From the author.

Syphilis and the Etiology of Atheroma.

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SYPHILIS AND THE ETIOLOGY OF ATHEROMA.

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In this paper I purpose shortly to consider the nature of arterial atheroma, more especially with regard to the part, if any, played by syphilis in its causation. Everyone is familiar with the appearance of atheroma in the aorta, the formation of thickened patches, the fibrous, pulpy, or calcareous formations in its inner coat. It is not my intention to describe these changes, which have already so often been described both macroscopically and microscopically, but to discuss certain questions in their etiology.

The importance of the part played by syphilis in the causation of aneurisms[1] must certainly be acknowledged, and hence some would argue that syphilis exerts a like influence in the production of arterial atheroma, but the latter conclusion is not a fair one. In order to show that such a conclusion is not justified it becomes necessary to make a digression and to discuss shortly the *rôle* of syphilis in the causation of aneurisms.

For this purpose it will be best to confine ourselves to aneurisms of the aorta, so as to exclude, as far as possible, aneurisms due to traumatism, bruising, and embolism, and especially to exclude those caused by septic inflammation of the arterial walls, set up by emboli in cases of infective endocarditis.[2] Aortic aneurism occurs chiefly at the middle period of life; out of ninety-two cases analyzed by Dr. Thomas Hayden, sixty occurred between the ages of thirty and fifty,[3] whereas the same author found that atheroma was most common after the age of sixty. In spite of this, however, Dr. Hayden evidently considered aneurism to be due to atheroma, or at least to antecedent changes in the vessel-walls, of which atheroma may be looked on as the type; this is what he said: "Thus, whilst deterioration of the arterial coats as typified in atheroma is most common after the age of sixty, one of its ordinary consequences,

[1] The statistics on this subject are, of course, as liable to error and as hard to ascertain correctly as those of antecedent syphilis in cases of tabes dorsalis. Professor Clifford Allbutt tells me he would say that in 90, or even 95, per cent. of aneurisms there has been previous syphilis. See also F. H. Welch, "On Aortic Aneurism in the Army." Med.-Chir. Trans., 1876, vol. lix.

[2] See J. Langton and W. Bowlby, "Multiple Embolism of the Arteries of the Extremities." Med.-Chir. Trans., 1887, vol lxx.

[3] See "Diseases of the Aorta," in Quain's Dictionary of Medicine, first and second editions. Other statistics agree in pointing to the period between the ages of forty and fifty as the commonest for aortic aneurism.

aneurism, belongs to an earlier period of life. The apparent discrepancy may be explained by the more frequent employment of men under fifty in severe labor, and their greater capacity for extreme muscular effort earlier in life, the condition of the arterial wall which favors aneurism having been already established."

That violent efforts and high blood-pressure are most important factors in the causation of aortic aneurisms there can be no doubt,[1] but I believe that the explanation given by Dr. Hayden is not sufficient to account for the discrepancy acknowledged by him between the favorite age for aortic aneurism and the period of greatest frequency of aortic atheroma. It appears to me more natural to conclude that ordinary atheroma is not, after all, the commonest cause of sacculated aneurism of the aorta, but that a localized inflammatory infiltration of the aortic wall[2] usually precedes the aneurismal dilatation.

There seems to be nothing against the view that such patches of subacute aortitis represent sometimes a true tertiary syphilitic process of the nature of a gummatous infiltration, and this view best explains the importance of syphilis as an etiological factor in aortic aneurisms.

In 1868 Prof. Clifford Allbutt,[3] when describing the histological character of the diseased cerebral vessels in a syphilitic man, aged thirty-one years, drew attention to a condition of chronic arteritis with great nuclear and cellular proliferation, which affected all the coats to some extent, but especially the middle and inner coats. He said, "The distinction between the coats was in many places lost; in other places the inner was detached from the middle coat by a nest of nuclei and granules. . . .

