STUDIES UPON CALCAREOUS DEGENERATION.*

V.—THE RELATION OF EXPERIMENTAL ARTERIAL DISEASE IN ANIMALS TO ARTERIOSCLEROSIS IN MAN.

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PLATE XXIV.

Since Josué first produced arterial changes in rabbits by means of adrenalin there has been a whole host of experimenters who have repeated and confirmed his work. Although Josué was the first to produce arterial lesions by means of adrenalin, he was preceded by Gilbert and Lion who were successful in bringing about arterial changes, by means of bacteria and their toxins; these lesions they believed simulated arteriosclerosis in man. Sumikawa, too, caused inflammatory changes near the arteries in rabbits, and believed that the vascular changes were identical with those found in arteriosclerosis. However, there is no doubt that arterial changes have been produced with most success by the inoculation of adrenalin. Erb, Baylad and Albarède, Külbs, Fischer, Scheidemandel, and Lissauer have experimented with adrenalin, and have noted the vascular changes. In the main their observations agree, but details of minor importance have been emphasized by some of them. B. Fischer has further found that digitalin when inoculated intravenously produces lesions similar to those caused by adrenalin.

The French workers, Josué and Baylad and Albarède, are most emphatic in maintaining that the intimal changes found in the vessels of experimental animals are of prime importance. The others, with whom I agree, hold that the medial lesions are the principal changes caused by adrenalin. The intimal changes,

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which are rarely found, are of a secondary nature, or else are brought about by a process quite distinct from that producing the medial changes.

On account of the importance of a proper interpretation of these experimental lesions, and of the relation which they bear to the diseases of the arteries in man, I feel justified in making a histological comparison of the experimental and human lesions. It is impossible to call the macroscopical changes in the rabbit's aorta atheroma or arteriosclerosis unless the histological examination supports this view. I do not doubt that some have been misled in the use of these terms by the naked-eye appearance of the intima, while others have used the term arteriosclerosis in its broadest sense. Should the latter course be adopted, it should be recognized that experimental arteriosclerosis in rabbits is entirely distinct from sclerosis of the aorta in man. Moreover, as I shall point out later, the term atheroma should not be used in connection with the adrenalin lesions.

It is unnecessary for me to give in detail the methods of experimenting on animals, further than to state that my methods resemble those of previous investigators and more particularly those described by B. Fischer. The pure solution of adrenalin chloride, one in a thousand, was injected into the ear veins of rabbits.

Microscopical lesions, such as dilatation of the blood-vessels, hæmorrhages in the brain, and aneurismal distentions of the larger vessels, were noted. The most frequent lesions were situated in the descending arch of the aorta, where white calcified plaques formed the chief naked-eye alterations. The aneurisms were found to be situated in the centres of these white plaques which have been described by some as atheromatous areas. Histological examination shows that these plaques, at an early stage, are situated entirely in the media and that the calcification which occurs here is the secondary result of a degenerative, chiefly fatty, change which takes place in the media. Calcification is never found in the intima, and only rarely are there any intimal changes. The intimal changes which occur are of two kinds: either there is a

local heaping up of endothelial cells at a point where no degenerative changes of any kind have taken place, or there is thickening of the intima underneath the endothelial cells, chiefly due to proliferation of the connective tissue, in which slight fatty changes may occur. Such being the case, the term atheroma must be discarded in describing the experimental arterial lesions in rabbits.

As I have pointed out elsewhere, the primary change in the media, preceding the stage of calcification, is fatty degeneration of the muscle cells, followed by fatty degeneration of the elastic fibres. In the earliest lesions, before any macroscopic change can be noted in the vessels, fine granules of fat are aggregated about the nuclei of the muscle fibres. These granules of fat have an arrangement not unlike that seen in fatty degeneration of the heart muscle. From this stage of degeneration the process advances rapidly so that in a few days the median zone of the middle tunic of the vessels is in an advanced stage of degeneration. Fischer has already noted the rapidity with which the muscle fibres change under the influence of adrenalin inoculation, and hence has applied the name arterionecrosis. Since the degenerative changes are not so rapid as to prevent the appearance of fatty degeneration, and since there proceeds with the apparent necrosis a process of calcification, the name proposed by Fischer is a little misleading. I must grant that sections stained with hæmatoxylin and eosin give a picture of an active necrosis, but with Weigert's stain alone. or combined with Sudan III, the necrotic appearance disappears.

My studies lead me to accept the histological descriptions given by Fischer and others, except, as I have stated, that I find fatty changes in the muscle and elastic fibres preceding the deposit of the calcium salts. The mode in which these calcium salts are laid down has also been discussed in full in another paper, but as regards the sites of the calcium deposit I wish to speak more fully.

