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FROM THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1909

Extracted from the American Journal of the Medical Sciences, October, 1909

THE NATURE OF THE ARTERIOSCLEROTIC PROCESS.[1]

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Surely all of us who are active pathologists have been impressed by the fact that the more autopsies we perform the larger does arteriosclerosis loom as the fundamental morbid process in the majority of deaths after the age of forty years. If trauma, malignant disease, and infections, such as pneumonia and the rarer tuberculosis, be eliminated, we are left with that vast mass of cases of cardiac incompetence, aneurysm, chronic bronchitis and emphysema, cerebral apoplexy, and chronic Bright's disease; and the more we study these cases the more it is borne in upon us that in these the terminal event is but an outcome of the one common underlying process of arterial disease. At the same time, the more carefully we study the arteries in these cases the more we recognize that we deal with an almost protean series of disturbances: now it is the upper portion of the aorta, the ascending limb, or the arch that shows the most pronounced and obvious lesions; now the abdominal aorta; in other cases the aorta is relatively free from sclerotic change, but its larger branches show irregularities, this with or without pronounced involvement of the smaller arteries, which in their turn are not equally affected; at times the renal, at times the cerebral, at times the arteries of the extremities are the seats of most advanced change. In the second place we find that the lesions are not all of one order, so much so that it may well be debated, as it is debated, whether one common name should be applied to the series. I am free to acknowledge that this name arteriosclerosis is not wholly satisfactory. Marchand[2] has recently recommended that of atherosclerosis, but this, like the older atheroma, is inadequate, in that it implies that the development of ἀθήρη, or a porridgy degeneration, is inevitable. Something might be said for this suggestion had we to deal only with the aorta and the larger vessels, although even in these there are developed sclerotic states—I refer to those of syphilitic origin—which do not by any means necessarily pass on to an ather-

[1] The annual address delivered at a meeting of the Pathological Society of Philadelphia, April 24, 1909.

[2] Verhandl. Deut. path. Gesellsch., 1906.

omatous stage. (These Marchand would place in a separate class.) It is, however, inadmissible for in the condition as found in the smaller sized arteries the sclerotic change is predominant, and the atheromatous or degenerative is characteristically absent. Again, it may rightly be objected that the atheroma is a secondary and not a primary condition; it is always the secondary outcome of fibrosis. "Arteriocapillary fibrosis," save for its flatulency, has more in its favor than atherosclerosis, but again is incorrect, for the capillary changes are not obvious, and, as I shall point out, when present must be regarded as secondary. We come back, therefore, to this, that the term "arteriosclerosis" is the most satisfactory name that has so far been afforded for this series of arterial changes, since sclerosis, which is equivalent to fibrosis, is the condition of commonest occurrence in the series of included conditions.

What, then, are the different forms that we have to take into account? So much has been written upon the subject of late years that I need only refer to the salient points, for doubtless the majority here present have as full a knowledge of this matter as have I who speak. And first as to the main orders of disturbance seen in the aorta and its larger branches—in the vessels, as we may term them, of the elastic type:

1. Most common is the ordinary nodose arteriosclerosis. This shows itself in the slightest cases as a thickening and sclerosis, more particularly at or around the origins of the side arteries, as yellowish, white thickenings notably affecting the origins of the series of intercostal arteries. Later these have grown in size, and some may have coalesced, forming in the opened aorta projecting flattened nodes, and now these may be scattered somewhat irregularly through the aorta, tending to be more abundant and more advanced in the abdominal region. It is this form that, more particularly, passes into the condition of atheroma, and of calcification of the intimal plaques.

2. Almost as frequent is a contrasted order of disturbances, in which clinically we have the most obvious proof of the existence of arteriosclerosis, in the presence of hardened and at times pipe-stem radials; but when we come to examine the aorta we may in the most typical cases find a complete absence of nodose thickening of the intima. In its place there is a diffuse dilatation of the aorta, affecting more particularly the thoracic portion. Instead of being thickened, the aortic wall appears to be thinned and the increased volume of the tube tends to show itself not only in breadth, but also in length, the vessel becoming somewhat tortuous; the arch takes a wider sweep, the abdominal section is curved. This I am inclined to regard as the uncomplicated senile type of the disorder. It is further characterized by the presence, in the common iliacs and the carotids, of slight depressions, tending to have their long axis situated transversely, in fact, by the very reverse of the sclerotic nodosities, a giving way taking the place of thickening of the wall.

And the question may well be asked: Should this be included? It is not a sclerosis, but merely a degeneration. This I freely admit, but would urge that the condition of the whole arterial tree has to be taken into consideration in making our diagnosis, and if we do this we find that in these cases the smaller arteries are markedly sclerotic, with localized areas of intimal fibrosis, with hypertrophy and fibrosis of the middle coat and often with well pronounced peri-arterial fibrosis. The sclerosis of the radials and other middle-sized arteries, often so prominent in these cases, is paradoxically not a sclerosis proper; it is not necessarily due to fibrosis of the intima or other coats. Sometimes there is a diffuse thickening of the intima of moderate grade, but that is not the cause of the hardening. As Dr. Klotz[3] has most serviceably pointed out, the essential change in vessels of this type is a calcification of the media, which I may add, following Russell,[4] is apt to be preceded by a marked hypertrophy of the middle-coat. For convenience, I would speak of this order of arteriosclerosis as Moenckeberg's sclerosis, Moenckeberg[5] having been the first to make a full study of what is the most striking feature, namely, the areas of giving way and slight sacculation seen in the main branches of the aorta due to degeneration of the media. But, doing this, I would impress upon you that uncomplicated examples of this order of disturbance are relatively uncommon. Quite the commonest condition in elderly people is a combination of these two types, having occasional nodes or plaques of sclerosis or atheroma in the aorta, more particularly in its abdominal portion, though by no means necessarily confined to this region, with this faint saccular giving way in the common iliacs and carotids, suggesting strongly that the same order of events leads now to the one, now to the other development; that, in fact, they are diverse manifestations of a common state.

