A STUDY OF THE ARTERIAL AND ARTERIOLAR ARCHITECTURE

IN NORMAL AND DISEASED HUMAN KIDNEYS

BY MEANS OF NEOPRENE INJECTIONS

by

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Introduction

This study was undertaken with the hope that the application of a new method to the study of an old problem might remove some of the contradictory ideas that exist concerning the blood supply of the normal and abnormal human kidney. The importance of an accurate knowledge of the blood supply in the normal and diseased human kidney is realized when we consider that for over one hundred years controversy has raged in regard to the relation of renal disease to hypertension. With the recent production (1932-1938) by Goldblatt and others of experimental hypertension by constriction of the main renal artery, the importance of a knowledge of the blood supply of the kidney in hypertension is more fully apparent. The association of chronic renal disease and hypertension as a frequent direct or indirect cause of death is revealed at autopsy and indicates that any work is of value which elucidates in any way the causation of hypertension in human beings. With the knowledge gained from experimental hypertension the problem now is to determine in man the relation of the hypertension to the changes in small arteries and arterioles of the kidney.

A study of the underlying processes of disease in any organ must start with a clear understanding of the normal anatomy and physiology of the organ concerned. Since it is only recently that the writers of text-books of histology have begun to agree regarding the blood supply of the normal human kidney, it has seemed of value to review briefly the literature tracing the steps whereby we have gained our present knowledge of the normal renal blood supply and then to discuss the views regarding the renal vasculature in disease. Secondly, it has seemed of importance to compare, using the same technique, the morphology of the arterial blood vessels of the normal human kidney in the different age groups, with the morphology of the renal arterial tree in kidneys from patients who had died with hypertension and who were in corresponding age groups.

Part I

REVIEW OF THE LITERATURE

Blood Supply of Normal Kidney

Much has been written about the blood supply of the kidney. A good deal of this has been repetitious and confusing. The progress of our knowledge of the blood supply of the mammalian kidney has been made by a relatively small number of investigators in a few bold steps. Only the ideas of those workers who have definitely advanced our knowledge are mentioned with the hope that this subject will not appear as complex and bewildering to the reader as it has to the writer.

General: According to Clendening, "Aristotle thought the bladder secreted the urine. Vesalius stated that the ureters carried the urine from the kidneys to the bladder." Then, as in all other branches of science, authority ruled throughout the dark ages and all progress towards truth ceased. Malpighi in 1666, broke this long silence and pleaded for people to be open-minded and to try again by their own observations to discover truth in nature. In De Viscerum Structura Exercitatio Anatomica, he said: "Do not stop to question whether these ideas are new or old, but ask, more properly, whether they harmonize with Nature. And be assured of this one thing, that I never reached my idea of the structure of the kidneys by the aid of books, but by the long, patient, and varied use of the microscope. I have gotten the rest by the dictations of reason, slowly, and with an open mind as is my custom." Malpighi noted that the kidney cortex was composed of tubules like a "coil of small worms." He also saw the branches of the vessels with the "globules" attached to them. "It is clear" he said, "that the extreme ends of these worm-like vessels, which form the outer part of the kidney, are continuous with the descending vessels which go to the pelvis. I confess that I have

never been able to demonstrate this continuity, either on account of my clumsiness, perchance, or on account of the crudity of my instruments." He believed that the trickle of urine from the kidneys resulted from a separation of the elements of the blood as it passed through this tubular system. This mistaken view was accepted for many years by others. Huschke in 1828 denied the existence of any connection between the Malpighian corpuscles and the uriniferous tubules.

The next definite contribution to the anatomy and physiology of the mammalian kidney came from Bowman in 1842. Using lead chromate, a rather new material for injections, he found that the capsule that invests the Malpighian corpuscle was the basement membrane of the uriniferous tube expanded over the tuft of vessels. He did not understand how the tuft of blood vessels was invaginated into the end of the uriniferous tubule for he said the capsule "is perforated by the afferent and efferent vessels and is certainly not reflected over them." He stated that "here is a tuft of capillaries extruded through the wall of the tube and lodged in a dilatation of its cavity, uncovered by any structure." Except for this one error, Bowman understood the circulation of the kidney almost as well as we do to-day. His ideas are summed up in the following passage. "All the blood of the renal artery (with the exception of a small quantity distributed to the capsule, surrounding fat, and the coats of the larger vessels) enters the capillary tufts of the Malpighian bodies; thence it passes into the capillary plexus surrounding the uriniferous tubes, and it finally leaves the organ through the branches of the renal vein. Thus there are in the kidney two perfectly distinct systems of capillary vessels, through both of which the blood passes in its course from the arteries into the veins." That he understood how well the circulation of the kidney and glomerulus are adapted for filtration (a concept which we accept at the present time as part of the mechanism of the formation of urine) is evident from the

following passage: "It would indeed be difficult to conceive a disposition of parts more calculated to favour the escape of water from the blood, than that of the Malpighian body. A large artery breaks up in a very direct manner into a number of minute branches, each of which suddenly opens into an assemblage of vessels of far greater aggregate capacity than itself, and from which there is but one narrow exit. Hence must arise a very abrupt retardation in the velocity of the current of blood. The vessels in which this delay occurs are uncovered by any structure. They lie bare in a cell from which there is but one outlet, the orifice of the tube." ..... "Why is so wonderful an apparatus placed at the extremity of each uriniferous tube, if not to furnish water, to aid in the separation and solution of the urinous products from the epithelium of the tube?"

Since that time the more gross architecture of the renal arteries has been fairly well established by numerous workers. Kölliker (1860) recognized that the main renal artery divided in the hilum of the kidney, supplied a few branches to the kidney pelvis and then continued on as several branches between the cortex and medulla. In the interval between the cortex and medulla there was repeated branching without anastomoses. From these branches small arteries arose at right angles, divided several times, and formed small branches which ran directly outwards between the cortical fasciculi. These terminal branches he called "arteriae interlobulares" and stated that except for a few fine twigs to the exterior these arteriae interlobulares were entirely consumed in supplying the "vascular coils." This brief statement is an almost accurate account of the renal arterial vasculature as we know it today. From the descriptions of Golubew (1893) and von Ebner (1899), the impression is gained that in a unilobular kidney the maih renal artery divides into a few large branches which pass between the medulla and cortex parallel to the surface of the kidney. When these vessels reach the base of the pyramid they arch over this. These

vessels were termed "arcuate arteries" because from their origin near the apex of the pyramid to their termination over the base of the pyramid they describe an arch. Vessels were described which arose at right angles from the convex surface of these arteries at regular intervals passing out perpendicular to the surface of the kidney and parallel to one another. These were called interlobular arteries because it was believed each supplied a kidney unit, the lobule. From them the small arteries to the glomeruli arose. Lee-Brown, as late as 1924, presented a description which gives a rather similar impression. Modern text-books of histology also do nothing to dispel this general impression.

In the interval between Golubew and the present time there have been two workers who have tried to give a slightly different and more accurate conception of the distribution of the intrarenal arteries. Huber (1906-07) employed a celluloid corrosion technique for injection of the renal arteries of cats, dogs and rabbits. He pointed out that while the divisions of the renal artery that gain the interval between the cortex and medulla ran parallel to the surface in the kidney, they divided repeatedly, each branch maintaining a course parallel to the surface of the kidney. All of these branches he called arcuate arteries. He stated that from the convex side of these arcuate arteries small arteries arose at acute angles. These were directed with a slight inclination to the cortex. From their outer surface arose small arteries which travelled towards the cortex and divided repeatedly into branches from which arose the interlobular arteries. Following this description he commented that - "If the designation arteriae arciformes is retained for arterial branches having an arched course, relatively large branches arising from these and passing through two to three further subdivisions need to be recognized before arterial branches known as the arteriae interlobulares are reached." Huber also could not agree with those who believed that the interlobular arteries each supplied a vascular unit of the kidney. He noted that

some of the interlobular arteries passed only part way through the cortex while others branched into further arteries of interlobular type.

Gross in 1917 departed still farther from the classical description of arcuate arteries. Using for his studies human kidneys, injected with radio-opaque material, he said, "One glance at the skiagraphs will show that there are no divisions of the renal artery which could possibly correspond to these so-called arcuate arteries, and that, instead, the renal arterial architecture resolves itself into a simple tree-like dichotomous arrangement of the branches of the principle afferent artery." Gross believed it would be wise to change the terminology of different components of the arterial tree of the kidney. He suggested that the large branches coursing between the cortex and medulla be called interlobar arteries; the small end-arteries running perpendicular to the surface be named intralobular arteries and the small arterioles running to the glomeruli should be called glomerular arteries. If we accept Traut's definition of a lobule the term intralobular artery would be incorrect, and, as will be seen later, it seems better to keep the term interlobular arteries for the small vessels giving origin to the afferent arterioles.

