THE EXPERIMENTAL PRODUCTION OF ARTERIO-SCLEROSIS.

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ON THE EXPERIMENTAL PRODUCTION OF ARTERIO-SCLEROSIS.

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Before taking up the study of the experimental production of arterio-sclerosis it is necessary to ask, What is arterio-sclerosis? (*a*) Is it an entity; or (*b*) are several distinct morbid conditions included under this one heading; or (*c*), what comes nearly to the same thing, in different states which we are accustomed to regard as arterio-sclerosis, do we find the different coats and constituents of these coats affected diversely?

It is necessary, to ask these questions, because, as I shall show, different procedures and reagents have different effects upon the arteries, and whether we are to regard these experimental results as arterio-sclerosis must depend upon our answer to these questions. The subject of classification has been taken by Professor Welch; fortunately, therefore, I need not discuss the various forms. All that I need say as indicating my point of view is that I do not agree with Jore's narrower definition. His extensive studies, which have received much attention, have led him to include only a particular histological change in the vessels as coming into the category of arterio-sclerosis, while the mass of other scleroses in the arteries remains unclassified. He and those who follow him would limit the term to conditions of intimal hyperplasia, with a peculiar splitting of the internal elastic lamina, conditions which can only be distinguished under the microscope.

Are we, then, to exclude the clinician from diagnosing arterio-sclerosis? The answer can but be, No! And this for the adequate reason, that such is not the sense in which Lobstein applied the term arterio-sclerosis in 1835. Let us preserve the broader meaning, and regard all scleroses or hardenings of the arteries as included under this general term, recognizing, if need be, distinct varieties.

Thus I would point out that arterio-sclerosis is not a simple disease. Although, in some instances, a single coat of a vessel is found affected by a fibrous or other allied change, in others several tunics of the same artery are involved. Again, we may find that in a certain form of

sclerosis particular tissue elements are picked out, while other tissues are unaffected, or that when muscle fibres are degenerating in the media the connective tissue elements of the intima are proliferating. Hence we may have two or more such processes inextricably mixed in a progressive disease of the arterial walls.

Of the more common forms of sclerosis of the arteries I would point out that the hard radial vessels by which the clinician makes his diagnosis of arterio-sclerosis is a widely different disease from that recognized by the pathologist at *post-mortem* examination of the aorta. The sclerosed radial vessels represent a disease which is peculiar to the media; it has its origin in the muscle cells of the middle coat, and the middle coat alone is damaged. The intima and adventitia are not essentially involved in the process, though occasionally a secondary intimal thickening accompanies the medial degeneration. The main changes in the media are a fatty degeneration of the muscle and later of the elastic fibres, both of which become calcified. It is through these calcareous plaques in the media that the beaded character is given to the radials. At these sites of medial degeneration and calcification the vessel wall is perceptibly thinned, so that many small pouchings result. These pouchings, though small, are true aneurysms distributed irregularly in the vessel wall, and when held to the light are seen to be thin and quite transparent. This type of disease, which is most frequent in the vessels of the extremities, I shall later speak of as the Moenckeberg type of arterio-sclerosis, and I shall point out how closely some of the experimental lesions resemble it.

On the other hand, the nodular aorta, which we so frequently meet with at autopsy, is the result of repeated insults telling upon the intima alone. The thickenings of the intima may again be entirely proliferative, and in this case represent a chronic inflammatory production. This I acknowledge is not the view held by all; those who still uphold Thoma's conception of the arterio-sclerotic process see also in the typical nodose sclerotic aorta a primary giving way of the media, and regard the intimal overgrowth not so much as an inflammatory as a compensatory process. Whichever view be accepted, or be correct, or whether, as would seem to be truly the case, we encounter both conditions, it is still an open question whether the newly-developed cells in the intima are of endothelial or of connective tissue origin; it may be again that both tissues take part in the overgrowth. At all events, few or many layers of cells, which are very like endothelial cells, are produced immediately beneath the endothelium, and it was the character of these cells which led Virchow to speak of "endarteritis chronica deformans."

When a similar intimal thickening, by the proliferation of connective tissue or endothelial cells, occurs in the smaller arteries, so that the lumen of the vessel becomes distorted, or even wholly obliterated, the condition is spoken of as "endarteritis deformans sive obliterans." I may, however, mention that seldom if ever is a vessel occluded by the overgrowth of its intima alone. The usual result is that after a vessel has been partly obstructed by the thickened intima, complete blockage is brought about by thrombosis.

Now although we have ample opportunity to study the damage that has been done by the various noxæ to the human arterial system, we are as yet largely without the means of recognizing which lesion has been produced by a particular irritant. It thus becomes evident that the histological changes in the arteries must be investigated by experimental means, for it is only in this way that the changes in the arteries produced by insults of different kinds can be followed step by step, and that a decision can be reached regarding the influence of the various injuries.