3. The third great type is the syphilitic. The aortic manifestations of this form are in the broad features so much of the same order as those of ordinary nodose arteriosclerosis that it is only during the last generation and, indeed, during the last seven years that the distinguishing features have attained general recognition. Thanks to the labors of Döhle[6] of Kiel and other pupils of Heller, and of Chiari,[7] we now have no difficulty in making the distinction, if not always by the naked eye, then surely under the microscope. The seat of election in the first place is in the ascending aorta and arch, and here the nodes are liable to lie in groups. These in their earlier

[3] Calcification of the Aorta in Rabbits after Injection of Adrenalin, Jour. Exp. Med., 1906, viii, 325; Calcification of the Media in Arteries of the Elastic Tissue Type, Jour. Exp. Med., 1906, viii, 330; The Relationship of Experimental Arterial Disease in Animals to Arteriosclerosis in Man, Jour. Exp. Med., 1906, viii, 304; Experimental Arteriosclerosis, Brit. Med. Jour., December, 1906; Experimental Work-Arteriosclerosis, Montreal Med. Jour., March, 1908, and Centralbl. f. allg. Pathol., 1908, xix, 535.

[4] Arterial Hypertonus, Sclerosis, and Blood Pressure, Edinburgh, 1907.

[5] Virchow's Archiv, 1903, clxxi, 141.

[6] Inaug. Diss., Kiel, 1885.

[7] Präger med. Woch., 1806, xxxi, No. 12; Verhandl. Deut. path. Gesellsch., 1904.

stage are large and, if I may so express it, succulent, with a semi-translucent or hyaline appearance; characteristically they have little tendency to atheromatous and calcareous change, but, on the contrary, exhibit a later scarring or central depression with some puckering. The reason for this is found upon microscopic examination. The primary disturbance here is subacute mesaortitis, with small-celled infiltration around branches of the vasa vasorum and absorption of the elements proper of the media. Coincidently there is overgrowth of the intimal tissues, and when, as a result, the deeper portions of the overgrowth exhibit necrotic change and degeneration, then the underlying inflammatory granulation tissue advances new capillaries into the necrotic area. The result is an absorption of the degenerated material, replacement by cicatricial tissue, shrinkage, and scarring. So far as my observations go, there is a striking lack of vascularization and replacement in the ordinary nodose arteriosclerosis. It does not occur during the necrotic atheromatous stage; I have encountered it when there is already pronounced intimal calcification and the necrotic change is extending into the inner layers of the media.

Here in connection with syphilis, and yet more markedly, there is to be observed that same paradox seen in connection with the Moenckeberg type; while the syphilitic virus leads to the more pronounced intimal overgrowth, at the same time it leads characteristically to the opposite condition of lack of intimal overgrowth, thinning of all the coats, and aneurysm production. It will be familiar to you that modern workers, with the exception of von Hansemann, ascribe from 60 to 85 per cent. of aneurysms to syphilis. How are we to reconcile these opposing results?

These are the main types. Acute changes do not come under the heading of arteriosclerosis, nor do simple degenerative changes without proliferation. The fatty streaks of the intima seen often after acute infection, are not here included, although these and certain other intimal changes may throw light on certain phases of the process. To them I shall refer later.

Turning now to the other arteries, we may, as regards arteriosclerotic change, divide them into the muscular arteries and the arterioles. As regards the former, the same changes, the ordinary thickening of the intima, the giving way of the Moenckeberg type, and the syphilitic changes may be seen as in the aorta, with, however, one or two modifications which would seem to be a function of relative size. Thus we do not encounter anything like the same extent of atheromatous and degenerative change. Compared with the size of the artery, the areas of intimal thickening may be extreme; nevertheless, in absolute size they do not compare with the plaques seen in the aorta. And it may be reasonably suggested that degeneration when it occurs is due to cutting off of the nutritive lymph supply by the development superficially of layer after layer of dense new connective tissue, and that in general the size of those plaques

in the arteries (save in the larger cerebral vessels and the coronaries) is not sufficient to inhibit the percolation of lymph and arrest of nutrition of the more central areas. This does not, however, mean that there may not be extreme calcification, more especially in the middle sized arteries; only that calcification affects, more particularly not the intima, but the media.

This brings us to the second point of difference, namely, that in these arteries the media exhibits much more obvious alteration. Where there are relatively large plaques of intimal thickening there beneath them, even with the naked eye, the media is seen to be notably thinned. But, on the other hand, it may exhibit diffuse thickening from hypertrophy of its muscle tissue, with little obvious intimal change. On the other hand, there may be degeneration of the muscle and replacement by connective tissue; in some regions this may be associated with giving way and dilatation of the arterial lumen with associated intimal thinning; in others there is seen a more or less diffuse thickening and overgrowth of the intima, suggesting compensatory change. Passing to the arterioles, we find, it is true, the same series of changes, but here the relationships are significantly altered. There has been active debate as to their significance and relative frequency. In one order of cases the muscular hypertrophy of the middle coat has been the dominating change. This is especially well seen in certain kidneys, so much so that sundry observers have laid stress upon this as the cardinal change. In another series fibrosis is the most evident alteration—fibrosis of the *intima*, fibrosis replacing largely the *muscular* tissue of the *media*, fibrosis and pronounced overdevelopment of the *adventitia*. So that other observers have waved the muscular change to one side and regarded the fibrotic change as the all-important condition.

Yet another state has also been dwelt upon, particularly in association with the infectious type, as seen in tuberculosis, syphilis, and chronic glanders, namely, the active cellular proliferation of the intimal endothelium leading to an obliterative endarteritis. It is still unsettled whether this proliferation is directly connected—as Baumgarten believes it to be—with the production of the intimal fibrosis—whether, that is, the endothelium directly gives origin to the connective tissue overgrowth of these arterioles, or whether the processes are distinct. Provisionally I incline to Baumgarten's opinion.

How now are we to harmonize and bring into a common scheme these various lesions? What, in short, is the fundamental underlying change—if there be any—common to be different conditions? The answer to this question can be approached in two ways—either by an exhaustive analysis of the factors seen to be in action in the various types of arteriosclerosis; or by taking one form in which the causative factors have been most fully determined and applying the results gained from the study of this form to the other cases, to observe whether any common general principles are capable

of application to all. Both, I believe, lead surely to the same end result, and let me confess that I have been puzzled as to which method to employ. It seems to me, however, that the former would consume too much time; it would demand a preliminary discussion of the minute anatomy and of the physiology of the arterial tree, of the regulation of the blood pressure, and the influence of contraction of the arterioles upon the aorta and the aortic conditions. It is true that, employing the other method, reference must be made to most if not all of these matters, but I imagine that it will be less wearisome if I take up a concrete case and then proceed to apply the results gained from that to a consideration of the other cases.