[1] Hence the much greater frequency, so often alluded to, of aortic aneurisms in men than in women, and in men who make great muscular efforts than in men who do not. This is confirmed by the fact that the aortic arch, where naturally the strain is greatest, is the most common site for aneurisms. Strain probably acts likewise as a predisposing cause of atheroma. The arteries of the lower extremities, which are more liable to strain than those of the upper extremities, are likewise more liable than the latter to atheroma; the pulmonary artery, where the blood-pressure is much lower than in the aorta, is seldom affected by atheroma, except when the blood-pressure in the pulmonary artery is pathologically increased by pulmonary emphysema, disease of the mitral valve, etc. (See S. Wilks and W. Moxon, "Lectures on Pathological Anatomy," 3d ed., 1889, pp. 155–57.) Precisely how strain can induce atheroma remains doubtful. A discussion as to whether a chronic inflammatory process plays an intermediate part in these cases would be unprofitable, but we may bear in mind that, though moderate functional activity and mechanical movements must be regarded as natural stimulants tending to the proper nutrition of the tissues, excessive functional activity and mechanical strain may probably cause malnutrition and irritation, giving rise to chronic degenerative and inflammatory changes. It is not then a matter for surprise that strain sometimes helps in the production of atheroma; the part, however, which it plays in the production of atheroma is probably quite different to the part which it plays in inducing aneurism. In the latter case the usual action of strain is most likely the mechanical thrusting out of a part of the vessel-wall already softened by some true inflammatory process.

[2] The very first stages of a sacculated aneurism of the aorta are, however, not likely often to fall under the notice of the pathological anatomist.

[3] "Cerebral Disease in a Syphilitic Patient," St. George's Hospital Reports, 1868, vol. iii. p. 61. What appear to have been miliary gummata had already, in 1863, been noticed by Dr. S. Wilks in the bloodvessels of the brain in the case of a syphilitic woman, aged 38. See Guy's Hospital Reports, 1863, 3d series, vol. ix. p. 45.

in other places, again, pear-shaped processes, thrust inward from the middle and inner coats, projected into the lumen of the vessel, carrying the inner coat before them. . . . Their contents were chiefly of an opaque granular character. I found, however, no dark layers of fatty degeneration like those we see in common atheroma; and on the whole the degeneration was not of so low a kind as in atheroma, the products being generally of higher physiological value." Although this account and the subsequent paper by Heubner,[1] of Leipzig, described syphilitic disease of the small arteries, it may be inferred that there is also likely to be a difference between a chronic or subacute syphilitic inflammation in the aorta and ordinary atheroma.[2]

I now return to the original question: the nature of aortic atheroma and its relation to syphilis. The digression was undertaken to point out that syphilis may play a much greater part in the production of aortic aneurism than it does in the production of atheroma, not to urge that syphilis was of no account in the causation of atheroma.

Any local inflammation seems to predispose to chronic atheromatous changes. It is an old observation that atheromatous changes are very likely to be found in valves which have been slightly affected by previous rheumatic endocarditis. Chronic atheromatous thickening is not rarely seen in congenitally malformed cardiac valves, such as when there are only two instead of three aortic or pulmonary valves. In these cases one of the valves is often divided into two parts by what John Hunter, in describing the condition, termed a "crossbar."[3] Probably such valves are sometimes the result of intrauterine endocarditis,[4] the "crossbar of Hunter" representing the part where two valves during fœtal life have undergone inflammatory adhesion so as subsequently to form a single valve in the adult; it seems, therefore, fair to consider that when such valves undergo chronic thickening the intrauterine inflammation, like ordinary rheumatic endocarditis, or any other inflammation, has acted as a predisposing cause to the subsequent degenerative changes of atheromatous nature supervening in adult life.

A patch of syphilitic aortitis, besides its chances of giving rise to an aneurism, would, like any other inflammation, predispose to a subsequent atheromatous process, and this is, I believe, the chief part played by syphilis in the causation of atheroma.

Some would make of atheroma itself a chronic inflammatory process, but of this I think there is not sufficient evidence. As in the case of

[1] Professor O. Heubner: Die leutische Erkrankung der Hirnarterien, Leipzig, 1874.

[2] See S. Wilks and W. Moxon: Lectures on Pathological Anatomy, 3d ed., 1889, p. 152.

[3] Sir James Paget, in 1844, drew attention to the frequency of disease affecting the aortic and pulmonary valves, when there were congenitally only two instead of three of them. Med.-Chir. Trans., vol. xxvii. p. 188. See also Dr. J. B. Peacock: Monthly Journ. Med. Science, May, 1853, vol. xvi. p. 387.

