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CONCERNING COMPENSATORY HYPERPLASIA OF
THE INTIMA

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Reprinted from THE JOURNAL OF EXPERIMENTAL MEDICINE, Vol. XII., No. 6, 1910.



CONCERNING COMPENSATORY HYPERPLASIA OF THE INTIMA.¹

By OSKAR KLOTZ.

Plate LXIX.

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In 1885 Thoma set forth his views concerning the fundamental principles underlying arteriosclerosis. From the first Thoma's attention was concentrated on the intimal thickening which occurred in various arteries, and more particularly upon those developing in the aorta. His studies of these lesions were chiefly concerned with the general characters of the disease, to some extent with the nature of the tissues involved, and occasionally with the degenerative processes which develop in these intimal thickenings. According to his observations the intimal thickenings had common characteristics in their development, but only two types of the disease were recognized. In one instance the intimal thickening was diffuse and uniform, sometimes encircling the entire artery; in other cases nodular thickenings were evident, which might or might not be associated with the openings of smaller arteries. In his opinion the intimal thickening of both types developed in a process of connective tissue hyperplasia which was associated with a widening of the vessel lumen.

Thoma had previously convinced himself that shortly after birth there was an increase in the connective tissue of the intima of the aorta, extending from the mouth of the ductus arteriosus to and into the hypogastric arteries. His explanation for this development of connective tissue was that the loss of the placental circulation at birth led to the disproportion of the blood content to the vessel wall; that is, he believed that after birth the amount of blood in the vessels forming the foetal circulation was less than was

¹Received for Publication June 11, 1910.

present during intra-uterine life, and hence, to compensate for this diminished amount of blood, a new layer of connective tissue developed in the lumen, in order to make the tube narrower.

Although it has been found that there is a gradual development of intimal tissues with progressive age, no association can be demonstrated between the loss of placental circulation and the tissue hyperplasia. Nor can we support Thoma's findings that this new tissue in the intima is confined alone along the path of the fetal circulation. Moreover, the hyperplasia which occurs in the intima often involves elements other than connective tissue. Furthermore, the principle of compensation between the fluid of the body and the fixed tissues is usually balanced by other means. Under ordinary conditions the diminished amount of blood in the vascular system is readily compensated by the absorption of fluid from the surrounding tissues. How frequently during life must there be a temporary disproportion of the fluid blood to the arteries! Severe hemorrhages following trauma, hemorrhages occurring in typhoid and dysentery, and loss of blood occurring in cases of hemophilia all lead to this disproportion of blood content to the vascular system, and yet in these cases the disproportion is but temporary and the proportion can be easily reestablished by the absorption of fluid. Moreover, in none of these diseases do we see a process of compensatory hyperplasia such as is described by Thoma.

This general principle of compensatory hyperplasia, which Thoma claimed for the connective tissue growth in the intima of the aorta of children, was also adapted by him for the explanation of the intimal thickening occurring in later life. Thoma discusses the subject in a general way only, and he avoids minute histological descriptions.

In 1886 Thoma carried out a series of experiments to demonstrate compensatory hyperplasia. He filled the fresh aorta in the cadaver, or aortæ recently taken from the cadaver, with melted paraffin under a pressure about equal to the blood pressure in the aorta. These injected preparations were kept at this internal pressure until the paraffin had thoroughly hardened. The aorta was then split open and the paraffin core removed. On examining these wax models Thoma claimed that the surface was uniformly smooth,

and that opposite the sites of nodular sclerosis the paraffin showed no indentation such as might be expected from localized intimal thickenings.

Moreover, on examining the arterial wall, which had been subjected to the continuous pressure of the paraffin, he found that the intimal surface was quite smooth and free from the endarteritic irregularities such as are found in the collapsed arteries at post-mortem.

Thoma further examined cross-sections of these arteries and found that not infrequently the media was thinned opposite the endarteritic plaque. He stated also, elsewhere, that the thickened intima might overlie an area of the media which appeared normal or even hypertrophied.

From his various observations Thoma deduced his well-known theory, the main features of which are briefly these: (1) the beginning of an arteriosclerosis, either endarteritis nodosa or diffusa, results from a weakening of the media which allows the artery to dilate either over a small circumscribed area or one involving a considerable portion of the arterial wall; (2) this dilatation of the arterial wall causes a widening of the lumen, which in turn induces a slowing of the blood current at this point. This slowing of the blood stream now acts as a local irritant leading to his so-called "compensatory hypertrophy of the intima."