Now undoubtedly we possess the clearest and most indubitable data regarding the syphilitic form. There is no question nowadays that the primary lesion in syphilitic aortitis is a granulomatous condition or small-cell infiltration immediately surrounding the terminal vasa vasorum in the media; the primary condition is, as Chiari describes it, a syphilitic mesaortitis, and this involves in the first place the outer half or two-thirds of the aortic media. Certain of the vasa only are affected. Here, just as in acute mycotic aneurysm, as shown by Dr. J. McCrae's[8] study of a case published from our laboratory, the infective agent gains entrance into and lodgment in particular vasa. And here it may be noted that several observers have discovered the spirochete in the aortic lesions. With this infiltration there is, as Dr. Klotz points out in an article shortly to be published, a remarkable dissolution of the elements of the media. They seem literally to melt away. This explains the thinning and depressions which may occur, so that, as Aschoff points out, placed against the light these areas are semitranslucent. To what an extent this process may extend is well shown in the accompanying specimen (Fig. 1) which Dr. Klotz has been so good as to permit me to demonstrate to you. This has been stained to demonstrate the elastic tissue. You will observe that in the region where there is the most extensive small-cell infiltration the elastica has completely disappeared.

I will not say that this dissolution is specific. I do not believe that it is. I am inclined to think that it may be the outcome of local inflammation, due to more than one cause, with swelling, degeneration, and necrosis of the cells of the involved area. But undoubtedly the most frequent cause is syphilis. Here, therefore, is the onset of the syphilitic or mycotic type. It will be readily understood how such extreme destruction of the media, the main sustaining coat of the aorta, leads on to aneurysm. In fact, we may say that it is universally acknowledged nowadays that degeneration of the middle coat is the dominant cause of aortic aneurysm. But such extreme destruction of the middle coat as here shown is the exception and

[8] Jour. Path. and Bact., 1905, x, 373.

not the rule; so again in syphilitic aortitis aneurysm production is the exception; what is far more common and widespread is the production of intimal thickening. How is this to be explained? I doubt if there be any more obvious example of compensation in the whole of pathology; degeneration of the one coat, the media, is accompanied or followed by overgrowth of the other, the intima; nay, more, as Dr. Klotz's example illustrates very beautifully, and as I confess I had not previously realized, in connection with the aorta there may[9] be a coincident and very pronounced hypertrophy of the adventitia (Fig. 1).

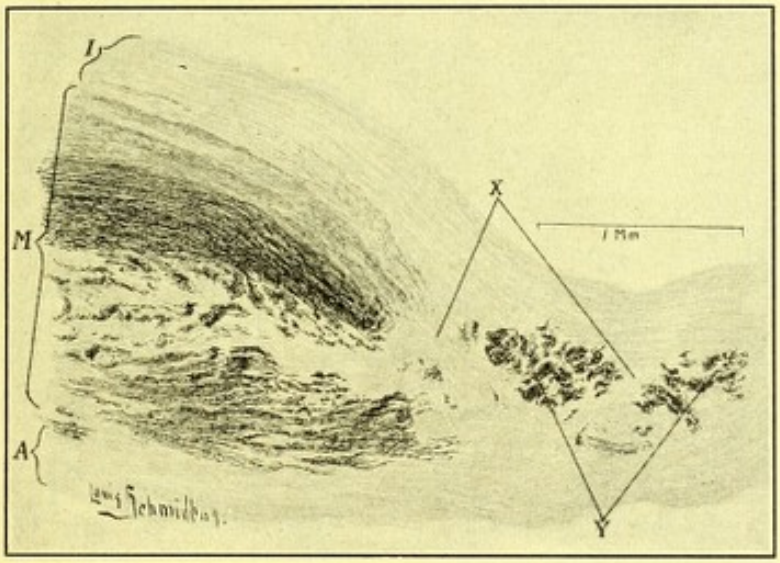

FIG. 1.—Section from a case of syphilitic mesaortitis stained by the elastic-tissue stain to demonstrate the extraordinarily degenerated and diseased appearance of the elastic tissue through syphilitic mesaortitis. It will be seen that at *X* the elastic fibres have completely disappeared; at *Y* they are reduced to irregular masses. There is some definite hypertrophy, both of the intima, *I*, and of the adventitia, *A*, but this has been insufficient to prevent a certain giving way of the wall. (From a specimen prepared by Dr. Klotz).

Certain points stand out very prominently regarding this intimal thickening. In the first place, it exhibits none of the ordinary earmarks of an inflammation. There is no formation of granulation tissue properly so-called; no new vessels; no small-cell infiltration, and, notwithstanding this, the new connective tissue formation attains to large proportions. The intima, it is true, is in itself non-vascular; it receives its nourishment by diffusion from the plasma within the aorta, as, indeed, would seem to be the case with the innermost layers of the media. But if we take any other non-vascular region, the cornea for example, and induce in that an inflammation by any of the accepted methods—by the injection of bacteria or the employment of caustic agents—within a short time new vessels make their way to the injured area from the periphery. Save as a late event, as already

[9] Since this address was delivered, J. H. Wright and O. Richardson have also called attention to this thickening of the adventitia with extensive necrosis of the media. Boston Med. and Surg. Jour., 1909, clx, 539

noted, we do not encounter this in the intimal thickening in syphilis even when there is an active granulation tissue formation in the media. This is a very remarkable fact; the intimal overgrowth is essentially and purely hypertrophic. The internal elastic lamina constitutes as it were a barrier. We do not deal with an endarteritis, and Virchow was wrong in labelling it with this name; as again have been Thoma and other later writers (Fig. 2).

