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Arteriolosclerosis : a consideration of the pathology and etiology

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ARTERIOLOSCLEROSIS

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INTRODUCTION

This thesis is presented as a review of certain facts and theories pertaining to a branch of one of the most interesting and disputed subjects in the field of medicine today. In the light of modern scientific and medical advancement Arterial Sclerosis furnishes a very fertile field for the development of knowledge.

In addition, this branch of Arteriosclerosis is intimately tied up with Hypertension--another enigma of medicine.

These two afflictions have for many years been subjects of bitter and profound controversy, and rightfully so, for both are processes which seem to be ultimately connected with our common heritage: Senility and Death.

These arguments have resulted in establishing definite fields of investigation, and in an assortment of facts. In keeping with modern methods and ideas, endeavor has turned more and more to the essentially basic elements of the afflicted vascular system. The arterioles constitute a very important part of the basic element, or peripheral vascular system.

Arteriolosclerosis, chiefly as regards etiology and pathology, then will form the subject matter of this thesis.

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HISTORY, DEFINITION AND ETIOLOGY

ARTERIOLOSCLEROSIS

Attempts at defining and classifying arteriolosclerosis are similar to like proceedures for arteriosclerosis, in that they are always open to criticism.

There is first the question, whether or not arteriolar sclerosis should be made a part of the general term arteriosclerosis.(1) This has been done by many authors and workers, and still is done, but many now feel that the term is too inclusive. Pal,(2) expresses this when he suggests that all so called sclerosis, fibrosis and calcification, of the vascular system be subdivided into intimasclerosis and mediasclerosis.

Fritz van Mueller, is credited with first using the term arteriolosclerosis in 1817. He used it to designate an independent arteriole sclerosis--a pronounced systemic disease.(2) In 1842 Jean Cruveillier, in his "Atlas of Anatomy" mentions arteriole changes and a little later he describes extreme sclerotic changes of the arterioles, in his extensive series on"Pathology".

Although Bright in his treatise on the "Diseases of the Kidney" mentions sclerosis of the walls of the larger arteries, seen in kidney affections, George Johnson, in 1852, is given credit for first describing a thickening of the minute vessels in post-inflammatory contraction of the kidneys.

It was in 1872, that Sir William Gull and Henry Sutton edited

their paper on the "Pathology of the Contracted Kidney in Bright's disease", and used the term "Arterio-Capillary Fibrosis" to describe the change seen in the small vessels. This paper is perhaps the best known of the earlier papers and is credited with being the first paper on arteriolosclerosis per se. In 1876, following the early extended use of the ophthalmoscope, Gowers, an ophthalmologist, called attention to the generalized reduction in the size of the retinal arteries in certain nephritics. Raehlmann published the first extensive description of sclerosis of the retinal arteries in 1889. Marcus Gunn 11 years later elaborated and extended this work.(4)

Concerning the work of Johnson, Gull and Sutton and the other even earlier workers, Allbutt,(5) and Kernohan(6) have said that although it is classic and pioneering, it is not especially valuable now because of their inferior technique.

Jores is probably the first to have done any extensive work on arteriolosclerosis using modern equipment and methods. This was done in 1904, and has been constantly referred to by countless workers and writers since.(6)

In so far as the literature and work done before 1904 are only of minor value, we shall refer to it as infrequently as possible, except in a historical interest.

Aschoff in defining arteriolosclerosis is particular to see that it is distinguished from arteriosclerosis, he says:"In contr-

distinction to arteriosclerosis which is an affection of the arteries properly so called, arteriolosclerosis is an affection of the precapillary arterioles usually manifesting itself by hyalin and lipoid imbibitions on the part of the vascular wall."(1)

Friedenwald also makes a distinction:"Distinct from this atheromatous disease is the condition of arteriolosclerosis which is characterized by hyalin-lipoid infiltration of the intima and media of the vessels"(7)

Ophuls,(8) on the other hand would make arteriolar sclerosis simply a diffuse hyperplastic sclerosis of the arterioles, which is the intimasclerosis of Pal. Pal however says they are not the same, and that sclerosis of the arterioles holds an independent position; being either a partial manifestation of a general intimasclerosis or a special affection. Bell and Clawson,(9) put it a little differently-"Arteriolosclerosis is not a distinct pathologic entity but an extension of arterial disease into the terminal branches". Neuberger takes much the same stand as Ophuls.(10) Stieglitz,(11) simply states that arteriolar sclerosis is a fibrosis of the walls of the arterioles.

Because even the term arteriolosclerosis is an inclusive one attempts have been made to subdivide and simplify it.

