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# ARTERIOLAR SCLEROSIS IN HYPERTENSIVE AND NON-HYPERTENSIVE INDIVIDUALS *

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## INTRODUCTION

The association of cardiac enlargement and renal contraction has been recognized since Bright's classical case reports in 1836. Shortly thereafter Johnson added diffuse disease of the smallest arteries to the pathological anatomy of Bright's disease and in 1873 proposed the theory that renal disease was primary with subsequent diffuse thickening of the walls of the smallest arteries leading to increased peripheral resistance, elevated blood pressure and cardiac hypertrophy.

Subsequent observations added complexity rather than simplification to the problem. Gull and Sutton reported widespread small vessel disease called by them "arterio-capillary fibrosis," and observed that "these changes are, or may be, independent of renal disease, and that the renal change in chronic Bright's disease with contracted kidneys, when present, is but a part of a general morbid condition." They concluded that the diffuse vascular disease was a primary pathological change responsible for

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increased resistance to blood flow. Confirming this general hypothesis were the early clinical observations on blood pressure by Mahomed to the effect that high blood pressure precedes the clinical signs of renal damage.

There were then three divergent views as to the pathogenesis of chronic hypertension: (1) that the renal disease was primary; (2) that the renal disease was but a part of a diffuse primary vascular disease; and (3) that the hypertension itself was primary, the renal and the vascular changes being secondary to it.

The recognition by Jores of two types of contracted kidneys, inflammatory and arteriosclerotic, provided the anatomical basis for differentiating nephritic from essential hypertension. The latter, according to Fishberg's definition which is representative of the majority opinion, is chronic hypertension which neither on clinical nor anatomical grounds can have been caused by preceding inflammatory or obstructive renal disease. It has become generally accepted that the primary change in nephritic hypertension is the renal injury, but the relation of the contracted kidney of nephrosclerosis to hypertension has remained a controversial subject. It is generally believed that the renal vascular disease leads to renal atrophy and contraction but there is a divergence of opinion about the relation as to the cause and effect between the hypertension and the renal vascular disease. Certainly, essential hypertension commonly precedes any clinical evidence of renal insufficiency. Whether or not chronic hypertension precedes the vascular disease that so frequently leads to renal atrophy is the controversial point.

This divergence of opinion as to the relation between essential hypertension and vascular disease may be illustrated by citing the opinions of Volhard and Fahr. Volhard recognized two principal types of hypertension, "pale" and "red." "Pale" hypertension is secondary to renal insufficiency. The renal insufficiency may be due to primary renal disease (glomerulonephritis, and so on) or to the renal vascular damage caused by "red" hypertension, and the "pale" hypertension is the immediate result of the action of pressor substances causing spasm of arterioles throughout the body. "Red" hypertension is primarily a functional derangement to which certain persons are constitutionally predisposed and in which the general distensibility of small arteries is impaired and

blood pressure elevated entirely without primary organic arteriolar contraction. In regard to the "red" or "essential" hypertension his views are based on "the assumption of an early senescence of the whole arterial system, a fatigue of its different structural units, microscopically visible in diminution of internal muscular layer, defects in the elastic layer and over-stretching, all processes commencing while a normal pressure still exists and followed by an increased tonus of the arterioles via vaso-vascularis reflex." This places the cause of essential hypertension outside the kidney except in those instances where the hypertension itself causes renal damage and thus establishes a vicious circle. Fahr, on the other hand, was of the opinion that hypertension is a secondary phenomenon in relation both to inflammatory and to arteriosclerotic renal disease. The primary change is renal and the mechanism by which blood pressure is elevated is, according to him, "compensatory." Bell and Clawson have attempted to harmonize these contradictory views by admitting the absence of any real evidence as to which is antecedent, hypertension or renal vascular disease, but opined that "it is, however, probable that when severe arteriolar sclerosis of the kidney has developed, the circulatory obstruction tends to raise the blood pressure to higher levels."

Critical commentators, such as Hewlett and Boyd, have expressed the belief that the primary change in essential hypertension is functional in the form of arteriolar spasm with resulting increase in peripheral resistance and a later development of permanent structural changes in the form of arteriolar sclerosis which fixes the hypertension by organic narrowing of vessels. Christian and O'Hare felt that the present evidence as to the cause and effect relation of chronic hypertension and arteriolar sclerosis is inadequate to support any definite conclusion as to sequence.

Excluding such possible causes of hypertension as nephritis, urinary obstruction, obesity, hyperthyroidism, pituitary tumor, lead poisoning, adrenal tumor, aortic insufficiency, coarctation of the aorta and arteriovenous aneurysm, there remain the following general conceptions as to the cause and effect relation of arteriolar sclerosis and chronic hypertension:

1. That chronic hypertension is the result of primary renal arteriolar sclerosis, either because a generalized reflex spasm of peripheral vessels is initiated in the ischemic kidneys, or because

of the retention or elaboration of pressor substances incident to a reduced blood flow through the kidney.

2. That chronic hypertension is the result of increased resistance to blood flow caused by widespread primary arteriolar sclerosis with resulting narrowing of vessel lumens.

3. That chronic hypertension is due primarily to arteriolar spasm and that the arteriolar degenerative changes in the kidney and elsewhere are secondary to the increased intravascular pressure and may or may not serve to increase the severity of the hypertension because of organic lumen narrowing.

There is an almost equal lack of agreement as to the character and distribution of vascular lesions in association with essential hypertension. Johnson and Ewald described medial hypertrophy as being a predominant arteriolar change and observed it as occurring generally throughout the body. Gull and Sutton described an equally wide distribution of the arteriolar lesions but believed them to represent degeneration rather than hypertrophy. Jores reported widespread arteriolar intimal hyalinization but failed to find vascular changes in the skeletal muscles. Evans observed medial hypertrophy as well as intimal proliferation and hyalinization in many organs of hypertensive individuals but together with Fishberg and Bell and Clawson failed to discover arteriolar disease in the skeletal muscle. The interest that has been manifested in the occurrence or non-occurrence of arteriolar disease in the skeletal muscle in essential hypertension has been stimulated by the fact that the skeletal muscles constitute so large a part of the peripheral vascular bed. Kernohan, Anderson and Keith reported that the arterioles in skeletal muscles of persons with essential hypertension very frequently showed hypertrophy of the media, proliferation of the intima and reduction of lumen caliber. Scott, Seecof and Hill reported a high incidence of arteriolar lesions in the skeletal muscle of hypertensive patients and Andrus observed more severe fibrosis of the media of arterioles from the skeletal muscles of hypertensive than of non-hypertensive individuals but did not believe that there was wall thickening or reduction of lumen caliber.

The determination of the relation that arteriolar disease bears to chronic hypertension is obviously of more than academic interest especially with the advent of the surgical treatment of the disease.

If permanent organic changes are primary, less can be expected of operations designed to relieve vascular spasm than if the vascular spasm were primary and the organic changes secondary. In the elucidation of the problem it was felt that a clear understanding of the pathological anatomy of hypertension would be of value. Many careful and comprehensive investigations of the pathological anatomy of hypertension have been made and it appeared that the only hope for further morphological or statistical investigations would be the employment of different methods. So far as could be determined no purely objective and yet comprehensive study of the pathological histology, distribution and relative severity of arteriolar lesions in the various organs and tissues of a large number of individuals has been heretofore reported. The correlation of these objective findings with the clinical and anatomical data assembled later was undertaken in the present investigation.

Prior to this objective study of arteriolar disease a general survey was made of the clinical and pathological characteristics of cases of essential hypertension based on the records of the departments of medicine and pathology of Western Reserve University and The University Hospitals.

## General Characteristics of the Population of a Representative Chronic Hypertensive Group

The clinical and autopsy records of 200 consecutive cases of chronic hypertension were studied to determine the age, race and sex characteristics of the disease. These were cases in which there was no significant degree of inflammatory heart disease. They were known to have had prolonged elevation of systolic blood pressure over 150 and diastolic pressure over 100 mm. of mercury, and to have had heart weights in excess of 400 gm. in males and 350 gm. in females. In the presence of obliterative coronary arterial disease heart weights in excess of 500 gm. were required for acceptance. No case was included in this series unless death was due to uremia, cardiac decompensation or cerebral hemorrhage.

The group was comprised of:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 116 | males | with | a | mean | age | of | 52 | years |
| 84 | females | " | " | " | " | " | 50 | " |
| 60 | blacks | " | " | " | " | " | 47 | " P.E.m. 0.9 |
| 140 | whites | " | " | " | " | " | 55 | " P.E.m. 0.5 |

In this series the mean age of females was 2 years lower than the age of males at the time of death. This was not a statistically significant difference. The mean age of blacks was 8 years lower than that of the whites at the time of death which was 7.5 times greater than the P.E. of the difference.

A comparison of the race and sex population of the hypertensive group to the race and sex population of 1177 consecutive autopsies of all kinds performed on individuals over 30 years of age between the years 1930 to 1935 in the same laboratory is shown below.

| | Whites | Blacks | Males | Females |
|---|---|---|---|---|
| | % | % | % | % |
| Cases of chronic hypertension ..... | 70 | 30 | 58 | 42 |
| General autopsy series ..... | 80 | 20 | 60 | 40 |

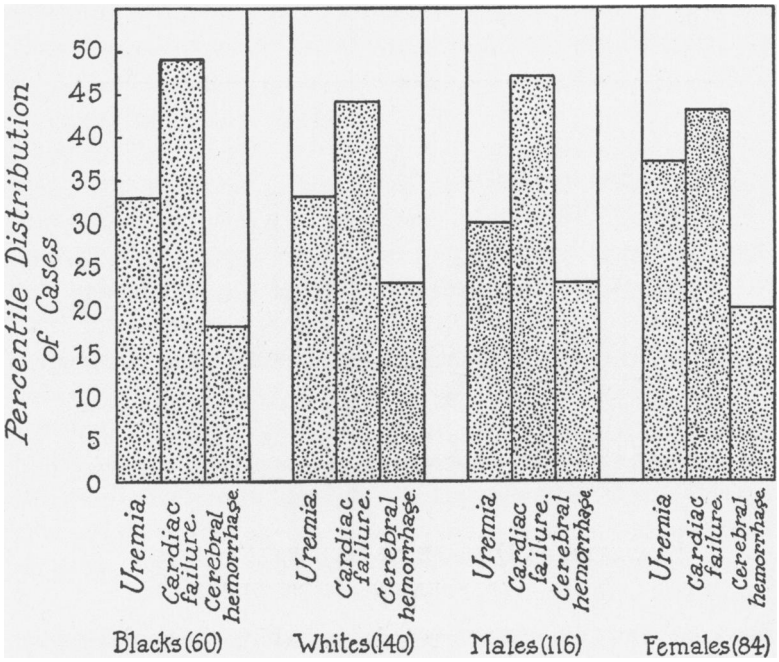
The only significant difference in the population of the chronic hypertensive group as compared to that of the general autopsy series is a racial one. Blacks were encountered with greater relative frequency in the hypertensive group than would be expected from the racial constitution of the general autopsy series. There are 50 per cent more blacks in the hypertensive group than the incidence of the blacks in the general autopsy population would indicate. In contrast there are 13 per cent fewer whites in the hypertensive group than would be expected if whites and blacks had the same degree of mortality from conditions related to chronic hypertension.

Two conclusions appear to be justified as far as this group of 200 cases is concerned: one is that the blacks with chronic hypertension died at a younger age than did whites; and the other is that the percentage of blacks in the hypertensive group was higher than the percentage of whites if the racial constitution of the entire autopsy population was considered.

An investigation was next made of the relation of race and sex to the mode of death in cases of essential hypertension. In the entire group it was found that there were 68 cases in which death was due to uremia, 89 to cardiac decompensation and 43 to cerebral hemorrhage. In Text-Fig. 1 it may be seen that in the different race and sex groups there were no very striking differences in the proportion of each group dead of uremia, cardiac decompensation and cerebral hemorrhage.

The greater susceptibility of blacks over whites to death from

hypertension or its complications was not reflected in the manner in which blacks with hypertension died. About the same percentile proportions of death from uremia, cardiac decompensation and cerebral hemorrhage were seen in blacks, whites, males and females.

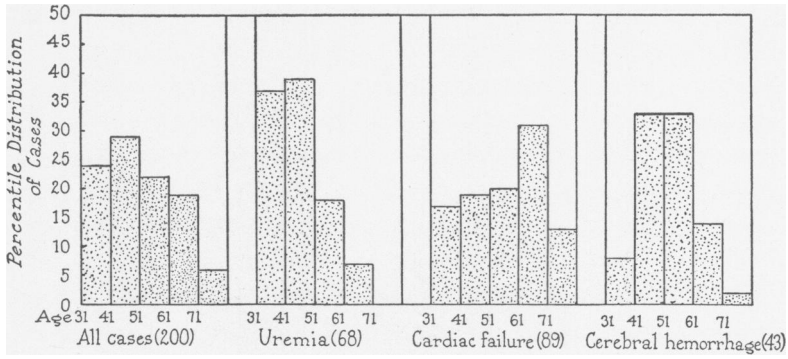



Text Fig. 1.- Relation of race and sex to mode of death in 200 consecutive cases of chronic hypertension.

The correlation of age and mode of death showed striking differences in the age at death of the various types of chronic hypertension. In Text-Fig. 2 it may be seen that the highest incidence of death from uremia was in the 4th and 5th decades. Seventy-five per cent of all the individuals dead from uremia died under 51 years of age. The age incidence was quite different in the groups dead of heart failure and cerebral hemorrhage. In these, death occurred after the age of 51 in 64 per cent and 49 per cent respectively.

Of some significance is the high incidence of obliterative coro-

nary arterial disease in the group of chronic hypertensives dead of heart failure. Forty per cent of all those dead of heart failure were found to have either remote coronary thrombosis or obliterative coronary sclerosis. The incidence of severe coronary arterial disease in the chronic hypertensives dead of cardiac decompensation began at 27 per cent in the 4th decade and rose to 60 per cent in the 7th.




Text Fig. 2. Age at death of 200 consecutive cases of chronic hypertension in which death was due to uremia, cardiac failure or cerebral hemorrhage.