[4] See Dr. J. B. Peacock: Monthly Journ. Med. Science, May, 1853, vol. xvi. p. 385.

arterio-sclerosis, and as in some cases of granular contracted kidney,[1] and of chronic fibroid changes in the cardiac muscle,[2] the question arises in this case, also, what definition of inflammation we are to accept as our criterion in judging whether inflammation is present or not. The "rubor, tumor, calor et dolor" of Celsus, though still of great service as ordinary clinical tests for inflammation when occurring in extensive areas accessible to touch or view, is hardly satisfactory as a scientific definition. For the present purpose I would prefer such a modification of modern definitions as that suggested in my recent paper on "Arterio-sclerosis,"[3] namely, that inflammation is "the series of tissue-changes caused by an injury or by the presence of some harmful irritant, and usually leading to an accumulation of cells in the part affected."

This includes the cell-accumulation resulting from proliferation of the fixed cells as well as that resulting from the migration of leucocytes. It includes tuberculous affections and the other infective granulomata; it will also include cancer and sarcoma, if ultimately the presence of coccidia-like organisms should be proved to be necessary to their development. The occurrence of necrobiosis, secondary to inflammation or due to the same original cause, will not confound the definition.

If we accept such a definition, does atheroma fall under the head of inflammation? The cell-accumulation is certainly present, but an injury or irritant cause is probably not essential to the production of atheroma, unless, indeed, deficient nutrition be regarded as an irritant cause. Mere malnutrition and deficient nutrition are causes of necrobiotic and degenerative changes, acute and chronic; but, if they should be regarded as irritants, it would become hard, indeed, to separate chronic inflammatory from degenerative processes.

It is doubtful whether in many conditions it is possible to draw a hard-and-fast line between chronic inflammation of tissue and chronic degeneration of tissue. One can understand that the blood by deficiency in quantity, or, at least, by deficiency in its chief nutrient components, may give rise to a process of simple malnutrition. Besides being merely deficient in quantity or nutrient quality the blood supplied to the tissues may contain injurious substances owing either to excessive formation in some tissue of the body of a natural toxic product of tissue-metabolism, or to its deficient excretion from the body,[4]

[1] Especially those cases chiefly seen in old people, in which the capsule of the kidney strips off quite readily, though the surface of the cortex appears somewhat pitted or granular, and the cortex of the whole kidney is slightly diminished in size.

[2] See H. Huchard: Maladies du Cœur et des Vaisseaux, 2d ed., Paris, 1893, pp. 170 *et seq.*

[3] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, September, 1894, p. 287.

[4] Or to deficient washing out of products of catabolism from some particular organ. Thus, the increase of fibrous tissue taking place in the liver and spleen from passive congestion may be due not merely to the passive hyperæmia, *per se*, nor to increased venosity of the blood, but rather to the accumulation of the products of tissue-catabolism occurring in the congested organs owing to the local stagnation of the blood.

or to the formation by diseased tissue-metabolism of toxic substances (true auto-intoxication) not formed at all in the healthy body, or, lastly, owing to the formation within the body of toxic products resulting from the metabolism of parasitic microbes. Such toxic substances circulating in the blood may, of course, act as irritants and cause inflammatory changes in the tissues, the effects of inflammation then becoming added to those of simple degeneration. It is not surprising, therefore, that just as the causes of simple degeneration may be associated with those of inflammation, so the pathological alterations in tissues due to mere degeneration are frequently associated with those due to inflammation.

The difficulty of distinguishing between a simple degenerative process and the results of chronic inflammation is especially great in the case of atheroma, which is certainly often accompanied and preceded by undoubted inflammatory changes. Dr. W. Moxon[1] thought that atheroma was in continuity with arteritis, graduating from a condition in which no inflammatory results can be found into one in which inflammation is distinctly present. According to Dr. Thomas Hayden,[2] however, "Atheromatous transformation of the coats of arteries is a result of malnutrition, and essentially degenerative," though "not infrequently the products of a low form of inflammation of the internal and middle coats are combined with those of tissue-degeneration." Dr. Douglass Powell[3] considers atheroma of the aorta to be a degeneration, the result most commonly of preceding inflammatory change, but sometimes occurring primarily as fatty transformation from senile decay.

The difficulty is increased, since it is possible that in cases of tissue-degeneration the products of degeneration may themselves, if unremoved, even without the presence of microbes, act to some extent as irritants to the surrounding tissues. In this way a condition of secondary chronic inflammation would be induced, although the primary condition was one of simple degeneration. On the whole, although atheroma may be frequently preceded or even accompanied by inflammation[4] the weight of evidence seems to be that it may likewise occur as a primarily degenerative process.

