. Much more accurate data regarding this should be forthcoming with the terminal study of the Quarter-Century Victory Medal diabetics reported by Joslin.[12]

Do cases of diabetes differ in some subtle and as yet undetected way? We can only speculate on this. To assume that the knowledge obtained from experiments on diabetic animals can be applied to human beings is hazardous. Duff and others[13–15] have demonstrated that the development of atheromatous lesions of the aorta in cholesterol-fed rabbits was retarded in animals with alloxan diabetes. If the diabetes of these animals was treated with insulin the inhibitory effect was abolished and the lesions were similar to the nondiabetic cholesterol-fed controls. Similarly the majority of investigators of the cortisone-induced diabetes of rabbits report significantly less lipid deposition in the aorta, despite large increases in blood lipid fractions in the cholesterol-fed rabbits treated with cortisone in contrast to the nondiabetic cholesterol-fed controls.[16–18]

Little investigation of diabetes and atherosclerosis has been done in other species. Allen and Lisa[19] found no vascular lesions in a dog made diabetic for twelve years by partial pancreatectomy and with the diabetes controlled by diet and insulin. Dragstedt,[20] on the other hand, reports an increased incidence of arteriosclerosis in a series of 160 depancreatized dogs (15 per cent against 2 per cent in 400 controls). These observations were made on dogs of unknown age obtained from the pound.

If arteriosclerosis is due, at least in part, to a defect in lipid metabolism or lipid transport, it is entirely possible that the disturbance of carbohydrate metabolism in the diabetic contributes to this. Until comparatively recent years little has been known of lipid transport. The report of Barr[21] on the percentage of alpha and beta lipoprotein in diabetics four to thirty-five years of age is of great interest, for it is evident that their lipid pattern is almost identical with that of persons who have survived myocardial infarction and approaches that in rabbits and dogs rendered arteriosclerotic.

A rare disease of great interest is progeria and its variations, which masquerade under such names as Werner's syndrome in the adult and Rothmund's or Hutchinson-Gilford's syndromes in children. Advanced sclerosis of the arteries often leads to the death of children so afflicted before the age of ten. Diabetes is a common occurrence in this group of diseases.[22–24]

In view of the recent work of Friedenwald[25] and the correlation of the microaneurysms of the retina and glomerular capillary lesions in diabetic subjects, one cannot ignore the role that the capillary bed may play in accentuating the atherosclerotic lesions of the large arteries of diabetic subjects.

PROBLEMS IN ARTERIOSCLEROSIS

Ignorance of the pathogenesis of arteriosclerosis has resulted in a succession of theories, to be championed and discarded as their inadequacy became manifest. Current concepts tend to implicate a chemical or physiochemical disturbance of lipid metabolism, but the more recent papers also acknowledge the importance of the arterial wall. This fact is consoling to many pathologists who were beginning to suspect that arteriosclerosis was an "in vitro" disease.

Foremost among the difficulties of investigation is the fact that arteriosclerosis is a qualitative as well as a quantitative disease. One plaque strategically placed in a coronary artery can be fatal, yet individuals with hundreds of plaques in practically every artery, with aneurysms, with thrombi loosely attached to ulcerated surfaces, and with even complete occlusion of an artery may not only enjoy long life but remain asymptomatic. Secondly, arteriosclerosis is an almost universal disease in man, beginning early in life and continuing in episodic fashion until death. Because of these two facts the value of chemical tests designed to detect atherosclerosis or to measure its severity can be questioned.

EVALUATION OF PRESENT KNOWLEDGE

It is generally agreed that atherosclerosis begins early and progresses with age, although it is not necessarily associated with aging. The localization of atheromatous deposits about sites of injury and in particular areas in normal blood vessels and the acceleration of the disease in hypertension support the opinion that anatomic variation and hemodynamics play an important role.

The coexistence of early and advanced lesions in close proximity implies that the causative agent acts discontinuously, and offers some hope that it might be interrupted.

The predominantly lipid nature of the atheromatous material has led to the opinion that the vessel wall acts as a more or less selective filter, capable of holding back certain lipid fractions. Wilens,[26] who has filtered plasma with varying lipid content through excised human iliac arteries, has established that at least in vitro the arterial wall can retain certain fractions of plasma lipids as measured by chemical analysis and microscopic examination. Others have maintained that the vessel wall

disposes of lipids under normal conditions.

The precocious development of arteriosclerosis in diseases associated with abnormal lipid patterns, such as diabetes, nephrosis, myxedema, and familial xanthomatosis, has formed the foundation for the vast experimental work in animals.