Thoma's theories to-day are upheld by some and denounced by others. As we have improved our technique for pathological examination, it has been shown that some of his views are untenable.

During the foregoing winter, 1909, I repeated some of Thoma's experiments, but had little success in the use of paraffin as an injection fluid. I found that paraffin was liable to produce artefacts which were misleading. When paraffin was injected into the aorta, the globules of water adhering to the fresh vessel wall produced irregularities in the mold of the hardened wax. I also found that the paraffin, after it had set and when the pressure of the fluid paraffin without had no effect upon it, underwent a considerable shrinkage, producing other artefacts, and in my specimens it always showed extensive irregularities of the intima on the paraffin core. In no instance could I substantiate Thoma's claim that the lumen

of an endarteritic artery was smooth and regular when under pressure.

However, remembering that there was considerable shrinkage in the paraffin while hardening, the possibility remained that when the vessel was properly distended at normal pressure or nearly so, the vessel wall was smooth, even with the presence of endarteritic plaques. It was, therefore, decided to use water for the injection fluid, and to fix the preparation by freezing. An apparatus was then devised so as to give any desired pressure, depending upon the height of the column of water above the aorta to be tested. When the proper pressure, equal to one hundred and sixty millimeters of mercury, had been obtained in the aorta, the whole apparatus was placed at a temperature of from 0° F. to -20° F. After an exposure of some hours the water in the specimen and apparatus was completely frozen and the character of the lumen was determined by sawing the frozen aorta into a series of small discs half an inch in thickness. The character of the lumen was easily distinguished in these discs, and impressions of the vessel wall in the distended state with the ice within were easily obtained. All the observations had, of course, to be made in the cold.

It was found that when the discs had been painted over with methylene blue and the excess stain had been removed with blotting paper, that accurate impression of the contour of the vessel wall could be obtained. Moreover, these impressions indicated with accuracy the contour of the lumen of the vessel while still under pressure. It is to be remembered that, as our specimens were filled with water under average high arterial pressure, the process of freezing, instead of relieving this pressure to some extent as is the case in the use of paraffin, actually increases the pressure, and hence would tend to obliterate still further the intimal projections and favor the views of Thoma.

In these experiments we were again unable to substantiate Thoma's contention. The intima with its white endarteritic thickenings could be quite readily distinguished from the media. Each of these endarteritic plaques formed a rounded bulging into the vessel lumen and nowhere could any weakening of the media be distinguished in the early intimal lesions. The small superficial



FIG. 1.



1.

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3.

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7.



8.

FIG. 2.

FIG. 1. Abdominal aorta of man aged 63, with extensive arterio-sclerosis and chronic endarteritis. Lumen much distorted.

FIG. 2. Aorta of man aged 75. Nos. 1, 2 and 3 are from thoracic aorta; Nos. 4 to 8 are from abdominal aorta. Chronic endarteritis with deep atheroma. Intimal lesions encroach into lumen. Media thinned in places.

fatty plaques which occur about the intercostal vessels were observed to rest upon the inner surface of the intima, like small masses of excess tissue. In many instances neither the deep intima nor the media showed any change in their structure or contour (Fig. 5).



FIG. 3. Arteries from man aged 75. Nos. 1 to 6 abdominal aorta; No. 7, common iliac. Moderate diffuse and nodular endarteritis. Pouching in iliac obliterated by internal pressure.

Pearly thickenings of the intima without atheroma, the true endarteritis chronica nodosa, occupied the whole thickness of the intima and projected to a considerable extent into the lumen of the aorta.

The media was unaltered and formed a circular band of tissue with no evidence of bulging opposite the intimal thickening (Fig. 4).

On the other hand, in the cases of chronic endarteritis in which a degenerative softening had taken place in the deep structures, the media was found to be involved to a considerable degree and showed distinct evidence of thinning. In these specimens the deep intimal degeneration was so closely involved with a degeneration in the inner layers of the media that these two portions were fused, making it appear that the thickening and degenerative process was situated in the intima alone. The media was obviously thinned opposite the degenerative process, but there was nothing in the remaining media to indicate a primary weakening or change in these muscle



FIG. 4.