Allbutt recognized at least three types of renal arteriolar sclerosis. 1.Arterioles damaged and sharing in a general vascular decay. 2.Arterioles affected by some infective cause. 3.Arterioles

damaged by long continued high pressures.(5)

Wagener has distinguished four types of retinal sclerosis: 1.Consecutive--hypertension. 2.Primary--inflammatory 3.Secondary--post-inflammatory 4.Senile. He adds a word of explanation:"I attempted to distinguish from among the general signs of sclerosis those signs which were especially characteristic of each of these groups. Thus I called attention to the relatively uniform involvement of the arteries and especially to their generalized constriction in the hypertension type, to the more irregularly distributed and the more obliterative character of the sclerosis in the primary type, to the predominance of perivascular changes in the sclerosis secondary to edema or inflammation of the retina or optic nerve, and to the general attenuation of the vessels, and their loss of sheen in the senile retina".(4)

Further consideration of this question will be taken up when the pathology of the arterioles is discussed.

The etiology of arteriolosclerosis is probably the most debated phase of the subject. This is also true of arteriosclerosis. Never the less, the theories and facts pertaining to one do not necessarily hold for the other, as will be illustrated.(1),(12)

Many attempts have been made to piece together the known facts on arteriolosclerosis and arrive at a definite etiological answer. To date, it is generally agreed, no sucess has attended these efforts. If anything, the mystery has deepened with the flood of literature and experiments and clinical reports.

If we are willing to admit several etiological factors, acting in different ways, and are not to inquisitve as to just how it all takes place we may be somewhat satisfied. At the present it is the best we have.

The one point of near general agreement is that there is a form of sclerosis attacking the vascular system thruout, which comes on with age and which may be termed involutionary sclerosis. (5),(13),(14). Under Allbutt's classification this is the first type or those arterioles sharing in a general vascular decay. We are left with two other forms, at least, as mentioned. Because of the convenience of such a classification it will be used. We must however recognize its faults. Not the least ones being that it is empirical and dogmatic.

While agreeing that there is an involutionary sclerosis, there is a lack of agreement as to why and how it takes place. Ophuls, (8), has this to say:"Various suggestions have been offered, such as the presence of constitutional inferiority of the arteries, the development of senile changes in them or other unknown physico-chemical changes, and finally functional wear and tear has been advanced as an adequate cause." Aschoff,(1a) in particular has emphasized the last, and formulates his ideas, for arteriosclerosis in general, as follows:"The functional wear and tear or excessive stresses cause a loosening of the ground substance of certain systems together with reactive proliferation of other systems.

The entering blood plasma renders apparent the functional deterioration, more or less clearly, according to its content of cholesterolesters or of calcium. In this manner it makes visible the fact that deterioration has occurred and by chemical changes and necrosis advances to the formation of calcareous plates or ulcerations which form the end links in a continuous chain of one and the same process."

This theory, of course, needs confirmation, but it is illustrative of the amount of unproven facts used, and needed, to explain a phase of the subject. We still know so little about the process of aging that any discussion of it is theoretical.

Concerning the infective cause of arteriolar sclerosis-as given by Allbutt, there is also much disagreement. Fahr,(15) was among the first to advocate arteriolar changes as inflammatory in nature and toxic in origin. However, he used the terms "necrotizing arteritis and arteriolitis" locally, and "malignant sclerosis" for the process in general. He has been widely criticized. Especial criticism has been directed at his use of the term "arteriolitis", in connection with sclerosis.(15) At the present time the field seems about evenly divided on the importance of infections in sclerosis of the arterioles. Many believe they are of paramount importance.(2),(16),(17). At the same time such men as Aschoff and Moschcowitz say that the only infectious sclerosis of any importance is that of syphilis, and some question whether this process should not be termed an arteritis instead of a sclerosis.

Finally we come to Allbutt's third type of arteriolosclerosis, in which the arterioles are damaged by long continued high pressure. In more recent times this has become a subject of great interest. This is because of its relationship to Hypertension.

It will be impossible to go very fully into a discussion of Hypertension, due to its present magnitude. Therefore, it will be touched upon only as to pathogenesis and etiology, other than a discussion of its relationship to arteriolar sclerosis. This is distinctly meant to infer that the pathogenesis and etiology of hypertension may or may not be related to a similar phase of arteriolosclerosis. This is for the future to decide.(8)

The meaning of hypertension varies as to persons, field of specialization, and even as to countries. The latter, perhaps, because of the difficulties between languages. In general we may say hypertension is a state of vascular tension above the normal. It has also been defined as an irritable vasomotor condition.(11a) The word "hypertonia", is often seen in literature, especially translations from German. Pal,(2) says it is used in the following two ways: Ordinary hypertension or high blood pressure, and to indicate increased proper tension of the arterial wall muscles.

For convenience it has been subdivided into the Benign, the Severe and the Malignant types. This grouping is based chiefly on the rapidity with which it develops and remains at any level. The difference between the three is apparently only in degree.(9), (12).