## Arteriolar Disease in Hypertensive and Non-Hypertensive Individuals

*Selection of Cases:* The material on which the major part of this study was made was comprised of 200 cases: 100 had no history of hypertension and the other 100 were known to have had chronic hypertension. Obviously, the possibility of hypertension having been present at some time in some members of the control group could not be positively excluded. The acceptance of a case as non-hypertensive depended on the fulfillment of two criteria. One was that there must have been repeated blood pressure determinations, none of which exceeded 140/90 and the heart weights in males were required to be less than 400 and the females less than 300 gm. As a further means of excluding cardiac hypertrophy, all hearts were examined microscopically and any showing histological evidence of hypertrophy were excluded. All cases selected for the chronic hypertensive group had repeated blood pressure determinations higher than 160/90 or 150/100. No male

was included in this group if the heart weighed less than 450 gm. and no female if the heart weighed less than 350 gm. Cases of inflammatory heart disease were excluded and if severe coronary arteriosclerosis were present, a heart weight in excess of 500 gm. was required for acceptance. The frequent occurrence of cardiac hypertrophy leading to heart weights up to 500 gm. in non-hypertensive individuals as the result of focal myocardial ischemia and dilatation in severe coronary disease has been described by Moritz and Beck. These cases were selected on the basis of the above outlined criteria and with no knowledge as to the presence or absence of renal or vascular disease. The selection was made in such a manner that the population of the two groups was similar in regard to age, sex and color. Approximately one-third of each group was comprised of individuals between 31 and 45 years of age, one-third between 46 and 60, and one-third 61 years of age or over.

*Size of Vessels Studied:* No satisfactory definition of an arteriole was found, other than that the smallest arteries are arterioles. A variety of criteria have been proposed to distinguish between small arteries and arterioles (Maximow, Cowdry, Benninghoff). These include the number of layers of smooth muscle in the media, the existence of an internal elastic lamella and the external cross sectional diameter of the vessel. We have not found any of these distinctions useful and propose to use the terms "arteriole" and "small artery" interchangeably. This investigation, however, was directed at arteries that had an external diameter of 100 $\mu$ or less.

*Methods of Investigation:* Various staining methods were found useful in a study of the exact anatomical character of certain arteriolar lesions. In addition to hematoxylin-eosin, the most important methods used were Weigert's for elastic tissue and van Gieson's for connective tissue. In studying a particular type of lesion, sections were cut in uninterrupted series and were stained in rotation with hematoxylin-eosin, Weigert's, van Gieson's, the Wilder method for reticulum, and the Mallory-Heidenhain azan-carmine method for connective tissue. In vessels chosen to illustrate certain types of vascular change, the hematoxylin-eosin stained preparation of the vessel was photographed and then the artist made a colored drawing using the photograph for structural

orientation and the slide for color detail. The same section was then decolorized and restained by the van Gieson method. The original drawing served for structural orientation and a second drawing was made again using the slide for color detail. The section was decolorized and restained for elastic fibrils and this time the drawing of the elastic fibrils was either superimposed on the drawing made from the van Gieson preparation or a third drawing of the same vessel was made showing the distribution of the elastic tissue with a neutral counterstain of the rest of the vessel.

Another useful method for the investigation of the pathological anatomy of arteriolar lesions was by means of uninterrupted series of sections. Nine uninterrupted series varying between 100 and 400 in each were prepared from various tissues to study the longitudinal extent and distribution of different types of arteriolar lesions.

*Recording of Data:* All of the sections of a given organ or tissue in each of the 200 cases were examined objectively with no knowledge as to the presence or absence of hypertension and a record was made as to the kind and severity of the arteriolar disease present. The severity of the arteriolar changes was recorded as mild, moderate or severe by the symbols +, ++ and +++. If the arteriolar disease was focal in a given tissue, a note was made as to the kind of lesion and the fact that it was focal, but such disease was ignored in the general classification of the severity of arteriolar sclerosis in a given tissue. Every organ finally classified as being the seat of mild, moderate or severe arteriolar sclerosis was characterized by the presence of diffuse vascular disease. In many cases of mild, and in some instances of moderate or severe sclerosis, all of the arterioles were not affected, but invariably enough were changed to constitute a general rather than a local process within that organ or tissue.

These degrees of change were not comparable to one another in different tissues. Severe arteriolar sclerosis in a skeletal muscle was not of the same grade of severity or even the same kind of vascular disease as was present in severe arteriolar sclerosis in the spleen. Mild, moderate or severe, refer to the three grades of severity in the particular tissue under consideration.

## Pathological Histology of Chronic Arteriolosclerosis

*Intimal Hyalinization:* This was the most common form of chronic arteriolar disease observed and consisted of a subendothelial accumulation of homogeneous, acidophilic material which appeared to represent an infiltration or expansion of the ground substance between smooth muscle of the media and the endothelium. Vacuolar degeneration, either fatty or hydropic, was common and although there was considerable variation in staining reaction of the hyalin, it usually stained deep blue with the Mallory-Heidenhain azan-carmine and the Mallory connective tissue methods, yellow with the van Gieson, and green with the Masson trichrome light green stain. The disposition of hyalin varied, being sometimes in the form of circumscribed subendothelial plaques (Fig. 1), sometimes a subendothelial collar of uniform thickness, and sometimes annular but of irregular thickness, so as to displace the lumen to an eccentric position (Fig. 2). The longitudinal distribution of the hyalin along a vessel was also variable with normal segments interspersed between diseased segments. Not all arterioles with intimal hyalinization had narrowed lumens and some actually appeared to be dilated (Fig. 3). This apparent dilatation was thought to be due to an increased resistance to postmortem contraction imparted to the vessels because of the hyalin, this view being supported by the frequent absence of undulation of the internal elastic lamella of such vessels.

The relation of the internal elastic lamella to the hyalin varied considerably. Although the principal mass accretion of hyalin was commonly inside of the internal elastic lamella (Figs. 1 and 3), it appeared that the hyalin actually enveloped the elastic lamella which in many vessels lay approximately in the center of the hyaline mass (Fig. 2). In such circumstances, elastic degeneration was invariable and was represented by swelling, disruption and dispersion of fibers with eventual complete disappearance.

*Medial Hypertrophy and Degeneration:* Two types of chronic medial change in the arterioles were observed. One was manifested by increased medial thickness due to an increase in the number or size of smooth muscle cells (Fig. 5), and the other was represented by a relative increase in the amount of intercellular collagen throughout the media (Fig. 6). Although these changes

did occur independently of one another, yet they occurred together (Fig. 6) with such regularity that in the grading of arteriolar lesions according to severity the two changes were treated as though they were part of the same process.

Variations in the degree of postmortem contraction of vessels seen in different individuals or in different vessels of the same individual frequently made it difficult to identify medial hypertrophy. When true hypertrophy of the media had occurred (Fig. 5) the increased thickness of the media was not associated with the same degree of undulation of the internal elastic lamella as was present in normal vessels (Fig. 4), which appeared to have thick walls because of excessive postmortem contraction.

In normal arterioles the media was seen to have three components — smooth muscle, intercellular collagen and occasional irregularly disposed elastic fibers. With the van Gieson method the collagen stained very faintly or not at all in normal arterioles (Fig. 4), but in arterioles the seat of medial degeneration, the increase in collagen was readily recognized (Fig. 6). The increase in collagen was not associated with penetration of the media by fibrocytes, was more pronounced in the inner than in the outer half of the media, and was in some instances associated with atrophy rather than hypertrophy of smooth muscle cells. Medial degeneration showed marked segmental variation, as was the case also in intimal hyalinization. In some segments the medial degeneration was associated with severe secondary degenerative changes so as to cause stenosis of the lumen (Figs. 7 and 8). As a rule this change occurred independently of any intimal disease.

*Endothelial Hyperplasia:* Endothelial hyperplasia regularly resulting in reduction in lumen caliber was seen most frequently in vessels over 50 $\mu$ in diameter, occasionally in arterioles down to 30 $\mu$ in diameter, but rarely under this. As a rule the hyperplastic endothelium of the larger arterioles gave way gradually to intimal hyalinization in the smaller arterioles. It was not possible to recognize endothelial proliferation with certainty when all of the endothelium was represented by lining cells. In such circumstances postmortem contraction of the vessels together with tangential section could give an illusion of endothelial hyperplasia. The piling up of endothelial cells layer on layer did, however, present a clear picture of endothelial hyperplasia (Figs. 9 and 10).

Such hyperplasia was in rare instances superimposed on a relatively unaltered internal elastic lamella (Fig. 9). More commonly, however, there was formation of new elastic fibers between the hyperplastic endothelial cells. In some vessels this new elastic tissue formed an irregular intercellular mesh, which in others was seen to be organized to form more or less concentric lamellas, the lamellas being separated from one another by newly formed endothelial cells (Fig. 10). As in the case of the media, there was no recognizable penetration of the intima by fibrocytes although the proliferated endothelial cells tended to become spindle shaped so as to resemble fibrous connective cells closely. As in the case of intimal hyalinization, the elastic fibers, both new and old, showed a pronounced tendency to degeneration, as manifested by swelling, disruption and dispersion of fibrils. This degeneration of elastic fibers was especially pronounced when the proliferated endothelium underwent hyalinization, which was a common secondary degenerative change in vessels affected in this manner (Fig. 10). A wide variety of acute secondary degenerative changes was seen and will be described later.

## Pathological Changes in Arterioles of Non-Hypertensive Individuals

As already indicated, this study was directed at chronic rather than acute arteriolar changes. Acute primary degenerative and inflammatory arterial and arteriolar disease have been discussed recently by Karsner and were not studied in this investigation.

The incidence and relative severity of arteriolar sclerosis in the various organs and tissues in non-hypertensives is summarized in Table I. The table does not include a record of the vascular changes in the female internal genitalia where cyclic hyperplasia and involution make their occurrence exceedingly common, or changes in various tissues not examined with sufficient frequency to make statistical comparisons profitable. The heart and lungs were not included in the table because of the rarity of arteriolar changes in those situations in this series of cases. Pulmonary (Parker and Weiss) and myocardial (Karsner and Bayless) arteriolar sclerosis is seen most commonly in cases of rheumatic carditis and since no individuals with cardiac enlargement were

## TABLE I

*The Relation of Age, Sex and Race to the Incidence and Severity of Arteriolar Sclerosis in Non-Hypertensive Individuals*

| Age Groups | Spleen | | | Pancreas | | | Adrenal | | | Gastro-Intestinal | | | Brain * | | | Skeletal muscle | | | Liver | | | Kidney | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total |
| *yrs.* | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % |
| 31–45 | 56 | 17 | 73 | 38 | 0 | 38 | 25 | 0 | 25 | 12 | 0 | 12 | .. | .. | .. | 17 | 0 | 17 | 3 | 0 | 3 | 7 | 0 | 7 |
| 46–60 | 63 | 19 | 82 | 33 | 6 | 39 | 39 | 5 | 44 | 16 | 0 | 16 | .. | .. | .. | 20 | 0 | 20 | 6 | 0 | 6 | 9 | 0 | 9 |
| 61 and over | 74 | 26 | 100 | 50 | 5 | 55 | 41 | 12 | 53 | 27 | 0 | 27 | .. | .. | .. | 13 | 0 | 13 | 24 | 5 | 29 | 16 | 0 | 16 |
| Total | 65 | 21 | 86 | 38 | 5 | 43 | 36 | 6 | 42 | 19 | 0 | 19 | 17 | 0 | 17 | 15 | 0 | 15 | 11 | 2 | 13 | 12 | 0 | 12 |
| **Sex Groups** | | | | | | | | | | | | | | | | | | | | | | | | |
| Male | 63 | 23 | 86 | 43 | 6 | 49 | 40 | 7 | 47 | 18 | 0 | 18 | .. | .. | .. | 12 | 0 | 12 | 10 | 2 | 14 | 12 | 0 | 12 |
| Female | 68 | 17 | 85 | 32 | 2 | 34 | 31 | 4 | 35 | 20 | 0 | 20 | .. | .. | .. | 21 | 0 | 21 | 13 | 2 | 15 | 10 | 0 | 10 |
| **Racial Groups** | | | | | | | | | | | | | | | | | | | | | | | | |
| White | 65 | 20 | 85 | 37 | 7 | 44 | 33 | 6 | 39 | 21 | 0 | 21 | .. | .. | .. | 13 | 0 | 13 | 10 | 2 | 14 | 13 | 0 | 13 |
| Black | 66 | 22 | 88 | 40 | 0 | 40 | 40 | 5 | 45 | 15 | 0 | 15 | .. | .. | .. | 18 | 0 | 18 | 17 | 4 | 12 | 10 | 0 | 10 |

* Brain examined in 29 cases only.

included in the control group most cases of rheumatic heart disease were automatically excluded.

*Distribution of Arteriolar Sclerosis:* An examination of the total incidence of arteriolar sclerosis in the various tissues of non-hypertensives showed a high incidence in the spleen (86 per cent), pancreas (43 per cent) and adrenal capsules (42 per cent). Of all the tissues recorded in Table I, the renal arterioles were found to be least frequently diseased. There were 12 instances of renal arteriolar sclerosis in the entire control group, and of these, the sclerosis was classified as mild in 10 and moderately severe in 2.

### *Occurrence of Various Histological Types of Chronic Arteriolar Changes in Non-Hypertensive Individuals*

*Intimal Hyalinization:* All three anatomical types of chronic arteriolar disease were seen. The most common was intimal hyalinization. In the control group this was more pronounced in vessels over 50 $\mu$ in diameter. It was found most commonly in the spleen, pancreas, the capsules of the adrenals, brain, eye and kidney. It occurred in vessels of the internal genitalia and in the hyperplastic intima of arterioles in regions the seat of chronic or healed inflammation. It was rarely found in the gastro-intestinal tract except in association with inflammation, in liver, skeletal muscle, subcutaneous tissue, lymph nodes or bone marrow.