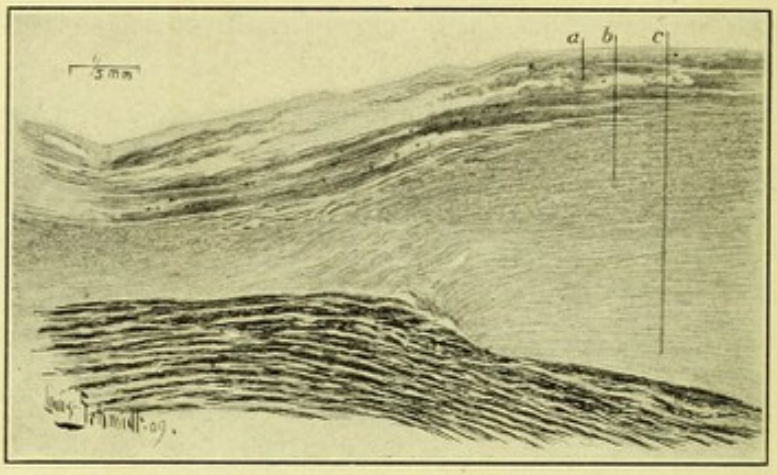

FIG. 2.—Section of an aorta from syphilitic mesaortitis with some narrowing of the media and great overgrowth of the intima. It will be observed that the layers of new tissue of the intima show a regular arrangement with absence of vessels and of small-cell infiltration. The outer layers, at *a*, in this case exhibited pronounced fatty change. The intermediate layer, *b*, took on a slight stain with the elastic tissue reagent, and under the high power this was seen to be due to the fine fibrils of what, from their arrangement, were young connective tissues, taking on the elastic tissue stain. Deeper down, at *c*, there was a complete absence of this reaction. The media, on the contrary, while narrowed, stained deeply with this stain. (From a specimen prepared by Dr. Klotz.)

But if an hypertrophy, how is it to be explained? We owe to Thoma,[10] in connection with ordinary arteriosclerosis, the first clear recognition that this is a compensatory hypertrophy—that in ordinary arteriosclerosis there is first a giving way of the media, and that the intima proliferates as a consequence. Thoma sought to explain this overgrowth as of nutritive origin, as due to alteration in the rate of blood flow at the region of bulging of the arterial wall. For myself, I must confess that I have never been able to grasp his explanation; what is more, I have never met anyone who has pretended to do so. Thirteen years ago, in an address before the New York Pathological Society, I afforded an explanation.[11] That also was not comprehended at the time. For example, Professor Mott[12] wholly mistook its drift. But I am more and more convinced that that explanation was rational, and, what is more, recent studies of a different nature have afforded a brilliant demonstration of its

[10] Virchow's Archiv, civ, and subsequent volumes.

[11] On the Relationship between Inflammation and Sundry Forms of Fibrosis, Middleton Goldsmith Lecture, Med. Rec., 1896, pp. 469 and 505; see also Discussion upon Arteriosclerosis, Brit. Med. Jour., December, 1906, ii.

[12] Allbutt's System of Medicine.

correctness. I laid down then that this regular development of layer after layer of new connective tissue was non-inflammatory, but was of the nature of *strain hypertrophy*—that just as increased pull or strain of the muscles upon their bony insertions leads in athletes to an increased development of the bony ridges, to a localized hypertrophy of bone, so within certain limits, increased tension or pull upon fibrous connective tissue favors its overgrowth, provided that adequate nourishment be afforded at the same time. It is but another example of the law, wholly misunderstood by Weigert, that increased functional activity within certain limits favors growth. I am glad to see that Professor Aschoff[13] explains the progressive increase in the elastic tissue of the aorta as being due to a like work hypertrophy.

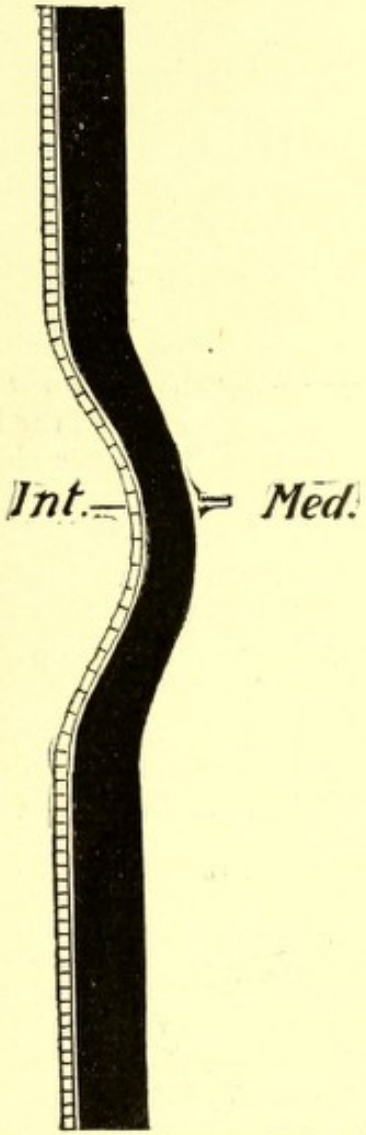

FIG. 3.—Schematic representation of the increased strain brought to bear upon the cells of the intima, *Int.*, when the media, *Med.*, undergoes a localized expansion through relative weakness.

I held, and so I still hold, that a moderate local giving way of the media under the pressure to which it is subjected by the blood within an artery causes an increased strain upon the overlying intima, which must undergo a certain amount of stretching, as it now becomes pressed outward to expand over the concavity afforded by the bulging of the media (Fig. 3). Herein is the stimulus to growth, and the growth continues, layer after layer, until not, as Thoma held, the concavity is accurately filled and the lumen restored to the status quo ante, but until the volume of the new tissue and the resistance that this affords to the mean distending force balances the loss sustained by the weakened media. In other words, when the resistance offered by the whole arterial wall at such a locality is equivalent to that of the rest of the aortic or arterial wall, then the strain is reduced and the process of hypertrophy becomes arrested. In these cases the youngest tissue is situated immediately beneath the endo-

[13] Beihefte zur med. Klinik, 1908, iv.

thelium, the oldest most remote and nearest to the deeper musculo-elastic layer. Unlike what occurs in the ordinary form of arterio-sclerosis, in syphilis this latter layer, so far as I have seen, shows comparatively little hypertrophy.

The convincing demonstration of the accuracy of this view has been afforded by one of Carrel's remarkable transplantation experiments. Carrel,[14] it will be remembered, removed a length of the cats carotid and replaced it by a length of vein from the same animal and of approximately the same caliber; under the increased blood pressure the vein exhibited dilatation, but left in situ for many weeks it presented at the end of the period a remarkable connective tissue hypertrophy of all its coats, so that its eventual thickness was distinctly greater than that of the artery at either end of the transplanted piece. The adequate and, in fact, as I freely admit, improved nutrition to which the vein is subjected, might by some be held to explain the hypertrophy of the intima, but at the same time the more that becomes sclerosed, the less becomes the nutrition of the deeper layers; but all the coats showed the connective tissue overgrowth. Add to this that cases in which increased nutrition, pure and simple, leads to hypertrophy are almost if not entirely wanting. I can bring to mind no single incontrovertible example. There is, I hold, no other satisfactory conclusion than that in this case it is the increased strain thrown upon the venous wall (coupled with adequate nutrition) that leads to the profound connective tissue hypertrophy.

