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ON CHRONIC ENDOCARDITIS REGARDED AS A FIBROSIS OF THE VALVES OF NON-INFECTIVE ORIGIN.

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In these days when bacteriology is dominant, if not indeed rampant, it is difficult to rid ourselves of the idea that fundamentally underlying one or other morbid condition of the tissues there is some primary microbic factor. Or perhaps, more accurately, our first inclination is to search after and seize upon evidences of present or past microbic activity, and, if we can find indications which with greater or less plausibility can be regarded as suggesting the outcome of microbic growth within the tissues, then we are satisfied to believe that we have grasped the etiology of the condition. If, on the other hand, we find ourselves compelled to fall back upon physical or metabolic factors as causes of tissue change, we do this with a certain distrust or discontent. For example, we have nowadays to accept such conditions as myxedema, acromegaly, Addison's disease, obesity, gout and acidosis as the resultants of disorders of the internal secretions or more broadly of cellular metabolism. But doing this, confessedly, it is difficult to form a mental picture of the succession of changes in the cells and tissues that lead to the anatomical manifestations of these different states. On the other hand, we have been drilled so thoroughly into an appreciation of the various stages which may result from an infective inflammation, and those stages, it may be added, are so many and so varied, that it is easy for us to imagine almost any morbid process as a resultant of some form of infection. Thus in the matter of valvular disorders—of endocarditis—I think I make a correct statement in saying that our tendency is to regard the valve changes as outcomes, whether recent or late, of some infective process, and, whether voluntarily or involuntarily, we find ourselves sceptical as to explanations of any other order.

Nevertheless, are we justified in considering chronic endocarditis as essentially of microbic origin? For myself, I must acknowledge that very early in my career a series of experiments by my old chief, the late Professor Roy, of Cambridge, published in our joint names, gave me food for thought. Among pathologists there has been no more brilliant mechanical genius than was Roy. His ability to devise instruments fitted to give records of one or other order was extraordinary. He devised and I noted. And incidentally in the course of our studies upon the effects of increased arterial pressure upon the volume and work of the dog's heart we found, that increased aortic pressure, produced by narrow-

ing the aorta was repeatedly followed by very definite changes in the aortic valves. These, we found, were not mere inert mechanical membranes, but reacted to their environment. The aortic cusps, it may be recalled, are normally devoid of vessels save near their bases. Their nourishment therefore is by means of blood plasma absorbed through or between the lining endothelial cells, or both, from the cardio-aortic blood. After extreme high pressure in the first part of the aorta we found that the cusps presented a series or chaplet of fine glistening bead-like elevations just below the line of their apposition. Evidently during diastole the high pressure acting upon their aortic aspect coupled with the low pressure on their ventricular aspect, and it may also be with expansion of the endothelial cells and increase in the intercellular spaces due to stretching of the cusps under the increased pressure; all these had led an increased percolation of "lymph" into the valve substance with a collection of the same along the line of greatest strain or weakness of the cusps. And Roy and I then called attention to the possibility that the thickening of the aortic valves in cases characterized by high blood-pressure might be a later outcome of this same process.

Now chronic endocarditis in elderly people is characteristically associated with the presence of nodose arteriosclerosis, and the two processes are, I would point out, of identical type. Both conditions involve intimal structures, (for the heart valves are but infoldings of the cardiac intima), and, histologically, they are of the same order, with overgrowth of the subendothelial connective tissue, the most recent layers being nearest the surface, the deeper layers exhibiting a series of degenerative changes which culminate in the development of calcareous plaques. I freely admit that in one order of arteriosclerotic changes a proliferation and swelling of the cells of the musculo-elastic layer immediately to the inner side of the internal elastic lamina is a prominent feature. In the cases that I here refer to these changes while they may be present are not dominant. What is especially significant is this laying down in an orderly manner of layer after layer of connective tissue parallel to the surface, whether of aorta or of aortic cusp. There are here none of the cardinal signs of inflammation or its after results; no accumulation of leucocytes or plasma cells, no entry and no formation of new vessels, such as we see, for instance, after the chronic inflammation of other non-vascular regions, as the cornea. As my old colleague, Professor Klotz, has demonstrated (although he does not see eye to eye with me in the explanation of these changes) a similar uniform connective-tissue hypertrophy with accompanying overgrowth of the musculo-elastic layer can be produced in the rabbit by purely mechanical means, namely, by periodical raising of the blood-pressure for a few minutes every day extending over several months. In the absence, therefore, of adequate evidence of infective origin in these cases, in the absence of signs of ordinary inflammation and from the histological features of the new tissue, it is neces-