*Medial Hypertrophy and Degeneration:* Medial hypertrophy and degeneration were seen in the gastro-intestinal tract in 19 per cent and in the skeletal muscle of 15 per cent of the non-hypertensives. In no instance was it graded as a severe change. This type of arteriolar disease was seen frequently in the spleen but was usually obscured by the more striking intimal disease.

*Endothelial Hyperplasia:* Intimal endothelial hyperplasia in the arterioles of the non-hypertensive group was seen principally in association with involutional or inflammatory changes. It was seen almost constantly in the ovary, uterus and Fallopian tubes. It was seen in the adventitial arterioles in syphilitic aortitis and in association with chronic peptic ulcer, cholecystitis and appendicitis and a variety of other chronic inflammatory conditions. Medial degeneration in the form of intercellular collagen as well as intimal hyalinization were frequently associated changes.

*Age and Sex Differences:* Table I shows the relation of age to the incidence and severity of arteriolar sclerosis in the non-hypertensive group. In practically all of the tissues examined the arteriolar lesions were seen with greater frequency and severity as age advanced. There were no consistent differences between males and females or between blacks and whites in regard to incidence or severity of arteriolar sclerosis.

## Pathological Changes in Arterioles of Hypertensive Individuals

The incidence and severity of arteriolar sclerosis in the various organs and tissues of the hypertensive group are shown in Table II. As in the case of Table I, the internal genitalia are not included because of the common occurrence of vascular changes associated with cyclic involution and hyperplasia. The heart and lungs were omitted because of the rarity of chronic arteriolar changes in these situations in hypertensives except in association with rheumatic heart disease.

*Distribution and Severity of Arteriolar Lesions:* An examination of the total incidence of arteriolar sclerosis in the various tissues shows approximately the same frequency in the spleen and the kidney, 98 per cent and 97 per cent respectively. In the hypertensive group there was approximately the same sequence of organs, according to the incidence of arteriolar disease, except for the kidney, which changed from being one of the organs least frequently the seat of arteriolar sclerosis in the non-hypertensives to sharing first place with the spleen in being most frequently the seat of arteriolar sclerosis. In every organ and tissue, however, there was an increase in both frequency and severity of arteriolar disease throughout the hypertensive group as compared to the controls.

In grading, arteriolar sclerosis was designated as mild, moderate or severe. In the hypertensive group, severe arteriolar sclerosis was observed in the kidneys (47 per cent), gastro-intestinal tract (15 per cent), skeletal muscle (14 per cent), liver (11 per cent) and brain (8 per cent), in contrast with the non-occurrence of severe arteriolar sclerosis in any of those situations in members of the control group. Although severe vascular lesions were ob-

## Table II

*The Relation of Age, Sex and Race to the Incidence and Severity of Arteriolar Sclerosis in Hypertensive Individuals*

| Age Groups | Spleen | | | Pancreas | | | Adrenal | | | Gastro-Intestinal | | | Brain * | | | Skeletal muscle | | | Liver | | | Kidney | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total | Mild or moderate | Severe | Total |
| *yrs.* | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % | % |
| 31–45 | 46 | 54 | 100 | 21 | 52 | 73 | 51 | 39 | 90 | 44 | 20 | 64 | .. | .. | .. | 64 | 17 | 81 | 38 | 9 | 47 | 33 | 67 | 100 |
| 46–60 | 39 | 61 | 100 | 28 | 62 | 90 | 56 | 38 | 94 | 64 | 15 | 79 | .. | .. | .. | 62 | 25 | 87 | 36 | 19 | 55 | 46 | 50 | 96 |
| 61 and over | 44 | 52 | 96 | 56 | 31 | 87 | 50 | 44 | 94 | 48 | 7 | 55 | .. | .. | .. | 48 | 3 | 51 | 41 | 6 | 47 | 72 | 22 | 94 |
| Total | 44 | 55 | 99 | 40 | 47 | 87 | 51 | 42 | 93 | 55 | 15 | 70 | 42 | 8 | 50 | 58 | 14 | 72 | 38 | 11 | 49 | 50 | 47 | 97 |
| **Sex Groups** | | | | | | | | | | | | | | | | | | | | | | | | |
| Male | 50 | 50 | 100 | 42 | 42 | 84 | 51 | 37 | 88 | 60 | 10 | 70 | .. | .. | .. | 58 | 12 | 70 | 36 | 7 | 43 | 47 | 51 | 98 |
| Female | 37 | 60 | 97 | 38 | 53 | 91 | 51 | 49 | 100 | 50 | 20 | 70 | .. | .. | .. | 62 | 16 | 78 | 40 | 18 | 58 | 54 | 41 | 95 |
| **Racial Groups** | | | | | | | | | | | | | | | | | | | | | | | | |
| White | 45 | 55 | 100 | 38 | 48 | 86 | 52 | 42 | 94 | 55 | 19 | 74 | .. | .. | .. | 55 | 18 | 73 | 33 | 15 | 48 | 45 | 51 | 96 |
| Black | 42 | 54 | 96 | 46 | 43 | 89 | 48 | 42 | 90 | 55 | 7 | 62 | .. | .. | .. | 68 | 4 | 72 | 48 | 3 | 51 | 59 | 41 | 100 |

* Brain examined in 33 cases only.

served in the spleen, pancreas and capsules of adrenals of some of the controls, the incidence of severe arteriolar sclerosis was more than doubled in those same organs in the hypertensive group.

*Age and Sex Differences:* In contrast with the control group in which the occurrence and severity of vascular disease increased with age, the general trend in the hypertensive group was for vascular disease to be less severe in the older individuals. An especially striking drop in the severity of arteriolar sclerosis with age was seen in the kidney, where the vascular disease was severe in 67 per cent of all hypertensives dead under the age of 45, in 50 per cent of hypertensives dead between the ages of 46 and 60, and in only 22 per cent of hypertensives dead after the age of 61 years.

No significant differences in the occurrence or severity of arteriolar disease could be seen in males and females or in blacks and whites within the hypertensive group.

### *Occurrence of Various Histological Types of Arteriolar Sclerosis in Hypertensive Individuals*

*Endothelial Hyperplasia:* In a discussion of the anatomical types of arteriolar disease seen in the various tissues in the hypertensive group the occurrence of intimal proliferation not demonstrably caused by inflammation of surrounding tissues appeared to deserve first consideration. This type of change was most pronounced in renal vessels over 30 $\mu$ in diameter, giving way to intimal hyalinization in the afferent arterioles. It appeared frequently to be associated with medial degeneration (intercellular collagen and thinning), and in many instances was complicated by hyaline, fat, mucoid or chromatropic degeneration, or necrosis of the hyperplastic intima as well as of the media. Although primary intimal hyperplasia was observed most frequently in the kidneys, it was seen occasionally in a variety of other situations. In no instance was it encountered in the skeletal muscle, subcutaneous tissue, lymph nodes or bone marrow, except in association with obvious local inflammation.

*Acute Arteriolar Lesions:* Acute degenerative, necrosing and inflammatory lesions were frequently superimposed on chronic arteriolar lesions of all kinds and were seen most frequently (38

per cent of all cases of chronic hypertension) in the renal arterioles, especially those showing intimal hyperplasia. The lesions varied greatly as to character and severity and were so obviously secondary that although they may have been significant in relation to the rapidity with which the disease progressed, they were not considered significant in relation to the inception of either the hypertension or the renal vascular disease. No tissue or organ was immune from the occurrence of these vascular lesions and, next to the kidney, they were seen most frequently in the gastro-intestinal tract.

*Intimal Hyalinization:* Intimal hyalinization occurred in the same tissues in the hypertensive as in the non-hypertensive group but with greater frequency and severity in the former. It was seen commonly as a generalized vascular disease in such tissues as the kidney, gastro-intestinal tract, liver and brain, where its occurrence in any degree of severity in non-hypertensives was rare. In the kidney and eye it was frequently associated with endothelial hyperplasia in larger arterioles (50 to 100 $\mu$ in external diameter). There was no qualitative difference in the intimal hyalin in the arterioles of the hypertensive and the non-hypertensive groups, although secondary degenerative changes were more common in the former.

*Medial Hypertrophy and Degeneration:* Medial hypertrophy and collagenous degeneration were widespread and common types of arteriolar changes in the hypertensive group. Without complicating intimal disease these changes were seen most frequently in the skeletal muscle. In a number of instances in which samples of more than one skeletal muscle from the same individual were examined, there appeared to be no significant difference in the severity of the vascular disease in various portions of the skeletal muscular system, with the possible exception of the diaphragm. Sections were prepared from the pectoralis major, rectus abdominis, quadriceps femoris, psoas and diaphragm from 6 individuals having severe generalized arteriolar sclerosis. With the exception of the diaphragm, the various muscles exhibited, as nearly as could be judged, the same degree of arteriolar sclerosis. In 3 of the 6, the diaphragmatic arterioles either appeared normal or mildly sclerotic, whereas in other muscles moderate or severe arteriolar sclerosis was present.

## Measurements of Wall Thickness of Arterioles

The claims of Keith, Barker and Kernohan to the effect that the thickening of the walls of the arterioles of skeletal muscle, due principally to medial hypertrophy, could be demonstrated by measurements in microscopic sections, deserved corroboration if their assumptions were correct. Their claims were made on a basis of measuring several arterioles from each of 50 control cases and from 143 cases of chronic hypertension. They found that arteriolar thickening was frequently present in hypertensive individuals and described five different types of chronic hypertension in which different mean wall to lumen ratios were observed. They did not state what the error of the method was or what the observed anatomical variations were. Bell, as well as Andrus, has denied the probability of medial hypertrophy of arterioles in the skeletal muscle of chronic hypertensives, but neither has presented quantitative data to refute the findings of Keith, Barker and Kernohan.

### *Variations in Measurements of Arterioles Not Related to Disease*

To determine the extent of the variation in arteriolar measurements incident to errors in mensuration or to differences in relative wall thickness related to different degrees of postmortem contraction or to actual anatomical differences, 15 samples of 75 arterioles each from the pectoral muscle of 1 non-hypertensive individual were measured and the mean external diameter, the mean lumen diameter and the mean ratio of wall thickness to lumen diameter were calculated. The 15 samples were fixed and prepared for microscopic examination by a uniform technic. The vessels were measured by the method described by Kernohan, Anderson and Keith, using an 8 mm. objective and a X 7 ocular containing a micrometer scale. Every arteriole between 18 and 72 $\mu$ in diameter was measured as it was encountered in cross section until 75 vessels had been measured. The outermost cells of the media were used to define the external diameter. To avoid measuring the same arteriole in succeeding sections, the sections from each block of muscle were cut at intervals of between 0.5 and 1.0 mm.

The means of the arteriolar measurements of the 15 samples of 75 arterioles each are given in Table III. This record indicates that the least variable mean was that of the external diameter of

a sample of arterioles having a fixed size range. In this instance it was 31.9 $\mu$ with a probable error of 1.5 $\mu$. The variation of the wall to lumen ratio was great, ranging from 1.0–1.4 to 1.0–2.5. It is apparent then that any difference in the wall to lumen ratio within the limits of 1.0–1.4 and 1.0–2.5 in 2 samples of 75 arterioles each, or less, would have no significance unless some more accurate method of measurement were employed than was used in

TABLE III

*Record of Measurements of 15 Samples With 75 Arterioles in Each From the Pectoral Muscle of 1 Non-Hypertensive Individual*

| Sample | Mean external diameter | P.E.m. | Mean internal diameter | P.E.m. | Wall to lumen ratio |
|---|---|---|---|---|---|
| | $\mu$ | | $\mu$ | | |
| 1 | 33.4 | 1.04 | 16.0 | 0.58 | 1 to 1.8 |
| 2 | 31.4 | 1.08 | 17.4 | 0.76 | 1 to 2.5 |
| 3 | 32.2 | 0.90 | 15.5 | 0.54 | 1 to 1.9 |
| 4 | 33.8 | 0.97 | 17.9 | 0.72 | 1 to 2.3 |
| 5 | 31.4 | 0.83 | 15.3 | 0.36 | 1 to 1.9 |
| 6 | 34.0 | 1.30 | 17.1 | 0.72 | 1 to 2.0 |
| 7 | 30.1 | 1.01 | 15.2 | 0.54 | 1 to 2.0 |
| 8 | 32.5 | 1.08 | 16.7 | 0.72 | 1 to 2.1 |
| 9 | 28.8 | 0.97 | 13.8 | 0.54 | 1 to 1.8 |
| 10 | 29.4 | 0.90 | 15.0 | 0.54 | 1 to 2.1 |
| 11 | 30.2 | 0.97 | 15.0 | 0.76 | 1 to 2.0 |
| 12 | 31.1 | 1.01 | 16.1 | 0.65 | 1 to 2.0 |
| 13 | 31.8 | 0.97 | 15.8 | 0.61 | 1 to 2.0 |
| 14 | 30.7 | 0.86 | 17.1 | 0.58 | 1 to 2.5 |
| 15 | 30.1 | 1.04 | 15.9 | 0.61 | 1 to 2.2 |

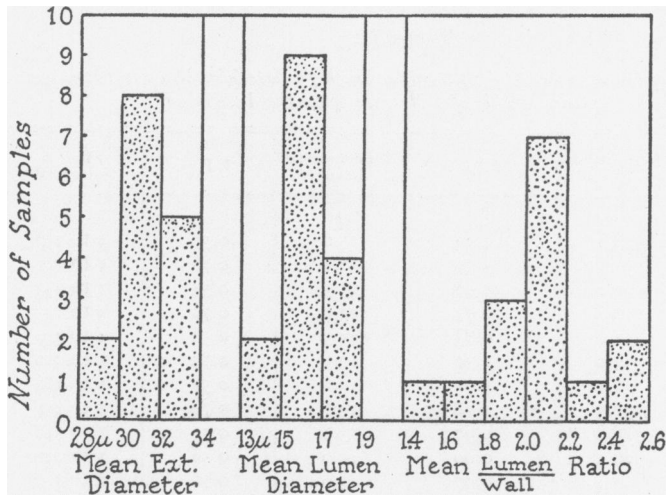
Mean external diameter = 31.4 $\mu$ P.E. $\pm$ 1.5
Mean internal diameter = 16.0 $\mu$ P.E. $\pm$ 1.0
Mean wall to lumen ratio = 1 to 2.0

this investigation. With such variation, it hardly seemed likely that the differences in the first decimal between mean ratios of wall thickness to lumen diameter in samples of undefined magnitude, such as reported by Keith, Barker and Kernohan, were significant. The distribution of each of the three means for the 15 samples is shown in Text-Fig. 3.