Looking at hypertension from the standpoint of a physiologist it seems to mean one thing in particular; A compensatory reaction designed to restore a normal blood supply to the tissues, such a reaction being brought on, usually, by the increased peripheral resistance.(18) Wiggers accepts this, but adds the factor of decreased elasticity of the aorta.(19) Stieglitz, however points out that any decrease in the elasticity of the aorta does not mean that the arteriosclerosis of the large vessel has anything to do with the hypertension.(11a) They are separate entities, and are simply superimposed, the hypertension then acting to aggravate the arteriolosclerosis.

From a pathological standpoint, this compensatory mechanism caused by an increased peripheral resistance, is not satisfactory. That is, it is not entirely satisfactory.(12),(20),(21). For, admitting this to be the main factor in hypertension, the natural sequence is that the lesions of arteriolosclerosis are responsible, in cases of long standing hypertension. The great majority of men working in this field do not believe this is true.(12),(1),(22),(23),(24),(9). Aschoff sums it up as follows:"If it is at all justifiable to advance an opinion at this time, it would seem that the hypertonia is to be regarded as the cause of the arteriolosclerosis of these vessels."

To explain hypertension, or rather the cause of it, from a pathological aspect many theories have been advanced. A few may

well be considered.

The theory that hypertension was primarily due to a renal condition, so popular years ago, seems to have been almost entirely disproved.(2)

At the present time the idea that there is a circulating toxin or pressor substance or hormone is the most debated. This substance whatever it is, supposedly circulates in the vascular system. By some it is supposed to directly attack the cells of the vessel wall, interfering with metabolism and causing a defensive elevation of blood pressure to hasten the removal of the offending substance.(13) Another view is that the substance directly affects or stimulates the vascular walls, in just what manner is not specified.(22),(25). Zimmer,(26) supported by work of Thomas,(27) and Heinbecker,(28) postulates a theory in which an imbalance of cations acts as a factor in producing hypertension by an alteration of the physiological state of the cell membranes, leading to an alteration of stimulus reception and conduction and increased irritability. Several other workers have supposed some sort of factor, other than an arteriolosclerosis, but offer no suggestions as to its nature.(29),(30),(21) An older view that adrenalin might be the causative factor seems to have been ruled out.(11),(21)

Opposed to the theory of a circulating toxin or pressor substance is the work of Moschcowitz and Allbutt. Moschcowitz,(14) has found an independence of incidence of arteriosclerosis in the

greater and lesser circulations. From this he says that it seems improbable that any toxins, metabolic products, food poisons, and so forth can cause arteriosclerosis, as the same blood bathes both circulations. Allbutt,(5) also holds this view. A recent paper by Wakerlin and Bruner,(31) states that no significant differences were found in the vasoconstricting properties of the hypertensive and of the normal serums. From which the conclusion was drawn, that there is no peripheral acting pressor substance in the blood of patients with Essential Hypertension.

Following along another line of reasoning are several theories which to date have never been definitely proved or disproved. Bordley and Baker,(32) have suggested;"That since arteriolosclerosis has been found without exception in the medulla oblongata in cases with a history of hypertension the localization of this process in the medulla oblongata may be the essential factor in the production of persistent high blood pressure." adding,"Although we recognize the objection that these changes may be secondary to the hypertension" Lange,(23) doubts this. Cutler,(33) concludes from his study:"If the high blood pressure is due to a lack of blood supply to the vasomotor center, it is evident from the studies that this abnormal condition is not caused by any demonstrable anatomic changes in the arteries of this region."

Other workers have reached the conclusion that the actual level of the blood pressure in hypertension is the sum of the local need for oxygen and the accumulation of lactic acid within

the vasomotor centers of the medulla as a consequence of local circulatory disturbance (spasms, sclerosis), plus the pathologically increased responses to the stimulus of the normal carbon dioxide tension of the blood and of different kinds of sensitive and emotional stimuli.(34)

Lange,(23) sums up the question of hypertension:"For the time being it will be wise to continue regarding hypertonia as a mere symptom and to search for the real cause of the disease. Just at present the further investigation of the humoral factors would seem to indicate the most promising direction for this search."

The relationship between arteriolar sclerosis and nephritis is still more or less of an open question. Some suggest the factor of the nephritic hypertension as the definite agent.(2),(12) Others believe a circulating poison is also the cause here.(25) Volhard and Fahr,(29a) suggested that there are two groups of nephrities. The one group typified by young subjects in which the nephritis is the initial lesion exciting the development of hypertension and arteriolar sclerosis. The other group, usually older, the arteriolar sclerosis is the initial lesion, exciting the hypertension with renal insufficiency eventually developing either from sclerotic strangulation of the glomeruli or from inflammatory processes added to the sclerotic strangulation.

Since it seems to be so universally agreed that hypertension is a causative factor in arteriolosclerosis, the question arises

as to the modus operandi.