It is the common fault of experimenters that, having been able to reproduce a disease in whole or in part by experimental means, the conclusion is drawn that all the features of this disease are due to this one cause. To avoid this common mistake we must advance very cautiously towards our conclusions.

THE EARLIER EXPERIMENTS.

In the earlier experimental attempts undertaken to produce arterio-sclerosis and aneurysms mechanical means were employed. Thus, Malkoff, and also Fabris, injured the vessel wall directly, either by forcibly pinching it through the skin or by laying it bare and crushing or by applying corrosive substances to its outer walls. That damages of all kinds were obtained in this manner we can readily understand, but that neither true aneurysms nor arterio-sclerosis resulted is just as clear. Thromboses and inflammation of the arteries were the most frequent results of these violent measures, but these studies have thrown little light on the process of arterio-sclerosis. Malkoff, however, made another interesting experiment, in which he laid the end of the carotid artery bare, and, ligating the vessel about an inch or so away, he put the isolated portion of the artery under artificial pressure and then returned it to its natural bed. This treatment he claimed led to a calcification of the media—a condition which he said was directly referable to the high pressure to which the vessel had been subjected.

Several authors claim to have obtained positive arterial lesions of the character of arterio-sclerosis by irritating or severing the nerves of

the leg. Of these, Lewaschew, Bervoets, and Fraenkel each described changes in the femoral and tibial arteries after performing these experiments, but in each case, as Czyhlarz and Helbing pointed out, the influence of the trophic inflammatory disturbances extending from ulcers about the limbs cannot be excluded. These experiments, thus, do not teach us more than that the coats of the arteries, including the intima, take part in an inflammatory process by direct extension from without. That the intima itself could become involved in an acute or chronic inflammation was denied by Roktitansky, who held that the thickening of this coat was the result of the organization of lymph thrown out of the blood. This contention has, however, been shown to be incorrect.

Soon after Thoma brought forward his theory that arterio-sclerosis is a compensatory thickening of a vessel in a region where the media has been weakened and the lumen of the vessel enlarged, several workers endeavoured to prove this by experimental means. Thoma, himself, undertook to show that the stimulus or irritation required for the proliferation of new tissue in the intima lay in the slowing of the blood current. By ligating a vessel he found that on the distal side of the ligature, as far as the first compensatory artery, considerable intimal thickening took place. However, Fuchs, who repeated the experiments, though he found the same changes to occur in the arterial walls, attributed the changes to a diminution of the blood pressure, while others again reported the occurrence of arterial thickening on both sides of the ligature, and ascribed its presence to local thrombosis and inflammation.

The inflammatory theory of arterio-sclerosis received further support in the experiments of Sumikawa, who irritated the vessels by painting them with turpentine or silver nitrate or infected them with bacteria. Vessels so treated showed an inflammatory condition in all the coats, or else in the intima alone. In each case there was a degeneration of the muscle fibres along with a small-celled infiltration along the vasa vasorum. His experiments with bacterial infection of the vessel walls bear out the pathological findings in man, where it is noted that inflammatory foci not only lead to a new formation of capillaries in the granulation tissue, but also of vasa vasorum in the neighbouring large blood vessels, and moreover, that the reaction in these blood vessels is accompanied by a connective tissue proliferation and thickening of the intima.

That lead, phosphorus, and mercury produce arterial lesions has long been described in medical text-books, and yet such lesions have not been produced experimentally. It is true that Lunz, in his experiments with these salts, has found that the elasticity of the vessels is dimin-

ished, but Jores could not verify these results, and was unable to find any change in the vessels of animals so treated.

THE MORE RECENT EXPERIMENTS.

Thus until 1903 little advance was made in the experimental production of arterio-sclerosis despite the many attempts. In that year Jores instituted a series of experiments at the Bonn Pathological Institute in which he fed animals on adrenalin extract, hoping thereby to test the effect on the arteries of raising the blood pressure. Whether he obtained any marked rise in the blood pressure he does not report. His results, however, on the arterial walls were negative. Josué, using the same substance, applied it in a different way. He repeatedly injected a solution into the ear veins of rabbits. After several weeks of this treatment, he found that the aorta of the animals showed distinct pathological change with aneurysmal dilatations. The lesions, which varied from the size of a pin's head to a split pea, were distributed irregularly over the thoracic aorta and over the abdominal aorta as far as its middle. The vessel changes consisted essentially of medial degenerations lying in the middle zone of this layer. The destruction of the muscle and elastic fibres with the later deposition of lime salts in them led to a thinning and weakening of the vessel wall, which later became the site of aneurysmal dilatations.