By altering the lipid patterns appropriately in various animal species such as the rabbit, chicken, dog, and recently monkeys, lesions resembling those of human disease can be produced. Arguments have been waged as to whether this disease is comparable to that in man, since development of the human lesion is apparently not dependent on such severe abnormalities of plasma lipids. Nevertheless, the production of the disease or at least a facsimile of it has offered the one useful approach toward an understanding of its pathogenesis. By observing the behavior of the lesions when the animal is taken off a regimen which entails the feeding of cholesterol-rich diets and is kept on normal stock diet for varying lengths of time, one can trace the pathways of removal of atheromatous material and the attempts at repair of the vessel wall. That an analogous situation exists in man is suggested by observations on human autopsy material where the lesions of those who were undernourished or who had lost considerable weight rapidly seemed to contain much less lipid than those who had not lost weight prior to death.[27]

The relation of obesity to arteriosclerosis has been emphasized.[28, 29] There seems little doubt that the presence or severity of arteriosclerosis is correlated with a state of good nutrition or overnutrition. Contrariwise, populations on low-fat diets seem to gain a measure of protection against the consequences of arteriosclerosis.[30]

We have limited knowledge of the influence of the endocrine factors on arteriosclerosis. For example, we know that it is impossible to produce arteriosclerosis in the dog by cholesterol feeding without depressing thyroid function either by thyroidectomy or the use of thiouracil.[31] Turner[32] and Katz[33] have prevented or suppressed the development of arteriosclerosis in rabbits and chicks by giving desiccated thyroid. Conflicting results have been obtained with the use of inorganic iodides.[34] Dinitrophenol, a drug which increases metabolism, is without influence on the production of lesions in the chick, suggesting that the action of thyroid is not simply a function of increased metabolism.[35] The administration of desiccated thyroid to dogs after withdrawal of the atherogenic regimen had no influence on the rate of regression of the lesions.[36]

One of the vagaries of arteriosclerosis that has been of great concern is the disparity in incidence of fatal coronary disease between the sexes. This lessens rather abruptly after the female menopause, until between fifty-five and sixty the ratio becomes almost equal. Thus attention has been focused on the possible role of estrogenic substances on the pathogenesis of arteriosclerosis. We have been unable to influence the rate of regression of atherosclerotic lesions in dogs by the administration of an estrogen orally.[36] However, Katz[34] and his co-workers report that in cockerels the administration of estradiol both prophylactically and therapeutically has selectively inhibited or prevented lesions in the coronary arteries but not in the aorta. Barr[21] and the Goldwater group[37] have given estrogens to males surviving myocardial infarction and have noted shifts in the lipid patterns toward so-called normalcy but have not noted clinical improvement in the anginal syndrome. Testosterone has exaggerated the abnormalities in the lipid pattern.

The influence of pancreatectomy in dogs has been touched on, and results by different investigators using various diets have been equivocal.[20] Alloxan diabetes and cortisone-induced hyperglycemia have prevented or inhibited lesions in cholesterol-fed rabbits. In contradiction there is a report of precocious atherosclerosis in children treated with cortisone.[38]

We still have insufficient knowledge of the enzyme systems necessary for the metabolism of lipid protein or carbohydrates, much less their intercepting pathways. Of interest are the recent investigations of the Harvard group,[39] who have succeeded in producing atherosclerotic lesions in methionine-deficient cholesterol-fed monkeys and have prevented their appearance by the addition of methionine to the diet.

Within the circumscribed field of the morphologist, restricted as it is by visual observation, there is a surprising lack of agreement. Interpretations of the nature and significance of the structural changes of atherosclerosis have differed widely. Duff and Leary[4] have long championed the importance of metabolism at the cellular level, especially the metabolism of lipids in the arterial intima. It is only when we know what goes on within the cell itself and its immediate environment that we can settle the argument as to whether increased or decreased permeability of the intima, or defense mechanisms inherent in the unaffected portion of the arteries operate to prevent the formation of lesions. Recent studies on the synthesis of cholesterol in arterial walls are contributing to our understanding of cellular metabolism. Further elucidation should come from studies of the ground substance of the intima, whose metachromasia and swelling are at present our earliest indication of the developing lesion.

SUMMARY

There is general agreement regarding the following observations: (1) Atherosclerosis begins early, progresses with age, and localizes in particular sites, especially in relation to injury and stress. (2) It is characterized by deposition of lipid material in the blood vessel wall. (3) The vascular change is accelerated by diseases in which there is disturbance of lipid metabolism.