### *Selection of Control and Hypertensive Cases for Arteriolar Measurements*

It was felt from this test of multiple samples from 1 individual that many samples of arterioles from the skeletal muscle of hyper-

tensives and non-hypertensives would have to be measured in order to determine whether real differences in relative wall thickness exist or not. Accordingly, 38 classical cases of essential hypertension, with death from renal insufficiency, heart failure or cerebral hemorrhage, were selected for study. These were about equally divided between males and females, between blacks and




Text Fig. 3. Histograms showing the distribution of 15 samples of pectoral muscle from one non-hypertensive individual according to the mean external diameter, the mean lumen diameter and the mean wall to lumen ratio of arterioles in each sample. Seventy five arterioles ranging between 18 and 72μ in external diameter constitute a sample.

whites, and between persons over and under 45 years of age. A control group of non-hypertensive individuals with comparable age, sex, and race population was selected. As in the case of previously reported measurements, the external and internal diameter of each of 75 arterioles within the limits of 18 and 72 μ in external diameter in samples of pectoral muscle from each of the 76 individuals were measured. These data are shown in Table IV.

## TABLE IV

*Record of Measurements of 75 Arterioles From the Pectoral Muscle of Each of 38 Non-Hypertensive and 38 Hypertensive Individuals*

| Non-hypertensive individuals | | | | | | Hypertensive individuals | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Sex | Color | E.D. | I.D. | Ratio | Age | Sex | Color | Cause of death | E.D. | I.D. | Ratio |
| *yrs.* | | | $\mu$ | $\mu$ | | *yrs.* | | | | $\mu$ | $\mu$ | |
| 43 | F | W | 31.7 | 15.1 | 1 to 1.7 | 37 | M | B | R | 38.2 | 11.5 | 1 to 0.9 |
| 32 | F | B | 29.2 | 11.9 | 1 to 1.4 | 59 | M | W | H | 41.8 | 15.8 | 1 to 1.2 |
| 41 | M | W | 33.8 | 18.0 | 1 to 2.3 | 50 | F | B | H | 33.8 | 14.8 | 1 to 1.5 |
| 46 | F | W | 32.4 | 16.2 | 1 to 2.0 | 43 | F | B | R | 37.8 | 16.2 | 1 to 1.5 |
| 48 | F | W | 30.6 | 11.9 | 1 to 1.2 | 50 | M | B | H | 36.7 | 14.4 | 1 to 1.3 |
| 53 | M | W | 34.2 | 19.1 | 1 to 2.5 | 54 | M | B | C | 44.3 | 19.1 | 1 to 1.6 |
| 38 | M | B | 34.9 | 19.8 | 1 to 2.5 | 38 | F | W | C | 46.1 | 14.0 | 1 to 0.9 |
| 36 | F | W | 34.2 | 16.6 | 1 to 1.9 | 50 | M | B | C | 39.2 | 10.4 | 1 to 1.1 |
| 36 | F | W | 36.4 | 21.6 | 1 to 2.9 | 38 | F | W | H | 31.3 | 13.7 | 1 to 1.6 |
| 48 | F | W | 30.2 | 15.1 | 1 to 2.0 | 49 | F | B | H | 33.5 | 14.4 | 1 to 1.5 |
| 38 | M | W | 31.3 | 15.5 | 1 to 2.0 | 58 | M | B | R | 41.0 | 16.2 | 1 to 1.3 |
| 50 | M | W | 34.9 | 18.7 | 1 to 2.3 | 54 | F | B | H | 34.2 | 12.6 | 1 to 1.2 |
| 57 | M | W | 30.2 | 15.5 | 1 to 2.1 | 33 | F | B | R | 34.6 | 14.8 | 1 to 1.5 |
| 52 | M | W | 36.4 | 18.0 | 1 to 2.0 | 40 | F | B | H | 36.7 | 17.6 | 1 to 1.9 |
| 40 | M | W | 31.3 | 16.6 | 1 to 2.3 | 58 | M | W | H | 39.2 | 20.2 | 1 to 2.1 |

E.D. = Mean external diameter of 75 arterioles varying from 18 to 72 $\mu$ in external diameter.
I.D. = Mean internal diameter of 75 arterioles.
Ratio = Unweighted ratio of mean wall thickness to mean lumen diameter of 75 arterioles.
Cause of death: H = heart failure.
R = renal failure.
C = cerebral hemorrhage.

TABLE IV — *Continued*

| Non-hypertensive individuals | | | | | | Hypertensive individuals | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | Sex | Color | E.D. | I.D. | Ratio | Age | Sex | Color | Cause of death | E.D. | I.D. | Ratio |
| *yrs.* | | | $\mu$ | $\mu$ | | *yrs.* | | | | $\mu$ | $\mu$ | |
| 57 | M | W | 32.8 | 13.0 | 1 to 1.3 | 58 | M | W | H | 34.2 | 13.3 | 1 to 1.3 |
| 36 | F | W | 33.1 | 16.2 | 1 to 1.9 | 50 | F | B | C | 33.8 | 16.2 | 1 to 1.8 |
| 62 | M | W | 30.2 | 11.5 | 1 to 1.2 | 41 | M | B | H | 39.2 | 13.3 | 1 to 1.0 |
| 49 | M | W | 30.2 | 15.8 | 1 to 2.2 | 51 | F | B | R | 38.6 | 16.9 | 1 to 1.5 |
| 58 | F | W | 32.8 | 16.9 | 1 to 2.1 | 40 | M | W | H | 37.1 | 17.6 | 1 to 1.8 |
| 34 | M | B | 30.6 | 15.1 | 1 to 1.9 | 40 | F | B | C | 36.4 | 18.4 | 1 to 2.0 |
| 41 | M | W | 36.0 | 16.2 | 1 to 1.6 | 37 | F | W | R | 41.8 | 14.8 | 1 to 1.1 |
| 44 | M | W | 30.2 | 16.2 | 1 to 2.3 | 36 | M | B | R | 36.4 | 14.4 | 1 to 1.3 |
| 55 | F | W | 32.8 | 13.7 | 1 to 1.4 | 34 | M | B | H | 36.0 | 16.2 | 1 to 1.6 |
| 49 | F | W | 32.0 | 16.9 | 1 to 2.2 | 36 | M | W | C | 32.8 | 10.8 | 1 to 1.0 |
| 37 | F | W | 29.2 | 14.0 | 1 to 1.8 | 55 | M | W | H | 43.6 | 20.2 | 1 to 1.7 |
| 54 | M | W | 30.6 | 14.4 | 1 to 1.9 | 50 | F | B | R | 34.2 | 15.1 | 1 to 1.6 |
| 58 | F | W | 36.0 | 18.7 | 1 to 2.2 | 44 | M | W | R | 41.8 | 13.3 | 1 to 0.9 |
| 34 | M | B | 32.4 | 16.9 | 1 to 2.2 | 45 | M | W | R | 46.1 | 17.6 | 1 to 1.2 |
| 34 | M | B | 33.1 | 16.6 | 1 to 2.0 | 37 | F | W | R | 42.5 | 15.5 | 1 to 1.1 |
| 45 | M | W | 33.5 | 17.6 | 1 to 2.2 | 36 | F | B | R | 42.1 | 15.5 | 1 to 1.2 |
| 50 | M | W | 29.9 | 11.9 | 1 to 1.3 | 31 | M | W | R | 36.4 | 13.0 | 1 to 1.1 |
| 35 | F | W | 28.1 | 13.3 | 1 to 1.8 | 48 | F | W | R | 47.2 | 14.8 | 1 to 0.9 |
| 38 | F | B | 32.4 | 16.6 | 1 to 2.1 | 36 | F | W | H | 36.7 | 15.1 | 1 to 1.4 |
| 38 | F | B | 29.5 | 12.6 | 1 to 1.5 | 58 | F | B | C | 33.8 | 16.2 | 1 to 1.8 |
| 52 | M | W | 33.5 | 17.3 | 1 to 2.1 | 51 | M | W | H | 39.6 | 20.5 | 1 to 2.1 |
| 59 | M | B | 29.2 | 13.0 | 1 to 1.6 | 53 | M | W | H | 35.6 | 13.3 | 1 to 1.2 |
| 40 | M | B | 33.8 | 16.2 | 1 to 1.8 | 45 | F | W | H | 44.6 | 16.6 | 1 to 1.2 |

*Comparison of Arteriolar Measurements in Control and Hypertensive Groups*

A comparison of the means of the mean external diameters for each group (hypertensives and non-hypertensives) shows:

32.2 P.E. ± 2.2 μ for the controls

and

38.4 P.E. ± 4.1 μ for the hypertensives

The difference is significant.

A comparison of the means of the mean lumen diameters for each group shows:

15.8 P.E. ± 2.3 μ for the controls

and

15.4 P.E. ± 2.4 μ for the hypertensives

The difference is not significant.

A comparison of the means of the mean wall to lumen ratio shows:

1.0–1.9 for the controls

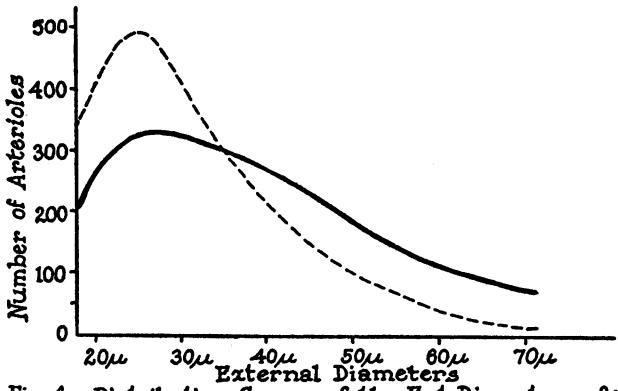
and

1.0–1.36 for the hypertensives.

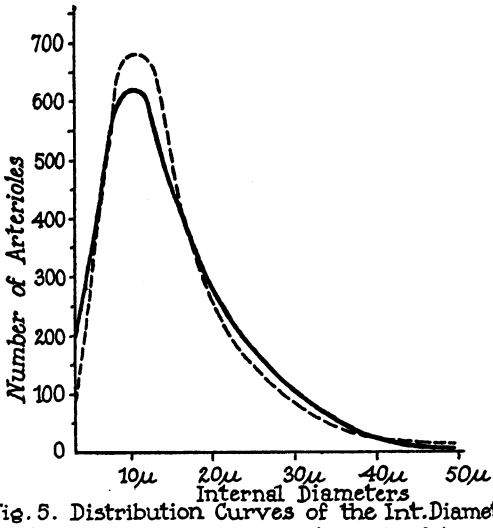
The difference is significant.

So far as the means of the various measurements of the arterioles of the hypertensive and the non-hypertensive groups are concerned, it appeared that the arterioles of the pectoral muscle of hypertensive individuals have relatively thicker walls than those of the non-hypertensives, that the arterioles are larger, as indicated by the mean external diameter, but that there is no real evidence that the arteriolar lumens of the hypertensives have been reduced.

A comparison of the external and internal diameters of arterioles in hypertensive and non-hypertensive individuals is shown in Text-Figs. 4 and 5. In Text-Fig. 4 the external diameters of 2850 arterioles of hypertensives and a like number of arterioles from non-hypertensives have been plotted against the number of vessels in each size group to establish two distribution curves. It may be seen that there are many more arterioles in the small vessel group




Text Fig. 4. Distribution Curves of the Ext. Diameters of:
——2850 arterioles in pectoral muscle of hypertensive individuals.
---2850 " " " " " non- " "




Text Fig. 5. Distribution Curves of the Int. Diameters of:
—— 2850 arterioles in pectoral muscle of hypertensive individuals.
--- 2850 " " " " " non- " "

75 arterioles ranging from 18 to 72μ in external diameter from each of 38 hypertensive and 38 non-hypertensive individuals, were measured.

(18 to 36 $\mu$ in external diameter) in the controls than in the hypertensives, and that over an external diameter of 36 $\mu$, vessels are more numerous in the hypertensive groups. This flattening of the curve represents an increase in the mean external diameter of arterioles in the hypertensive group.

In Text-Fig. 5 the internal diameters of the same arterioles have been plotted as abscissae against the number of vessels in each size group as ordinates. There is practically no difference in the two curves, which indicates that in so far as the two groups of cases (hypertensives and non-hypertensives) are concerned, the internal diameters of arterioles in the pectoral muscles are not significantly different.

No deductions can be drawn as to the relative patency of the two groups of arterioles in life. It is possible that medial degeneration rendered the arterioles in the pectoral muscle of hypertensives relatively resistant to postmortem contraction, so that although they appeared to have the same degree of patency as the more fully contracted normal arterioles in tissue sections, they may have had narrower lumens than normal vessels in life. It is equally possible that they were more fully contracted than normal arterioles and that the increased wall thickness in death is a reflection of a relatively greater lumen diameter in life. Differences in the functional state of arterioles in the skeletal muscle of hypertensive and non-hypertensive individuals cannot be conclusively determined from differences in measurements of postmortem material.