The success of Josué in producing experimental arterial lesions led immediately to like methods being employed by a large number of workers, and in the main their findings have agreed with one another and with Josué's original report. Fischer points out that the lesions produced by adrenalin are all of a medial nature, and that the process is really one of necrosis. He describes the elastic fibres lying more closely together, while the muscle cells between the elastic lamellæ are in part lost. Similar results have been obtained by Erb, Scheidemandel, Kurt Ziegler, Pearce and Stanton and others. Sturli found no difference between the lesions produced by synthetic adrenalin and the adrenalin extract. Opinion, however, remains divided as to whether we are right in comparing the experimental results in the lower animals with arterio-sclerosis as we find it in man. Some hold that the lesions are like those commonly seen in the human artery, while others again can find no similarity between the conditions.

Kurt Ziegler and I almost simultaneously compared these adrenalin lesions with the Moenckeberg type of arterio-sclerosis. We have both pointed out how in each the essential lesion is a degeneration of the muscular and elastic tissue of the media, while as a consequence

aneurysms are produced in the vessels. I have found that the degenerations in both instances are of the nature of fatty metamorphosis of the involved tissue, which later goes on to calcification.

Ziegler holds that the lesions produced by the inoculation of adrenalin are of a nutritional character, or, rather, due to lack of nutrition. Torri and others, on the other hand, regard them as the outcome of heightened blood pressure, while Fischer considers the process as a pure necrosis due to the direct action of the drug on the muscle cells. Observations in favour of the degenerative or necrotic theory have been recorded by Braun. He found that the combination of adrenalin with amyl nitrite neutralizes the pressure-raising power of adrenalin, but notwithstanding, the arterial changes manifest themselves just as when adrenalin alone is administered. A somewhat different result, however, was gained by Mironescu. He found that the inoculation of euthalmin alone had no effect on the arteries, while at the same time he noted that it produced a drop in the blood pressure. If after the inoculation of adrenalin the animals were also given a dose of euthalmin he found an initial rise with a secondary drop in the blood pressure, and that these aniamls showed arterial changes much sooner than those treated with adrenalin alone. Hence Mironescu concluded that it was the sudden change from a high to a low pressure that had a deleterious effect upon the arteries.

Harvey has recently demonstrated some very interesting experiments in regard to the degeneration of vessels. He notes that vessels under pressure undergo a more rapid destruction that those which are lax. This throws some light on the effect of high blood pressure in the arteries.

Experiments have also been undertaken by some to observe the effect of bacteria and their toxins on the vascular system. Gilbert and Lyon claim to have produced lesions similar to those produced by adrenalin.

In the main the different experimental results agree with one another, yet the inferences as to the nature of the lesions and the similarity with arterio-sclerosis in man differ widely; the majority of authors hold that the changes brought about in the arteries of animals are of an arterio-sclerotic nature, but in my opinion only one of them draws the proper inference and shows the identy of the changes in the vessels of the "adrenalin animals," and the Moenckeberg type of arterio-sclerosis in man.

THE AUTHOR'S OWN OBSERVATIONS.

It was the indefiniteness of the results obtained in the experimental work that prompted me to attempt the production of arterial lesions.

Simultaneously with Braun and Mironescu, I had conceived the idea of abolishing the high-pressure effects of adrenalin by combining it with a drug producing vasodilatation. I also observed the effect of adrenalin inoculated directly into the muscle tissue. Other substances, as digitalin and barium chloride, which have the effect of raising the blood pressure, were also tried. Lastly, the effect of producing a septicæmia with different organisms was studied, and in these experiments some interesting arterial lesions were obtained. In my series of observations over forty rabbits were used. In these animals I found that results are most easily obtained. Control animals were used in all cases where necessary, particularly in cases where the animals were inoculated with two substances simultaneously.

ADRENALIN CHLORIDE, BARIUM CHLORIDE, AND DIGITALIN.

Adrenalin chloride was administered intravenously to animals in doses varying from 0.3 c.cm. to 2.0 c.cm. of the 1 in 1,000 solution. The best results were obtained by giving large doses at intervals of three to four days. In several cases the animals died of acute œdema of the lungs immediately after the inoculation of the adrenalin, but I have never met with a case of death from cerebral hæmorrhage, as has been reported by others.

The arterial lesions varied in extent and severity with the length of time the animals were under treatment, with the quantity of adrenalin inoculated, and with the idiosyncrasy of the individual animals. The lesions were usually present at the end of two or three weeks, and the early changes consisted in small isolated plaques of calcification with pittings in their centres. When these grew larger, saccular aneurysms made their appearance. These lesions were distributed mainly over the thoracic aorta and in the abdominal aorta as far as the renal vessels.