Moschcowitz,(14) says that in as much as hypertension is merely an exaggeration of normal intravascular tension, it is logical deduction that given a sufficient span of time normal intra-vascular tension may produce arteriosclerosis. This accounts for decreseent arteriosclerosis-, Hypertension only brings about these changes sooner and more intensively.

Although this is somewhat explanatory it tells us nothing at all of the mechanics of the process. Stieglitz,(11) has probably done as much as anyone on the functional theory of hypertension and arteriolosclerosis. Because there seems to be no better explanation at the present time we shall use his.

Before going into this theory some review should be made of the anatomy and physiology of the vascular system, particularly in regard to the part played by the arterioles.

It might be well to define as nearly as possible what is meant by an arteriole. It has been used to include small vessels varying from the size of the afferent and interlobular vessels of the kidney,(Fishberg) to the precapillary vessels alone which are the size of the vasa afferentia in the kidney, by Bell and Clawson,(9) Kernohan, Anderson and Keith,(16) base their work on vessels measuring from 25 to 100 microns.

As a standard we may use Maximow,(35) who says the smallest arteries, .3mm in diameter and smaller, are usually grouped into

a separate class and are called arterioles. In the region of the transition between the arterioles and the capillaries some authors distinguish precapillary arterioles. Maximow says this is an ill-defined concept, and that the peculiarities in the structure of the different types of arteries are reflected in their physiologic significance.

In arteries with a caliber of .3mm or less all three coats are present. The tunica intime, the tunica media and the tunica adventitia. The elastic element seen in the greater vessels is almost entirely absent from the arterioles and the media consists of muscular fibres; chiefly circular, which is the most highly developed muscular layer in the vessels of the vascular system. Fishberg says this is an indication of the importance of the role played by changes in arteriole caliber, and that by contraction the arteriolar walls may completely occlude the lumen.

The importance of the arterioles in the regulation of blood pressure is often overlooked, whereas in reality the arterioles are the point of the chief gradient of blood pressure fall in the vascular system, this is said to amount to 20%.(11) The total bed of the stream in the region of the arterioles while greater than that of the arteries, is considerably less than that of the meshwork of capillaries, while difference between the diameters of the two is not very large. On this account the velocity of the blood in the arterioles is very much greater than that obtain-

ing in the capillaries, and since function, and therefore the resistance to the flow of blood through the arterioles must be greater than that often presented by the capillaries. The large part taken by the arterioles in determining the difference of pressure between the arteries and veins is shown by the fact that this difference can be diminished to one half by any means which causes a general dilitation of the arterioles.(36) The great influence of even small changes in the caliber of the lumen of the arterioles on the blood pressure is obvious from the laws governing the flow of fluids in capillary tubes. These laws first studied by Poisseulle and named after him are embodies in a definite equation.(12)

The control of the caliber of the arterioles is dependent upon the constant flow of impulses along the sympathetic nerve fibers to the smooth muscle in the vessel walls. Fluctuations in the intensity of these stimuli account for increased constriction with diminution of the volume of blood flow and increase in the intravascular tension, or for relaxation with greater volume flow and reduction in local blood pressure. The vasomotor nerves contain both constrictor and dilator fibers. Constant impulses thru these fibers are responsible for the normal continuous state of partial contraction or tonus of the vessels.

In summarizing the factors associated with the peripheral resistance, it is important to emphasize the phenomena of compensation and adaptation. The bed of the vascular tree is expansile

and contractile both generally and locally, so that the local demands for increased or decreased flow in certain areas may be met as the need arises. There are more small vessels, arterioles, capillaries and venules than tissue nutrition requires under ordinary circumstances.(11)