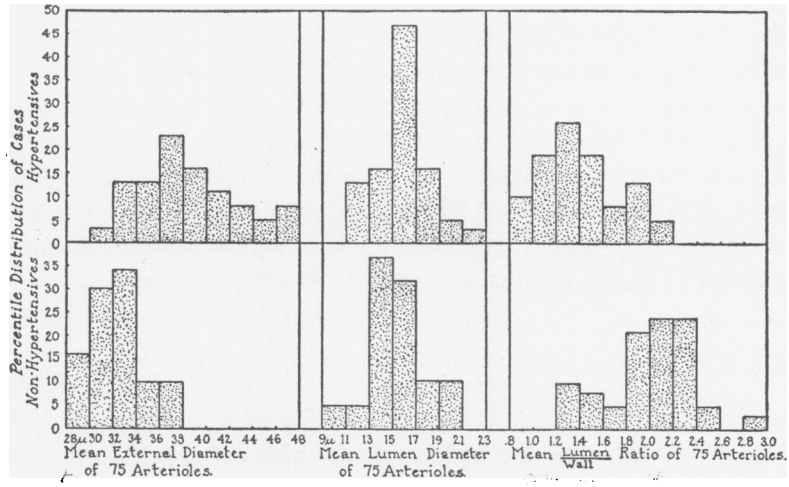
Table V shows the results of the arteriolar measurements in the various subgroups of the 38 hypertensive individuals. It is seen that so far as mean internal and external diameter, and mean wall to lumen ratio are concerned, there are no significant differences between individuals under and over 45 years of age, between males and females, blacks and whites, or between those dead of uremia, heart failure or cerebral hemorrhage.

Finally, in this consideration of the measurements of arterioles, attention was turned to the possible value of measuring arterioles in samples of pectoral muscle to distinguish between hypertensive and non-hypertensive individuals. Text-Fig. 6 was prepared to show the correlation of mean external and lumen diameter values, as well as mean ratios of wall to lumen thickness with chronic hypertension.

TABLE V

*Hypertensive Group*
*Skeletal Muscle*

| | No. of cases | Age | E.D. | I.D. | Wall to lumen ratio |
|---|---|---|---|---|---|
| | | *yrs.* | *μ* | *μ* | |
| Entire hypertensive group | 38 | 43.8 | 38.4 | 15.4 | 1 to 1.3 |
| 31 to 45 years of age | 20 | 38.4 | 38.7 | 15.0 | 1 to 1.3 |
| 46 to 60 years of age | 18 | 49.7 | 37.6 | 15.8 | 1 to 1.4 |
| Male | 19 | 43.7 | 38.2 | 15.4 | 1 to 1.4 |
| Female | 19 | 43.9 | 37.9 | 15.4 | 1 to 1.4 |
| White | 18 | 41.7 | 39.9 | 15.6 | 1 to 1.3 |
| Black | 20 | 45.7 | 37.0 | 15.2 | 1 to 1.4 |
| Death from heart failure | 17 | 46.6 | 37.2 | 15.5 | 1 to 1.4 |
| Death from renal insufficiency | 14 | 41.9 | 39.9 | 15.0 | 1 to 1.2 |
| Death from cerebral hemorrhage | 7 | 46.6 | 38.1 | 15.0 | 1 to 1.3 |




Text Fig. 6. Histograms showing the percentile distribution of 38 control and 38 hypertensive cases, according to the mean external diameter, the mean lumen diameter and the mean wall to lumen ratio of arterioles in samples of pectoral muscle from each. Seventy five arterioles ranging between 18 and 72μ in external diameter constitute a sample.

It was found that in 48 per cent of the hypertensives the mean external diameter of the 75 vessel samples was greater than that found in any of the control group. If the control cases were representative normals it might be said that whenever the mean external diameter of a sample of 75 arterioles, ranging between 18 and 72 $\mu$ in external diameter, exceeded 38 $\mu$ the sample was from a chronic hypertensive individual. Moreover, in almost half of the group of the chronic hypertensives the mean external diameter was greater than 38 $\mu$. The correlation of mean external diameter and a state of normal blood pressure was less striking. Sixteen per cent of the non-hypertensives had mean external diameters lower than those seen in any hypertensive. So far as these data were representative, it appeared that when the mean external diameter fell below 30 $\mu$ chronic hypertension could be excluded.

There was no significant difference between the contour of the distribution curves or the means of the internal diameters of the same 75 vessel samples of pectoral muscle of the hypertensive and non-hypertensive groups.

It has already been stated that the mean wall to lumen ratio of these same samples of arterioles was 1.0–1.9 in the controls and 1.0–1.36 in the hypertensives. The distribution curves of these ratios (Text-Fig. 6) showed a wide overlapping with only 29 per cent of the hypertensive group having a wall to lumen ratio less than that seen in any of the controls. It appeared that if the wall to lumen ratio of a sample of arterioles, such as were measured in this study, was less than 1.0–1.2, that sample was invariably from a hypertensive individual. The distribution curves showed that if the wall to lumen ratio was greater than 1.0–2.2, chronic hypertension could be excluded. Hypertension could be excluded in 32 per cent of the normals by this criterion.

### *Variations in Arteriolar Measurements Related to Differences in Methods of Tissue Preparation*

It was thought that differences in the time at which tissues were fixed in relation to death, differences in the duration of fixation, dehydration and clearing and differences in the time in the paraffin oven might lead to measurable differences in the dimensions of arterioles. To determine whether this were true or not, 8 samples

of pectoral muscle obtained from 1 non-hypertensive individual were prepared for histological examination by the various methods indicated in Table VI. Unless otherwise indicated the tissue was fixed during rigor and kept in 10 per cent formalin for 24 hours. The standard time allowed for dehydration and clearing was 12 hours and for embedding (paraffin oven) 3 hours. All sections were cut at a thickness of 6 $\mu$ and stained in the same manner. Seventy-five arterioles ranging from 18 to 72 $\mu$ in external diameter were measured in each sample.

Table VI shows that there were no differences between the means greater than the differences observed in samples subjected

TABLE VI

*A Comparison of the Mean External Diameter, Mean Internal Diameter, and Mean Wall to Lumen Ratio of Arterioles in 8 Samples (75 Arterioles Between 18 and 72 $\mu$ in External Diameter in Each Sample) From the Pectoral Muscle of 1 Non-Hypertensive Individual, to Show the Effect of Variations in Methods of Tissue Preparation On the Dimensions of Arterioles*

| Sample | Treatment | Mean external diameter | Mean internal diameter | Wall to lumen ratio |
|---|---|---|---|---|
| | | $\mu$ | $\mu$ | |
| 1 | Fixed before onset of rigor | 34.9 | 17.7 | 1 to 2.1 |
| 2 | Fixed during rigor | 31.6 | 16.2 | 1 to 2.1 |
| 3 | Fixed after dissipation of rigor | 32.8 | 15.8 | 1 to 1.9 |
| 4 | Fixed for 168 hours | 36.0 | 20.3 | 1 to 2.6 |
| 5 | Dehydration and clearing for 6 hours | 31.5 | 15.1 | 1 to 1.8 |
| 6 | Dehydration and clearing for 62 hours | 31.5 | 14.4 | 1 to 1.7 |
| 7 | In paraffin oven for 1½ hours | 32.3 | 15.2 | 1 to 1.8 |
| 8 | In paraffin oven for 24 hours | 34.6 | 18.3 | 1 to 2.2 |

to a uniform method of tissue preparation (see Table III and Text-Fig. 3.) Although this experiment does not prove that variations in technic do not influence the size of vessels in microscopic preparations, yet it does indicate that the anatomical variations and errors in mensuration under controlled conditions account for as great differences as result from deliberate variations in methods of tissue preparation.

*Variations in Arteriolar Measurements Related to Differences in the Physiological State of the Vascular System*

It was thought that differences in the functional state of arterioles (vasoconstriction or vasodilatation) at the time of death or at the time that the biopsy was taken might be reflected in differences in relative wall thickness in microscopic preparations. To determine whether this were true or not the following experiments were conducted on 4 dogs.

The dogs were mongrels, ranged from 8 to 12 kg. in weight, were mature but were of unknown ages. Each animal was anesthetized with ether and a carotid canula was inserted and connected with a mercury manometer and the systolic blood pressure recorded on a kymograph. As soon as the blood pressure had reached a fairly constant plateau, a biopsy of skeletal muscle was taken. Following this biopsy, the injection of 0.5 cc. per kilo of 1:1000 adrenalin was followed by a rise in blood pressure, at the peak of which another sample of skeletal muscle was taken. After waiting for 30 minutes, 0.5 cc. per kg. of a 1:1000 solution of nitroglycerin was injected intravenously and when the blood pressure had fallen below the original resting level the last biopsy of skeletal muscle was taken. All specimens were fixed for the same period and prepared for histological examination in the same manner. Sections were cut at intervals of about 0.5 mm. from each block of tissue and 50 arterioles ranging from 18 to 72 $\mu$ in external diameter were measured in each specimen. The results of these measurements are recorded in Table VII.

To determine whether the observed differences were significant or not, 7 samples of skeletal muscle were taken at the same time from the shoulder of 1 dog and the samples were prepared for microscopic examination in the same manner. Fifty arterioles (18 to 72 $\mu$ in external diameter) in each sample were measured as in the preceding experiment and the measurements were recorded in Table VIII. It was seen that the variations in mean external diameter, mean internal diameter and mean wall to lumen ratio, associated with differences in the physiological state of the vascular system, were no greater than those observed in the samples taken under uniform physiological conditions. Although this experiment does not prove that variations in the

TABLE VII

*A Comparison of the Mean External Diameter, the Mean Internal Diameter and the Mean Wall to Lumen Ratio of Arterioles in Samples of Skeletal Muscle (50 Arterioles Ranging Between 18 and 72 μ in External Diameter in Each Sample) in Different States of Arterial Hyper- and Hypotension from Each of 4 Dogs*

| Dog No. | Experimental conditions | Systolic blood pressure | Source of muscle | Mean external diameter of 50 arterioles | Mean internal diameter of 50 arterioles | Mean wall to lumen ratio of 50 arterioles |
|---|---|---|---|---|---|---|
| | | *mm. Hg.* | | μ | μ | |
| 1 | Resting | 160 to 180 | Shoulder | 32.4 | 14.8 | 1 to 1.7 |
| | After adrenalin | 270 | " | 35.3 | 15.5 | 1 to 1.6 |
| | After nitroglycerin | 140 | " | 37.6 | 17.3 | 1 to 1.7 |
| 2 | Resting | 150 to 170 | " | 29.5 | 15.8 | 1 to 2.3 |
| | After adrenalin | 240 | " | 29.2 | 15.1 | 1 to 2.1 |
| | After nitroglycerin | 120 | " | 29.9 | 15.1 | 1 to 2.0 |
| 3 | Resting | 160 to 170 | Thigh | 29.3 | 10.3 | 1 to 1.1 |
| | After adrenalin | 300 + | " | 27.7 | 8.4 | 1 to 0.9 |
| | After nitroglycerin | 150 | " | 27.4 | 10.3 | 1 to 1.2 |
| 4 | Resting | 160 to 170 | " | 28.1 | 10.6 | 1 to 1.2 |
| | After adrenalin | 280 | " | 27.4 | 10.6 | 1 to 1.3 |
| | After nitroglycerin | 140 | " | 31.9 | 12.3 | 1 to 1.3 |

physiological state of vessels do not influence their size in microscopic preparations, yet it does indicate that anatomical variations, together with errors in mensuration under controlled conditions, account for as great differences as were observed in varying physiological states.

TABLE VIII

*A Comparison of the Mean External Diameter, Mean Internal Diameter and Mean Wall to Lumen Ratio of Arterioles in Each of 7 Samples (50 Arterioles Ranging Between 18 and 72 μ in External Diameter in Each Sample) Taken at the Same Time and Subjected to the Same Methods of Tissue Preparation From the Shoulder Muscle of a Dog*

| Sample | Mean external diameter | Mean internal diameter | Mean wall to lumen ratio |
|---|---|---|---|
| | μ | μ | |
| 1 | 30.2 | 16.2 | 1 to 2.3 |
| 2 | 27.4 | 14.8 | 1 to 2.3 |
| 3 | 26.3 | 13.3 | 1 to 2.0 |
| 4 | 27.0 | 13.7 | 1 to 2.1 |
| 5 | 25.9 | 12.6 | 1 to 1.9 |
| 6 | 28.1 | 13.7 | 1 to 1.9 |
| 7 | 28.8 | 16.9 | 1 to 2.8 |

## PATHOGENESIS OF ARTERIOLAR SCLEROSIS

Impressions as to the pathogenesis of the various types of arteriolar sclerosis based on a statistical and morphological study of the disease were obviously inferential but certain relations and general trends deserve consideration.

Of perhaps the greatest significance is the fact that no type of chronic arteriolar disease was of and by itself pathognomonic of hypertension. Every type was found in persons known to have had normal blood pressures.

Intimal hyalinization appeared to be the arteriolar counterpart of simple arteriosclerosis (Plate 98), was essentially an aging phenomenon which developed precociously in some individuals and was seen most frequently in the abdominal organs supplied by relatively large short branches of the aorta (spleen, kidney,

pancreas and adrenals) as well as in the brain, spinal cord and eye. It was seen with greater frequency and severity in hypertensives than in non-hypertensives and in hypertensive individuals extended into vascular beds where its occurrence in non-hypertensives was very infrequent (liver and gastro-intestinal tract). Since intimal hyalinization appeared to be a simple "wear and tear" type of tissue reaction, and since it was reasonable to assume that chronic hypertension might augment arteriolar "wear and tear," it is not unreasonable to expect the lesion to be more widely distributed and more severe in hypertensives than in non-hypertensives. It is also possible that the arteriolar changes secondary to chronic hypertension frequently effect such widespread organic reduction in lumen caliber that the severity of the hypertension is increased, thus establishing a vicious circle. There was, however, no proof that hypertension initiated intimal hyalinization. The development of visible arteriolar disease in the retinal vessels in the course of essential hypertension and the later development of renal failure due to advanced nephrosclerosis do not necessarily indicate that these vascular changes are due to the high blood pressure. They may as well represent the further extension of a primary morbid process which causes hypertension. Neither does recovery from a state of chronic hypertension indicate that the disease is primarily functional rather than organic. Certainly organic vascular disease is not necessarily an irreversible process. The possibility that high blood pressure causes intimal hyalinization cannot be denied, but there is no conclusive evidence that such is the case and it is known that intimal hyalinization does occur quite independently of hypertension.

Another possible explanation for the increased severity of intimal hyalinization in hypertension is that only the more severe forms of arteriolar disease may in some way have been responsible for hypertension. Still another possible explanation is that the factors (humoral or reflex) that cause the arteriolar spasm that produces the increased peripheral resistance may also injure vessels with resulting intimal degeneration.