In sections stained with hæmatoxylin and eosin, it is seen that the lesion lies in the middle zone of the media and that in the early stages the muscle fibres become granular and lose their nuclei. With this degeneration of the muscle fibres, which must

necessarily be accompanied by softening of the tissue, the elastic fibres are packed more closely together, leaving less room between them for the muscle cells. At these points, where there is a loss of the muscle elements, the vessel wall is distinctly weakened, and partially gives way, leading to small aneurismal sacculations. In advanced lesions these aneurismal dilatations are the most marked macroscopic changes that are found.

When the muscle cells in the media have undergone fatty degeneration, the condition advances, until the cells become fairly loaded with the fat granules. Nuclear degenerations then become apparent and soon the cells die, leaving only their outline marked by the deposit of the fat granules which were in them. These fat granules do not coalesce but remain as isolated particles. Passing through the stage of fatty acids and soaps[1] they are converted into calcium compounds of the fatty acids, and hence the calcium deposit occurs as a fine sandlike material distributed in the sites of the former fatty granules. Following closely upon this change, the elastic fibres also become fatty, as Jores has observed, and go through the same process of calcification as the muscle cells. There is now a fine granular deposit of calcium at the site of the muscle fibres and rigid zig-zag calcified elastic fibres lying between them. This picture is not seen in the advanced stages of the calcification of aorta in rabbits, for the calcium salts have coalesced more or less to form larger masses, so that the former histological structure of the media is entirely lost. In no instance of experimentally calcified vessels in animals has primary calcification of the intima been noted. Occasionally I have seen very advanced experimental arterial disease in which the calcification of the media extended immediately below the intima.

If we are to accept Jores's definition of arteriosclerosis, namely, that the disease consists of a hyperplasia with degeneration of the musculo-elastic layer of the intima as seen in the human aorta, these experimental lesions would not fall in this category. I am not, however, inclined to accept this restricted

[1] See the studies upon calcareous degeneration by the writer. *Jour. of Exper. Med.*, 1905, vii, 633.

definition of arteriosclerosis, particularly as regards the human disease.

Lissauer compares the experimental lesions in arteries of rabbits to syphilitic arterial disease in man, pointing out that syphilitic arteritis attacks particularly the media. He falls short of a proper comparison. The main factor in the experimental lesions is the calcification of the muscle and elastic fibres in the media, and this never takes place in syphilitic disease of the vessels. In syphilitic arteritis the main reaction, consisting of an inflammatory change with new formed blood-vessels, an infiltration of small cells, and later the production of connective tissue, takes place in the outer third of the media. The blood vessels affected by adrenalin, on the contrary, show no reparative reaction in the media, the process being entirely a degenerative one. If a reaction does occur, it is secondary to a medial degeneration, and this reaction consists of a heaping up of the endothelial cells in the intima.

I would point out that although the lesion does lie in the media—and especially in the middle zone of the media—there are no changes in the vasa vasorum. All the hypotheses, maintaining that the action of adrenalin on the vasa in the vessel wall is the prime factor in the production of the necrosis, are based upon general inferences regarding the action of this drug in other parts; the histological appearances give no support to this theory.

A second arterial disease which Lissauer wishes to compare with the vascular changes caused by adrenalin is the so-called neurotic angiosclerosis. He points out that Lewaschew and also Fraenkel found that by injuring or cutting the nerve supply of vessels, they became infiltrated with connective tissue, and that the change lay only in the media. Their results are quite contrary to those of Jores, who found that neither injury to a nerve nor the complete severance of it had any effect on the histological structure of the vessel it supplied. In syphilitic arterial disease, as I have mentioned, and in the neurotic lesion, calcification of the media is never seen.

There is, however, an arterial disease in man which simulates the

experimental arterial degenerations in every respect. This disease I have spoken of elsewhere as Moenkeberg's type of arteriosclerosis. This disease, as Moenkeberg and others have pointed out, affects the vessels of the extremities—the vessels of the muscular type—that is, arteries in which the muscle tissue predominates in the media. From this lesion the clinician makes the diagnosis of arteriosclerosis when he finds the radials hardened like "pipe stems" or "beaded like a trachea." It is now definitely known that this form of arterial disease is distinguishable from arteriosclerosis as we find it in the human aorta. Moenkeberg's type of arteriosclerosis affects the media alone, causing degenerative changes. The intima is affected neither by degenerative nor by reparative changes, or if such changes are present they are secondary to or parts of another disease and not associated with changes taking place in the media. This disease of the media affects the vessels of the extremities—the femorals, tibials, internal and external iliacs, radials, and brachials being particularly susceptible.