FIG. 5.

FIG. 4. Female aged 53. No. 1 thoracic aorta. No. 2 abdominal aorta. Showing early endarteritis in the thoracic portion projecting into the lumen, also irregular lumen of extensive sclerosis of abdominal portion.

FIG. 5. Female aged 26. Thoracic aorta. Showing early endarteritis. Endarteritic areas project into lumen of vessel.

fibers which could secondarily induce intimal hyperplasia to excess with degeneration (Figs. 1 and 2).

By these same methods I also examined some vessels, particularly the iliac arteries, in which known lesions of the media were present. Some of these vessels showed typical Moenckeberg's arteriosclerosis with degeneration and calcification of the middle coat, while the

intima showed little or no change over these areas. Macroscopically, and in the relaxed condition, these vessels showed small pouchings and transverse grooves on the inner surface. There were no nodular thickenings of the intima to be seen. When, however, these vessels were subjected to a hydrostatic pressure equal to one hundred and sixty millimeters of mercury and allowed to freeze, the longitudinal section of the artery showed quite a smooth intimal surface. The ridges and pouchings in the vessel wall had been obliterated (Fig. 3). Obviously here the more normal part of the vessel wall had, under pressure, dilated equal to the pouching present in the diseased areas. This is exactly what we should expect in comparing the results with the histological preparations. It has been repeatedly commented upon by various authors that the sclerosed and calcified areas of the media in Moenckeberg's disease diminish the elasticity of the media and fix the muscular tissues in a rigid state. In life this sclerosis takes place while the vessel is under pressure and hence the tissues become fixed and rigid while fully dilated. Under ordinary conditions of life, these sclerosed areas need not be more widely dilated than the adjoining more healthy arterial wall, as is shown in our experiments. Immediately on relaxing the blood pressure at death, the active and more healthy portions of the vessel wall contract, leaving the sclerosed portions as transverse areas to form the pouchings, as is seen at autopsy.

Here, then, we have a process exactly contrary to Thoma's theory. We find that in the areas where the media is diseased there is a pouching of the wall when the vessel is relaxed, and that these areas of medial disease are not covered by a thickened intima of compensatory hyperplasia.

But besides this macroscopic demonstration, we possess clearer evidence that the lesions of the intima are to a great extent independent of medial changes. Dividing the diseases occurring in the intima of arteries into the productive and the degenerative types, we shall, in this paper, confine ourselves to those lesions which lead to the development of new tissues. Nor is it within the province of this discussion to consider the final outcome of intimal hyperplasia, whether this leads to a process of degeneration or continues in the production of new tissue.

One meets not infrequently with specimens of *endarteritis chronica nodosa* in the aorta in which various grades of the disease can be recognized. The inner surface of the aorta is studded with pearly intimal thickenings of all sizes and in all stages, from the earliest beginning to the large plaques showing deep fatty change.

If, however, we confine our attention to those small islands of fibroses (be these of endothelial or connective tissue origin), which are just visible macroscopically, and study the microscopic characters of these specimens, we find that the diseased process is confined wholly to the intima with no change in the media. It is well to exclude, as far as possible, the presence of senile changes in the media of the aorta, and hence only vessels of adults under thirty-five years should be examined. By none of the known methods of staining can we demonstrate associated lesions in the media in these early processes of *endarteritis*. Fat and hyaline changes are wanting, calcareous salts have not been deposited, and the elastic fibers of the media show no inequality in staining. In short, we have to deal with a process which is confined to the intima.

This disease of the intima falls into two classes, according to the classification of Jores, (1) the hyperplastic, and (2) the regenerative.

Jores clearly points out that the hyperplastic thickening of the intima, which leads to an excessive development of the musculo-elastic layer, is a "hyper-physiological" process. There are many factors in the life-history of every individual which throw an increased strain upon this muscle layer of the intima of the arteries, and which, if not too persistent, lead to this natural hypertrophy. When, however, these factors are excessive, degenerative changes develop in the hypertrophied tissues. This result is a common, if not the usual finding in hyperplastic intimal thickenings in later life.