Again, in other cases it was found that the entire thoracic aorta, half of the abdominal aorta, the vessels of the neck and those of the abdomen were completely calcified. The thoracic aorta, however, alone showed a diffuse aneurysmal dilatation, beginning at the aortic opening and reaching as far as the diaphragm. Neither the abdominal aorta nor any of the smaller vessels were involved in this dilatation.

The results obtained by the inoculation of barium chloride were exactly the same as those produced by adrenalin; in fact, the similarity is so striking that the lesions cannot be distinguished from one another either macroscopically or microscopically. In several cases I was able to produce the diffuse aneurysm of the aorta by the use of barium chloride, and in each example it was striking how the aneurysm was

isolated to the thoracic portion of the vessel and did not advance beyond the diaphragm.

Fischer's experiments, too, of producing arterial lesions by the intravenous inoculation of digitalin, were also repeated, and I agree with his findings that the arterial lesions isolated in the aorta are similar to the milder adrenalin destructions.

It was further found that, if the pressure-raising effect of adrenalin be abolished by the use of nitroglycerin, although the arterial lesions were not as extensive as when adrenalin alone was used, nevertheless, tissue degeneration in no way differing from that produced by adrenalin did still occur in the vessel walls.

In such cases where the arterial lesions were just beginning there was change to be noted in the vessels macroscopically. I might point out, too, that in none of the vessels that I have obtained from animals treated with adrenalin was I ever able to make out any naked eye changes in the intima. This coat was at all times stretched smoothly over the damaged media. The earliest damage was always found in the muscle cells of the middle zone of the media. Here patches of homogeneous tissue were met with, where the muscle nuclei were lost, but where the elastic fibres passed through these areas unaffected. With the loss of the muscle cells the parallel elastic fibres were crowded closely together by the blood pressure within the vessel.. This crowding of the elastic fibres from within outwards naturally led to a small dimple at this point and this was the beginning of a saccular aneurysm.

The loss of the muscle cells takes place by a form of necrosis, as was pointed out by Erb and Fischer. The elastic fibres later become affected, losing their elasticity and contractile power. This degeneration of both muscle and elactic fibres occurs through a process of fatty change, which is in some cases difficult of demonstration, but which is, however, readily brought out out in those cases where the metamorphosis is slower. With the high calcium content of the rabbit's blood these areas of fatty degeneration in the media of the aorta and other vessels are converted into calcified plaques by the process described by me elsewhere. Microscopically, no connexion could be linked between the positions of the vasa vasorum and the arterial degenerations, and a true mesarteritis, as noted by Fischer, was not met with.

In no instance have I found a primary change occurring in the intima after any of the above treatments, though in one or two specimens I did note the slight thickening of the intima at the margin of the aneurysm.

It is to be noted, too, that with the abolition of the physiological effects of adrenalin, the arteries are still affected, though more slowly

and to a less degree than where the vessels are under tension. Boveri claims to have abolished the effects of adrenalin on the blood vessels by combining it with "Iodipin," though he was not able to prevent the toxic effect on the muscle cells.

The effect of adrenalin chloride inoculated directly into the skeletal muscle depends upon the strength of the dose given. When the undiluted 1 in 1,000 solution of adrenalin chloride is inoculated into the muscle tissue the cells are killed outright, so that the nuclei and cell membrane disappear. Weaker solutions produce a fatty degeneration of the muscle cells. It was found also that the animals receiving the adrenalin treatment over an extended time developed fatty degeneration of the heart. So we can but conclude that adrenalin has a selective action on muscle tissue, and that its toxic effect thereon is the primary cause of the arterial lesions. The same holds true for barium chloride and digitalin. The three substances are thus similar in their effects, differing only in the intensity of their reaction.

The influence of high pressure in producing arterial change is well brought out in these experiments. We have noted that the most frequent site and the most severe changes occur in the thoracic aorta, and that the vessels in the remote parts of the body are only affected when advanced lesions are present there. We must admit that the inoculated substances are distributed equally to all parts of the body, and that from toxæmia alone all vessels of similar structure should suffer equally. But the normal amount of work done, besides the increased strain that is produced by raising the blood pressure, is felt most severely in the aorta, mainly in the thoracic portion. As a result of this combined degeneration and high pressure, the thoracic aorta exhibits a fusiform aneurysm, extending from its origin to where it passes behind the diaphragm. From this localization of the diffuse aneurysm to the thoracic aorta, it is evident that the aorta opening in the diaphragm acts as a flood-gate in letting through only given quantity of fluid. By this mechanical device the abdominal aorta is relieved of having an increased volume of blood thrown into it by the overworked heart, and thus is not subjected to the double degenerative forces of toxæmia and high blood pressure, as is the thoracic portion. Focal degenerative lesions are nevertheless found in the abdominal aorta.