Traut, in 1923, in a very careful and accurate study, attempted to correlate the finer blood supply with the structural units of the kidney. By injection, either the tubules or blood vessels were stained lightly with Prussian blue. The whole kidney was macerated in 50% hydrochloric acid. When the ground-substance and connective tissue were sufficiently macerated the kidney was teased gently. Traut observed that the kidney was easily separated into pyramidal units which he called structural units. These presented the following architecture: They varied slightly in shape and size depending on their position in the kidney. But in general those subjected to equal pressure on all sides were pyramidal in shape possessing four triangular sides with the bases at the periphery of the cortex and the apices in the medulla, where each unit ended in a collecting duct of the 8th order, each apex being equidistant

from the tip of a papilla. In the cortex, the centre of this structural unit was composed of collecting tubules, which at the level of the cortex and medulla ended in four collecting ducts of the tenth order. Packed around the collecting tubules and completely surrounding them were numerous coils of the convoluted tubules. In the cortex the four surfaces of the pyramid were covered by glomeruli. These glomeruli were supplied by glomerulus-bearing end-arteries which arise from branches of the so-called arcuate arteries. Traut here recognized that there were arterial branches interposed between what might strictly be called arcuate arteries and the final small arteries giving rise to the afferent glomerular arterioles. There were no arterial anastomoses between adjacent lobules, and in the cortex and medulla, capillary anastomoses between adjacent lobules was very slight. Traut pointed out that when a kidney is cut in the coronal plane the exposed surface of these tetrahedral lobules is identical with the medullary rays as they pass out into the cortex. The red lines extending out between the medullary rays represent the interlobular arteries extending out through the cortex between the lobules. He said: "And so it would seem that the lobule is a unit from the point of view of its blood supply, as well as from its gross point of view." All of this would indicate that in this unit structure the lobule is formed essentially on the basis of the tubular architecture and that the lobular distribution of the blood supply was acquired secondarily. This whole description appears reasonable and seems founded on excellent work. It gives some meaning to the irregular divisions of the interlobular arteries, and considers the renal structural unit to be of rather small size.

More interest has been attached to the finer parts of the renal blood supply including that of the glomeruli, the afferent and efferent arterioles and the route of the blood supply to the parenchymal capillary plexus. Opinions have varied a great deal regarding the exact nature of these finer structures

and many workers have made detailed studies of one or other aspect of this portion of the renal circulation. For this reason it seems advisable to discuss the more minute parts of the vascular bed under appropriate headings.

Glomeruli: Bowman recognized the essential vascular nature of the glomerulus when he described corpuscles like apples upon an arterial tree. "The Malpighian body I saw to be a rounded mass of minute vessels invested by a cyst or capsule..... The capsule is seen to pass into the basement of the tube as the body of a Florence flask into its neck." He did not recognize that the glomerulus was invaginated into the upper end of the uriniferous tubule. Johnston (1899) studied the minute structure of the glomerulus by reconstruction from serial sections. He came to the conclusion that the afferent arteriole breaks up into five main divisions as it enters the glomerulus. Each of these main divisions forms a capillary plexus. These capillary plexuses in turn anastomose within themselves and with one another. The efferent vessel is formed opposite the afferent vessel and passes within the glomerulus to the hilum where it makes its exit. In his material he found that the efferent vessel was smaller than the afferent but he believed this might be due to differences caused by the preliminary injection of a supersaturated solution of Berlin blue. Morrison (1926), Vimtrup (1928), and others agreed that the afferent glomerular arteriole divides into approximately two to six primary divisions.

There has been much difference of opinion regarding whether or not there are anastomoses within the glomerulus between capillaries arising from different primary divisions of the afferent vessel. Vimtrup (1928) believed that the glomerulus is too complicated a structure to study by any method of reconstruction. From a study of the glomerulus injected with gelatin and Berlin blue and then teased apart, he drew the conclusion that the larger lobules of the glomerulus correspond to the main divisions of the afferent arteriole. He found no anastomoses between capillaries of the same primary

division or between capillaries of different primary divisions of the afferent arteriole. This actual dissection seems the most accurate approach to the study of a structure so delicate and so complicated as the glomerulus.

Bowman believed that the glomerular tuft was suspended in the upper end of the uriniferous tubule uncovered by any tissue. Opinions on this question have varied a good deal since that time. On the basis of his own work and many others, Ludwig in 1872 stated "..... the walls of the capillaries are not in immediate contact with its fluid contents, a layer of not very well defined cells with spherical nuclei investing their surface. It is apparently stretched uniformly over each lobule of which the glomerulus is composed, and consequently binds the several vessels together; on the other hand, it is not extended from lobule to lobule, but if continuous at all, is only so at their roots." Von Ebner (1902) believed there was epithelium on the surface of the glomerulus, while the greater mass of cell nuclei deep in the glomeruli belonged to a syncytium connecting the capillary loops. Vimtrup in 1928 concluded that in the human kidney each capillary loop early in its development gains a complete epithelial covering.

Various methods have been used at different times to count the glomeruli of a kidney. Traut in 1923, by a maceration technique, separated human kidneys into structural units. He was able to count the number of glomeruli in each of these units. Then, on the basis of the number of ducts opening on a papilla, he calculated the number of lobules in a kidney. Multiplying these figures he obtained glomerular counts for single kidneys ranging from 3,862,000 to 5,700,000. In 1928 Vimtrup, by an injection technique similar to that used by Traut, stained the glomeruli with Prussian blue. Then all of the cortex was stripped from the medulla. With microscope and a ruled glass slide the glomeruli were counted in a section of cortex of known weight. By proportion the number of glomeruli in the total weighed cortex was calculated

from the number of glomeruli in the small section of cortex of known weight. This work was done on kidneys of the dog, cat, child, and in the adult man. He presented a figure of 887,399 glomeruli for the kidney of a child, and in the adult the figure varied from 867,177 to 1,233,360. He concluded that there was a marked increase in the number of glomeruli with increasing weight of the kidney. This is true in comparing the glomerular counts of dog and cat with man. But no such conclusion can be drawn from his figures of the glomerular count of a child and adult. In one large adult kidney the count was high but this would be consistent with the variation found between different individuals. Moore, in 1931, also counted glomeruli, staining them first with an injection of Prussian blue and then macerating the kidney. He too counted the glomeruli in a known weight of cortex and from this he calculated the number of glomeruli for the whole kidney. He obtained a figure which ranged from 700,000 to 1,200,000 as the average glomerular count in each kidney of an adult man. He concluded that there was no nephrogenesis after birth and that the glomerular count decreases with age. Thus, Moore and Vimtrup, using almost the same method, obtained very similar results but their conclusions were diametrically opposed. It seems clear that Moore's conclusions are the only tenable ones.

Afferent Glomerular Arterioles: Most writers agree that the majority of glomeruli are suspended from the arterial tree by small arterioles which arise from fine end-arteries in the cortex. As pointed out above in this connection, the differences of opinion have been over the exact position in the arterial tree of these end-arteries from which the afferent arterioles arise. But most writers (Lee-Brown, Kölliker, Golubew, Huber, Morrison, Gross, Miller) agree that the majority of the afferent arterioles arise in the cortex from small end-arteries of fairly uniform size and appearance termed interlobular arteries. It has been stated that there are a few afferent arterioles near the cortico-medullary junction which arise from the convex sides of the larger

vessels in this area (Morrison, Huber, Traut, Miller). Those afferent arterioles arising close to the medulla are in general longer than those in other areas of the cortex (Lee-Brown, Morrison).

Efferent Glomerular Arterioles: Bowman noted that the blood of the kidney passed through two sets of capillaries before passing into the veins. He likened this to a portal system with the efferent vessel connecting the two capillary systems. Since that time much attention has been given to the nature and distribution of these vessels. Kölliker in 1860 stated that "the vasa efferentia although arising from capillaries are still not veins, but have the significance, and in part the structure, of small arteries." Bensley, in 1929, using a special silver stain, found that there were special cells closely applied to the endothelium of the vasa efferentia. These cells he termed pericytes. He did not claim that they were of contractile nature but suggested that if they were, the vasa efferentia were admirably suited to alter the intraglomerular pressue. He did not agree with those who held that the difference in pressures between the glomerular and tubular capillary plexuses was due to the smaller diameter of the vasa efferentia. In discussing the distribution of the vasa efferentia Bensley agreed with Kölliker (1860), Lee-Brown (1924) and others, who stated that the termination of the vasa efferentia depended on their position in the cortex of the kidney. In the outer cortex the vasa efferentia were called the subcapsular type. These ran towards the capsule for a considerable distance before breaking up into a dense intertubular capillary plexus. In the middle of the cortex there were the cortical type. These after a short distance gave off a few capillaries and then broke up into an intertubular capillary plexus. Those arising from glomeruli near the medulla were called the cortico-medullary type. These were directed towards the pelvis. They broke up by repeated divisions into long vessels of large diameter which ran in a straight course between the collecting tubes of the medulla. These straight vessels were called arteriolae rectae and ended in a capillary plexus near the pelvis.