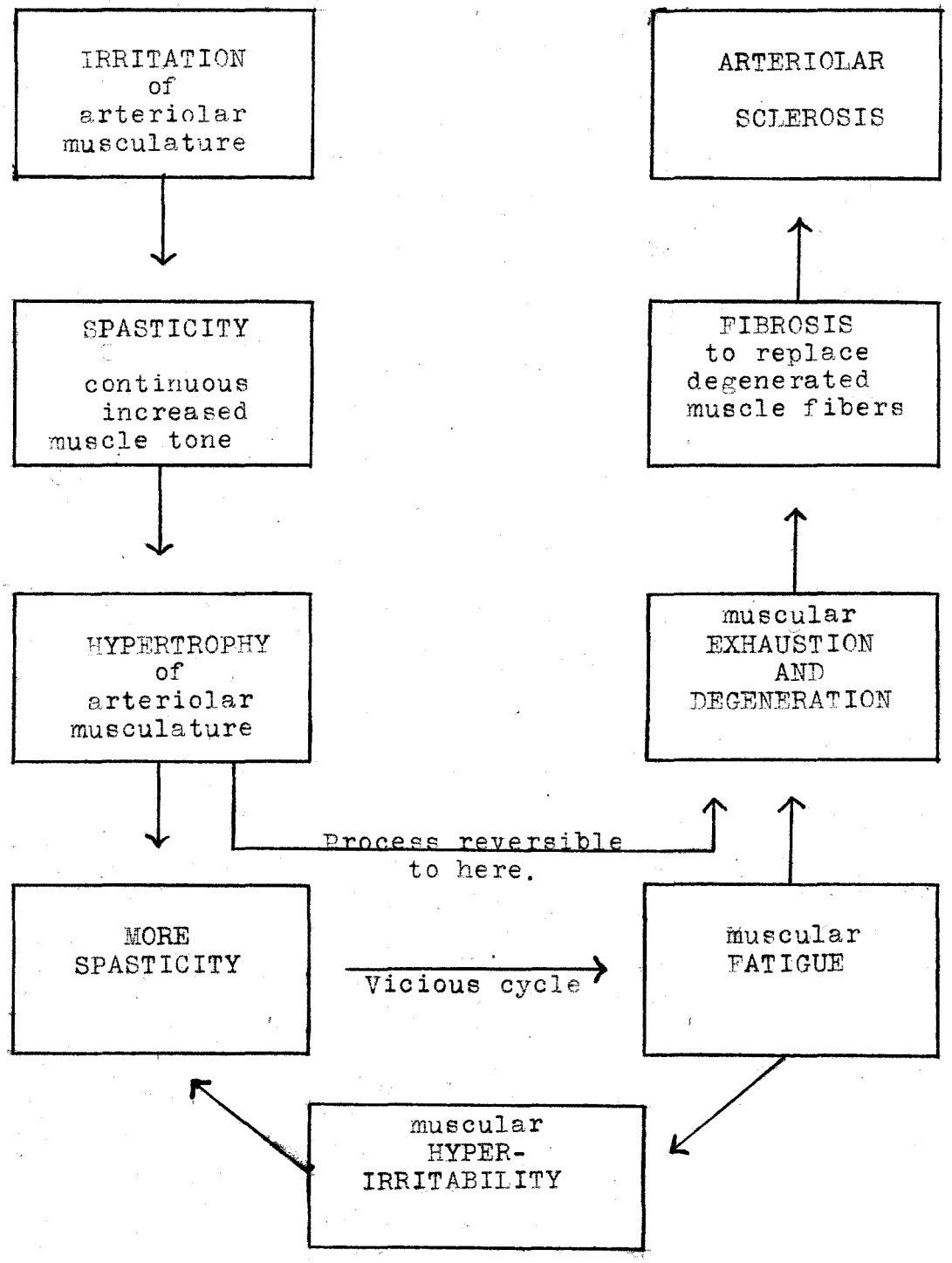
Because the functional theory takes these previously mentioned physiological functions into account it seems all the more rational.

To illustrate this theory the following diagram and explanation are given as presented by Stieglitz.(11)

Chart given on following page.

The process begins with direct or nervous stimulation of the arterial musculature, this leads to increased tonus or spastic contraction. With the continuation of this over a period of time such as weeks or months, the arteriolar musculature hypertrophies, as would any muscle structure under the influence of increased work. As the biceps increase in size in the arm of the practiced rower, the muscles of the medial layer of the arterial walls increase in thickness, both by the addition of more muscle fibers and by augmentation in size of those already there.(6) This has been questioned by Allbutt,(5) but seems logical. This hypertrophy then adds to the degree of vascular constriction by enhancing the strength of the contractile portion of the vessel walls. The same degree of nervous stimulation produces a much more energetic

Diagram from Stieglitz(11)



response in this type of vessel as in a muscular, robust vigorous individual than in a weak vessel or an asthenic frail person. This is the first step in the pathologic processes of hyperpiesis and could best be described as the "initiating process of hypertension."

But muscle fibers are not naturally adapted to continuous load or continuous excess contraction. Fatigue, particularly fatigue resulting from continuous strain, is associated with and the cause of an increased irritability. Fatigue reduces the threshhold of stimulation making for exaggerated response to lower degrees of stimulation. Fatigue, in the sense used here, must be sharply differentiated from exhaustion, when response to stimulation ceases. It has been shown that fatigue, at least muscular fatigue, is a chemical phenomenon, associated with an accumulation of lactic acid and that upon excessive accumulation the power of contraction ceases.(11b) Substances which in greater concentration are toxic or depressant, are in lesser amount or lower concentration distinctly stimulating in effect. -Not only do changes in the concentration of lactic acid play a role in producing the hyperirritability associated with fatigue, but changes in the hydrogen-ion concentration greatly affect muscular response.(11)

The continuous spasticity therefore leads first to hypertrophy, then to fatigue and finally to hyperirritability, and of course to a further increase in the arterial muscular spasticity.