The important role that the muscle fibres of the media play in the strength of the arterial wall is well known. In fact, it is pointed out that they are the mainstay of the vessel. This fact is exemplified in these experiments, where it is found that with the primary degeneration in the muscle cells the vessel wall begins to give way in this region. The

elastic fibres at this time, though themselves not visibly altered, no longer take on the wavy contour which is characteristic of them in a relaxed vessel. It would seem from this that the apparent elasticity, as shown by their undulations, is not an inherent quality, but is due to the contraction of the muscle fibres surrounding them—or, otherwise, that when the artery is in a condition of tonus, its contracted state is due mainly, if not entirely, to the muscle fibres; when dilated it is probable that the elasticity of the elastic fibres comes into play.

A proliferation of the intimal tissue in these cases is to be regarded as secondary to degenerative processes in the media. The proliferation is either of the character of a hypertrophy of the musculo-elastic layer or of the subendothelial tissue. Whether this subendothlial tissue had its origin in connective tissue or endothelial cells we cannot discuss here.

INFECTIVE ARTERIO-SCLEROSIS.

I have also undertaken the production of experimental arterial lesions with infective agents. For this purpose B. typhosus and streptococcus were used in separate experiments, while again in others diphtheria toxins were inoculated. Each of these agents was inoculated intravenously into rabbits.

The results obtained with B. *typhosus* and the streptococcus were of the same order. The first part of the pulmonary artery and the ascending limb of the aorta showed warty thickenings of the intima. There were no anerysmal sacs nor any sign of a calcareous degeneration of the media. Microscopically there was a fatty degeneration of the subendothelial tissue, while there was, however, much connective tissue advancing into the degenerated area. A small-celled infiltration was wanting, as was also any sign of calcification. At the areas of thickening of the intima it was found that the internal elastic lamina had split into several parallel layers, which were stretched between the proliferating cells. The area affected included the intima and the inner layer of the media. Thus we find that these infective lesions (of *B. typhosus* and streptococcus) differ entirely from those produced in our adrenalin series. What we may term the adrenalin group are agents producing destruction of tissue leading to a calcification with little or no local repair to make up for the lost tissue, while the mild infections lead to a slight degeneration of the vessels coats, though the process is followed step by step by the process of repair, and instead of getting a thinning of the vessel wall there is an actual thickening. It becomes self-evident that with the absence of extensive destruction of the muscle fibres in the media no aneursyms were formed.

In our experiments it must be remembered that we dealt with cultures of low virulence. The possibility must not be overlooked that virulent micro-organisms gaining entrance in to the adventitia through the vasa vasorum, and proliferating there, might invade the media and induce local degeneration and destruction, and if the reparative process could not keep pace the weakening of the media might result in aneurysm formation. Such lesions would correspond to the mitotic aneurysms in man, which have been described by McCrae and others; nay more, the observations of Heller, Chiari, and others upon syphilitic mesaortitis, afford a like explanation for aneurysms in the syphilized.

The presence of lesions in the pulmonary artery is worthy of note in comparing the distribution of the lesions with those of the adrenalin series. In the later, the aorta and its branches were alone involved, while the heart became hypertrophied—a feature that was not seen after the bacterial inoculations.

The repeated inoculations of diphtheria toxin into rabbits gave surprising results. Here, instead of meeting with proliferative changes, such as the B. typhosus and streptococcus produce in the aorta, there were only lesions of a degenerative character. The degenerations were isolated to the first part of the aorta, and were identical with those produced in the adrenalin series. The thinning of the arterial wall, with calcification and aneurysmal dilations, were all present, and the microscopical examination showed the lesions to be confined to the media. No proliferative or inflammatory changes were present in the intima, nor was there any change about the vasa vasorum.

Hence we have before us two interesting groups of arterial lesions resulting from infective conditions. On the one hand, lesions are intimal and proliferative, while on the other they are of a purely medial degenerative nature. The free toxins of diphtheria have a predilection for the muscle tissue of the circulatory system, whereas the endotoxins of typhoid and streptococcus infections are in small doses rather of a stimulating nature to the connective tissue and endothelial cells.

If, then, we are to consider the nature of the lesions produced in the arteries as a criterion in classifying the toxins, we must place the diphtheria toxin along with the adrenalin series, while the endotoxins, the stimulating or proliferative agents, form another. The marked differential characters which are brought out by the two series in experimental animals make it more than probable that such differences also exist in man—that is, that typhoid or streptococcus infection will lead to an endarteritis, while diphtheria will produce lesions of a degenerative character, affecting chiefly the muscle cells.