Direct Blood Supply to Cortical and Medullary Capillary Plexuses

Since Huschke's and Bowman's time the greatest differences of opinion regarding the blood supply of the kidney have arisen concerning the question whether or not all of the blood of the renal artery first passes through the glomeruli before reaching the tubular capillary plexus of the cortex and medulla. Various ideas have also been held concerning the question of anastomoses between the capsular and interlobular arteries. These differences of opinion are partly due to errors inherent in the various techniques applied and partly to the conclusions drawn regarding the blood supply of the human kidney from observations on abnormal kidneys and the kidneys of other animals. For instance, there must always be a tendency to error in the reconstruction of complicated structures from serial sections. In the injection of vessels there is always the difficulty that the injection mass may go too far and completely obscure the structures to be studied, or it may not penetrate far enough. Then, too, in some injection techniques the finer structures may be broken. It is known that there is good collateral circulation in the kidney of a dog between the capsule and parenchyma. The application of conclusions from experiments on such animals to man must be guarded. As MacCallum in 1939 pointed out "many of these observations when analyzed are actually not in conflict but are mutually confirmatory."

The different views concerning the finer blood supply of the kidney fall into three groups. The first view (Huschke 1828, Bowman 1842, Huber 1906-07) is that all of the renal arterial blood normally passes first through a glomerular capillary tuft before reaching the secondary cortical and medullary peritubular capillary plexuses. According to the second view (Schweigger-Seidel, 1865) most of the medullary and many of the cortical peritubular capillary plexuses normally have a direct non-glomerular arterial supply. The third view (Golubew 1893) is a compromise between the first and second: the normal

supply in the normal mammal is both indirect or glomerular and direct or non-glomerular in both cortex and medulla.

Cortical Capillary Plexuses. As pointed out above, most writers believed that the renal arteries finally terminate in small branches called interlobular arteries which give origin to the afferent arterioles of the glomeruli. Huschke (1828) believed that all of these small branches of the renal artery gave origin only to afferent arterioles which ended in glomeruli. He thought that all of the blood of the peritubular capillary plexus of the cortex came from the efferent vessels of these glomeruli. Bowman injected the renal arteries of different kidneys with one or other of two kinds of injection mass and then studied sections with the microscope. Lead chromate was one of the materials used and the other was vermilion-stained size, a gelatinous material used for stiffening cloth. Bowman believed that all of the blood of the renal artery except for a small amount of blood to the capsule, pelvic atructures and walls of large blood vessels, first passed through glomeruli before reaching any further capillary plexus. He commented at some length on this aspect of the circulation of the kidney in the following words: "There are in the kidney two perfectly distinct systems of capillary vessels, through both of which the blood passes in its course from the arteries into the veins: the first; that inverted into the dilated extremities of the uriniferous tubes, and in immediate connection with the arteries; the second, that enveloping the convolutions of the tubes and communicating directly with the veins. The efferent vessels of the Malpighian bodies, that carry the blood between these two systems, may collectively be termed the portal system of the kidney." These conclusions of Bowman's are essentially accurate even though the observations from which these conclusions were drawn are not all that could be desired.

Ludwig (1844) believed that the blood to the cortical intertubular capillary plexus first passed through glomeruli, but he thought that some of

the interlobular arteries terminated near the surface of the kidney by greaking up dinrectly into a capillary plexus. He found an occasional small twig arising from afferent arterioles just before they entered a glomerulus. This twig passed directly to the cortical capillary plexus and later became known as Ludwig's arteriole. Kölliker (1860) agreed essentially with Ludwig. He stated that a few of the interlobular arteries terminated in a subcapsular capillary plexus without passing through glomeruli and some of the interlobular arteries penetrated directly to the fibrous capsule. Virchow (1857) also agreed with this opinion feeling that most of the blood of the interlobular arteries passed through glomeruli although a few branches terminated either directly in the subcapsular capillary plexus or penetrated the fibrous capsule. In all of these views it is hard to differentiate between observed fact and mere opinion.

In 1885 Steinach introduced the idea of direct communication between arteries and veins on the basis of injection experiments on living animals. In kidneys injected through the artery with a suspension of lead chromate in gelatin he found some vessels in the boundary zone between the cortex and medulla containing injecting material, even though the glomeruli were only partly filled and the efferent vessels in this region contained none of the injection mass. He concluded that these were veins which had been injected by some more direct route than through glomeruli. He claimed to have confirmed this view by injecting lycopodium spores which were too large to pass through the glomeruli or through ordinary capillaries, into the carotid artery and recovering them in the blood of the renal vein. This seems open to serious doubt since these lycopodium spores, supposed to be incapable of passing through ordinary capillaries, must have passed through the capillaries of the head and lungs to have reached the left side of the heart.

Golubew (1893) injected arteries with silver nitrate and claimed that this had the advantage of defining the structure of the vessel wall as well as marking out the course of the vessel. He confirmed by direct observation the view of Steinach that there were some direct connections between arteries and veins. He also described small vessels arising from vasa efferentia close to the glomerulus and going directly to the intertubular capillary plexus of the cortex.

Huber (1906-07) employed a celluloid corrosion technique for the study of the renal arteries. This method had the advantage of allowing a great many vessels to be studied at one time throughout their entire length. Moreover, observations in three dimensions of injected arteries seemed to afford greater accuracy than observations of reconstructions from serial sections. The injection mass was made of photoxylin camphor, stained red with alkanin. The corrosion of kidney tissue was carried out with strong hydrochloric acid. The kidneys of dogs, cats, rabbits and guinea pigs were used in this study. Huber was convinced that all of the blood of the interlobular arteries reached the cortical capillary plexus only after passing through glomeruli. He stated: "So far as may be determined in corrosion preparations in which the peripheral portions of the interlobular arteries appeared completely injected, they end in afferent glomerular branches and do not present terminal branches which end in capillaries in the peripheral portion of the cortex." "Now and then, and more particularly in the dog, have I found an interlobular branch which did not completely break up into branches within the renal cortex, but could be traced beyond the outer border of the cortex anastomosing, as it would appear, with capsular branches." He concluded this very important study with the following remarks: "From my observations on corrosion preparations of the dog, cat, rabbit, guinea-pig and rat, in which it is possible to trace the renal arteries through their several branchings to their termination, including the branches which go to the glomeruli, the glomeruli themselves, the branches leaving the glomeruli, and often the

capillary plexuses formed by these, the conclusion seems warranted that practically all of the blood found in the capillaries surrounding the different portions of the uriniferous tubules is blood that has first passed through the glomerular vessels." He commented that this was so clearly stated by Bowman many years before that he should be given full credit for discovering the truth of this aspect of the circulation in the kidney. This was undoubtedly the best injection study of fine vessels of the kidney up to this time and in the main the observations agree with what now seems to be fact according to the best authorities.

Lee-Brown (1924) believed that he could settle these controversial points by preparing material which could be photographed. His photographs appear to be of sections in which the vascular tree has been injected but it is impossible from his paper to understand anything about the technique employed. He claimed that interlobular arteries besides terminating in glomeruli may either break up into a subcapsular cortical capillary plexus or perforate the capsule. He also believed that the interlobular arteries deep in the cortex give off branches very occasionally which break up into an intertubular capillary plexus without passing through glomeruli.

Morrison (1926) using the celluloid corrosion technique of Huber with slight modification prepared specimens of which he was able to get some excellent photographs. The material was derived from human autopsies varying in age from birth to seventy-five years and also kidneys from dogs, cats, rats, rabbits and guinea-pigs. His descriptions and photographs of the vessels show that interlobular arteries may either terminate in a subcapsular capillary plexus or may penetrate the capsule. He also showed a picture of a vessel which arose from an interlobular artery deep in the cortex and which broke up into a capillary plexus without passing through a glomerulus. From this study he believed that fundamentally the architecture of the renal blood supply was designed to allow all of the blood to pass through glomeruli before reaching the tubular capillary plexuses, but that occasionally there were direct nutrient arteries from the

branches or the termination of the interlobular arteries. He felt that these two additional non-glomerular sources of nutrient supply were, however, so infrequent as to be negligible from a physiological point of view. The photographs of his material showing structures down to the size of glomeruli make this work a valuable contribution to the literature of renal vascular architecture in man.