The regenerative lesions of the intima are processes taking place in the tissues superficial to the musculo-elastic layer, and occur quite apart from any changes in the deep intimal tissues. This regenerative process is regarded by Jores and others as a connective tissue proliferation of the nature of an inflammation but lacking, at the same time, the features of inflammation, as found in other tissues. A study of the earliest changes occurring in the development of these minute plaques shows that they are a result of the proliferation of

the superficial cells. At the beginning, only a single type of cell, which by some is regarded as of endothelial origin, by others as of connective tissue origin, is found to take part in the proliferative change. Later, fine elastic fibrils are found to permeate the intimal plaque.

Such proliferative changes are most commonly met with in bacterial infections, and occasionally in association with poisons.

These lesions may progress to a considerable size before there is any evidence of change either proliferative or regenerative in the media, and no rule can be followed which will indicate the changes in the media during any particular stage of the disease. Moreover, it is not possible to determine any association between the development of these medial lesions and those of the intima. It would seem that, in these cases, the conditions in the media and in the intima arise wholly apart from each other, though they may result from a common cause.

From these cases we must clearly differentiate the lesions which arise in the media as a result of advanced intimal change. This is familiar to all and is quite a different process. When intimal lesions have been progressive and the thickening of this layer has become so advanced that nutrition is no longer able to pass from the lumen of the vessel to the innermost border of the media, nutritional degeneration, with a deposit of fat in the tissues, will take place. In these instances, the medial lesions are obviously secondary to an intimal disease.

Let us, for a moment, give our attention to the diseases affecting the media of the peripheral vessels and determine the part played by this coat in intimal hyperplasias. For this study the iliac, femoral, mesenteric or brachial arteries and their branches serve very well. Particularly in the case of the iliac and femoral arteries, can the medial diseases be studied from their first beginnings to the severest lesions.

The media of the peripheral vessels, as has repeatedly been indicated, is a functional muscular structure which has to do with the control of the blood supply of the part. Under conditions of stress the muscle tissue of the artery is active, and controls the amount of blood passing to the limbs or organs. Where the blood pressure

and the velocity of the blood is increased, a smaller arterial lumen is required to give an equal amount of blood to the tissues, as under normal conditions. This diminution of the lumen is controlled alone by the media. Under ordinary circumstances the media can adequately control this blood supply, but when from various causes, such as hypertrophy of heart, Bright's disease, or excessive physical work, this blood pressure remains high for a long time, the media reacts by hypertrophy while the nutrition to its walls is adequate. When, however, the nutrition fails, this hypertrophied media slowly undergoes retrogressive changes. In the first degenerative changes of the media, the muscle fibers show an accumulation of fat granules in their protoplasm which continue to fill the cells until the muscle fibers undergo complete destruction. Later these areas of degeneration become calcified and in the superficial vessels are readily recognized as beaded tubes.

Such degenerations of the media are not accompanied by any inflammatory reaction and appear to be the result of over-strain or over-stimulation of the muscle elements. The condition can, in short, be considered as a process of fatigue of the muscle fibers coupled with nutritional disturbance. In consequence of the medial fatigue, there is a localized weakness of the wall, which is evidenced by the pouching that results in the areas of least resistance.

These progressive medial degenerations occurring in the peripheral vessels are readily studied in all the stages, and not infrequently several stages can be observed in the same artery. It is occasionally found that vessels show a considerable microscopic degeneration in the media before any pouching or dilatation results. This is probably due to the fact that the media had previously undergone an hypertrophy sufficient to withstand the heightened blood pressure even after some of the muscle lamellae had been destroyed.

These peripheral vessels showing medial degeneration show irregular conditions of the intima. In many cases the intima is found in a normal condition over lesions of various grades in the media. I have observed the successive changes in the media, from those showing the earliest sign of hypertrophy to the advanced changes in the media with pouching and calcification, without meeting with any condition of endarteritis nodosa or diffusa over the

lesion. It is true that vessels with medial calcification not infrequently show a condition of endarteritis, but this endarteritis is found to bear no direct or secondary relation to the medial disease, save that both may be produced by the same injurious agent.

What is true of medial degeneration and dilatations of the peripheral vessels also holds true of the aorta. In the diffuse though not severe degenerations of the media in the aorta in old age, there is sufficient reason to believe that the arterial wall is materially weakened and that the vessel may be locally or diffusely stretched. Nevertheless, from this medial process alone we cannot predict what changes have occurred in the intima. Occasionally in such vessels the intima is without endarterial change.