The fact that the streptococcal and typhoidal infections lead to a splitting of the internal elastic lamina with a proliferation of the sub-endothelial tissue (and also the musculo-elastic layer) places the lesion in very close relationship with arterio-sclerosis in man, as it is described by Jores.

To sum up the results of my experiments, I find that:

1. The effect of the high-pressure drugs (adrenalin chloride, digitalin, and barium chloride) on the arteries is a degenerative one, as was described by Fischer and Erb for adrenalin.

2. The muscle cells of the media are first attacked, while the elastic fibres of this layer are also involved later.

3. At a proper stage of the degeneration, a fatty change can be demonstrated in the tissues, followed by calcification.

4. The middle zone of the media is always involved.

5. Occasionally secondary reactions occur in the intima which are of a proliferative nature.

6. The effect of adrenalin is not abolished by lowering the blood pressure with nitroglycerin.

7. The aneurysms are produced as a result of the destruction in the media.

8. These experimental lesions are in every respect similar to the Moenckeberg type of arterio-sclerosis.

9. The effect of diphtheria toxins on the arteries is similar to that of the adrenalin series.

10. Typhoid and streptococcus infections produce little destruction of tissue cells, but tend to stimulate cell proliferation in the intima and inner layer of the media.

11. Vessel changes are brought about by these infections which correspond to arterio-sclerosis, as described by Jores.

12. Contrary to the general conclusions reached by Thoma, these experiments show that there is definitely a form of arterio-sclerosis in which, not a preliminary weakening of the media, but a primary proliferation of the intima, including the musculo-elastic layer, is the prime feature. To what extent this essentially proliferative type is to be encountered in the human aorta and other vessels must be left an open question. Undoubtedly in the medium-sized arteries, the Moenckeberg type of medial degeneration is common. Undoubtedly also in syphilitic as well as other cases, we encounter in the aorta a secondary and adaptive or compensatory over-growth of the intima—secondary that is, to the medial degeneration.

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DISCUSSION.

DR. PEARCE said experimental lesions were not analogous to those of man, but of great value in explaining degenerative and regenerative changes in vessels. Physiological studies of the action of adrenalin were of great value in explaining problems of cardio-vascular pathology.

PROFESSOR CLIFFORD ALLBUTT said: I must begin my remarks, Sir, by thanking you for the compliment you pay me in calling upon me, who am no expert in pathology, to speak in this Section. The discussion of this morning is peculiarly instructive and gratifying to me in so far it has come to the support of the doctrine in which for so many years I stood alone—the doctrine of the mechanical origin of a certain large group of cases of arterio-sclerosis, a group which includes that of chronic renal disease, and especially of granular kidney, but is by no means confined to cases of renal disease. And although it is true that mechanical causes, which we may express pretty nearly in terms of arterial blood pressure, operate in all cases of arterio-sclerosis, of the group of which I am now speaking it is virtually the sole cause; in other words, the arterial damage is due, and stands in proportion to a period or periods of excessive pressures, an excess which, in the first instance, is antecedent to the arterial disease, and may even within some such term as four or five years be subdued, and the arterial damage thus averted—an opportunity which we must be ever more and more on the alert to seize and to turn to advantage. But this mode of arterial disease, the mode which I have

called that of hyperpiesis, is by no means the only one. Speaking as a physician, I recognize two other classes, at least, of arterial disease—classes which I have named respectively the toxic and involutionary classes—each of great extent and importance. In these classes the arterial pressure are not characteristically high. Tension or strain (which, of course, cannot be excluded) is not the prime factor in setting up the arterial disease. In these two classes, indeed, the arterial pressures often run low, and—intercurrent contingencies apart—do not exceed the average for the time of life of the individual. The mechanical wear and tear would be harmless but for some causes of other kinds which produce in the vessels a morbid liability to yield under ordinary stresses. Now it is here that as a physician I come to the pathologist to inquire if, in accordance with these several clinical features, he can separate arterio-sclerosis into corresponding histological varieties? I would suggest—and my own cruder efforts in pathology lead me to think—that in the arterial disease of toxic origin the poisonous agent enters by the adventitia and vasa vasorum, whence it penetrates to the intima, but on its way leaves the adventitia and the media not without traces of its deteriorating influence; that in the arterial disease of involutionary origin the disease begins early, if not first in the media, by spots and streaks of decay going on to calcification; that in the hyperpietic disease the damage begins by tearing and shearing stresses, by shears, or even by rents, which, indeed, do not always elude the microscopical eye. These shears act chiefly in the plane *minoris resistentiae*—the plane of opposition of the intima and the media. When the rents are manifest to the eye, they lie tangentially to this plane, and the elastica is fragmented, or is reduced to common fibre. Such, however, is the consequent obliteration of normal landmarks that we know too well how difficult it is to be topographically exact in these descriptions. From such considerations as these I have urged that the clinician should discard the name of arterio-sclerosis as the name of a disease, and be content to speak of arterial disease as of several kinds, or, at any rate, as a result of many maladies, maladies which are divisible between at least three different classes. With what reserves and distinctions the pathologist is to use the term it would not become me to discuss before this audience. In addition to the surmises I have just ventured upon, I may, however, propose one more consideration, namely, that in arguing upon the relative meanings of arteritis, arterio-sclerosis, atheroma, and so forth, we must constantly bear in mind the stage, the rate, and the place of the process in each particular case. Different as such processes