Intimal proliferation (Plate 101) was seen under three circumstances: (1) it was seen very frequently in association with chronic inflammation and apparently represented the characteristic vascular response to chronic inflammation in hypertensive

as well as non-hypertensive individuals; (2) it constituted a secondary adaptive change in arterioles supplying tissues that had undergone parenchymatous atrophy with a consequently diminished capillary bed and diminished blood flow (ovary and uterus); and (3) it was seen commonly as an independent and apparently primary morbid process most frequently in the kidney and occasionally in other tissues (pancreas, adrenal capsules, gall bladder, seminal vesicles, spleen, gastro-intestinal tract, and eyes of hypertensives.

The pathogenesis of the intimal hyperplasia in the first two of the above considered conditions seems to be primary exudative or non-exudative arteriolitis or arteriolar involution. The third consideration is best exemplified by the obliterating arteriolar intimal hyperplasia of nephrosclerosis in chronic hypertension and may be the result of inflammation, involution, neither or both. It is possible or even probable that this is a form of arteriolitis, occurring either as an augmented type of "wear and tear" arteriolar degeneration (Herxheimer) or as a primary independent arteriolar inflammation (Fahr). It is also possible that some or all of the arteriolar endothelial proliferation in the contracted kidney represents arteriolar involution secondary to obstruction proximal to it by spasm or distal to it by glomerular contraction (Volhard, Fishberg). It has been suggested by Moschcowitz that the endothelial proliferation is caused by the hypertension and in support of this theory he cites the endothelial hyperplasia of pulmonary arterioles in cases of mitral stenosis. The analogy is obviously not entirely applicable, inasmuch as in mitral stenosis there is, in addition to pulmonary arterial hypertension, stasis and cardiovascular inflammation.

Medial hypertrophy and degeneration uncomplicated by intimal thickening (Plates 99 and 100) were seen with greater frequency and severity in hypertensives than in non-hypertensives. The change appeared to be structurally analogous to the hypertrophy of any other hollow muscular structure. It is not known that arteriolar dilatation occurs in life as a result of high blood pressure, but it is presumed that arteriolar constriction does occur. Increased peripheral resistance to blood flow due to vasoconstriction is a *sine qua non* of chronic hypertension. Arteriolar dilatation is then the apparent antithesis of the vascular state of hypertension.

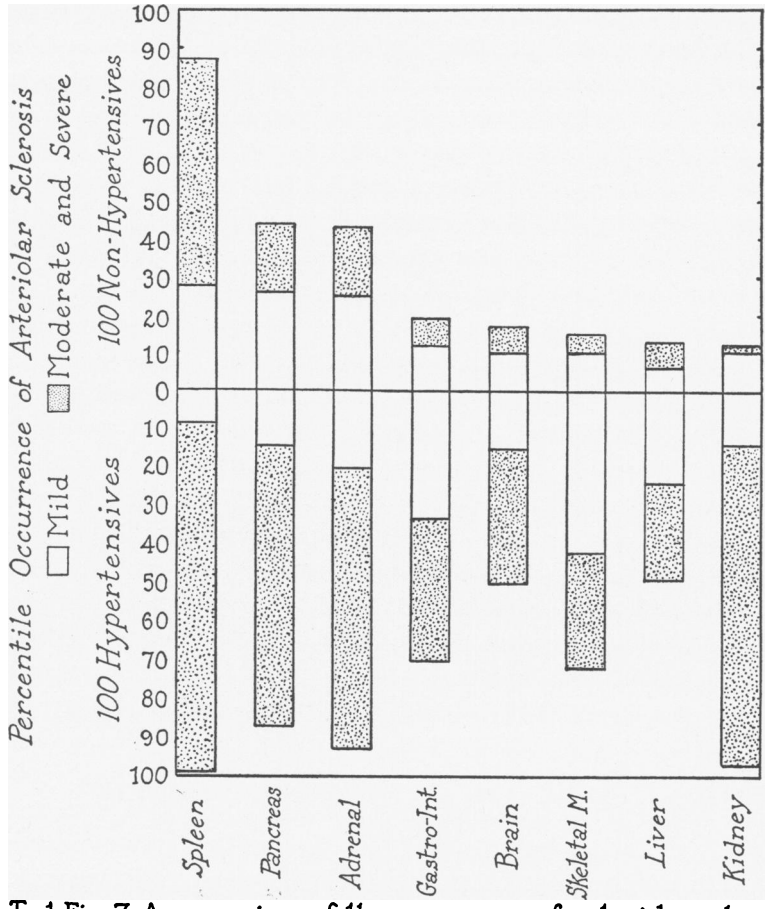
The microscopic changes in this type of arteriolar disease were similar to those occurring in other hollow muscular structures subjected to increased internal expansile pressure. It is not known whether vasoconstriction in hypertension is segmental or general, but if it is segmental it can be understood how dilatation might take place proximal to contracted segments or, as suggested by Volhard, may antedate the distal arteriolar spasm which results in the abnormal peripheral resistance. If medial disease is in some circumstances primary, it is conceivable that wall stretching might occur even with normal blood pressure and medial hypertrophy result. Although no conclusive evidence has been offered in support of the view that this medial change is secondary to stretching, such an explanation appears tenable.

In summary it may be said that the two most prominent and frequently occurring types of arteriolar disease, intimal hyalinization and intimal hyperplasia, appear to be primary pathological processes. The former is an aging phenomenon and the latter appears to be either an accelerated type of the former or an independent, non-exudative, productive arteriolitis. Medial hypertrophy appears on anatomical grounds to be a secondary phenomenon, probably related to stretching of vessels by the intravascular bursting tension. The medial degeneration may be in part primary, leading to smooth muscle stretching in non-hypertensive as well as in hypertensive individuals. Severe forms of arteriolar medial disease were seen only in persons with chronic hypertension.

## Correlation of Arteriolar Sclerosis and Chronic Hypertension

In the foregoing review of the histological types, relative severity and distribution of arteriolar sclerosis in hypertensive and non-hypertensive individuals, two very pertinent facts have emerged. One is the high degree of correlation between renal arteriolar sclerosis and hypertension, and the other is the extreme rarity of more than a very mild degree of renal arteriolar sclerosis in non-hypertensive individuals (Text-Fig. 7). It should be recalled that the tissues from these 200 cases were examined objectively. Renal arteriolar sclerosis was recorded as being present in 109 persons. In 97 of these 109 cases of nephrosclerosis an

examination of the clinical records, corroborated by heart weights, revealed chronic hypertension to have been present. This permits the conclusion that at the time of death almost every chronic




Text Fig. 7. A comparison of the occurrence of arteriolar sclerosis in the various organs and tissues of 100 hypertensive and 100 non-hypertensive individuals.

hypertensive (97 per cent) has renal arteriolar sclerosis in some degree, that few non-hypertensives (12 per cent) have any renal arteriolar sclerosis, and that in only 2 per cent of the non-hypertensives is there more than mild arteriolar nephrosclerosis (see Text-Fig. 7). No comparable correlation could be found in the

case of any other organ or tissue. Although in hypertensives the arterioles of the spleen were frequently as sclerotic as those of the kidney, they were also found to be diseased in 86 per cent of the non-hypertensives. With the exception of the kidney, correlation of arteriolar sclerosis and hypertension is either not constant enough to indicate a significant relation or the organ or tissue shows arteriolar sclerosis so frequently in non-hypertensive persons that the significance of the positive correlation is destroyed.

Inquiry should next be directed at the causal relation of renal arteriolar sclerosis to hypertension. The two obvious possibilities are: (1) that hypertension causes the sclerosis of renal arterioles; and (2) that renal arteriolar sclerosis causes the hypertension.

The first explanation would attribute to the renal arterioles an extremely high degree of selective vulnerability to high blood pressure, since they were affected in almost every case of hypertension but were rarely diseased in any other circumstances. At the same time it would be necessary to attribute to the renal arterioles a high degree of resistance to every injury except the mechanical damage incident to elevated blood pressure. Arterioles in many parts of the body were found to be severely diseased in hypertensives, but with the exception of the kidney the same relative susceptibility of tissues to arteriolar sclerosis was seen in hypertensive and non-hypertensive individuals.

The second possible explanation, namely, that renal arteriolar sclerosis causes hypertension, is far more tenable. Arteriolar sclerosis occurs as a primary pathological change. It is entirely reasonable to assume that this primary vascular disease may affect the renal arterioles as well as those in the spleen, pancreas, adrenals and other tissues. When the renal arterioles become sclerotic, hypertension is almost invariably present. This conclusion is based on objective evidence in human postmortem material and is of especial significance because of the close correlation it establishes between essential hypertension in man and the experimental production of chronic hypertension in dogs by Goldblatt and collaborators. Goldblatt's original observations, subsequently confirmed by Page, Elaut, Wood and Cash, Collins, Harrison, Blalock and Mason, and Prinzmetal and Friedman, that reduction in blood flow through the main renal arteries of dogs by the use of clamps invariably led to chronic hypertension, is in entire accord

with the pathological anatomical findings in chronic hypertension in man. The renal arteriolar sclerosis in man appears to have the same functional effect as the silver clamp around the main renal arteries in dogs.

The fact that renal arteriolar sclerosis does in some instances occur without an associated hypertension in no way detracts from the major hypothesis. It is obvious that the reduction of blood flow through the kidney is not the entire mechanism involved in the production of chronic hypertension. Some humoral or reflex influence must lead to the generalized spasm of arterioles which makes hypertension possible. Even though the renal vascular disease with resulting reduction of blood flow through the kidneys is present, it is conceivable that other conditions are not favorable for the development of hypertension. A certain degree of myocardial competence and a sustained resistance to blood flow through the peripheral vessels is obviously necessary for the maintenance of high blood pressure. It is possible that as a result of natural causes or surgical intervention the functional response (hypertension) to reduced blood flow through the kidneys (arterial or arteriolar nephrosclerosis, chronic diffuse glomerulonephritis, congenital polycystic renal disease, and so on) may in some instances be inhibited. Furthermore, it is not possible to translate accurately structural change into functional effect. What appears morphologically to be mild arteriolar disease may in reality account for considerable reduction in renal blood flow, and the converse is equally true.

In this consideration of the correlation of chronic hypertension and the distribution of arteriolar sclerosis, attention must be paid to the 3 cases of chronic hypertension in which there was no significant degree of renal arteriolar sclerosis (see Text-Fig. 7).

The 1st case was a female, 54 years of age, who died of cardiac tamponade following the rupture of an aortic aneurysm. Blood pressure determinations prior to her terminal illness varied about the figure of 220/120. The heart weight was 450 gm. and there was severe renal arteriosclerosis.

The 2nd case was that of a female, 75 years of age, who died of pulmonary embolism following a period of mild cardiac decompensation. Her mean blood pressure during the period of observation was 160/90 and the heart weight was 680 gm. with-

out significant concomitant heart disease. At autopsy severe renal arteriosclerosis was observed and there were obstructing annular plaques around the aortic ostia of the renal arteries.

The 3rd case was a male, 60 years of age, who died of cardiac rupture through a myocardial infarct. Preceding the terminal infarct, blood pressure of 190/110 was observed. The heart weighed 500 gm. and there was a severe renal arteriosclerosis, with scattered coarse scars throughout both kidneys.

All 3 had renal arteriosclerosis of sufficient severity to constitute an independent postmortem diagnosis. If it be assumed that these were undoubted cases of chronic hypertension, their hypertension is susceptible to the same explanation as might be offered in the case of renal arteriolar sclerosis. The vascular changes are consistent with, although not definitely confirmatory of, reduced blood flow through the kidneys.

## Types of Chronic Hypertension

In these 100 cases of chronic hypertension there were neither clinical nor pathological criteria for establishing definite subgroups. Certainly there were some cases in which the disease ran a more acute course than in others, and such disease was found more frequently in persons under 45 years of age and usually terminated in death from renal insufficiency. This vaguely defined group has been spoken of as "malignant hypertension" in contrast to "benign hypertension" which affected an older group, progressed more slowly and characteristically terminated in heart failure or cerebral hemorrhage if not interrupted prematurely by accident or unrelated illness.

In reviewing the clinical data it appeared to be much easier to identify cases of chronic hypertension as malignant or benign in retrospect than it was to prognosticate the course of the disease from its beginning. There appeared to be no way of predicting the speed at which the disease would progress except on the basis of the rate of the cardiac or renal deterioration that had already occurred. Certainly the height and fixation of the blood pressure provided no constant index of the rapidity with which the disease would progress, nor did observation of the severity of vascular changes by ophthalmoscopic examination, except as they indicated the degree to which the disease had already progressed. Measure-

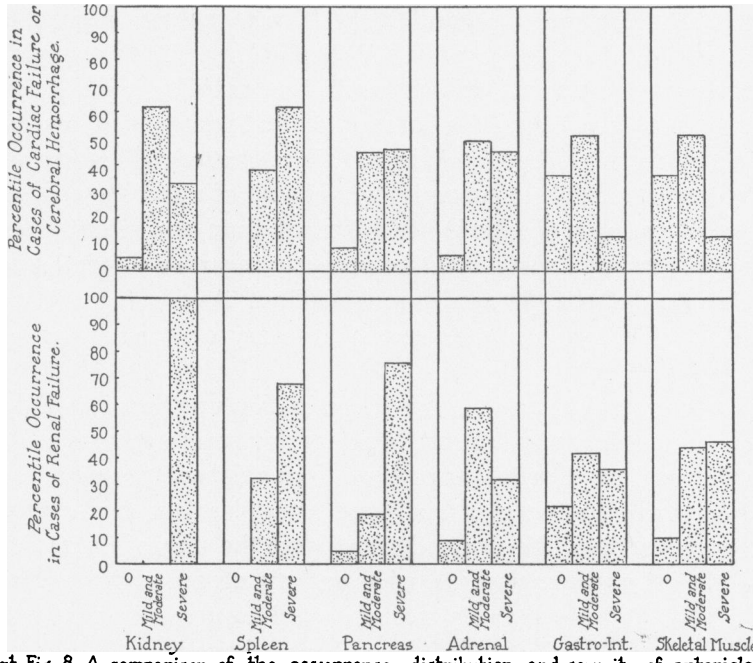
ments of a large number of arterioles in biopsy of pectoral muscle did not make it possible even to identify the presence of hypertension in more than half of the cases in which high blood pressure was present for a long time and provided no useful information in distinguishing between the "benign" and "malignant" form of the disease.