Medullary Capillary Plexuses. Many opinions have been expressed concerning the route taken by blood reaching the medulla. Huschke in 1828 stated his belief that all of the blood to the medullary capillary plexuses first passed through the cortical capillary plexuses and reached the medulla by a series of straight vessels. Bowman (1842) thought that all of the blood to the medulla passed through glomeruli but believed that the straight vessels arose directly from glomeruli adjacent to the medulla, and not from the cortical capillary bed. Ludwig (1844) accepted the opinion of Huschke that the straight vessels to the medulla arose from the cortical capillary plexuses. Virchow (1857) and Kölliker (1860) agreed essentially with Bowman that the straight vessels of the medulla arose from adjacent glomeruli. Kölliker called these arteriolae rectae after Arnold. Virchow also thought that some of these straight vessels arose directly from branches of the large renal arteries adjacent to the medulla (arteriolae rectae verae). Golubew in 1893 expressed the opinion that the straight vessels to the medulla originated from three sources. Most of them arose from the efferent vessels of glomeruli adjacent to the medulla. However, he believed that some of the arteriolae rectae had a direct origin from the afferent arterioles of adjacent glomeruli and from the arcuate arteries. He also described a new type of structure which he called retia mirabilia renum nova. These were small simplified glomeruli lying near the corticomedullary junction. Golubew thought these were newly developed glomeruli. As will be seen later others placed a different interpretation on these structures.

Gross injected the renal arteries with gelatin coloured with Prussian blue. He noted that in the normal human kidney the cortex stained while the medulla remained unstained. This appearance was almost reversed in small contracted kidneys. Gross thought that these findings indicated that in the contracted diseased kidney either the injection was forced into other normal but more direct channels to the medulla because of the glomerular obstruction or else this appearance indicated newly formed direct vessels to the medulla. To settle this question he hardened the cortex of a normal kidney with formalin and then injected it. No material reached the medulla. He concluded from this that in a normal kidney all of the blood of the medulla first passed through the glomeruli but that in the chronically diseased kidney new direct channels were formed to supply the medulla. This idea will be discussed more fully below along with the opinions of others.

Lee-Brown in 1924 said that he saw nothing clearly that could be called arteriolae rectae verae. Morrison (1926) stated that aside from the straight vessels to the medulla arising from adjacent glomeruli, there were some straight vessels arising from branches of the arcuates. These branches possessed thickenings in some cases. Morrison thought that these thickenings represented either Golubew's retia mirabilia renum nova, or the small glomeruli which Huber and Lee-Brown thought represented atrophic glomeruli lying close to the medulla, as a result of degeneration of nephrons in this area.

MacCallum in 1926 and 1939 wrote two excellent papers which cleared up much of the confusion that had existed regarding the finer blood supply of the kidneys. A combined method was used which consisted of staining the vessel wall and then injecting the lumen with material of another colour. Vital staining of the vessel wall was carried out with Janus green and the vessels were injected with carmine gelatin. The animals used included the rabbit, dog, guinea-pig, rat, cat and opossum. The stained and injected kidneys were studied

in serial sections. This method has the advantage of indicating what part of the vascular tree is present in the sections and so preventing some of the errors occurring when tracing a given vessel in serial sections. This is very important when drawing conclusions from serial sections where artery and vein lie parallel and close to one another. In his first paper MacCallum came to the conclusion that interlobular arteries always terminated in glomeruli. He considered that the suggestions of those who believed that interlobular arteries could terminate directly in the subcapsular capillary plexus were founded on errors of observation due to the fact that the arterioles from the end of interlobular arteries were in the same line as the artery. If the glomerulus was missing it appeared as though the interlobular artery continued on to end directly in the subcapsular capillary plexus. In one dog MacCallum found an interlobular artery which penetrated the capsule. In the following quotation MacCallum gives a clue to the conclusion he was able to make in his later publication. He stated in regard to the arteriolae rectae verae, "I have failed to find in the animals mentioned a single instance of such a vessel arising directly from the arterial arcades or interlobular arteries and breaking up directly into straight vessels in the medulla. It would be unwise, however, to draw the conclusion that such vessels never occur, for I have found in some instances atrophic glomeruli in which the afferent and efferent vessels were still patent, and it seems probable, as suggested by Huber, that the disappearance of the glomeruli and of the tubules to which they are related, either in the course of development or as the result of disease, would result in the persistence of their afferent and efferent vessels in such a way as to give the appearance of direct arteriolae rectae arising from an artery and not through the intermediary of a glomerulus. The instances which I have found of such a partial disappearance of glomeruli were not, however, in the lowermost areas of the cortex, and in relation with the larger arteries, but at the upper level of the cortex. In

two instances in guinea-pigs, vasa afferentia went to glomeruli which consisted of a single U-shaped loop, but were surrounded by a capsule and then continued on with undiminished calibre as efferent vessels." He believed at that time that a slow obliteration of the glomerulus might allow the blood finally to pass through just one of the short circuits within the glomerulus described by Johnston and so result in a structure which looked like a direct artery to the capillary bed. He insisted on the relative unimportance of such an occurrence from the standpoint of the theory of normal urine secretion.

MacCallum in 1939 was able to give a very comprehensive description of the steps leading to the development of direct vessels in the cortex and medulla. The same technique, and animals of the same species were used as in his previous study. MacCallum's findings showed that in a glomerulus the site of disease, most of the capillary loops became compressed and obliterated, until the afferent and efferent arterioles are joined by a single endothelial channel through a fibrotic glomerulus. At this point the efferent vessel acquires a definite coat of circular muscle so that there is a direct vessel to the capillary plexus of the kidney composed of two arterial segments joined by a capillary loop. From this point further changes occur which may be divided according to MacCallum into: "Type 1, <u>vascular unit obliteration deviation process</u>", or "Type II, <u>vascular unit non-glomerular transformation process.</u>" In the change of type I the capillary loop is compressed, the efferent vessel collapses and finally the lumen of the afferent arteriole is completely obliterated leaving no trace of the afferent arteriole glomerulus and efferent arteriole. In the type II process, the endothelial channel through the fibrotic glomerulus enlarges, acquires a muscle coat, the efferent arteriole increases in diameter so that finally there is a single glomerulus-free arterial vessel uniform in size and structure. MacCallum stated that depending on whether this vessel is in the cortex or close to the medulla, "this new type non-glomerular vessel is the controversial medullary true straight artery, arising directly from arciform

or interlobular artery and the direct glomerulus-free end or lateral branch of the interlobular artery which joins the cortical peritubular capillary plexus without first having broken up into a glomerular capillary tuft and recombined." MacCallum described many variations of this direct artery to the cortical and medullary capillary plexuses. He mentioned that all of these vessels previously described in pathological human material have been observed in the kidneys of his apparently normal animals. He felt that all of these represent either intermediate or end-stages or variants of a pathologically induced series of circulatory readjustments. MacCallum concluded his discussion by expressing the opinion that the controversy of the past was due to a failure of workers to define normality and to use what could definitely be called normal kidneys in their studies. He stated that the renal blood supply is exclusively glomerular until pathologically induced circulatory readjustments make it otherwise and he went on to say: "When these relatively infrequent pathological departures from the normal are noted in text-books of normal anatomy or physiology, it should be pointed out definitely that they are pathological in character."

Summary of present Status: While there has been a great difference of opinion regarding the blood supply of the kidney it now seems clear that in the normal human kidney the fundamental plan of the renal vascular architecture allows all of the blood to pass through glomeruli before supplying the capillary plexus of the cortex and medulla. The majority of afferent arterioles and glomeruli are suspended from arteries of rather uniform and small size which in general are directed from the medulla towards the surface of the kidney. These small arteries giving origin to most of the glomeruli are end-arteries and may conveniently be called interlobular arteries. Occasionally direct vessels to the capillary plexus of the cortex and medulla do occur, and in the human kidney there are sometimes anastomoses between interlobular arteries and the capsular vessels. MacCallum's work seems conclusive in confirming the

opinion of Huber, Gross and Morrison that the direct vessels to the capillary plexuses are rare and occur as the result of the changes in the kidney consequent on age and disease. As will be seen later, Oliver and his co-workers have discussed more fully the development of these direct channels in chronic renal disease and have attached a definite significance to their presence in the diseased kidney.