Thus a vicious circle is set in operation.(11c) The continuation of the cycle of spasticity, fatigue, hyperirritability, more spasticity, fatigue, etc., is the second physiologic phenomena and can well be called "the perpetuating process of hypertension" in contrast to the "initiating" process already discussed.

Mumford,(11d) has pointed out that a vessel by constant use of its power of contraction may acquire the habit of so responding to the same degree when the stimulus is lessened or when another form of stimulus is received. Such hypersensitivity may remain in a vessel for a considerable time as a result of habit and represents another aspect of the factor of hyperirritability and the "perpetuating factor".

Fatigue is then followed by exhaustion if exertion continues. Fatigue may be likened to a warning of catastrophy, whereas exhaustion represents the catastrophy. Certain of the muscle fibers, unable to stand the continuous strain, degenerate and die. Their place is taken by collagenic connective tissue. This gradual replacement of smooth muscle fibers with connective tissue is due to the primary degeneration and is not invasive on the part of the connective tissue. As this process continues we have represented the phenomena of arteriolar sclerosis or fibrosis of the walls of the arterioles. Lange,(11e) and others attribute the lack of normal vasomotor response in arteriosclerotic individuals to muscular fatigue. The presence of the fibrosis or "sclerosing

connective tissue" represents an attempt at compensation in giving support to the weakened, degenerating vascular walls and must not be confused with an invasive degenerative process found in the atheromatous arteriosclerosis of larger vessels.

In leaving the question of etiology it must be recognized that many decisive points are as yet undecided. It is also well to remember the remark made by Evans, and reiterated by Bell,"No matter what view one adopts as to the cause of arteriolosclerosis the same difficulty is encountered, viz., why certain arterioles are affected more than others."

PATHOLOGY

In considering the problem of arteriolosclerosis I have followed a suggestion made by Stieglitz,(11) "The usual sequence of discussion of the pathology of a disease is first a description of the anatomic changes and then a discussion of the phenomena causing this. More logical is a description or discussion of the physiologic disturbance followd by a description of the anatomic pathology resulting therefrom. This is particularly true in instances of disturbances of vascular tension because the pathologic changes are the result of the physiologic disturbances and not the cause thereof."

We have already discussed the physiology of the arterioles and seen what changes may lead to sclerosis. Here we shall deal with the changes proper and the sclerosis, chiefly from an anatomic standpoint.

Much of the work on the pathology of arteriolosclerosis has centered about the kidney and to a lesser degree about the eye. There are several reasons for this. In the case of the kidney: It is primarily an organ of excretion and as such has to deal with many of the toxins and metabolic products found in the body. Furthermore the kidney has an intricate and extensive vascular system, predisposing it to circulatory disturbances which if they lead to an increase of the intra-vascular pressure, will cause changes in the vessels.(22) Changes in the renal vessels are intensified and appear earlier than in most other vessels.(12)

In the case of the eye: The changes in the vessels of the eye are important for a different reason than in the case of those of the kidney. For one thing the retina is the only organ whose vascular system is available for direct clinical observation. Fortuneately too, the metabolic requirements of the retina, especially in regard to oxygen, are of such a high order that one would expect functional impairment of the circulation here to produce demonstrable symptoms at a much earlier stage than in almost any other organ. A second reason is that the whole intraocular course of the retinal artery is morphologically equivalent to the terminal arterioles of other organs and is capable of being affected over its entire course with the hyaline degeneration characteristic of arteriolar sclerosis.(7)

In spite of these facts, there still is the question whether clinical changes in the retinal vessels are a very accurate criterion of vessel change elsewhere in the body.(7),(37),(38). Cohen, (39) has found microscopic evidence of sclerosis of the retinal vessels, in cases where they could not be noted clinically.

As the majority of pathological studies on arteriolosclerosis have been made on the vessels of the kidney, they will be the ones considered here.

From the discussion of the functional theory, the first change anatomically apparent should be the relaxed arterioles due to the exhaustion of the muscle cells of the vessel walls.

This has been done, Lohlein,(22) is said to have first described them and later work by Jaffe,(22), McGregor,(40) and Fishberg, (12) have substantiated this. Jaffe, however, has offered another explanation of the dilitation. He says:"I would suggest that the primary renal lesions should be sought in the tufts of the glomeruli. The fatal spasms occur in these. They result in a sudden interruption of the glomerular circulation and in an increase of the pressure in the afferent arterioles. The increased pressure distends the arteriolar wall. This is the first change remaining visible after death". McGregor,(40) does not uphold Jaffe's explanation for she finds that the arteriolar sclerosis preceeds glomerular change. If the glomeruli are damaged the arterioles are sclerosed, but the glomeruli often are not damaged tho the arterioles are.

We might expect the next change to be a partial replacement of the muscle cells of the arteriole walls by connective tissue. This too has been found.