When, on the other hand, the destruction of the media is more widespread and, we must presume, more acute, then, as in aneurysm formation, we encounter not intimal overgrowth, but the reverse. In other words, the expansion of the intima which has wholly lost its main support, the media, is now so great that we pass from the state of *strain* to that of *overstrain*, and now with the overstrain in place of hypertrophy we tend to get atrophy.

We thus arrive at the following conclusions regarding the effects of syphilis upon the aorta: (1) The primary disturbance is a granulomatous, inflammatory degeneration of the media. (2) This leads to a local giving way of the aorta. (3) If this be moderate it results in a strain hypertrophy of the intima and of the adventitia, with the development of a nodose intimal sclerosis. (4) If it be extreme, there results on the contrary an overstrain atrophy of the intima and aneurysm formation. (5) The intimal nodosities are here not of inflammatory type and are non-vascular, although, with the progresive laying down of layer upon layer of connective tissue on the more internal aspect of the intima, the earlier and deeper placed layers of new tissue gain less and less nourishment, and so are liable to exhibit fatty degeneration and necrosis. (6) These products of necrosis exert a chemiotactic influence upon the nearby

[14] Jour. Exp. Med., 1908, x, 130.

vessels of the medial granulation tissue, with, as a result, (*a*) a secondary and late entrance of new vessels into the early and deeply placed atheromatous area; (*b*) absorption of the necrotic products; (*c*) replacement by granulation tissue; (*d*) contraction of the granulation tissue; and (*e*) depression and scarring of the sclerotic nodules so characteristic of syphilitic sclerosis.

Can we apply these deductions to ordinary non-syphilitic nodose arteriosclerosis and to the Moenckeberg's type already noted? I think we can, or otherwise, and this is the crucial point, we can demonstrate that the ordinary arteriosclerosis of advancing life exhibits a primary giving way of the media, and we can do this both histologically and by experiment. First, as regards the histology, a most interesting study has been published recently by Professor Aschoff regarding the progressive changes that are undergone by the aortic media in the course of life. I will not go into all the details, but merely epitomize his main conclusions. In infancy the elastic laminæ of the media stand out sharply defined, well separated from each other by the muscle layers, which are well developed. There is, that is to say, sharp alternation of muscle and elastic layers. From childhood there is to be observed a slowly progressive increase in the elastic elements of the media. Not only do the individual lamellæ seen in cross-sections become thicker, but also they afford an increasing number of fine secondary filaments feathering off from these and crossing the muscle layer, so that now they are no longer sharply defined, but more ragged upon cross-section. This progressive increase attains its maximum at or about the age of thirty-five, and from now on for the next fifteen years the condition is relatively stationary. After fifty, according to Aschoff, there is to be observed a slowly progressive atrophy of the elastica. The media becomes obviously thinner and presumably weaker.

Independently, Dr. Klotz has been studying the same subject for some years and for the last twelve months Mr. Foster, under his direction, has examined a long series of aortas, from those of infancy up to those of advanced age. His work is on the eve of publication. Again, not to enter into details, I may say that these observers are wholly in agreement with Professor Aschoff's findings up to the age of thirty-five and in practical agreement up to that of fifty. But, as Klotz has already pointed out on more than one occasion, the subsequent degenerative process is one showing itself histologically not so much in connection with the elastic lamellæ as with the intervening muscle. This from the age of thirty-five onward begins to exhibit fatty degeneration, although it is only after fifty that, as a rule, this becomes at all marked. And now one or both of two processes may occur. Either, as shown by Klotz's admirable studies, the fatty gives place to a calcareous infiltration, fine calcareous granules appearing in the course of the muscle fibers—a sign of necrosis of these fibers—or they undergo complete absorption. Per-

haps most frequently both processes are to be made out. As a result the intervening spaces between the elastic lamellæ become smaller and smaller, and often there is afforded the appearance of thick lamellæ due to the approximation of two or more, which can be resolved under higher magnification. With this, whereas in the young aorta the lamellæ are wavy, due to the contraction of the intervening muscles fibers, now they are relatively straight. It is this muscular atrophy rather than atrophy of the elastic tissue that thus would seem to be the main cause of the thinning of the aortic media. I do not in the least mean to say that the elastica is unaffected in this process. At times the calcareous degeneration affects it also. Everything indicates that coincidently it *loses its elasticity*, becomes more rigid and more expanded as the result of internal pressure; it is unapt to return to its former length.

It is further to be noted that the calcification is unequally distributed. Frequently in Dr. Klotz's specimens of the Moenckeberg type it is most marked, and the thinning of the media is coincidently most pronounced, in the walls of the shallow sacculations already noted. The presence of the sacculations show that here are the regions of greatest weakening. But it is frequent to find that when there is marked nodose thickening of the intima then also the underlying aortic media is thinned. This, it is true, is most evident not in the aorta, but in its branches—in the carotids, the splenic artery, the coronaries, etc. In all of these there may be an extraordinary overdevelopment of the fibroid intima and an equally striking expansion and giving way of the media. All must be familiar with specimens showing this condition. On the other hand, it has to be admitted freely that there may be well-marked intimal nodes of the aorta when the underlying media shows no recognizable thinning. Apart from possible exceptions to be subsequently noted there is an explanation to be afforded for this state of affairs—an explanation along the lines of Thoma's well-known observations upon the disappearance of the projecting intimal nodosities when the aorta is filled with melted lard under pressure. This is most rapidly afforded by the accompanying diagram (Fig. 4), which represents a length of aortic wall, in which the midportion has become weaker than the rest. This portion under internal pressure will be liable to give way, and, while thus bulging, will of necessity exhibit a definite grade of thinning, with compensation or strain overgrowth of the intima tending to fill the concavity. If, as occurs postmortem, the internal pressure be removed, then the natural elasticity of this midportion of the wall, which has not been wholly lost, will result in a disappearance of the concavity, the wall now appearing to be of normal thickness of media with a projecting nodosity of the intima. The same will naturally appear in sections prepared under the same conditions.