Arterial and Arteriolar Changes in the Kidney in Hypertension

General: Observations on autopsy material that indicate some association between renal disease and hypertension have been noted for over one hundred years. But it was not until Riva-Rocci in 1892 developed the method of measuring blood pressure with the pneumatic cuff and mercury manometer that hypertension was recognized as a definite clinical entity., It was only after this time that people began to investigate the specific pathology of this disease. Whether or not disease of the kidneys plays a primary rôle in the development of hypertension has been a question for speculation and controversy for a long time. Richard Bright, in 1836, in discussing the clinical picture of acute glomerulonephritis, mentioned the presence of a "full and hard" pulse in these patients. In speaking about contracted kidneys he said: "The first circumstance which strikes the mind, is the extent and frequency to which the derangement of one organ is connected with the derangement of several others: Yet we are not at liberty to assume that the disease of the kidney has been the primary cause on which the disease of the rest depended." That he recognized changes which must have been due to the hypertension in these cases is apparent from his comment that the hearts in many cases showed a marked hypertrophy, particularly of the left ventricle, for which no cause could be found in the heart or large arteries. He observed that the degree of hypertrophy paralleled the progress of disease in the kidneys for the hypertrophy was most marked when

of this hypertrophy to be due to a demand for increased effort on the part of the heart and thought this might be a result either of an altered state of the blood or of an increased resistance in the finer circulation. That he even anticipated the much later classification of contracted kidneys as being due to chronic glomerulonephritis and arteriolonephrosclerosis, seems apparent from his comment that at autopsy he found contracted granular kidneys which should have come from patients with a history of albuminuria, but no such history could be obtained. He also found that there was an increased resistance to perfusion of nodular contracted kidneys. Toynbee (1846) showed that this difficulty was due to thickening of the walls and narrowing of the lumens of the intrarenal vessels. Johnston (1858) found a similar thickening in the small vessels of other organs, but he believed the primary disease to be in the kidney. He thought that the purpose of the thickening was to prevent the accumulated noxious substance from passing into the tissues.

Gull and Sutton (1872) described a widespread "hyalin-fibroid" thickening of small vessels in the kidneys and other tissues from autopsy cases in which there were contracted granular kidneys. They also found similar but slight changes in the small vessels of kidneys which were finely granular, of normal size and presented no marked changes in the kidney parenchyma. From these observations they concluded that the first step in the development of chronic Bright's disease was this thickening of small vessels throughout the body. They believed that this widespread thickening and constriction of fine vessels, which they called arterio-capillary fibrosis caused an increased peripheral resistance resulting in the cardiac hypertrophy. It seems evident now that without realizing it they were describing the kidneys of the early stages of benign arteriolar nephrosclerosis, and from their observations drawing the conclusion that arteriolar constriction was the cause of all renal contraction and granularity.

But it was not until the work of Jores (1904) and Volhard and Fahr (1914) that contracted granular kidneys were clearly differentiated into two types: one the kidney of chronic glomerulonephritis and the other the kidney of arteriolar nephrosclerosis. Clinically it was known that contracted kidneys were associated with arterial hypertension in most instances. The hypertension associated with chronic glomerulonephritis was generally regarded as of renal origin while the hypertension associated with arteriolar nephrosclerosis was considered to be the essential hypertension of Frank and the problem became one of determining the pathogenesis of this form of arterial hypertension.

It soon became apparent that the arterio-capillary fibrosis of Gull & Sutton was not sufficiently widespread to cause an increase in peripheral resistance adequate to produce persistent hypertension. Albutt (1915) expressed his belief that a generalized vasoconstriction was responsible for essential hypertension and that the vascular disease was secondary, appearing as a consequence of the hypertension. Attention was now directed toward finding the cause of this primary generalized vasoconstriction and for some years no serious thought was given to the kidney as a primary source of this widespread disturbance of vascular tone. But as time went on some workers had kept insisting that there must be some significance to the constant association of chronic renal disease and hypertension. Various methods have been used to study the blood vessels of the kidney from cases of hypertension, all of them yielding contradictory results. More recently, the production of experimental hypertension by constriction of the main renal artery by Goldblatt and others has awakened tremendous interest in the question of the relation of renal vascular disease to hypertension and a marked impetus and direction have been given to all of these studies.

Goldblatt (1932-38) reawakened the waning interest in the problem of the relation of chronic renal disease to hypertension. Goldblatt (1932) was successful in producing experimental hypertension in dogs by markedly constricting

the main renal arteries with the production of marked renal ischaemia. Since then in a series of brilliant papers he has confirmed the results of the first experiments and extended the observations in an attempt to define the mechanism operating in the production of this form of hypertension in dogs. These same results have been confirmed in dogs and obtained also in rabbits, cats and monkeys by other investigators.

Goldblatt started with the hypothesis that hypertension associated with narrowing of intrarenal arteries was caused by this arterial narrowing through the reduction of renal blood flow which he assumed would result from the presence of such vascular lesions. If this hypothesis were correct, the experimental production of intrarenal vascular sclerosis should be followed by the appearance of hypertension. No experimental method was available for producing the requisite lesions in the intrarenal arteries, and for this reason Goldblatt adopted a method by which he could at least simulate the presumable functional effect of arterial narrowing by reducing the blood flow through the kidney. A special clamp was devised which could be fitted around the main renal artery and by means of which the artery could be compressed and constricted to any desired degree with consequent renal ischaemia.

Briefly stated, the results of these experiments on dogs are these: Constriction of rather marked degree of one main renal artery causes a rise of diastolic and systolic blood pressure which persists for about one month but gradually falls again to normal. When a similar constriction is applied to both main renal arteries usually a persistent hypertension occurs. If constriction is carried out on the aorta just above the renal arteries, hypertension occurs in the body above the constriction, but if the constriction of the aorta is below the renal arteries no rise in blood pressure occurs.

The proof that ischaemia of the kidney is in some way responsible for this rise in blood pressure is shown by the following experiments. If ischaemia of only one kidney is produced and then, while the blood pressure is still

elevated, either the ischaemic kidney is removed or the arterial constriction relieved, the blood pressure falls promptly to normal. If, when hypertension has been produced by constriction of both renal arteries, either one clamp or both clamps are removed, the blood pressure returns to normal — this fall of blood pressure being most rapid when both clamps are released. When one kidney is removed and the other transplanted to the neck, constriction of the blood supply to the transplanted kidney results in an elevation of the blood pressure, proving that the mechanism of this form of hypertension is not reflex in nature. Bilateral nephrectomy is not followed by persistent hypertension indicating that renal insufficiency is not necessary for the development of hypertension. In conclusion, Goldblatt stated that: "These results constitute evidence that the kidney is responsible for the effect and that it must be present in the body in order for hypertension to occur." Since then the study of experimental hypertension has been directed towards determining the mechanism of this form of experimental hypertension. All of these findings have stimulated the study of the renal vasculature in cases of hypertension in man in order to determine whether renal ischaemia may be responsible for essential hypertension in man as it is in the experimental animals.

The studies of the renal vasculature of abnormal kidneys both before and after Goldblatt's work have been carried out by the use of three main methods. Three-dimensional studies have been made by various injection techniques, by microdissection and by reconstruction or a combination of these. There have been some excellent studies made on histological material. Others have attempted to study this problem by perfusion experiments.

Histological Investigations: Fishberg (1925) defined essential hypertension as a persistent hypertension which neither on clinical or anatomical grounds can be regarded as being caused by inflammatory or obstructive disease of the kidneys. In a study of tissues taken at autopsy from 72 cases of essential hypertension he found sclerosis of small renal cortical arteries and

arterioles in every case. He concluded that arteriolosclerosis was a natural phenomenon of ageing, accelerated in its development by the wear and tear of hypertension. He believed the renal lesion could not be held responsible for the hypertension. In drawing this conclusion he seems to have been influenced by lack of evidence of renal insufficiency in most cases. Since this work preceded that of Goldblatt, Fishberg was not aware that experimental hypertension of renal origin can be produced without significant impairment of renal excretory function.

Bell & Clawson (1928) made a very careful histological study of the renal arteries and arterioles of the kidneys from 420 cases of essential hypertension. Cases were accepted as instances of essential hypertension when either there was a persistent systolic blood pressure of 150 mm. of mercury or more, not associated with any disease known to cause hypertension, or when there was an idiopathic hypertrophy of the heart exceeding 450 grams in the female and 500 grams in the male. From these studies they concluded that thickening of the elastic lamina of vessels down to the afferent arteriole was no indication that the patient had suffered from hypertension unless these changes were extremely severe. Restricting the term arteriole to the afferent glomerular arterioles they stated that: "No instances of definite sclerosis of the afferent glomerular arterioles were observed in whichhypertension could be excluded with certainty, so that we are inclined to consider this lesion pathognomonic of hypertension: but further studies should be made before we conclude that this relationship is without exception." Ten percent of their cases of hypertension did not show renal arteriolar sclerosis. They believed that there were sufficient studies available to indicate that generalized arteriolosclerosis was not a common accompaniment of hypertension. They thought that on histological grounds alone a fundamental distinction could not be made between arteriosclerosis and arteriolosclerosis. In discussing the possible causes of

hypertension they stated their belief that renal disease could not be held as the cause of essential hypertension. They believed that primary hypertension was not caused by vascular disease but that it put an additional strain on the arterial system which intensified and accelerated arterial degeneration throughout the body and especially in the kidney. At the time of their work they were not influenced by Goldblatt's results. In 1939 Bell had altered his opinion slightly and stated: "It is clear that severe renal arteriosclerosis may cause or intensify hypertension and it appears probable that hypertension may intensify arteriolosclerosis."