Saccular aneurysms of the aorta not uncommonly show some thickening of the intima, but, as has been shown by others (Osler, Chiari), these aneurysms are most frequently the result of a syphilitic mesaortitis, and the intimal overgrowth is associated with the syphilitic process before an actual weakness or stretching of the vessel wall has shown itself. The mesaortitis is essentially an inflammatory process to which the neighboring intima reacts.

From our observations on the medial lesions occurring in the human blood vessels, we are unable to make any general statements associating these with the thickening of the intima, nor does there appear to be any "compensatory" reaction on the part of the intima due to medial weakening.

The experimental lesions in the arteries, too, have been of considerable value in the study of intimal hyperplasias. Some have contended that, as spontaneous disease may occur in the arteries of the experimental animals, or that the lesions experimentally produced were not comparable to the disease in man, no conclusions could be drawn from the work in experimental arteriosclerosis. Without discussing the right of this opposition, we need only point out that the study of the arterial lesions, as they occur in animals, has assisted to a great extent our knowledge concerning progressive and retrogressive changes of the various coats of arteries in general.

Various investigators studied the arterial lesions following mechanical injury (D'Anna, Malkoff, Israel). In all of these, varying grades of inflammatory reaction were obtained. The inflammation

extended from the adventitia through the media to the intima. When healing was allowed to take place, there was a connective tissue replacement of the arterial wall, while the intima showed a nodular thickening over the injury. In some instances (Israel) the intimal thickening was followed by degenerative changes. It appears evident that in the intimal thickening we have to do with an inflammatory repair of the injured coat, although in the later stages all evidence of acute inflammation is wanting. It is probable that all vessels which are disturbed from their normal bed of *vasa vasorum* will later show inflammatory and degenerative processes.

Similar inflammatory changes of inconstant characters were obtained when large nerve trunks (sciatic) were interfered with (Bervoets and Fraenkel). However, it was later shown by Czylharz and Helbing that the vascular reactions were secondary to trophic lesions (ulcers) which occurred on the limbs of the animals. When no trophic changes were present, no arterial lesions developed. Hence the loss of nervous control of the arterial wall with the dilatation of the channels, was in itself not sufficient cause to produce intimal hyperplasia.

The arterial changes produced by the inoculation of adrenalin are interesting and have been thoroughly studied by some fifty-five investigators (Saltykow). The nature of the lesions is well known. In the majority of cases, the thoracic aorta was the site of predilection, though in a number of instances some of the peripheral vessels were also affected. These lesions most frequently consisted of primary degenerative processes in the media, affecting both the muscle and the elastic tissues. The muscular elements were first destroyed, and the whole vessel wall became thinner. In the early stages, with the loss of the muscle elements, the elastic fibers of the media were crowded closer together. Eventually the affected area became calcified and remained as an isolated mass in the middle zone of the media, with relatively healthy adventitia and intima on either side of it.

In only a few instances was any thickening of the intima observed over or associated with the medial degeneration. This thickening of the intima was in part a hypertrophy of the deep muscle coat of this layer along with some fibrous tissue overgrowth close beneath

the endothelial surface. In some instances the hypertrophy of the musculo-elastic layer was quite remarkable, and in studying the various stages of the thickening of the intima in these lesions it was seen that the muscle hypertrophy preceded any development of connective tissue in the intima. Later, this development of muscle tissue in the intima was followed by degenerative changes simulating atheroma.

Although the medial degeneration was the most constant observation made by various investigators, none of them found sufficient evidence in their studies to associate relationship between the medial degeneration and the thickening of the intima. Ziegler, however, noted in his specimens, that the intimal overgrowth assisted, in some measure, the smoothing out of the depressions produced by the giving way of the media.

In other experiments we have more direct evidence of the production of intimal hyperplasias. Sumikawa found, when the femoral artery of rabbits was laid bare and was painted with a four per cent. solution of silver nitrate or with turpentine, that a localized inflammation followed in the tissues with an intimal thickening. The author concluded that the intimal reaction was a secondary one, following the general inflammatory process of the other coats.