Preceding the deposition of calcium salts in the media, there are degenerative changes which consist chiefly of fatty degeneration, which is visible to the naked eye, and can be distinctly traced in the media when the vessel is cut open longitudinally. This early fatty degeneration in the media differs from that of arteriosclerosis of the aorta in that the fatty plaques do not stand above the surface of the intima, but can be seen through this membrane. One is convinced by the microscopical picture, that in the early stages the muscle cells undergo a fatty degeneration characterized by the deposition of the finest fat globules. The calcium salts, too, are found to be deposited as fine sandlike granules in the degenerated muscle fibres. In the early stages of degeneration, calcium granules are found in double wedge-shaped aggregations lying between the elastic fibres, and this grade of calcification is not to be recognized by the naked eye. However, with the constant accumulations of fresh calcium deposit, the granules lie very close together and then coalesce. At this stage, when the calcium granules are becoming densely aggregated, we find that the vessel wall decreases in thickness; there is a thinning of

the media with a bulging outward of the wall at this point. Distinct multiple aneurismal dilatations are of common occurrence in these vessels, so that the outer contour of the vessel is quite irregular. From the inner surface of the vessel it is seen that the calcified areas form depressions which are lined by smooth and unchanged intima. Microscopically, the elastic fibres are seen to be stretched into straight lamellæ and no longer show the wavy character found in healthy vessels. The elastic fibres, too, are calcified and are lying more closely together, although in advanced cases this is difficult to distinguish, as the calcium deposit in the muscle and elastic fibres have run together into a solid mass. In consequence of the constant tension and stretching of the elastic fibres, they have become calcified in the position that they had in these vessels, and thus we find the straight calcified laminæ. Where calcification of elastic fibres has advanced beyond the general area of calcareous degeneration, and, too, where contractile muscle fibres have persisted between them, these elastic fibres have taken on a zig-zag outline due to fractures.

Microscopically one can demonstrate that the running together of the calcium granules takes place in the middle of the media, and that at either end of such a mass are outrunners of calcified elastic fibres and granular degenerated muscle fibres. The internal elastic lamina is stretched as it passes over the calcified and aneurismal portion of the media.

The intima occasionally shows some reaction over the areas of medial degeneration, the endothelial cells being heaped up. This intimal change is, however, entirely secondary and has nothing to do with the primary cause of the medial change, and further is not a necessary accompaniment of the medial degeneration.

Moenkeberg holds that the adventitial changes are in great part confined to thickening of the intima of the vasa vasorum, but points out that this limitation is not a constant feature in the disease. There are some who claim that the degeneration of the media is due to occlusion of the vasa vasorum causing poor nutrition of the media. However, the changes in the vasa vasorum are too inconstant to allow us to draw any definite con-

clusion, and, moreover, it is very hard to estimate the amount of change in these small arterioles with no definite wall, especially when they are collapsed and empty.

Pure medial calcification is commonly found as an accompaniment of advanced age, occurring most frequently after the age of fifty. But, as Marchand has pointed out, it occurs also in young individuals. The disease affects males more frequently than females, the ratio being about six to one. It is further of interest that medial calcification occurs in the vessels of those extremities which are most active; thus in right-handed individuals it is found more pronounced on the right side, while in those whose duties keep them constantly on their feet the femorals are most affected. Again, the disease is particularly common among the laboring classes.

When the experimental lesion in animals and the medial arteriosclerosis in man are compared, they present great similarity in their anatomical, histological, and, it may be, their etiological characters. In each case the essential lesions are confined to the media, the changes in the intima being of a secondary nature or else the result of a different disease. In both lesions the process in the media rapidly leads to calcification of the muscular and elastic elements, fatty change preceding the deposition of the calcium salts. Aneurismal dilatations at the sites of the calcium deposits in the media often occur with both lesions, and in the dilated part the vessel wall is much thinned as the result of the loss of muscular elements and the packing together of the elastic fibres.

Both diseases are brought about or accompanied by an increased blood pressure; in the one it is artificially produced by the use of adrenalin and involves the general circulation, while in the other it is localized in parts, the extremities, where increased work, straining and constriction of the muscles, lead to heightened pressure. Whether this heightened blood pressure acts directly on the vessel walls to cause the medial degeneration, or whether by the stretching of the arteries the vasa vasorum are in part or wholly pinched off, leading to focal necrosis in the media, is not wholly clear. Certainly from the focal character

of the experimental lesions and from the annular arrangement of the degeneration in the vessels of the extremities in man, I should feel very much inclined to think that the vasa played an important rôle in the production of these changes. However, we must not lose sight of the fact that in the experimental animals the toxic character of the substances inoculated may be an important factor in the production of the lesions, as Fischer has pointed out.