may be—as indeed I have urged—yet we are apt, I think, at times to forget that in comparing tissues from a very slow case with those of a case whose course has been quicker, or in comparing, in the same case, a muscular artery with a piece of the aorta, or, again, in comparing an earlier stage of disease in a patient cut off by contingent causes with a later or final stage in another patient, we may in the differences of time and place overlook essential similarities or even identities. May I say, in conclusion, a few words on arterial hypermyotrophy? Whether there be in arterio-sclerosis a true hypertrophy of the muscular coat is a fallacious question, if so be that arterio-sclerosis is a general term including several kinds; for this hypertrophy may occur in one or more of the kinds, but not in all. This, in my opinion, is the case: arterial hypermyotrophy occurs in the kind of arterial disease I have called the hyperpietic—that in which the disease is a result of excessive pressures within the vessels, but does not occur in either of the kinds which I have called toxic and involutionary; unless, perchance, their ordinary course is modified by some incidental burden of blood pressures. Leaving these two kinds, then, and turning our eyes to the arterial disease of high pressures only, we shall find if time be given, the first deviation from the normal to be this hypermyotrophy. At this stage, if the abnormal pressures be permanently reduced within normal limits, the hypermyotrophy will disappear also. Such transitory phases are best witnessed in young, or comparatively young, subjects. If, on the contrary, excessive pressures persist, unrelieved by nature or art—say for more than four or five years—this hypertrophied coat seems to lose its specific quality and to deteriorate into fibre of inferior rank, but perhaps capable of more tenacious resistance. This process is deferred, I think, in small arteries in which constriction has been especially dominant, a constriction whereby the pressure within them and the consequent tension of their coats are reduced. This vascular hypermyotrophy was described first by George Johnson, and Dr. Savill and other recent observers have verified rather than enlarged his description. It fell to me, perhaps to point out that this hypertrophy of the media is not confined to granular kidney, but arises in all cases of continuously high arterial pressure—all cases, that is, in which these parts are nutritionally capable of re-adaptation. Gull and Sutton erred, as I pointed out in a contemporary number of the *British and Foreign Medico-Chirurgical Review*, not in describing other kinds of pathological change in the arteries but in doing so to the exclusion of Johnson's kind. The problem in this hypermyotrophy now to be decided is whether spasm of the vessels concerned, under the influence, let us say, of some poison

acting upon them directly or indirectly through the vasomotor centre, suffices to produce it, or, as I have ventured to urge, that it is due in the vessels, as in the heart, to enhanced dilating stresses. The answer is not easy, as the closer the constriction in any vascular area the lower must be the pressure, which, *caeteris paribus*, is converted into velocity. Perhaps if the resistance distal to the area of constriction be high, spasm and high internal pressure may co-operate to produce hypermyotrophy. That the muscular arteries on the hither side of areas of spasm will dilate and hypertrophy under the rise of pressure caused by it needs, I think, no asseveration. And how, thereafter, under this strain, arterial disease arises—hypermyotrophy is scarcely to be called disease—I have already stated; this is, of course, a later phase, a phase in which the state of the vessel passes into the irremediable. But for a moment I may return to calcification. Calcification rarely occurs in the arteriosclerosis originating in high pressures; it is characteristic of the involutionary kind. But it is a common error to suppose that calcification is a very slow process, or one confined to old age. It may scatter itself widely and profusely in comparatively short periods, and it may attain even extreme degrees so early as the fifth decade of life, possibly in rapidly decaying individuals, even sooner. On the whole, then, calcification is, clinically speaking, a presumption against hyperpiesis, present or past—hyperpiesis, that is, above the degrees usual for the time of life. Notwithstanding, I have records of a few cases, primarily of hyperpiesis, observed over long periods of time, in which calcification supervened—exceptions which test the rule. For in these it was apparent, on consideration of all the facts of each case—facts clinical as well as pathological—that the calcification appeared when the processes of hyperpiesis had ceased or become subordinate, and the life of the patient had been spared to undergo the ordinary involutionary changes which are present in the vast majority of elderly persons.

