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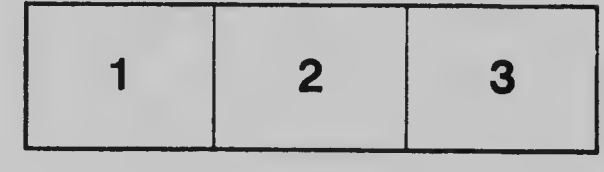

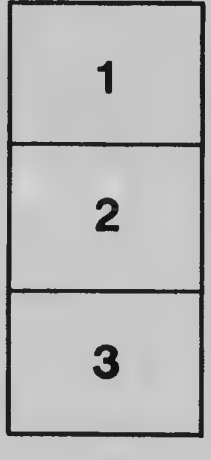

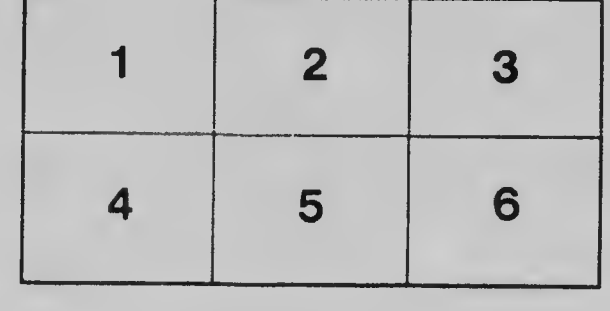

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EXPERIMENTAL STUDIES IN ARTERIOSCLEROSIS.*

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Our conception of the pathology of arteriosclerosis has recently been so altered, that much confusion exists at the present date, as to what form or forms of arterial disease should be considered under this term. There were and are still many who would limit the term to a single kind of lesion, while others again are more liberal, and use this appellation to include the great mass of arterial diseases which eventually lead to a thickening of the vessel walls. The author of the term leaned towards using the word "arteriosclerosis" for all conditions of hardening of arteries, and with this meaning the old anatomists expressed themselves, reserving, however, the term "atheroma" for another distinct lesion. However, Virchow's description of endarteritis chronica deformans, as the commonest type of arteriosclerosis, has led to the adoption of these expressions interchangeably, and has found the most favor recently. In my own studies I have given the wider use of the word, and include under arteriosclerosis, as was formerly the case, all hardening of the arterial coats. This, you will agree, is more in accord with the findings of the clinicians, for, *intra vitam*, they can in no wise differentiate the various histological forms of arteriosclerosis. It is necessary to bear in mind

* Read before the Medical Association of the Greater City of New York, Jan. 21, 1907.

this wide definition I have given to the term, for otherwise it may be held up to me that arteriosclerotic lesions were not obtained in the experimental work.

One must also not lose sight of the diverse functions which the vascular system has to perform, and how the manifold work of the arteries is at the bottom of their histological structure. The arteries of the uterus, which are well supported by the muscle tissue of the organ, are rich in muscle fibers, while the quantity of elastic fibers falls much in the background. These uterine arteries require this abundant muscular development for the periodic congestion at menstruation and pregnancy. On the other hand, the splenic arteries which within the organ have a poor supporting framework must rely entirely on their own strength to withstand the blood pressure. This extra strength of the arteries is obtained in a well developed adventitia, strengthened by elastic fibers.

The intima, too, of the different arteries varies in its constituents. Thus the arteries of the first order possess a muscular layer in the intima which is not present in the smaller arteries. Certain diseases therefore can and do occur in the intima of these larger vessels which can in no way be developed in their branches.

The experimental production of arteriosclerosis in animals is of fairly recent origin. The first experiments undertaken were by the direct injury, as crushing of an artery. In this way the experimenters had hoped to bring about sufficient change in the vessel walls to lead to aneurism. They were disappointed in this, but instead of an aneurism they found that certain local inflammatory changes with endothelial proliferation were produced. It has since

been shown in all cases where an artery is disturbed in its natural bed, thereby affecting the vaso vasorum, that an inflammatory reaction is the result.

From a study of these inflammatory processes two important facts were noted. Firstly, that an inflammatory reaction in the media is evidenced by a leucocytic infiltration about the vasa vasorum and in the lymphatic channels; and secondly, that a lesion of the media of inflammatory nature may lead to a chronic proliferation in the intima. This intimal proliferation is the result of endothelial and connective tissue overgrowth and is similar to the disease which Virchow called "endarteritis chronica deformans" in man, while the medial inflammation is like Koester's "mesarteritis." This mesarteritis passes gradually from the acute inflammatory stage into the process of chronic healing in which fibrous tissue is laid down in the middle coat of the artery. In man the most severe form of this disease is met with in syphilitic arteritis, but no doubt other infections can lead to the same results.