sary to look for some other, non-microbic, causative agent in the production of these two conditions, and I cannot but conclude that in both we deal with stress or perhaps, more accurately, strain upon the affected part, coupled with adequate, or indeed increased nutrition; I say *strain* rather than *stress,* regarding the latter as the normal condition to which the vessels are normally and periodically subjected.* *Strain* I regard as a more abnormal pathological condition leading to one order of conditions of the nature of increased reaction, and *overstrain* as a still more aggravated condition having, however, results of a different nature—namely, to absence of reaction. What seems to me characteristic of all the conditions, here referred to, of valves and arteries is that either we have clinical indications that the tissues are already weakened, so that what under normal conditions would be a stress, now becomes a strain (where it does not become an overstrain), or, on the other hand, that the tissues in the intima are in their normal state, but are subjected to increased blood-pressure, to an actual rather than a relative strain.

There is, it may be laid down, a normal environment for the cells of every tissue under which those cells attain unto a certain limit of growth and do not exceed this limit so long as environment remains unchanged, but, at the same time, it has to be recognized that even such inert tissues as bone show us clearly an increased growth under conditions of moderate increase of the work they are called upon to perform. For example, increased muscular exercise demonstrably leads to increased weight and size of the skeletal bones, and development of their bony ridges where these muscles are inserted. And so with the intima of the aortic cusp: subject this to a moderate strain and it undergoes thickening. The prettiest example of this that I have come across has been in three cases of functional incompetence of the aortic valve, through widening of the aortic ring. All three of these cases were relatively early; under the hydrostatic test each exhibited a roughly-triangular orifice where the three corpora Arantii did not meet, and it was very striking to notice that just at this region the edge of each cusp had undergone thickening and rounding, with distinct fibrosis. The cause here was purely mechanical; just those portions of the cusp that did not come into apposition were subjected to the greatest strain, and, as a consequence, the cells had proliferated and produced increased fibrous tissue.

But it may be objected that in the case of the mitral valve, for example, in the typical endocarditis of the young individual, due to rheumatism, we have evidence of the same fibroid thickening of the valve which is of undoubted microbic origin, since everyone nowadays either believes, or is prepared to believe, in the infective nature of acute rheumatism.

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*In those conceptions of what is usually understood by *stress* and *strain* respectively, I recall, while revising my proof, that I am at variance with that master of English, Sir T. Clifford Allbutt. My only consolation is that he, at an earlier period, made a similar misuse of terms and, in fact, has helped to crystallize it in medical literature.

It is quite true that these cases so far as we can follow them, (where death occurs in the acute condition), begin with indications of a true inflammation, with destruction of the endothelium, formation of vegetations, as also vascularization of the valve. The early stages here are identical to all intents and purposes with those following upon an acute microbic ulceration of the cornea.

Now I wholly admit this infective origin of these mitral cases and, indeed, also of a certain proportion of cases of aortic endocarditis. I would only urge, however, that *the progressive thickening and contraction of the mitral valve is an interval occurrence, and is not directly due to the microbic irritation.* I am inclined to believe, that whether by the deformity of the valve produced in the region of actual ulceration, or merely through the focal growth of the micro-organisms, the valve becomes weakened and no longer functions so perfectly as before; and, as a consequence, is subjected to a relative strain. In a certain proportion also of these cases there are indications of increased blood-pressure and actual, rather than relative, strain upon the cusps. Thus it is this secondary strain that is responsible for the diffuse and generalized mitral thickening seen in these cases, rather than the primary irritant—the cause of acute rheumatism.

We have here another example to add to the abundant instances of the existence of "Vicious Circles" recently accumulated by Dr. J. B. Hurry.* Whether from extrinsic or intrinsic causes, the cusps become subjected to strain, and reacting, there is tissue growth with thickening and fibrosis. This very thickening makes them function less perfectly, and as a result they are subjected to more strain. More strain leads to further fibrosis—and so progressively there are developed those conditions of extreme diffuse thickening, contraction, deformity and degeneration of the heart-valves, with which we are so familiar. Here, indeed, Ossa is piled on Pelion, for the incompetency of the fibrosed valves leads to hypertrophy of the ventricular muscle in order that the circulation may be preserved. This hypertrophy results in more powerful contraction, with resultant heightened intracardiac pressure. The forces thus acting upon the damaged valves and inducing strain are not constant, but exhibit progressive augmentation. There is no "let up" to the process until the strain on the heart walls gives place to overstrain and cardiac failure is the result.

*Vicious Circles in Disease. J. and A. Churchill, London, 1911.