Professor Adami said: While appreciating fully the distinction which Professor Clifford Allbutt has drawn between compensation and adaptation, I feel bound as a pathologist to cross blades with him regarding the importance and the frequency of adaptive conditions; nay, more, I would go so far as to lay down that pathological processes so far as they are reactive are coincidently adaptive to a very great extent. As pathology widens itself from a study, histological and otherwise, of morbid states, to one of morbid processes, so inevitably are we driven to realize that this is so. I need but recall that the abundant and valuable recent studies upon acquired immunity, upon hæmolysins, cytolysins, and the like, recall to us a vast series of these adaptations. And here,

in connexion with the ordinary type of arterio-sclerosis, it has for long seemed to me that we encounter some of the most striking instances of adaptation. The studies made by me some years ago, to which I have referred in the Middleton-Goldsmith Lectures of 1896 upon Fibrosis and Inflammation, led me to support and confirm Thoma's contention that in the commonest type of aortic arterio-sclerosis there is (as in the later experimental researches of Josué, Pearce, Klotz, and so many other workers with adrenalin and allied drugs) a primary degeneration and giving way of the media. To that view, despite Jore's important studies, I still incline, and would harmonize the divergent opinions by laying down that while the primary lesion manifests itself in the media, the primary reaction to that lesion occurs in the intima. It is this reaction—this overgrowth of the musculo-elastic layer—that Jores has so serviceably brought to our notice, an overgrowth which may or may not be accompanied by coincident hyperplasia of the subendothlial connective tissue of the intima. No one nowadays regards this intimal hyperplasia as strictly inflammatory, as a direct reaction to injury; it has none of the characteristics of inflammatory new growth; there is no primary new formation of vessels, no small-celled infiltration; it is a hyperplasia pure and simple, occurring not in the tissue primarily injured, the media, but in another tissue, the intima. But it is secondary to the giving way of the media, and to that extent reactive, and can, I think, only be regarded as adaptive, tending towards a restoration of the original lumen of the vessel and a strengthening of the wall at the region of giving way. I have elsewhere explained this overgrowth as an effect of strain within certain limits. Just as increased strain, up to a certain grade, favours muscular hyperplasia, and as exercise, by causing increased pull upon the tendinous insertions of the muscles is followed by overgrowth of the bony ridges of attachment of those tendons, so I hold that when the media gives way locally to a slight extent the overlying intimal tissue becomes stretched and strained, and as a result exhibits hyperplasia. Too severe and sudden an expansion of the intima arrests any such tendency to overgrowth. Thus, it is significant that in aneurysms intimal thickening is lacking. There is a similar lack of overgrowth in these aortas from rabbits treated with adrenalin and barium chloride, with their aneurysmal pouchings, as, again, in the pouchings of human iliac and femoral arteries of the Moenckeberg type. I shall not be surprised, however, if further observations demonstrate that the common or Jore's arterio-sclerosis and the Moenckeberg or medial degenerative type are the effects of common noxæ acting with

different grades of intensity, and, as Professor Aschoff suggests, upon arteries of different constitution. I am inclined, that is, to think that the experiments made so far with adrenalin have been somewhat severe, leading to an acute type of medial degeneration, and that slighter grades of intoxication conducted over long periods will afford the reactive overgrowth of the intima, such as we see in human arterio-sclerosis of the ordinary type; indeed, from Dr. Pearce's published description of certain of his experiments, which tended to fulfil these conditions—experiments in which he gained not merely medial giving-way, but also intimal hyperplasia—it would seem that this relationship between the two types is in a fair way to receive its proof. While saying this I need scarcely add that, as demonstrated by Dr. Klotz's most valuable observations upon the effects of bacterial toxins on the aorta, there is a wholly different type of sclerosis in which we have to recognize a primary intimal overgrowth after the type of chronic endarteritis proliferans, as also yet another important type, as demonstrated by the Kiel school and Chiari, that following upon a chronic mesaortitis—the syphilitic type.

[The remarks of PROFESSOR ASCHOFF, who led the discussion, given in German and not reported by the British Medical Journal, were to the effect that there is perhaps too great a tendency to regard the arteries in general as of like structure. This is far from being the case: there is an essential relationship between function and structure and the function of the arteries of different regions varying we must be prepared to find, and, in fact, do find, that there is marked variation in the relative development of the different coats. From this it follows that one and the same noxae must be expected to have different effects upon different arteries, while certain noxae may attack one group of arteries and not others. We must be prepared to find in the future both that what appear to be distinct lesions in different parts are due to the common cause, as conversely that distinct noxae act specifically upon particular arteries setting up distinct forms of arterio-sclerosis.]