Certain group differences in the pathological anatomy of the so-called "benign" and "maligant" hypertension were apparent. The essential difference appeared to lie in the rapidity with which the vascular disease progressed in the kidney. If the arteriolar nephrosclerosis progressed with sufficient rapidity, renal insufficiency developed before the duration of the hypertension was sufficient to determine death from heart failure or cerebral hemorrhage. However, a number of examples were found of a rapidly progressing renal vascular disease in which heart failure or cerebral hemorrhage interrupted what might be properly regarded as the natural termination of the disease by renal failure. As a rule such cases were of older persons with severe coronary or cerebral arterial sclerosis.

In the material on which this investigation was based, in all the cases of so-called "malignant" hypertension severe generalized arteriolar nephrosclerosis was present. Not only was there occlusive intimal hyalinization of the afferent arterioles, but the small arteries from which they were derived were the seat of obliterating endothelial proliferation. A wide variety of acute degenerative and inflammatory changes was observed to occur in vessels already chronically diseased. These changes have been discussed in detail by Fahr, Klemperer and Otani, and Schurmann and MacMahon. An examination of Text-Fig. 8 suggests that on anatomical grounds this type of hypertension does not differ qualitatively from "benign" hypertension but is an accelerated and more severe type of vascular disease than is seen in the benign form. This conclusion is in essential agreement with the opinion of Herxheimer and Löhlein. This was especially true in the kidney, for in 100 per cent of the cases with death from renal failure, the vascular disease had been graded as severe.* In every organ and

* This does not imply that severe vascular changes are regularly seen in all cases of death from renal failure. In the 100 cases of chronic hypertension on which this study was based, all instances of death from renal insufficiency were by chance in cases of severe arteriolar nephrosclerosis.

tissue examined the arteriolar disease occurred with greater frequency and severity in the "malignant" than in the "benign" types of hypertension. Exclusive of the acute secondary arteriolar lesions, there was no type of vascular change in any tissue or organ that provided absolute grounds for distinguishing between malignant and benign hypertension. Although 100 per cent of the kidneys in cases of malignant hypertension showed severe




Text Fig. 8. A comparison of the occurrence, distribution and severity of arteriolar sclerosis in chronic hypertensives dying of renal failure and those dying of cardiac failure or cerebral hemorrhage.

arteriolar disease, equally severe renal arteriolar sclerosis was observed in 23 per cent of the cases of benign hypertension. Although 41 per cent of the cases of malignant hypertension had severe arteriolar lesions in skeletal muscles, 10 per cent of the benign hypertensives had equally severe arteriolar lesions in the skeletal muscles.

In both forms of hypertension the vascular disease was characteristically generalized and was represented by the same histological types of arteriolar lesions which were more severe and as a rule more widely distributed in individuals dying of renal

TABLE IX

*The Number of Patent Renal Glomeruli in Various Types of Chronic Hypertension* *

| Death due to renal failure | | | | | Death due to cardiac failure or cerebral hemorrhage | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Age | Sex | Heart weight | Renal arteriolar sclerosis | Total No. of patent glomeruli | Age | Sex | Heart weight | Renal arteriolar sclerosis | Total No. of patent glomeruli |
| *yrs.* | | *gm.* | | *thousands* | *yrs.* | | *gm.* | | *thousands* |
| 55 | F | Enlarged | Severe | 101 | 67 | M | 780 | Severe | 378 |
| 27 | F | 450 | Severe | 169 | 64 | M | 500 | Severe | 452 |
| 58 | M | 460 | Severe | 240 | 38 | F | 510 | Moderate | 490 |
| 48 | F | Enlarged | Severe | 243 | 70 | M | 550 | Severe | 645 |
| 35 | M | 650 | Severe | 254 | 46 | M | 875 | Moderate | 703 |
| 41 | M | 470 | Severe | 269 | 50 | M | 650 | Moderate | 749 |
| 49 | F | 430 | Severe | 386 | 62 | M | 500 | Moderate | 834 |
| 44 | M | 600 | Severe | 422 | 41 | F | 830 | Severe | 908 |
| 49 | F | 500 | Severe | 412 | 70 | M | 700 | Mild | 908 |
| 40 | F | 450 | Severe | 459 | 57 | F | 600 | Moderate | 972 |
| 58 | M | 740 | Severe | 510 | 52 | M | 600 | Moderate | 988 |
| 40 | F | 540 | Severe | 654 | 40 | M | 600 | Mild | 980 |

* The authors wish to express their appreciation to Dr. J. M. Hayman, Jr., for the glomerular counts.

insufficiency than in those dying of heart failure or cerebral hemorrhage.

Quantitative estimations of the degree of renal destruction by means of glomerular counts corroborated the impression gained from the histological examination and from the clinical course of the disease. Glomerular counts by Vimtrup's method were made on the kidneys of 24 chronic hypertensives (Table IX).

These 24 were comprised of two groups of 12 cases each. The mean age of the first group at the time of death was 45 years and of the second group, 55 years. Hypertension was generally of shorter duration in the first group in which death was the result of renal insufficiency. The second group had longer records of known chronic hypertension and death was due either to heart failure or cerebral hemorrhage. There were no significant differences in the degree of hypertension in the two groups. Cardiac hypertrophy was more pronounced in the group dying of heart failure or cerebral hemorrhage than in the group dying of renal insufficiency.

There was a striking difference in the numbers of patent glomeruli per kidney in the two groups. It has been shown by Moritz and Hayman that 1,250,000 is the approximate number of patent glomeruli in the normal kidney. In most of the individuals dead of renal failure there was a pronounced reduction in the number of injectible glomeruli, as compared with those dead of heart failure or cerebral hemorrhage. With full regard for the fact that a patent glomerulus is not necessarily a normal one, it is apparent that although the degree and duration of hypertension seem to be independent of the actual amount of renal destruction, death from renal insufficiency is associated with a measurable increase in the amount of glomerular destruction.

## Conclusions

### *General Characteristics of Essential Hypertension*

The mortality and probably the morbidity of essential hypertension was greater in blacks than in whites and the mean age at the time of death was lower in blacks than in whites.

The proportion of cases of essential hypertension with death

from renal insufficiency, heart failure and cerebral hemorrhage was the same in blacks as in whites.

There were no differences between males and females in mortality, cause of death or age at time of death from chronic hypertension.

The mean age at the time of death was lower in individuals dying of renal failure than in those dying of heart failure or cerebral hemorrhage.

In almost half of all cases of essential hypertension with death from heart failure, postmortem examination disclosed occlusive coronary disease.

### *Histological Types of Chronic Arteriolar Disease*

The three principal histological types of chronic arteriolar disease included: (1) intimal hyalinization; (2) medial hypertrophy and degeneration; and (3) intimal proliferation.

All three types, separately and in combination, were found in non-hypertensives as well as in hypertensives. Although no direct information was available as to the etiology of the three types there was indirect evidence in support of the view:

1. That intimal hyalinization is the arteriolar counterpart of simple arteriosclerosis, is essentially a degenerative change, and becomes more widespread and severe with advancing age.

2. That medial hypertrophy and degeneration are changes resembling those following distention of any hollow muscular structure, and although medial degeneration may be primary in some instances, yet the medial hypertrophy is probably secondary to stretching and was seen with greater frequency and severity in hypertensives than in non-hypertensives.

3. That endothelial hyperplasia with increase in elastic tissue and secondary degenerative changes was seen: commonly in association with inflammation where it was properly called endarteritis obliterans; commonly as an adaptive involutional change in vessels whose capillary beds have been reduced by parenchymatous atrophy; and commonly in cases of hypertension where it may have represented a primary vascular inflammation or an accelerated form of arteriolar sclerosis.

### *Measurements of Arterioles (Medial Hypertrophy)*

Neither the mean wall to lumen ratio, the mean external nor the mean internal diameter of large samples of arterioles from the skeletal muscle were useful in distinguishing between hypertensive and non-hypertensive individuals. Relative arteriolar wall thickening was a group characteristic for the hypertensives and, so far as histological preparations of tissues were concerned, the thickening resulted in an increase in external diameter rather than a decrease in the lumen diameter. The most useful numerical value in distinguishing hypertensives from non-hypertensives was the mean external diameter of arterioles within a fixed size range. It was possible to identify 48 per cent of the hypertensives by measurements that were in excess of those seen in any non-hypertensives, and it was possible to identify 16 per cent of the control cases by measurements lower than were observed in any of the hypertensives. Measurements of arterioles were not useful in distinguishing between various types of essential hypertension.

Neither the physiological state of the vascular system at the time the specimens were obtained for microscopic examination nor variations in the methods used in preparing tissues for microscopic examination led to changes in arteriolar dimensions that were greater than those resulting from anatomical variations or errors in mensuration under controlled conditions.

### *Correlation of Arteriolar Disease and Chronic Hypertension*

The objective examination of arterioles in all parts of the body of 100 control cases and 100 cases of chronic hypertension disclosed only one situation in which the presence of arteriolar sclerosis was almost invariably associated with hypertension and where the absence of arteriolar sclerosis almost invariably betokened an absence of high blood pressure. This was in the kidneys. Renal arteriolar sclerosis was present in 109 of the 200 cases studied, and 97 of these 109 proved to be cases of chronic hypertension. No comparable correlation could be found in any other organ or tissue.

It was felt that these facts, together with the information gained from a study of the histological characteristics of arteriolar disease in hypertensive and non-hypertensive individuals, supported

the conclusion that renal arteriolar sclerosis is the most common cause of chronic hypertension. This conclusion is in accord with the recent demonstration by Goldblatt that chronic hypertension is regularly produced in dogs and monkeys by reducing the blood flow through the kidneys (renal ischemia). The effect of the renal arteriolar sclerosis in human hypertension appears to be the functional analogue of the renal arterial clamp in experimental hypertension. In both instances hypertension appears to be produced by reduction in renal blood flow which does not necessarily lead to a sufficient degree of ischemia to impair renal function measurably.

It is concluded that the only significant site of arteriolar sclerosis so far as the causation of hypertension is concerned is the kidney.

### *Types of Chronic Hypertension*

The material on which this investigation was based did not include cases in which the hypertension could be attributed to chronic nephritis, congenital polycystic renal disease, urinary obstruction, obesity, hyperthyroidism, aortic insufficiency, aortic coarctation, pituitary or adrenal tumors, or arteriovenous aneurysm. Such causes of hypertension were not excluded deliberately but were simply not encountered in the selection of cases by the criteria outlined in the early part of this report. A survey of the rate of progress of the disease, the mean age at the time of death and the cause of death disclosed two groups which were best separated by the manner in which the disease terminated. One group died of renal insufficiency and for several reasons was most adequately described as "malignant" hypertension in contrast with a group that died of heart failure or cerebral hemorrhage which was designated as "benign" hypertension. The application of the terms "malignant" and "benign" denoted group characteristics applicable in retrospect rather than constituting useful terms in predicting the course of the disease in its early stages. The factor which determines that some cases of essential hypertension will run a more rapid course with early death from renal insufficiency does not appear to be the degree of the hypertension but rather the rate of renal destruction incident to the progressive character of the renal vascular disease. Although no correlation could be established between varying degrees of renal vascular disease and vary-

ing degrees of blood pressure elevation, there did appear to be a correlation between the amount of renal atrophy, as indicated by glomerular counts and the mode of death.

Note: The authors wish to express their indebtedness to Miss Theodora Bergsland for the colored illustrations.

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## DESCRIPTION OF PLATES

### PLATE 98

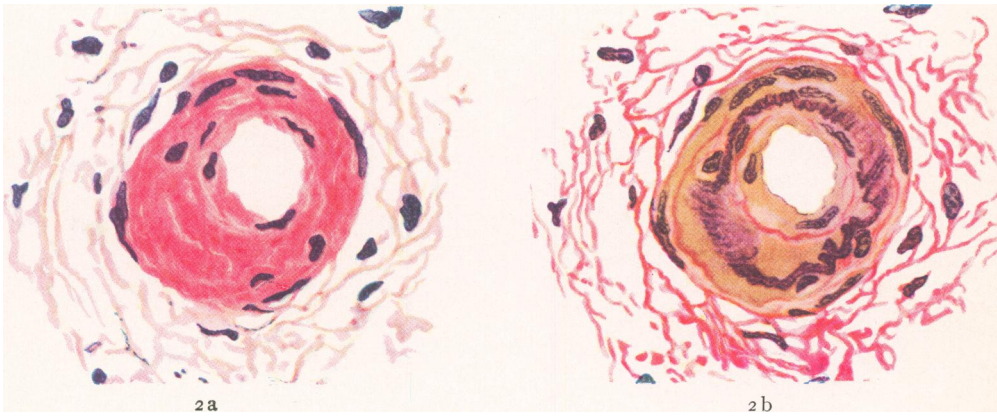
### Intimal Hyalinization

FIG. 1. Arteriole showing plaque of intimal hyalin.
a = Hematoxylin-eosin stain.
b = Combination of van Gieson's and Weigert's elastic methods on same section. × 500.