Since the above mechanical experiments were made, several other ways were found to bring about the same results. The chronic endarteritis has been brought about by the intravenous inoculation of bacteria of low virulence. Thus I have been successful in producing an endarteritis chronica deformans in the arch of the aorta and sometimes in the abdominal portion by the injection of old laboratory stocks of the streptococcus or B. typhosus. A true inflammation of the media (a mesarteritis) I have not succeeded in obtaining except when an injury had been induced close to the vessel itself. In this case the inflammation of the surrounding tissue spread into the arterial wall.

The experimental endarteritis chronica deformans has histological characters quite similar to that in the human arteries. The lesion is composed of a heaping up, layer by layer, of the endothelial cells, while the connective tissue underneath the endothelium is also undergoing a proliferation. The result is that a white, pearly plaque is produced, under which degenerative changes of a fatty character may develop in the deeper part of the intima.

Whether these pearly plaques in the human or experimental arteriosclerosis are composed wholly of endothelial cells, or of connective tissue, or both, is quite immaterial at present. The result is the same, the production of a nodular hyaline mass of tissue on the surface of the intima. Such a thickening of the intima has a disastrous effect on the tissue just underneath it. The intima and the inner third of the media derive their nourishment from the lumen of the vessel, and the production of a firm mass of tissue at one point in the intima cuts off the supply of nourishment to the cells underneath it. From this there follows the fatty change in the deep layers of the intima and the inner portion of the media, a condition which is so often seen in the aorta.

The experimental lesions which have of late received the most attention are of a different nature. I have just pointed out that the endarteritis chronica deformans is essentially of a proliferative character, and that degenerative processes, if they occur at all, are secondary to this. We have, however, on the other hand, been able to produce pathological conditions which from the first are degenerative in nature. By the use of adrenalin, digitalin, nicotine and barium chloride, it has been shown that *the muscle cells in the middle zone of the media are*

primarily attacked, and according to the intensity of the intoxication of these drugs, the cells either undergo a fatty degeneration or complete destruction. Along with the death of the muscle cells, the elastic fibers in the media are also affected and, like the former, they either become fatty, or with more severe intoxication, undergo necrosis. However, in each instance the muscle fibers are primarily affected. These lesions, it is obvious, have destroyed the most important tissues in the artery, and have weakened the vessel wall very considerably. Aneurisms are commonly to be found at the sites of medial change while little if any intimal compensation occurs. Thoma's dictum, therefore, that intimal compensatory hypertrophy follows medial weakening is not universally true. This type of arterial disease, in which the media is first destroyed, is spoken of as "Moenckeberg's arteriosclerosis."

Not alone was the medial degeneration with calcification produced by means of drugs, but I have also obtained it by the inoculation of the diphtheria toxin. This is important in demonstrating that the effects of diphtheria are not confined to nervous tissue and heart muscle, but that the muscle elements of the vascular system are also attacked. It may be that the intoxication in cases of diphtheria is an important agent in bringing about Moenckeberg's arteriosclerosis, such as is seen in the radials and other peripheral vessels.

This latter form of medial degeneration with aneurismal pouchings has also its analogy in the peripheral arteriosclerosis in man. The greater majority of the cases of arteriosclerosis which are diagnosed from the condition of the radial arteries are of this type. The beadings so often noted in the radials of old people are the small pouchings in the vessel wall that have become calcified.

It is therefore evident that, if the term arteriosclerosis is to be retained for the use of the clinician, this form of arterial disease, which is most commonly seen at the bedside, must be included under it.

The calcified plaques of the aorta or the calcareous beadings in the radials and other peripheral vessels are in each case secondary to a previous fatty change of the tissues. Experimentally these deposits of lime have been produced in connection with the medial destruction, when both muscle and elastic fibers become fatty. It is interesting to trace the course of the muscle tissue through the process of fatty degeneration with a subsequent death of the cells. The fine fat droplets within the cells are converted into the fatty acids by the lipase of the blood and serum, following which the salts of lime form a stable compound with the fatty acid in the form of lime soaps. These fatty acids and soap compounds are readily demonstrable by special staining. From the calcareous soaps the phosphate and carbonate of lime become deposited later.

Thus, up to the present, we have at our command the production of three types of arteriosclerosis, namely, (1) endarteritis chronica deformans, (2) mesarteritis, (3) Moenckeberg's type of arteriosclerosis. Each of those experimentally produced arterial diseases follows the same course and has the same ultimate result as in man. However, as the lesions are produced in healthy animals, which have power to compensate the effect of extreme arteriosclerosis, fewer symptoms are to be noted. The heart rapidly becomes hypertrophied and is able to carry the new load with comparative ease.