Better results were obtained by the bacterial or toxin inoculations. In using various kinds of organisms, *B. typhi*, *Streptococcus pyogenes*, *Staphylococcus aureus* and others, it was found that considerable change occurred in the intima of the arteries, while the media showed little or no change (Saltykow, Crocq, Gilbert and Lion, Sumikawa, Klotz). Endothelial proliferations were seen early followed by an edematous or hyaline-like degeneration of the newly developed layer. In some cases a fatty degeneration was noted in the intima, so that the lesion resembled very closely the early atheroma of man. There was apparently a selective action on the part of the bacterial poisons which acted more particularly upon the tissues of the intima. On no account could the intimal hyperplasia, with splitting of the intimal elastic lamina, and its secondary degeneration be associated with a weakening or disease of the media. The hyperplasia of the intima was, in these infections, primary.

In my own experiments, which had been undertaken to eliminate as far as possible the action of poisons and toxins, it was found that increased work on the arterial wall, when carried on for an excessive period, had a double effect on the arterial tissues. On the one hand, it was found that, in those arteries which were subjected to the greatest stress and where that stress no longer acted as an irritant but as a damaging factor, the middle coat of the artery, and particularly the muscle cells therein, showed degenerative changes, even to destruction. The appearance of these vessels was quite similar to that which was obtained when adrenalin and other pressure-producing drugs were inoculated into animals. Quite similar to the adrenalin experiments, there was relatively little reaction in the intima over the medial lesions. On the other hand, in some of the smaller arteries, particularly in the carotid, where the damaging factors were not so severely felt, the artery reacted to some degree by a hypertrophy of its various coats. This hypertrophy was to be seen especially in the musculo-elastic layer of the intima. The size of the muscle bundle was distinctly increased and there appeared to be not only an increase in the size of the muscle cells but also in their number. This, in itself, assisted in thickening the vessel wall. Later changes were, however, prone to occur. In irregular areas this hypertrophied musculo-elastic layer became swollen and with ordinary staining appeared edematous. The tissue was loose and the connective tissue fibres about this layer had a hyaline appearance. In these areas great quantities of fat were readily demonstrated and it was found also that the internal elastic lamina had split into several layers, changes quite similar to those found in this band in arteriosclerosis in man. Other than the hypertrophy, the media showed no definite change, although in the areas where the fatty degeneration of the intima was extensive, a similar condition was found in the inner layer of the media bordering the intima. The mid and external zones of the media showed in no instance any feature which would indicate a weakening, and the slight amount of fatty change seen in the inner zone of the media was readily recognized as being secondary to the lesion in the intima (Plate LXIX, Figs. 1, 2 and 3).

Some have referred to the apparent intimal hyperplasia which

occurred in transplanted vein segments as instances of Thoma's compensatory intimal hyperplasia. Since the valuable work of Carrel and Guthrie, indicating the manner in which arteries and veins might be successfully sutured, a number of operators have devised unique experiments on tissue transplantation. Fischer and von Schmieden have recently repeated the experiments of arterio-venous anastomosis and of the transplantation of a vein segment into the course of an artery. After allowing a complete healing of the sutured edges, the transplanted veins were examined after varying periods of time. The experiments were undertaken in answer to two questions: (1) Does a healthy vein become unduly dilated (varicosed) when under high pressure? and (2), Does the intima of the vein show a functional connective tissue hyperplasia? From their observation in their own experiments, they conclude that veins when under arterial pressure do not become unduly dilated, but after a time show a narrowing of the lumen, due to hypertrophy of the media by an increase in the muscle and connective tissue. The adventitia too was found to increase its connective tissue elements. The authors could find no compensatory hyperplasia of the intima, although nodular thickenings with inflammatory surroundings were occasionally observed. These nodules of the intima occurred most frequently about the sutures, and not in the most distended part of the vein, which was away from the suture line. In other words, the reaction in the vessel wall due to the increased function was found mainly in the muscle cells as an hypertrophy.

With reference to Thoma's views upon compensatory hypertrophy, it may be said that Adami has expressed views which, while subscribing to the idea that compensatory hypertrophy occurs, tend to ascribe it to other reasons. Both of the theories of Thoma, and those of Adami, assume a medial weakening antedating the growth of the tissue cells of the intima. Thoma contends that this weakening led to a dilatation of the artery with sufficient slowing of the blood current to cause reactionary proliferation of the intima; Adami, on the other hand, believed that the medial weakening and dilatation caused a tugging or stretching of the intima and its cells, and that these physical agencies were the stimuli for growth. However, the fundamental principle upon which both these theories are

based, namely, a primary weakening of the media, remains unproved, and I would even say stands contrary to many observations on this point.