Volhard (1935) stated that the dominant idea in the theories regarding the cause of hypertension was that the increased resistance was functional and not organic throughout the body. He divided hypertension into two distinct forms: the "pale hypertension" of renal origin due to generalized vasoconstriction caused by the presence of pressor substances in the body; and "red hypertension" (or essential hypertension) which was not of renal origin. He believed that red hypertension developed on the basis of an early senescence of the whole arterial tree. He explained the initial rise in systolic pressure on the basis of a loss of elasticity of the larger arteries. This resulted in an overdistension of smaller arteries which then underwent changes which converted them into rigid tubes. As a result, a more direct pressure was transmitted to the smallest vessels which were first reflexly contracted and then later became hypertrophied, resulting in an increased peripheral resistance. The changes in the larger arteries of these two forms of hypertension he thought could be distinguished. The vessels from cases of red hypertension showed a diffuse loss of the muscle coat with some hypertrophy of the outer coat and an increase in the elastic and collagen fibres and dilatation of the lumen, while in the vessels from cases of "pale" or renal hypertension there was a disseminated muscular hypertrophy and no dilatation of the lumen. To Volhard the

hyaline changes in renal arterioles were not sclerotic but rather soft in character ("arteriomalacia"). These changes he believed were due to a disturbed and inefficient blood supply to vessels of this size due to the changes occurring in the vessels proximal to them. Because of the changes occurring in the arteries proximal to the arterioles, he believed that the high blood pressure was not transmitted to the arterioles and therefore changes in arterioles could not be explained on the basis of an increased strain.

Moritz and Oldt (1937) noted an almost complete lack of agreement as to the character and distribution of vascular lesions in association with essential hypertension. They believed that a simple morphological study of this problem should be capable of accurate analysis. With this end in view they made a careful histological study of the arterioles of the kidney, spleen, pancreas, adrenal, gastro-intestinal tract, skeletal muscle and liver from 100 cases of hypertension and 100 cases known to have been non-hypertensive. Vessels of 100 μ or less in diameter were considered arbitrarily as arterioles. The criteria for hypertensive cases included a history of persistent hypertension higher than 160/90 or 150/100 together with a heart weight of 450 grams or more in the male and 350 grams or more in the female. Cases presenting any obvious cause for the cardiac hypertrophy such as valvular lesions were not included. The non-hypertensive control cases were required to have had repeated blood pressure readings of less than 140/90 and heart weights less than 400 grams in males and less than 300 grams in females. They described three types of change in the arterioles studied which they termed intimal hyalinization; intimal proliferation; and medial hypertrophy and degeneration. They concluded that the first two of these were primary pathological processes occurring in both hypertensive and non-hypertensive cases. The intimal hyalinization was more frequently severe in cases of hypertension than in non-hypertension.

The medial hypertrophy they believed to be a secondary phenomenon representing a compensatory reaction to dilatation of the arterioles which may have resulted either from increased arterial blood pressure or medial degeneration. This type of change was definitely more common in cases of hypertension. The only positive and definite correlation of arteriolar disease and hypertension was found in the kidney. Ninety-seven percent of the cases of hypertension showed renal arteriolar sclerosis, while renal arteriolar disease of more than mild degree was found in only two percent of the non-hypertensives. It seemed to Moritz and Oldt that the only two possible explanations of these findings were that hypertension causes sclerosis of renal arterioles or that arteriolar sclerosis causes hypertension. They thought that the first view attributed an extremely high degree of selective vulnerability on the part of renal arterioles to injury of a purely mechanical nature causes by the high blood pressure since the arterioles of other organs frequently were normal. They believed it was more reasonable to assume that primary sclerosis of the arterioles in the kidney was the cause of hypertension, and pointed out that this belief was in harmony with the mechanisms concerned in the experimental production of hypertension by constriction of the main renal arteries (Goldblatt). This was the first time in many years that a serious study had led to the implication of sclerosis of renal arterioles in the human kidney as the primary factor in the causation of essential hypertension. Since their observations were essentially the same as Bell and Clawson in 1929, it seems likely that the findings of Goldblatt strongly influenced their interpretation of the relation of renal arteriolosclerosis to hypertension.

Williams and Harrison (1937) studied the relation of changes in the renal arterial and arteriolar vascular bed to age and hypertension. They examined histological sections from normal kidneys, kidneys of chronic glomerulonephritis, benign nephrosclerosis and malignant nephrosclerosis. They found

an association between age and hypertension on the one hand and sclerosis of renal vessels of all sizes on the other. The atherosclerosis of the larger vessels was most commonly associated with age while the changes of small vessels and arterioles were most commonly found in cases of hypertension. They considered that some cases of essential hypertension may arise on the basis of a severe degree of renal arteriosclerosis, but to them it seemed most likely that the changes in small arteries and arterioles in cases of hypertension were secondary to the hypertension. This opinion is in accord with that of Bell and Clawson and opposed to the views of Moritz and Oldt.

Since Goldblatt's work a number of cases have been reported purporting to show that obstruction of the main renal artery in man can produce hypertension. From these the following two cases were selected as the best examples to illustrate how the Goldblatt mechanism of hypertension might apply to some cases of hypertension in man. Leadbetter and Burkland (1938) reported a case of hypertension of three years' duration in a boy of $5\frac{1}{2}$ years of age which was cured by unilateral nephrectomy. In the main renal artery of this kidney there was a smooth muscle plug almost completely filling the entire lumen of the main renal artery. Boyd and Lewis in 1938 reported a case of persistent hypertension in a man of 30 years of age cured by unilateral nephrectomy. The kidney was the site of a marked arteriosclerosis of the large vessels. In one main branch occlusion had occurred producing an infarct. It seems likely that the hypertension in both of these cases is explained on the basis of renal ischaemia due to marked obstruction of the large renal arteries.

Undoubtedly there are other cases in which hypertension developed on the same basis. But when these cases come to autopsy it is impossible to prove that such a mechanism operated in the production of the hypertension. Moritz and Oldt (1937) reported three cases of chronic hypertension which showed a marked arteriosclerosis of the large vessels of the kidney and no

arteriolar sclerosis. In one case there were obstructing annular plaques around the aortic ostia of the renal arteries.

Oppenheimer, Klemperer and Moschkowitz (1939) were the first to study the relation of arteriosclerosis and narrowing of the main renal arteries to hypertension. They found that out of 18 cases which came to autopsy with unilateral narrowing of the main renal artery, 15 had had hypertension during life. All of the cases of hypertension also showed sclerosis of intrarenal vessels while the three without hypertension showed no change in the intrarenal vessels. Blackman (1939) made a similar study. He examined and measured cross sections of the main renal artery from 50 cases of chronic hypertension and 50 non-hypertensive control cases in approximately the same age groups. The main renal artery in 54 percent of the cases of chronic hypertension showed a marked narrowing, the degree of which can be best appreciated by examination of the series of photographs accompanying his paper. The lumina of both renal arteries in 5 of these cases was reduced to 1.5 mm. or less in width and in 11 of the cases the lumen of one renal artery was reduced to 1.5 mm. or less in width. These were the only cases where the mechanism of Goldblatt could be seriously considered to have exerted its influence on the production of hypertension. Another 32 percent of the cases of hypertension showed a moderate degree of arteriosclerosis of the main renal artery, while the remaining 14 percent showed no significant narrowing of the portion of the renal artery available for examination. Only 50 percent of these cases showed a "vascular nephritis." No striking difference was found in the incidence and degree of stenosis of the main renal arteries in the cases of hypertension with vascular nephritis and those without vascular nephritis. While there was definite arteriosclerosis of intrarenal vessels in all of the cases of hypertension, there was no correlation between the degree of arteriosclerosis of the intrarenal vessels and the degree of stenosis of the main renal artery.

In the 50 control cases there were five (10 percent) with significant arteriosclerosis and stenosis of the main renal arteries. Blackman felt, in view of this evidence, it seemed probable that in the cases reported, the marked occlusion of the main renal artery of over 50 percent of the cases of hypertension was an important factor in the pathogenesis of the hypertension. But he thought the five control cases which showed stenosis of the main renal arteries without hypertension indicated that other factors were necessary for the development of hypertension besides partial occlusion of renal arteries. In agreement with others, he believed that a pressor substance was produced as a result of the renal ischaemia. He suggested that the mechanism responsible for this type of hypertension might fail if the pressor substance were not produced, if the reaction at the site of peripheral vessels failed, or if the heart should fail to respond to the heightened peripheral resistance by an increase in its work. The important fact from both these papers is the constant association of sclerosis of intrarenal arteries and arterioles with hypertension while the arteriosclerosis and stenosis of the main renal artery is a variable finding.

Investigations by Injection, Microdissection and Reconstruction Techniques.