Fishberg,(12) however, has found in his studies that the histological picture of arteriolosclerosis is different in the smallest artericles, the vasa afferentia, than in the next larger vessels, the vasa interlobulares. Never the less, the changes in both these sizes of vessel occur together and are both due to the same pathogenic factor, the hypertension; the morphological differences between the lesions produced in arterioles of different

sizes are evidently the expression of the divergences in the structure of the walls of the arterioles of unequal size. In the earliest stages of the arteriolosclerosis process in both afferent and interlobular arterioles, the media does not present any marked changes. Later, a progressive atropy of the muscle layer with fatty and hyalin change sets in. Finally, the muscle layer may completely disappear with fibrous replacement.

The question of whether the media hypertrophis or atrophies was introduced as far back as 1868 when Johnson described hypertrophy of the media as being often found pertaining to high blood pressure.(5) A few years later Gull and Sutton,(41) wrote:"Dr. Johnson states that the change in the minute arteries is simply hypertrophy of the muscular coat. But our examinations show that in fact they are thickened by a "hyalin-fibroid formation," and that the muscular coat is often variously atrophied." Allbutt,(5) doubts the hypertrophic nature of the media. Evans,(42) a few years ago, found that the media is thicker than normal as a result of hypertrophy and that the muscle cells may be made out, arranged distinctly in circular rings two or three cells thick. Stieglitz, (11) and others,(6),(23) insist upon a hypertrophy predeeding exhaustion in cases of hypertension, although admitting atrophy to occur a little later. Fishberg,(12) admits a medial hypertrophy in the renal arterioles of young individuals who die in the malignant phase of essential hypertension, especially if the vessels

donot show notable arteriolosclerosis.

To continue then with the morphological changes. In the smallest arterial vessels, of the size of the afferent arterioles of the kidney, the first change noted is hyalin degeneration.(12) The hyalin substance is deposited directly under the endothelium. (9) Longitudinal sections show that the hyalinization does not occur uniformly along the course of the vas afferentia, but usually begins close to the junction with the glomerular tuft. Nor is the hyalinization always uniform circumferentially. The highly refractile hyaline appears pink in ordinary hematoxylin-eosin prep-ararions and yellowish-orange in sections stained by Van Gieson's method. In the early stages this hyalin is not stained by Sudan III or other fat and lipoid reagents, but it subsequently, usually though not always, undergoes fatty change and gives the corresponding staining reactions. But it is to be emphasized that the fatty change is secondary and not an essential part of the arteriosclerotic process; the absence of the microchemical reactions for fat and lipoid should not lead one to consider the arterioles unchanged. In the earliest stages of the arteriolosclerotic process in both afferent and interlobular arterioles, the media does not present any marked changes. Later, a progressive atrophy of the muscle layer with fatty anf hyalin change sets in. Finally, the muscle layer may completely disappear with fibrous replacement.(12)

In the larger interlobular arterioles, the first change ob-

served is hyperplasia of the internal elastic membrane with reduplication and the formation of multiple, interwoven elastic lamellae (Jore's hyperplastic type of intimal thickening). The hyperplastic elastic tissue undergoes regressive changes marked by the appearance of fatty and hyalin substances and reactive proliferation of connective tissue cells resulting in the formation of collagenous connective tissue in the intima. These changes gradually result in marked narrowing of the lumen which may go on to complete obliteration.(12) Evans,(42) says this apparent obliteration of the arteriole lumen is an artafact, often. He adds that the the presence of an internal elastic lamina and its undulating form give an approximate idea of the extent of this medial contraction. He also mentions the frequent increase of fibrous tissue around the vessel due to an increase in the advential layer, or due to perivascular fibrosis.

It might be well to mention, that although obliterative endarteritis shows some likenesses, it is probably a distinct pathological entity.(7) On the other hand while the pathology seen in the malignant phase of hypertension was considered an arteritis by Fahr, it is now considered an extreme form of sclerosis.(9),(44).

Klemperer and Otani,(15) have presented a fairly thorough histological study on the malignant sclerosis of the kidneys. They have found the most outstanding changes not to be those of the glomeruli but necrosis of the arterioles and cellular intimal

proliferation of the distal portions of the interlobular arteries. Which is much like the changes found by Fishberg in less severe forms of arteriolar sclerosis, as mentioned. They, Klemperer and Otani,(15) also observed that a distinquishing feature between subacute glomerular nephritis and this condition is that in glomerular nephritis though necrosis may be present there is always intravascular and perivascular accumulations of polymorphonuclear leukocytes. This is not found in sclerosis.