Let us now turn to the experimental evidence. The active dis-

cussion as to whether the lesions caused by adrenalin, barium chloride, nicotine, and other drugs in the rabbit are to be regarded as in any way equivalent to arteriosclerosis as seen in man, will be familiar to all of you, and many of you may have come to very definite conclusions upon the matter. Certainly these lesions do not resemble the ordinary nodose arteriosclerosis, but, as all must admit, the constant feature is a giving way of the middle coat, and this to such an extent that at times definite aneurysmal pouches are produced, at others and frequently those more shallow sacculations, scarce to be designated as aneurysms proper. As Klotz and K. Ziegler[15] independently pointed out, the appearance is identical with that noted by Moenckeberg in his type of arterial change. Medial degeneration and giving way is the dominant lesion of adrenalin disturbances. I took occasion to point out at the discussion on Arteriosclerosis, at the Toronto meeting of the British Medical Association in 1907, that the reason for the lack of intimal overgrowth might well be the acute development of the medial degeneration, resulting in rapid expansion of the intimal sheath and overstrain rather than strain, and I suggested that less extreme degeneration would be found to result in a more typical arteriosclerosis with intimal hypertrophy. Since then Dr. Klotz, by a different method, has demonstrated the truth of this surmise on my part. He has set up arterial disease in the rabbit without the use of any drug whatsoever, and that by merely suspending a (previously) healthy well-grown buck for three minutes daily by the hind legs—head downward. This naturally caused *pro tem.* an unaccustomed blood pressure in the thoracic, cervical, and cranial vessels, a reduced pressure in the abdominal and other arteries of the hinder end of the body. After this is continued for one hundred to one hundred and twenty days the heart is found greatly hypertrophied, the arch and the thoracic aorta are dilated, with very distinct thinning of their walls; the abdominal aorta, on the other hand, is unaffected; the carotids are

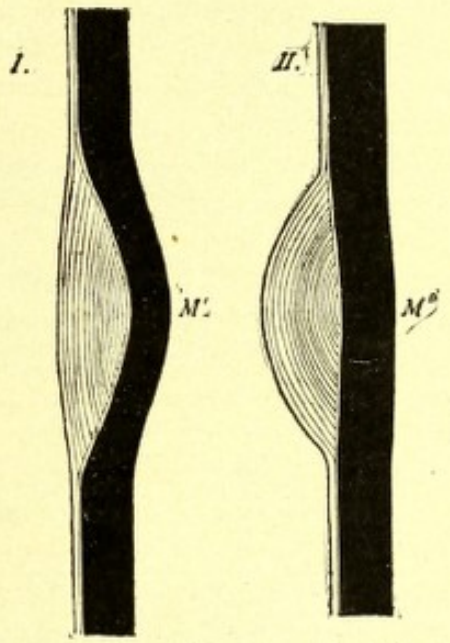

FIG. 4.—*I*, media weakened at M' with overgrowth of intima filling in the depression. *II*, with postmortem rigor and contraction of the muscles of the media and removal of the blood pressure from within, the stretched media at M'' contracts; the intimal thickening thus projects into the arterial lumen.

[15] Ziegler's Beiträge, 1905, xxxviii, 229.

larger than normal, and—this is the important point—they exhibit a typical irregular intimal sclerosis. There is pronounced connective tissue thickening of that intima.

These results can only be explained in one way, namely, as the effects of the daily temporary suddenly increased blood pressure brought to bear upon the vessels of the anterior half of the body.

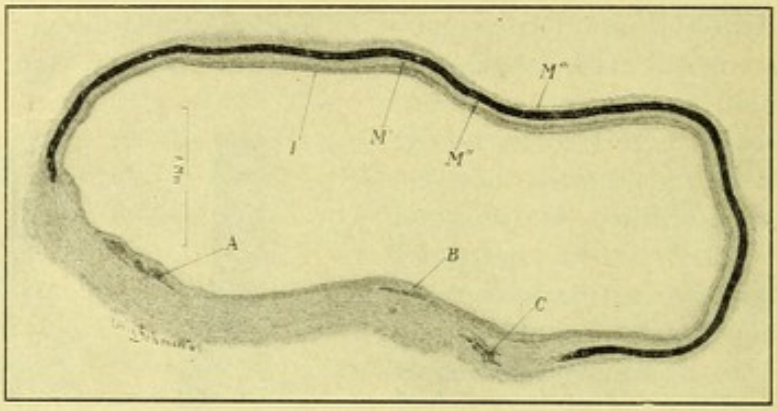

FIG. 5.—Section through the aorta of a rabbit that had been suspended for three minutes daily by the hind legs, for one hundred and thirty days, to demonstrate dilatation and relative absence of intimal proliferation. Around the greater part of the organ there is pronounced thinning of the media with calcareous degeneration of the middle layer (M''). This dilatation and thinning are less marked round about one-third of the organ, and here there is a slight grade of patchy hypertrophy of the intima at *A* and *B*. This hypertrophy here particularly involves the deeper musculo-elastic layer. At *C* there is beginning calcification of the media. (From a specimen stained with Sudan III and silver nitrate by Dr. Klotz.)

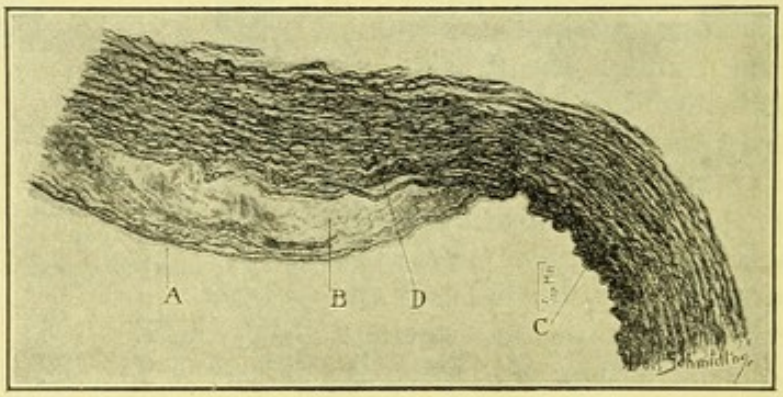

FIG. 6.—Section from the carotid of the same rabbit (higher magnification) exhibiting at *A* well marked nodular sclerosis of the intima. At *B* the deeper layers of the hypertrophied intima are already showing degenerative changes. *C*, normal intima. *D*, media. (From a specimen by Dr. Klotz).