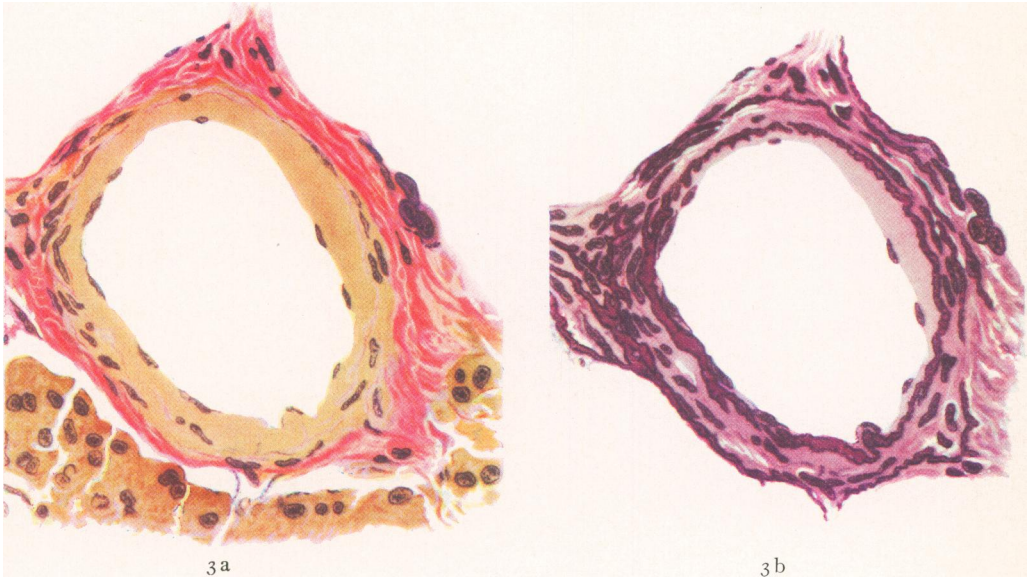
FIG. 2. Annular form of intimal hyalinization showing beginning degeneration of internal elastic lamella incorporated within the hyalin.
a = Hematoxylin-eosin stain.
b = Combination of van Gieson's and Weigert's elastic methods on same section. × 500.

FIG. 3. Intimal hyalinization in a dilated, thin-walled vessel.
a = Van Gieson's method.
b = Weigert's elastic method on same section. × 500.

1a 1b



2a 2b



3a 3b

PLATE 99

Medial Hypertrophy

FIG. 4. Normal arteriole showing increased wall thickness as the result of pronounced postmortem contraction.

a = Hematoxylin-eosin stain.

b = Combination of van Gieson's and Weigert's elastic methods on same section. × 500.

FIG. 5. Hypertrophy of media.

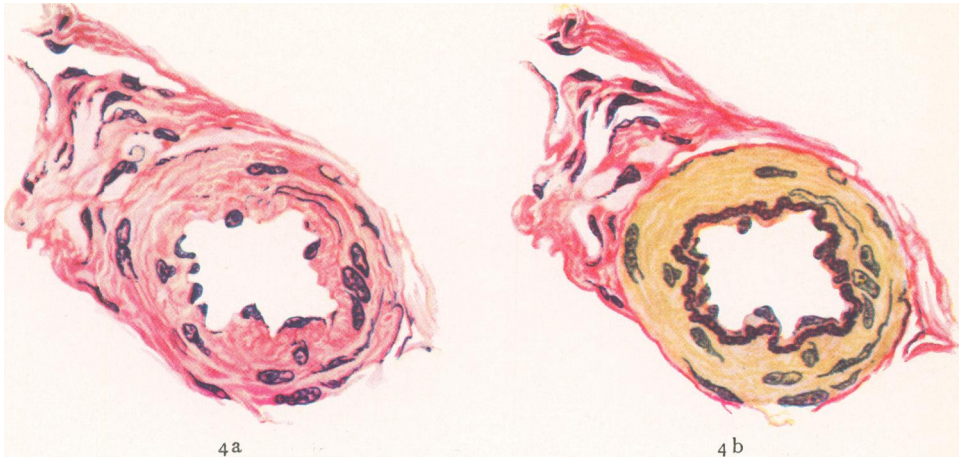
a = Hematoxylin-eosin stain.

b = Combination of van Gieson's and Weigert's elastic methods on same section. × 500.

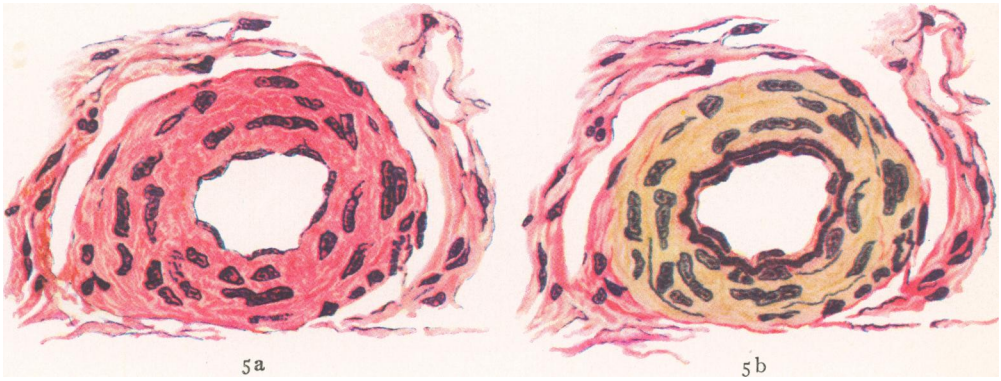
FIG. 6. Collagenous degeneration and medial hypertrophy.

a = Hematoxylin-eosin stain.

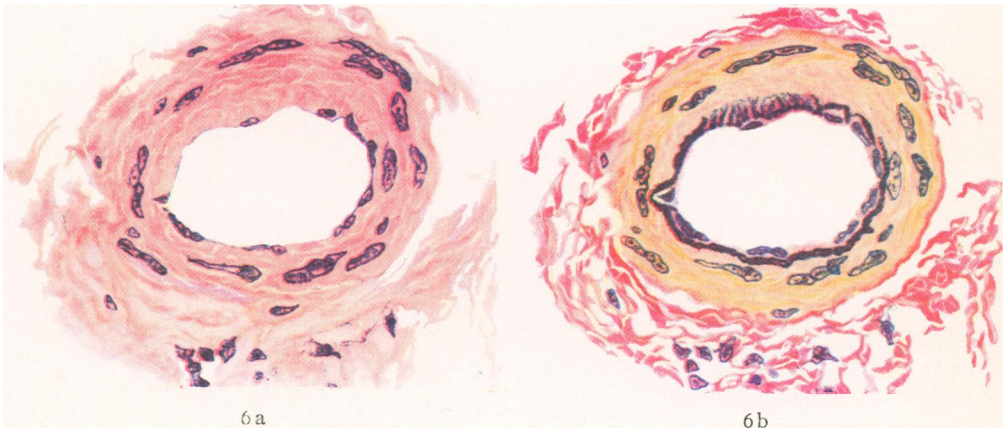
b = Combination of van Gieson's and Weigert's elastic methods on same section. × 500.



4a 4b



5a 5b

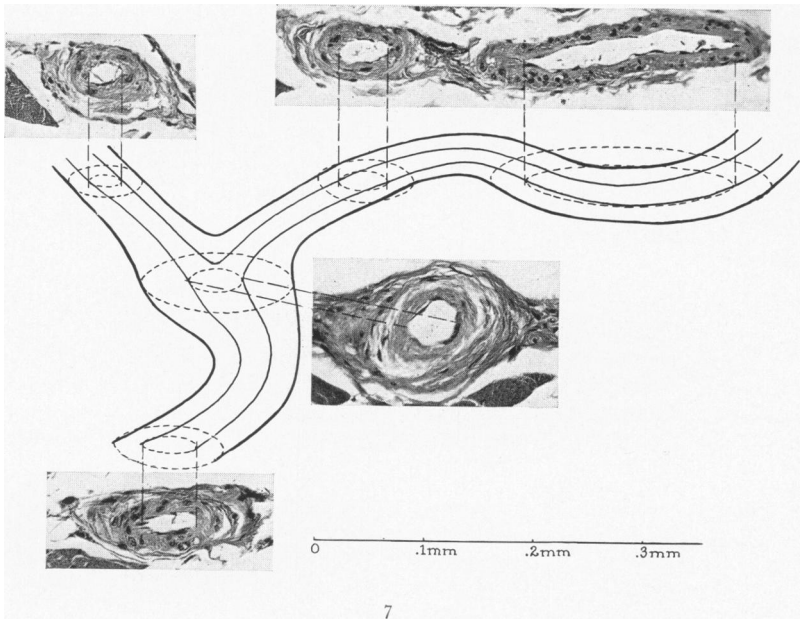


6a 6b

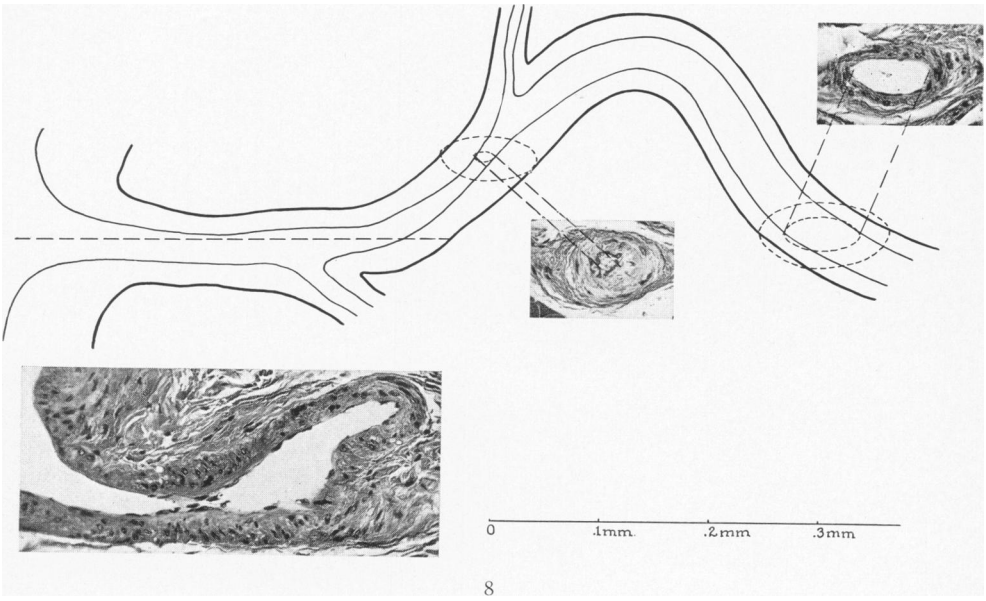
PLATE 100

FIG. 7. Reconstruction of an arteriole from the pectoral muscle of an individual with chronic hypertension showing the non-uniform character of the vascular disease in different segments of the same vessel.

FIG. 8. Reconstruction of an arteriole from the pectoral muscle of an individual with chronic hypertension showing the non-uniform character of the vascular disease in different segments of the same vessel.




7




8

## Plate 101

### Endothelial Hyperplasia

Fig. 9. Endothelial hyperplasia within an intact internal elastic lamella with pronounced intimal thickening and reduction in lumen caliber.

a = Hematoxylin-eosin stain.

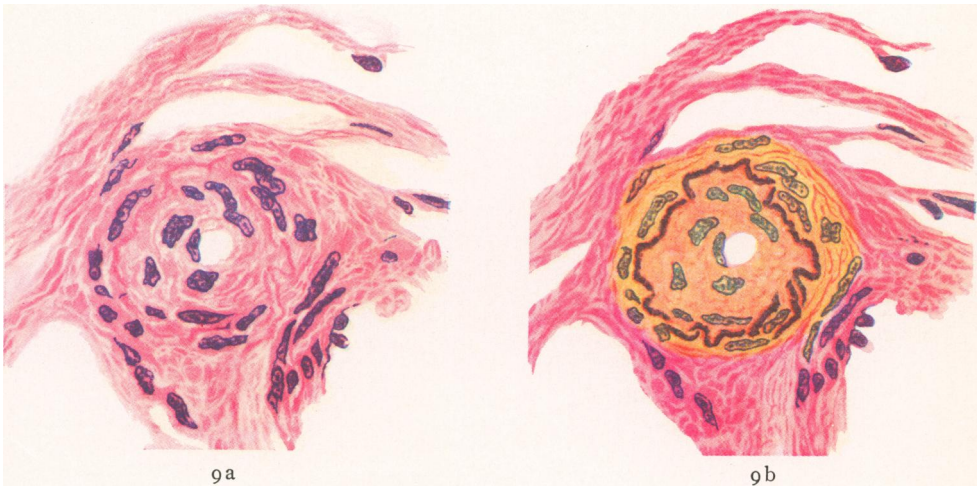
b = Combination of van Gieson's and Weigert's elastic methods on same section. × 500.

Fig. 10. Endothelial hyperplasia associated with reduplication of internal elastic lamella and degeneration of old and new elastic tissue.

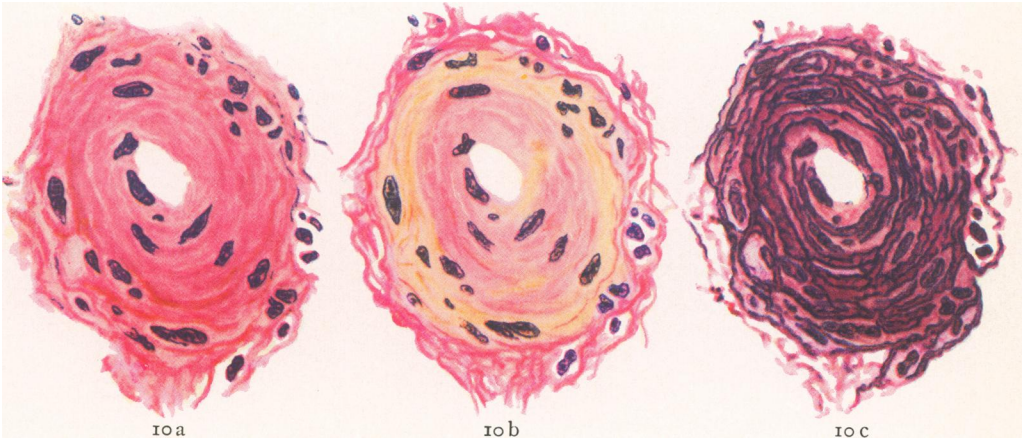
a = Hematoxylin-eosin stain.

b = Van Gieson's method.

c = Weigert's elastic method. × 500.



9a 9b



10a 10b 10c