From their studies they concluded that the cellular intimal proliferation was also arteriosclerotic in nature, the more so because no definite inflammatory reaction, such as intravascular or perivascular infiltration, could be observed. The proliferated cells suffered severe hyalin degeneration and fatty infiltration. The presence of foam cells next to the lumen caused marked narrowing, occasionally complete closure. The histologic picture suggested a rapid intimal proliferation with acute secondary degenerative changes. This acute narrowing could well have been responsible for ischemic changes in the arterioles and glomeruli and explained satisfactorily the ensuing circulatory disturbance of the remaing glomeruli. The arteriolar necrosis and the glomerular changes are conspicuous features which permit the diagnosis of malignant sclerosis, but they are not conclusive of an inflammatory origin of the renal disease. In fact, they are only secondary to a rapidly developing sclerosis of the interlobular arteries.

Murphy and Grill,(44) have called attention to the varying degrees of arteriolar damages that may exist. Vascular lesions may vary from the pre-necrotic stage characterized by advanced arteriolosclerosis with complete occlusion of the lumina of the arterioles to an extensive arteriolonecrosis accompanies by peri-arteriolar and interstitial leucocytic reactions. It has recently been pointed out that there is a definitely increased ratio of the thickness of the wall of the vessels to the diameter of the lumen.

Whether malignant hypertension is a diffuse arteriolar involvement in contra-distinction to benign hypertension--a focal arteriolar involvement, as Jores,(6a) believed, has not been settled as yet.(44) It seems that Jores is probably wrong inat least one respect. That is, in so far as the arterioles of nearly the entire body have been shown to be involved in even cases of benign arteriolosclerosis by Kernohan, Anderson and Keith.(6) And again more recently by Pilcher and Schwab.(46)

Two organs behave peculiarly towards sclerosis of their arterioles. One is the heart; Bell,(20) and Fishberg,(12) have stated that arteriolosclerosis is rare in the cardiac muscle. Recently, Pilcher and Schwab,(46) have been unable to find it all. In view of their findings, they have suggested that perhaps the increased demand for blood on the part of the hypertrophied heart, so uniformly seen in these cases, resulted in the formation of new blood vessels. Unlike in all these respects is the spleen. Here the

occurence of arteriolosclerosis is so frequent that it is now generally accepted as physiological. It has been found present as frequently as ninety-two out of one hundred cases of individuals dying in the ninth decade from a variety of diseases. From the same statistics, fifteen percent of individuals dying in the first decade showed it.(20a) From a pathological aspect the studies are interesting. The arteriole wall shows a hyalin degeneration which involves the entire wall. The wall is irregular in thickness, and the lumen is usually narrowed or completely closed. Lipoid may usually be demonstrated in the hyalin material. No elastic fibers are seen. Herxheimer,(20a) who gave the first complete account believes the process begins in the media but this has been questioned. The muscle of the media is transformed into a homogeneous substance. Occasionally in association with chronic hypertension with renal insufficiency, the small arteries and arterioles are so severely involved with hyalin degeneration that they become completely closed in mumerous places, giving rise to multiple small infarcts throughout the spleen.(20)

No discussion will be presented concerning the changes in the arterioles of the uterus and ovaries as they cannot rightfully be considered an arteriolosclerosis.(20)

In conclusion, it might be said that although at present the functional theory of the cause of arteriolosclerosis seems very attractive, there are many questionable steps. Until such a time as these are proven, an open opinion leaves the best means of retreat.

SUMMARY

In briefly summarizing, we have:

1. Arteriolosclerosis first named in 1817 by Meuller.

2. Gull and Sutton published first comprehensive paper on the subject in 1872. They termed the change arterio-capillary fibrosis. Recognized hyalin-fibroid deposit and atrophy of media.

3. Gowers, in 1876, notes arteriole changes in eye by use of ophthalmoscope.

4. Jores does first modern work in 1904.

5. No generally accepted definition of the subject.

6. Allbutt suggests at least three causes--Infective, senile and hypertensive.

7. Prolonged hypertension intimately related to arteriolar sclerosis.

8. Circulating toxin or pressor substance most accepted probable cause of hypertension.

9. Anatomy and physiology of arterioles discussed.

10. Functional theory of arteriolosclerosis seems most rational at present time.

11. Chief pathological work done on kidney vessels, much clinical work done on eye vessels.

12. Pathological studies to date seem to uphold the functional theory.

13. Chief pathological features apparently are:

    a. Varations in different size vessels.

b. Early hypertrophy of media, followed by atrophy. Subsequent hyalin-fibroid deposit.

c. Comparative little attack on endothelium.

14. Obliterative endarteritis a distinct pathologic entity.

15. Arteriolar changes in malignant form distinct, but probably sclerotic in nature.

16. With few exceptions arteriole change seen through out the body. Exceptions being: a. No sclerotic arterioles seen in the myocardium.

b. Splenic arterioles so often affected considered physiological.

17. Arteriole changes seen in the uterine and ovarian vessels not true arteriolosclerosis.

18. May conclude that the functional theory while best at present needs much additional support.

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