That has resulted in diffuse dilatation of the larger vessel, the aorta, without intimal overgrowth, and in pronounced intimal overgrowth of the smaller vessels, the carotids. Here for the first time, I think, we have an absolute demonstration that one and the same cause is responsible for the two orders of conditions, the demonstration that the arterial thinning of the Moenckeberg type and the intimal thickening of ordinary (senile) arteriosclerosis are diverse mani-

festations of a common process. The greater circumference and the relatively slighter resisting or accommodative force of the aortic wall due, I may say, to its anatomical structure, has led to overstrain and dilatation, and as a consequence absence of intimal proliferation; the lesser circumference of the carotids and their proportionately greater resisting strength has been followed by a relatively slighter dilatation, tending to be localized to particular areas, and here as a result there has been strain, not overstrain, of the intima and a resultant connective tissue hypertrophy. I must add in justice that another Canadian worker, Dr. Harvey, of Toronto, continuing work begun under Professor J. J. MacKenzie, has independently, in the laboratory of Professor Dixon, of Cambridge, England, brought about the same diffuse dilatation of the aorta and cardiac hypertrophy by temporal digital compression of the rabbit's aorta extending over long periods. He does not, however, in his communication call attention to the coincident sclerotic change in the smaller vessels.[16]

Here then we arrive at a common order of events in the two great types of aortic sclerosis—the syphilitic and the ordinary nodose forms. In both we find weakening of the media as the primary disturbance; in both, if this be above a certain grade, there is pronounced giving way without intimal compensation; in both, if below this grade, a strain hypertrophy of the intima is manifested, leading to the production of intimal thickening. Only, in syphilis the giving way of the media is the more extreme, and so we more frequently encounter advanced aneurysmal formations as contrasted with the shallower sacculations of the Moenckeberg type, and in this, also, occurring as a rule earlier in life, there is a more exuberant regenerative power exhibited by the intima.

This view, it will be seen, demands that strain or pressure is the cause of the intimal overgrowth in both orders of disturbance; it demands also that the giving way of the media in the first place is due to a local weakening sufficient to render the arterial wall unable to resist the outward thrust of the column of blood. Nay, more, Klotz's experiment shows that increased intravascular pressure alone may be the cause of the medial degeneration and weakening in the first place, of the giving way of the arterial wall in the second, and of the intimal hypertrophy in the third. We are brought thus face to face with the time honored problem—to what extent is heightened arterial pressure—or, as Sir Clifford Allbutt would seek to have us call it, *hyperpiesis*—a factor in arteriosclerosis?

From the data already afforded, it is evidently not an essential factor in the syphilitic cases. Undoubtedly when present it may

[16] Personal communication from Professor MacKenzie and Sir Clifford Allbutt. I was of the impression that Harvey's results had been published, but can find no reference the Index Medicus or elsewhere.

accelerate the process in these, but infection is here the primary agent in causing the atrophy and absorption of the media.

As regards senile arteriosclerosis, the observations of Aschoff, Klotz, and Foster show that after fifty there is to be determined a physiological atrophy of the media; obviously the degeneration of the muscular layers and the further indications of change in the elastic lamellæ indicate a weakened media. It is not necessary in these cases to demand an increased blood pressure. The normal blood pressure must eventually be adequate to cause giving way of the media with or without consequent intimal hypertrophy.

Granting this for senile cases, then for the presenile arteriosclerosis, we are, from Klotz's experiment, forced to recognize that high intra-arterial pressure, and this alone, is sufficient to bring about a nodose arteriosclerosis with all its possible dangers. That experiment affords the experimental proof of the danger of heightened blood pressure, which from practical experience clinicians have so learnt to fear—and this in a perfectly clear manner, with no ambiguities or possibilities of lack of appreciation of other factors. High pressure, and high pressure only, can be invoked to explain the results which I have demonstrated to you.

We then reach the following conclusions, namely: That *like results may ensue when, on the one hand, the artery has undergone weakening and the blood pressure is normal, and when, on the other hand, the artery has no preliminary degeneration of its media and the blood pressure is above the normal.* What is of importance is that, as shown by this experiment, it is not necessary to have a blood pressure which is permanently above the normal; an acute rise for a short period frequently repeated will bring about the result.

I would greatly like to enter into a discussion of the mechanism of increased arterial pressure in relationship to peripheral arterial sclerosis, but have already taken so much of your time that I can venture at most to suggest the headings. I would call your attention to the fact that it is the arterioles through the body and their tonus that determine the existence of the normal blood pressure; that heightened blood pressure in the larger vessels means increased contraction of the arterioles of important areas; that thus to changes in the arterioles and smaller arteries we must eventually look for the explanation of hyperpiesis; that it is by contraction of the arterioles that adrenalin, digitalin, barium chloride and the other raisers of blood pressure produce their effects; that in this contraction we have the elements necessary for the establishment of a vicious cycle; that, as shown by Leonard Hill, the arteries react normally to increased internal pressure not by dilatation, but by contraction; that thus the higher the blood pressure the more contracted do the smaller arteries tend to become; and that, if the heart responds to the increased work thrown upon it, the higher still becomes the blood pressure. Along these lines it will be seen that rise of blood pressure tends in the

first place to throw increased work upon the musculature of the smaller arteries, tends, that is, to cause their hypertrophy; if the rise is progressive, then this hypertrophy gives place to exhaustion, muscular degeneration, and dilatation of the arteries (and arterioles). As a result strain hypertrophy of the intima shows itself with thickening, and it may also be of the adventitia, resulting in chronic periarteritis. And now, with continued degenertion of the medial muscle in those muscular arteries, fibrosis of the media may also show itself. I would thus regard muscular hypertrophy of the arteries and fibrosis of the different coats as different stages in one and the same process. Whether these peripheral changes are the more marked, or the central, depends, I would suggest, upon the relative resisting power of the elastic and the muscular arteries of the individual respectively.

Lastly, it may be asked, have I included here all the forms of arteriosclerosis and intimal hypertrophy? I certainly believe that I have referred to the more important, though I have not exhausted the forms. There is, for example, a form which Aschoff would term functional sclerosis, seen in the ovaries and uterus, in the ovaries after menstruation and ovulation, in the uterus after menstruation and placentation. The sclerotic change here may be extreme, and again is of a hypertrophic and regenerative type—so much so that in the uterus there may be encountered, as shown by Sohma,[17] the development of what is practically a new artery within the old, with endothelial, intimal, muscular, and even what corresponds to an adventitial coat. Here, I would hazard, the same priniciple is at work. The extreme congestion and dilatation of these arteries in menstruation and placentation leads to an overstrain of their walls with consequent overexpansion and degenerative weakening, to such an extent that at the conclusions of these physiological events, when there is no longer a call for dilatation of the arteries, they still remain expanded. Nor is there any adequate mechanism on the proximal side (toward the aorta) to cut off fully the blood supply. There is still, therefore, a certain amount of strain exerted upon the arterial walls from within, and this leads now to secondary overgrowth.