Both of these lesions must be distinguished from the intimal form of arteriosclerosis as found in the aorta, and the presence of one condition does not indicate the presence of the other.

Several clinicians have made the observation that when pure medial arteriosclerosis is present in the vessels of the extremities without any changes in the aorta there is no hypertrophy of the left heart, while, on the contrary, if the aorta is affected with arteriosclerotic changes the heart shows hypertrophy. This fact suggests that while the aorta is healthy and elastic, it relieves, to a great extent, the increased blood pressure which would naturally follow the hardening of the peripheral vessels, while, on the other hand, if the elasticity of the aorta is destroyed, the increased pressure is directly transferred to the heart, leading to hypertrophy of the organ. The experimental hardening of the walls of the aorta apparently confirms this view, since hypertrophy of the heart frequently occurs with it.

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Fig. 1.

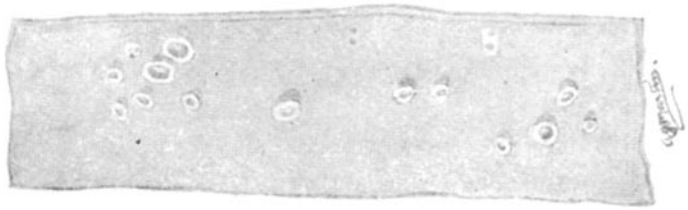

Fig. 2.

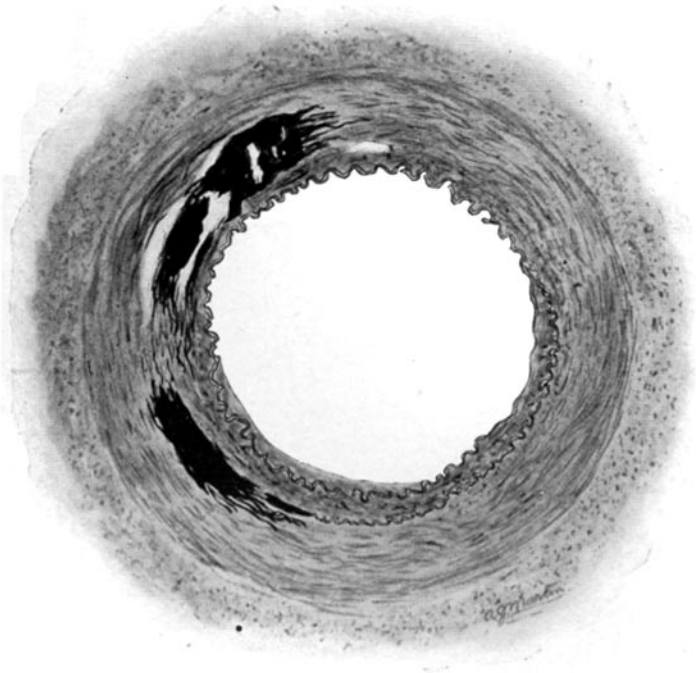

Fig. 3.

Fig. 4.

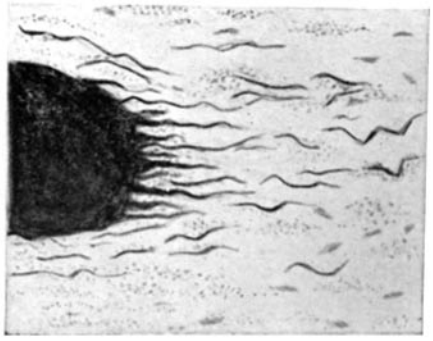

Fig. 5.

Pearce and Stanton.—*Trans. Assoc. of Amer. Phys.*, 1905, xx, 513.
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EXPLANATION OF PLATE XXIV.

Fig. 1.—Femoral artery (natural size), showing pittings and small aneurismal dilatations in the areas of calcification of the media.

Fig. 2.—Aorta of rabbit (enlarged x 2), after injections of adrenalin, showing small calcified plaques with depressions and aneurismal bulgings in their centres.

Fig. 3.—Femoral artery (low power, Leitz obj. 3, ocular No. 2), showing calcification of the media with little change in the intima other than splitting of the internal elastic lamina.

Fig. 4.—Aorta of rabbit after injections of adrenalin (low power), showing calcification in the media with no change in the intima. Vessel wall shows aneurismal dilatation.

Fig. 5.—Femoral artery (high power), showing densely calcified media, along with a less intensely calcified area in which the elastic and muscle fibres are in the early stages of calcification.