No one will doubt, I believe, that active work associated with an adequate nutrition will bring about hypertrophy or hyperplasia of many tissues. This increase of work may be, on the one hand, of a physical nature, or, on the other, of increased secreting function. In each case, the result is the same. While the nutrition remains sufficient for the needs of the tissue and the hypertrophied structures, a progressive increase in the number and size of the cells results. In other words, work in its various forms acts as a stimulus for cell growth, as long as the nutrition is adequate.

The tissues most affected in the arteries by the stresses of physical agents, such as high blood pressure, are the muscle cells and, to a less extent, the elastic tissue fibers. When arteries are stimulated in this manner, these cells are the first to react, as is evidenced by the early hypertrophy of the media and of the musculo-elastic layer. These same cells are also those which suffer the effects of overstimulation, or fatigue, and in them degenerations appear early. In examining my specimens, Professor Adami, while recognizing the hypertrophy of the musculo-elastic layer, believed, nevertheless, that the overgrowth of the overlying connective tissue of the intima proper, as it showed no earmarks of inflammation, indicated a strain hypertrophy.

Much of this newly developed muscular tissue in the deep layer of the intima is followed later by very extensive fatty degeneration, so that much of this tissue is again lost. Over the hypertrophied muscle layer there is at times a development of a loose fibrous stroma, appearing hyaline or edematous. There is every evidence to believe that this superficial tissue, be it of endothelial or connective tissue origin, has developed secondary to the degenerative processes in the deep part of the intima.

Notwithstanding this, Adami believes that a share of the increased work of the arteries falls upon the superficial cells of the intima, and that the stretching of this lining causes a proliferation of the cells.

Concerning the reaction seen in the intima in syphilitic disease

of the aorta, we incline to the view that it is secondary to the inflammatory processes of the media. Our increasing familiarity with syphilitic mesaortitis indicates that the lesions in the arteries are of an infective nature and that this infection lies in the adventitia and media. With this infective process there is truly a destructive process in the media, but there is also a concurrent inflammation which we feel convinced affects the intima.

The effect of moderately increased work upon the arterial walls leads to an hypertrophy of the muscle elements, giving way not infrequently to a later degeneration. The degeneration becomes most evident in the musculo-elastic layer which gives rise to atheroma. The growth of connective tissue elements over this degeneration is secondary.

When increased work exceeds the capabilities of the arterial tissues, degenerative changes set in from the first and no intimal hyperplasia is evident.

CONCLUSIONS.

We agree with Jores and others that not one but many factors may be at work leading to intimal hyperplasia. Among these factors may be mentioned infection, bacterial toxins, organic poisons, inflammation and increased arterial tension.

The theory of Thoma that the connective tissue developed in the intima is compensatory cannot be sustained.

From the evidence which we have at hand it is not possible to state that the proliferative changes in the intima are uniformly secondary to the weakening of the media.

Common influences may act simultaneously upon the media and the intima.

Progressive medial degeneration of the peripheral arteries (Moenckeberg's sclerosis) is the result of muscle fatigue coupled with nutritional disturbance.

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FIG. 1.

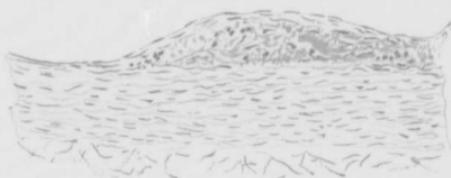


FIG. 2.



FIG. 3.

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EXPLANATION OF PLATE LXIX.

The tracings, including those in the text figures, are from impressions made from transverse sections of different aortas while frozen under pressure.

FIG. 1. Carotid artery of rabbit, daily inverted for five minutes for 120 days. Showing hypertrophy of musculo-elastic layer.

FIG. 2. Carotid artery of same animal as Fig. 6, in which hypertrophied musculo-elastic layer shows much fatty change.

FIG. 3. Carotid artery of rabbit treated for 135 days, in which the thickened musculo-elastic layer is very fatty, with a thickening of the subendothelial layer (endarteritis chronica).