There appears to be evidence that: (1) Atherosclerosis can be produced in animals by altering lipid patterns. (2) It is capable of regressions. (3) It is associated with good nutrition in man.

There is need for more knowledge of (1) the influence of endocrine products and specific enzymes, and (2) the metabolism of lipids at the cellular level.

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DISCUSSION

AARON KELLNER, M.D., (*New York*): Dr. Bevans has summarized in an exceedingly able and concise fashion our present knowledge, or lack of knowledge, of atherosclerosis. I was particularly pleased at the emphasis that Dr. Bevans placed upon morphology. The pendulum, as you well know, has swung away from morphology in recent years, and it is distinctly out of style to be a morphologist today. Yet, much remains to be learned by carefully thought out and well-directed morphological studies. This is particularly true of atherosclerosis which, despite the advances that have been made in our knowledge of lipid metabolism and lipid transport, is still defined in morphological terms. As a matter of fact, we are not even sure whether what we so define in morphological terms is one disease or a group of diseases.

Dr. Bevans emphasized quite correctly the importance of the very early lesions in atherosclerosis, what pathologists refer to descriptively as metachromasia and swelling of ground substance. It is here that morphological studies need particularly to be focused, making use of the newer optical and histochemical technics, because at the present time we do not know what the very early stages of this disease are, and we are not even certain whether lipids are in fact the primary offending agents, as many of us think, or whether, as others think, they are secondary phenomena.

Our experience at the New York Hospital with diabetes and atherosclerosis has been similar to that of Dr. Bevans and most others. It is our feeling that diabetics have considerably more atherosclerosis as a group than do nondiabetics of comparable age, and we, too, have been impressed by the fact that although females under the age of forty-five have a remarkable relative immunity to atherosclerosis, this immunity is abolished by diabetes or by hypertension.

Despite the fact that atherosclerosis seems to be more severe, more common, and to occur at an earlier age in diabetics, we are every now and again surprised to see a diabetic well on in years who has had diabetes for twenty or thirty years, who comes to post-mortem examination and is singularly free of atherosclerosis. This is a natural experiment which bears careful consideration. It may be that diabetes is a different disease in some individuals than in others. Perhaps not all diabetes is at its root the same disease.

Finally, I should like to ask Dr. Bevans whether she has had an opportunity to study the anatomical changes in the lower extremities of diabetics. Bell, in a study some four or five years ago, found that occlusive vascular disease of the lower extremities was forty times as common in diabetics as in nondiabetics. If this is due entirely to atherosclerosis, there must be something unique about the vessels of the lower extremities, because the coronary arteries of diabetics are not forty times as vulnerable to atherosclerosis. Diabetics do not have forty times as many myocardial infarctions nor forty times as many aneurysms of the aorta as nondiabetics. Is there something unique about the vessels of the lower extremities, perhaps some still undefined disease of the blood vessels, which occurs in diabetics and not in nondiabetics?

DR. BEVANS (*closing*): In answer to Dr. Kellner's question, I have had some experience in dissecting limbs of diabetics but not in recent years, however, when I might have been more interested than I once was. A rather intriguing thought occurred to me as I was writing this paper and that is that the cerebral lesions in diabetics are no more common than those in the nondiabetic population, but as we progress distally in the body, the lesions of the aorta seem to be more severe in diabetics, the lesions of the coronary arteries more severe, and so on down to the lower extremities where, as Dr. Kellner says, they are forty times as severe in diabetics. I think this warrants a little thought.

SUMMARIO IN INTERLINGUA

Lesiones Atherosclerotic in Diabete

Le sequente observationes es generalmente acceptate como ver: (1) Atherosclerosis comencia a bon tempore, progrede con le etate del patiente, e se localisa in sitos particular, specialmente in consequentia de vulnere o stress. (2) Atherosclerosis es characterisate per le deposition de materia lipide in le pariete del vaso de sanguine. (3) Le alteration vascular es accelerate per morbos in que le metabolismo lipide es disturbate.

Le sequente observationes es supportate per certe demonstrate datos: (1) Atherosclerosis pote esser producite in animales per alterar le balancia normal del lipidos. (2) Atherosclerosis pote passar per periodos de regression. (3) In homines atherosclerosis es associate con bon nutrition.

Le sequente problemas require studios additional: (1) Le influentia de productos endocrin e de specific enzymas. (2) Le metabolismo del lipidos in le cellula.