It is probably best to look on such primary atheroma as a process occurring in the larger arteries corresponding (etiologically, though not anatomically) with arterio-sclerosis[5] in the arterioles. According to this view, the same condition of malnutrition (whatever the primary cause of

[1] Guy's Hospital Reports, 1871, vol. xvi.

[2] Diseases of the Heart and of the Aorta, 1875, p. 1073.

[3] Reynolds' System of Medicine, 1879, vol. v. p. 19.

[4] Virchow and Niemeyer, however, considered inflammation a necessary antecedent to the changes found in atheroma. See R. Virchow's Die Cellular Pathologie, 1858, p. 319; and Felix von Niemeyer's Lehrbuch, 9th ed., Berlin, 1874, pp. 443 *et seq.*

[5] In the present paper the word "arterio-sclerosis" is used as synonymous with the arterio-

this malnutrition may be) which induces arterio-sclerosis in the walls of the smaller vessels may act on the coats of the aorta and larger vessels so as to induce atheromatous changes.

With regard, however, to the anatomical difference between the process of arterio-sclerosis in the small vessels and that of atheroma in the large ones, it must be remembered that, since the walls of the larger arteries are thicker than those of the smaller ones, the former are especially dependent for their nutrition upon the condition of their vasa vasorum.[1] The peculiar feature of atheroma is the cell-accumulation which takes place in the deeper part of the tunica intima (*i. e.*, that part of the intima nearer to the tunica media) of the affected artery. This is the portion of the arterial wall which is naturally worst nourished, for its blood-supply must be obtained from the vasa vasorum, whereas that of the immediate inner surface of the artery is derived from the blood which constantly bathes it. Consequently, when the vasa vasorum of a large artery are in any way stenosed the deeper (external) layer of the tunica intima is the first part to suffer in its nutrition. It has, indeed, been pointed out[2] that the position of the cell-accumulation in atheroma may be partly due to stenosis of the vasa vasorum by Bright's disease or syphilis.

Stenosis of the vasa vasorum, from whatever cause, is, then, likely to induce atheromatous change in the part of the arterial wall in which the vasa vasorum are affected. H. Huchard,[3] of Paris, has gone so far as to make of atheroma a "localization of arterio-sclerosis;" that is to say, he makes it due to a process of arterio-sclerosis affecting not to the same extent the arterioles over the whole body, but localized to the vasa vasorum of certain arteries, the stenosis of the vasa vasorum causing atheromatous changes in the walls of the affected arteries.

It is evident that alterations in the quality of the blood induced by gout, syphilis, and alcohol, and all the asserted causes of arterio-sclerosis may likewise be alleged as causes of atheroma. On these questions[4] I shall not enter in the present paper, but shall content myself with having

capillary fibrosis described by Gull and Sutton in 1872 (Med.-Chir. Trans., vol. lv.). This restricted use of the term is both usual and convenient.

[1] This difference in the conditions of nutrition between the main arteries and the small arteries has been aptly compared to the laws which the Romans made for the maintenance of their celebrated roads. The large arteries have their vasa vasorum, just as the Roman *primæ viæ* had their independent maintenance; whereas, just as the *viæ vicinales* had to be kept in repair by the neighboring populations, so the nutrition of the walls of the smallest arteries largely depends on the state of the organ which they themselves supply. See S. Wilks and W. Moxon, op. cit. 3d ed., p. 159.

[2] See Dr. F. W. Mott's paper on "Cardio-vascular Nutrition," Practitioner, 1888, vol. xli. pp. 161–173.

[3] Maladies du Cœur et des Vaisseaux, 2d ed., Paris, 1893, pp. 96 *et seq.*

[4] To some extent I have entered on these questions in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, September, 1894.

summed up, I hope intelligibly, the evidence in favor of the views (certainly not new ones):

1. That atheroma of the aorta, though often preceded or accompanied by inflammation, is itself a merely degenerative process: that syphilitic or other inflammation may locally predispose to atheroma.

2. That aneurism of the aorta is induced more often by the yielding of a portion of its wall affected by syphilitic or other inflammation than of a portion affected by simple atheroma.

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