Secondly, Dr. Klotz has shown experimentally, and Saltykow[18] has confirmed, that certain bacterial toxins, *e.g.*, the diphtheritic, lead to medial degeneration, others, like typhoid toxins, have no recognizable effect upon this coat, but induce a primary intimal proliferation. I freely accept the existence of such primary intimal overgrowth. I have to confess, however, that I have some doubts as to its frequency as a cause of extensive arteriosclerosis in man. When it is at all well developed, then I would point out, the superficial intimal overgrowth

[17] Archiv f. Gynäk u. Obst., 1908, lxxxiv, 84.
[18] Ziegler's Beiträge, 1908, xlii, 187.

cuts off the due nutrition of the musculo-elastic layer, and, indeed, of the innermost layer of the media; degeneration and weakening of these is the natural result, and there is established a vicious circle; the greater the intimal thickening the greater becomes the weakening of the lower intimal layer, and so of the arterial wall; nor is the ful picture of arteriosclerosis attained until both events are present.

The same picture is afforded in the arterioles. My former colleague, Dr. Duval,[19] now professor of pathology in Tulane University, then pathologist to the Montreal General Hospital, published certain most interesting studies upon the effects of attenuated glanders bacilli upon the vascular system of the rabbit. In these he demonstrated most clearly that these bacilli induce an active proliferation of the endothelium of the smaller arteries, and he gives a figure of a later stage in which a well-marked sclerotic node of the intima has associated with it a bulging and thinning of the media. If these two pictures represent successive phases of one process—and of that I am not wholly convinced—it must still be admitted that medial weakening, whether by the direct action of the glanders toxin or by arrest of nourishment of the media through the intimal hypertrophy, is an essential part of the process. Endothelial proliferation alone does not constitute arteriosclerosis.

Lastly, and perhaps of the greatest present importance, there is the consideration of the part played by the deeper or musculo-elastic layer of the aortic intima in the arteriosclerotic process. Following the lead of Jores,[20] the majority of the recent German writers on the subject lay stress upon the degeneration and hypertrophic processes found in this as being the fundamental change in arteriosclerosis. Here I have an objection to make of the same order as my criticism of the use of the term atherosclerosis, namely, that aortic disturbances are dwelt upon to the exclusion of the concomitant changes in the arteries of muscular type. It is only in the larger branches of the aorta—those of the intermediate type—that this layer continues to be a factor of any importance. As we pass into the smaller arteries its development becomes so slight that it cannot possibly be a factor of the first order.

In the aorta its fully developed structure—of longitudinally arranged plain muscle fibers and abundant elastic fibrillæ—renders it akin to the media. At most, the longitudinal arrangement of its elements suggests that its function is to oppose elongation rather than dilatation of the vessels in which it is present. Simple hypertrophy must connote increased strength of the arterial wall; degeneration must signify weakening of the wall as a whole. Now, significantly this layer is curiously apt to exhibit degeneration. Why this should be so is not wholly understood. I would suggest that its position relative to sources of nutrition is largely at fault. The

[19] Jour. Exp. Med., 1907, ix, 241.

[20] Ziegler's Beiträge, 1902, xxxii, 146.

internal elastic lamellæ of the media largely cut it off from nutrition from without; the plasma from the interior of the vessel has to pass through and be acted upon by the more superficial layers of the intima before reaching it. It has no independent source of nutrition, and more particularly if the superficial layers of the intima have undergone thickening, the factors favoring degeneration are clearly greatly increased. The striking picture that this layer presents in the earlier stages of degeneration—the swollen condition of its cell elements, the œdema of its interstitial substances, the diffuse soapy and fatty change that it undergoes—all, I am inclined to lay down, tend to arrest the attention and tend thus to a neglect of the concomitant medial and superficial intimal changes. And this point of view is supported by the existence of degenerative changes in the layer unaccompanied by any other vascular disturbance. In cases of burns and of acute infections, and that even in the young, it is common to meet with fine fatty streaks in the aorta. And these streaks indicate a fatty degeneration of, in the main, this musculo-elastic layer. It is natural to imagine that here we have the first stage in the arteriosclerotic process. I am, however, convinced that the two have no necessary association. I would ask anyone who doubts this to follow the example of Drs. J. McCrae and Klotz in our service at the Royal Victoria Hospital, and make a note upon the postmortem report every time that these fatty streaks are present. It will surprise him to find how common they are; how frequently they are present in the quite young; how little obvious relationship they have to the arteriosclerotic state.

I do not deny that a weakening of the musculo-elastic layer weakens the whole arterial wall, and thus may be a factor favoring subsequent intimal hypertrophy. I only urge that this is not nearly so frequent or so important as is a weakening of the media.

Thus we revert to our main conclusions that the dominant primary event in the arteriosclerotic process—syphilitic, senile, or functional—is a localized or it may be a diffuse weakening of the arterial wall and especially of the media. This induces increased strain upon the remaining coats; and if this be not excessive, that strain leads more especially to connective tissue overgrowth and the development of the characteristic lesions of arteriosclerosis.

In the foregoing remarks I have repeatedly referred to the work accomplished in our Montreal laboratories, and more particularly to the studies of Dr. Klotz. When the chief of a laboratory quotes the work of those under him, it is usual to infer that the work is his under another name—that he has inspired the researches. In justice to my colleague, I may say that in this instance this most decidedly is not the case. I have quoted Dr. Klotz's work so frequently because I have followed it with very deep interest and know intimately its progressive developments, and further because

each step has, to my mind, confirmed and expanded the conclusions I reached long years ago regarding the essential nature of the arteriosclerotic progress. I appreciate too highly the originality of Dr. Klotz to claim more than having been fortunate in suggesting to him that line of inquiry into the nature of calcification which he carried out with so much distinction and of which much of his later work is, as it were, a natural evolution. I should be glad to regard this address, and to have this address regarded, essentially as a vehicle for bringing forward in a connected manner the observations of my colleague and my interpretation of them, which must not necessarily be thought to be his interpretation.