Gross (1918) studied the arterial system of contracted granular kidneys but he made no attempt to differentiate between the different forms of contracted kidney. Injections of the arteries were carried out either with coloured gelatin or with a radio-opaque injection mass. He described the withered and bare appearance of the arterial tree in contracted kidneys but from the pictures of the skiagraphs nothing can be seen of the intimate changes in the smaller vessels of the cortex. He believed that there was a readjustment of the circulation to account for his injections reaching the medulla in contracted kidneys and not in normal kidneys. No attempt was made to interpret the relation of these changes to the cause of high blood pressure.

Graham in 1928, using the technique of Hill, injected a series of 48 kidneys with radio-opaque bismuth oxychloride suspended in a 10% solution of acacia. Without defining what he meant by the term nephrosclerotic kidney, he claimed that in these the earliest and most striking change was a tortuous, gnarled-oak appearance of the arcuate and interlobar arteries. In the more severe cases tortuosity of the interlobular arteries and a loss of glomeruli could also be seen. He thought that this method of injection might differentiate between the vascular changes in nephrosclerosis and glomerulonephritis because he found in one kidney from a case of glomerulonephritis only a few glomeruli injected and the medullary vessels well injected, the only such result in his whole series. The results of this study are rather vague and inconclusive.

Baehr and Ritter in 1929, employing the injection technique of Gross, injected a series of kidneys which included kidneys from three cases of primary arteriolar nephrosclerosis complicated by a necrosing arteritis and arteriolitis, two cases each of acute and subacute glomerulonephritis and nine cases of chronic diffuse glomerulonephritis. They were especially interested in determining whether there was any difference in the arterial pattern of the kidneys of chronic glomerulonephritis and arteriolar nephrosclerosis. They felt that Gross had not differentiated between these in the injections of contracted kidneys and they believed that the one kidney of glomerulonephritis that Graham injected was not a definite case of chronic glomerulonephritis. In their material there were no significant alterations in the architecture of the arterial tree in kidneys of acute and subacute glomerulonephritis. The arterial and arteriolar pattern of both forms of contracted kidneys were alike, consisting of a loss of the finer interlobular arteries and arterioles, while the larger branches were tortuous and irregularly constricted. They concluded from their observations that the final pathological picture in both forms of contracted kidney was caused by thickening and narrowing of the smaller arteries

and arterioles and that this was responsible for the indistinguishable clinical picture. They also believed that it was futile to speculate on the primary importance of arteriolar sclerosis in the causation of arterial hypertension. Unfortunately, they did not make it clear whether they were referring to arteriolar sclerosis in general or as it occurs in the kidney. The work of Gross, Graham, and Baehr and Ritter, preceded the papers by Goldblatt and these investigators failed, therefore, to draw any conclusions as to the possible significance of the arterial changes in relation to the Goldblatt type of renal hypertension.

Oliver and Lund (1933), Oliver and Luey (1934 and 1935), Loomis (1936), and Oliver (1939), did much to correlate disturbances of renal physiology with the anatomical changes which occur in chronic Bright's disease. They pointed out particularly that disturbed renal function cannot be interpreted on the basis of purely quantitative changes in the anatomy of the kidney. They studied carefully the whole problem of kidney architecture in contracted kidneys by two methods. Reconstruction from serial sections were made by the Born wax plate method and on some kidneys microdissection was performed following maceration in hydrochloric acid after the method of Huber. The most important observation of these workers was the description of the aglomerular tubule, which they believed represented an adaptation of the tubule occurring in the diseased kidney to allow this portion of the nephron to perform under proper conditions some of the functions of the glomerulus which had been destroyed by disease. They considered the aglomerular nephron to be a reversion to the form of aglomerular nephron seen in some fishes. Coincident with the development of the aglomerular nephron there were corresponding adjustments of the circulation. The interlobular arteries and arterioles became tortuous, shrunken, beaded and angulated. These changes were considered to be of a regressive nature, due to disease of the vessel walls and of the surrounding parenchyma. More important were the changes of progressive character. These resulted in the development of a new

direct blood supply to the cortical capillary plexus either by short circuits through preexisting channels inside or outside of the glomerulus or by the actual development of new vessels. For the first time a real significance was placed on the new direct vessels to the capillary plexuses which Huber, Lee-Brown and MacCallum had stated occurred only as a result of age or disease. Regarding arteriolosclerotic renal disease, Loomis concluded that: "All these adaptive changes in the blood vessels are of the greatest importance since where they are effective the kidney can continue to function even when there has been fibrosis of the majority of glomeruli. The condition of the kidney at any stage of the arteriolar sclerotic disease is then the resultant of quantitative changes affecting the blood supply..... The tempo of the disease determines whether the progressive processes (hypertrophy of the nephron, development of new vessels) can successfully counteract the regressive processes. The continued function of the organ depends on this balance." It will be seen later that these findings have an important bearing on the interpretation of results obtained by perfusion of abnormal kidneys. The appearance of the vessels in chronic glomerulonephritis and arteriolosclerotic Bright's disease was similar. Even though Goldblatt had published his first paper at that time no suggestion was made that these renal vascular changes might produce ischaemia of the kidney sufficient to cause hypertension by a mechanism similar to that in experimental hypertension in dogs.

Investigations by Perfusion Techniques: Hayman (1929) wished to determine the importance of reduced renal blood flow due to mechanical obstruction of the renal circulation in the production of disturbed renal function in the different diseases of the kidney. He perfused human kidneys obtained at autopsy with Ringer's solution and acacia. The rate of flow of the perfusate from the renal vein was correlated with the histology and the appearance of injected specimens obtained by the technique of Graham. His results showed, in kidneys presenting arteriolosclerosis, a reduced perfusion rate per gram of tissue

proportional to the severity of the histological changes and to the degree of abnormality of the vascular architecture as seen in the roentgenograms of the injected kidneys. In kidneys with chronic glomerulonephritis the perfusion rate was reduced to the same degree and the histological picture and appearance of the injected kidney were of the same type as in the kidneys of advanced arteriolosclerosis.

Stimulated by the work of Goldblatt and others, Christian and Schlesinger (1939) tried to determine the degree of ischaemia in the kidneys of human beings suffering from hypertension. They believed that this problem could best be investigated by calculating the perfusion rate and by studying injected specimens of kidney from cases of hypertension with and without evidence of renal failure. Physiological saline and Lock-Ringer's solution were used for perfusion; no detectable difference was found in the rate of perfusion for the different types of perfusate. The rate of perfusion was calculated for every rise in pressure of 20 mm. of mercury between 60 to 240 mms. Only one kidney was used in each case. Injections were finally made with lead phosphate in agar and the kidney sectioned, x-rayed and dissected according to the technique of Schlesinger. Forty-six kidneys in all were studied, including 27 normal control kidneys, 7 kidneys from cases of hypertension without evidence of renal insufficiency, 3 kidneys from cases of hypertension with evident renal failure, and 8 kidneys from cases of inconstant hypertension. Perfusion rates calculated both on the basis of body height or weight of kidney tissue varied considerably within each group, but there was no significant overlapping between the perfusion rates of the control cases and those with hypertension. The perfusion rate of the kidneys from hypertensive patients even at high pressure did not equal the perfusion rate of the normal kidneys at normal pressure. This is contrary to the findings of Hayman, who found that when the perfusion pressure was raised to a level equal to that occurring in hypertension, the perfusion rate of an arteriolo-

sclerotic kidney equalled the perfusion rate of a normal kidney at a normal pressure. In Christian and Schlesinger's work, there was no great difference in perfusion rates of the hypertensive cases with or without renal insufficiency. No correlation existed between the perfusion rates and the degree of atherosclerosis seen in the injected kidneys. It is significant to note that rather marked constriction of the main renal artery did not alter greatly the renal blood flow. All of these results must be interpreted with the utmost caution because in the perfusion of a kidney, oedema of the interstitial tissue develops. The degree of this oedema may vary between the normal and abnormal kidneys. Another factor modifying the perfusion rates of abnormal kidneys is the development of new vascular channels. And the final and probably most important consideration in interpreting such results is the fact that we do not know how closely such perfusion experiments approach the conditions controlling the renal circulation during life.

Cox and Dock in 1941 thought that the results of any perfusion method used to study the renal vascular bed could not be considered valid unless the perfusion rates approximated the renal blood flow as determined clinically by the diodotrast clearance method in similar cases. Perfusion experiments in the past had yielded values much lower than those obtained by clinical methods. Cox and Dock realized that in post-mortem material it was impossible to duplicate the flow during life but they felt that by a suitable method, the maximum carrying capacity of the renal vessels could be determined. To combat the oedema that developed during perfusion experiments, they used kerosene as a perfusate. In order to break down all rigor mortis in the vessels, the kidney was kept for 24 hours at 4°C, and then perfused with a litre of kerosene at a pressure of 200 mms. of mercury. The maximum renal blood flow was calculated from the perfusion rates and this was compared with diodotrast clearance values for men of the same age. The perfusion rates obtained for normal kidneys were 50%

higher than the renal blood flow obtained by the diodotrast clearance method in men of the same age. They believed that this indicated that their method was a valid measure of maximum renal blood flow. There was a reduction in the perfusion rate of one-quarter between maturity and late middle age. Seventy-five percent of the hypertensive group had values within the normal range. The possible renal blood flow was reduced in kidneys from patients who had suffered from renal insufficiency due to a variety of pathological processes in the kidneys. They found that narrowing of a short segment of the main renal artery must be very marked before the perfusion rate is lowered, a finding in agreement with Christian and Schlesinger. They concluded from their observations that hypertension is usually not associated with renal arterial disease at its onset, and is usually not accompanied by significant reduction in the renal vascular bed. They believed that hypertension may initiate and accelerate degenerative changes in renal arterioles and that this accounts for the reduction in blood flow in some cases. As will be pointed out later, histological section of kidneys made after perfusion by this method reveals that in some kidneys the peripheral glomeruli are stuffed with red blood cells. This must affect to some degree the results obtained for any one kidney and therefore variations of perfusion rates between different kidneys must be interpreted with the utmost caution.

Summary of Present Status: All of these studies have resulted in confusing and contradictory observations and opinions. Many workers are agreed, particularly since Goldblatt's work, that disturbances of the renal vasculature in man are responsible for the production of esssntial hypertension. But no consistency of opinion exists regarding where these changes occur or what they are. Much of the difficulty lies in the inherent limitations of the methods used in these studies. Observations of histological material may be inaccurate because of the variation in shrinkage that may take place in vessel walls depending on whether they are healthy or diseased. These observations also have

the disadvantage of being only two-dimensional, and at the most only a small part of any one kidney can be studied. Conclusions drawn from the perfusion rates of abnormal kidneys must always have some degree of uncertainty because of the effect on the perfusion rate of the aglomerular blood channels that develop in chronic renal disease and, as will be shown later, may become quite extensive. Interpretations from reconstruction methods are limited because of the small amount of the kidney studied and because of difficulties of reconstructing accurately very complicated structures. Injection studies have yielded reliable information only of the larger vessels. Up to the present time, injections of kidneys from cases of essential hypertension have not given any clear and exact knowledge of the finer vasculature to which so much importance is attached owing to the changes seen in the small arteries and arterioles in histological section of such kidneys.

Part II

REVIEW OF INJECTION TECHNIQUES FOR THE STUDY OF BLOOD VESSELS

As Applied to the Kidney

The study of blood vessels by the injection of their lumina has been performed for many years. The methods employed resolve themselves principally into four methods.

(1) Injection of a coloured material into vessels followed by clearing by the Spalteholz technique or some modification. The vessel walls also may or may not be stained previous to injection.

(2) Injection of a coloured material followed by serial section of the organ from which drawings and reconstructions can be made. The vessel walls also may or may not be stained. Reconstruction may not require previous injection of the organ.

(3) Injection of a radio-opaque material followed by an x-ray picture of the injected organ.

(4) Corrosion technique: This method consists of injecting a material into the vessels followed by corrosion of the organ tissue by some reagent which will not destroy the injected material. This leaves a cast of the lumen of the vascular tree which can be studied in three dimensions.

The success of all of these methods requires the fulfillment of a few fundamental requirements. The organ to be injected should be as fresh as possible, whether the material be from animals or from human autopsies. The organ may be injected in the body or outside of the body. If it is to be injected outside of the body a long shank of the artery to the organ should be left attached to the removed tissue and a good deal of surrounding fat or other tissue should be removed at the same time. Preliminary washing by water or other fluid is carried out. At this time all leaks may be stopped by

ligating vessels and tissue showing any oozing. If the organ is in the body all vessels that can act as anastomotic channels between the organ to be injected and the rest of the body must be closed. This preliminary washing must be carried out until the organ is quite pale and generally speaking if this does not occur within the first few hours a poor result usually follows.

A brief review of the materials used in these various methods follows and the details in each instance can be found in the original papers.

Various methods have been used for the sole purpose of filling the vessels with a coloured material so that on section in various directions the course of blood vessels can be seen in any organ studied. Bright in 1842 used vermilion coloured size, a gelatinous material, for injection of the vessels of the kidney, and studied his material by merely sectioning the kidney in various directions and observing the course of the vessels by the naked eye. Gelatin coloured with Berlin blue, carmine (Gross 1917, and MacCallum 1926), and innumerable other dyes has been a favourite. Sometimes, in addition, the walls of the blood vessels have been stained as well. MacCallum (1926) accomplished this by use of janus green and Bensley used a silver preparation, both with the object of determining what part of the vascular tree was being studied when thick sections are observed under the microscope. Organs stained by these methods may be cleared. Spalteholz developed one of the original methods of clearing tissue. Gross in 1917 found that aniline oil worked well for clearing kidney sections. There is an obvious limitation to all of these methods when observation is limited to sections of the kidney. Clearing of such injected organs possesses the advantage of allowing a three-dimensional view of the injected material in relation to the parenchymatous structure. There is the definite disadvantage that even under the most favourable circumstances the clearing extends through sections only a few millimeters in thickness.

The coloured materials used for injections preparatory to serial section and reconstruction are similar to those described for use when the organ is to be cleared. MacCallum (1926) succeeded in developing a good injection technique for gelatin stained with carmine. The vessel walls may also be stained by the methods of MacCallum and Bensley previously mentioned. These injected organs are open to two methods of study. They may be cut in thick serial section, studied with a binocular dissecting microscope and drawings made from these observations. Reconstructions by the Born wax plate method can be made from drawings of serial sections of these specimens. Oliver and his co-workers in 1939 have described this reconstruction method in detail as it was applied to the uninjected kidney. The results of drawings or reconstructions from serial sections of injected or non-injected material are valuable in attempting to define fine complicated structures since they can be traced through their complete course at high magnification. The greatest disadvantage to this method lies in the fact that the final product, whether a drawing or reconstruction, is at best only a model and so subject to the inaccuracies of any such reconstruction. Moreover, only a limited amount of material can be studied because of the laborious nature of this method.

Another method which has been widely employed is the injection of the vessels of an organ with radio-opaque material followed by roentgenogram of the injected organ. Gross in 1917 used barium sulphate suspended in gelatin for this purpose. Baehr and Ritter used the same material in a study of renal blood vessels. Hill in 1929 improved this technique so that finer structures could be injected. He finally used bismuth oxychloride in acacia and found that by varying the concentration and forcing the solution through cloth that he could govern the size of particles and so the size of the vessels to be injected. Graham used this technique for an extensive study of the kidney's vascular tree. The x-ray pictures that he presents show the interlobular arteries and glomeruli

quite well. He claimed that stereoscopic films of such kidneys allowed an accurate study of the finer structures. These methods, depending on the use of radio-opaque material, allow an excellent study of the relation of the vessels of an organ through the whole depth. While this is of value for an accurate understanding of the blood supply of an organ, it does not compensate for the fact that the finer structures cannot be isolated from one another and hence cannot be studied individually with any assurance of accuracy.

Possibly the commonest technique used for the study of the blood supply of an organ is that termed the corrosion method. According to Narat, Swammerdam first applied this method in 1670. Wearn states that Ruyich (1704) introduced the corrosion methods in studying the finer arterial branches of the myocardium. Since that time many substances have been used including white wax, cellulose, celloidin and paraffin. Ghoreyeb (1916) studied the finer blood supply of the kidney by the use of Woods' metal. The interlobular arteries were injected but not the afferent arterioles or glomeruli. Within the last forty years celluloid and related substances have been used more widely than other materials. Huber (1906-07) used celluloid to inject the arteries of the kidney and corroded the kidney with hydrochloric acid. He presented plates prepared from drawings showing the arterial tree of the kidney injected down to the glomeruli. Barker (1928) used celluloid in a study of the blood supply of normal and abnormal human kidneys. Morrison in 1926, using celluloid, presented some excellent photographs of the arterial tree of the kidney proving that this method is capable of injecting glomeruli. More recently various plastics have been used. Narat (1936) used Vinylite resin and coloured this with "Luxol Fast" dyes. These dyes were obtained in various colours and were resistant to the acid used in corrosion. With such materials arteries, veins and ureters could be injected separately and in the same kidney their relation to one another studied easily due to the different colours. None of the pictures presented gives convincing proof that the finer

structures could be injected with vinylite resin. The corrosion methods have the advantage of allowing a study of the lumina of blood vessels in three dimensions. In all of these corrosion methods the greatest objections arise from the possibility that the material may shrink as it hardens and so may not leave an accurate cast of the vessel lumen. Moreover, the final specimen is brittle and the finer structures cannot be traced out and separated from one another for study under the microscope.

Lieb in 1940 described a corrosion technique using a liquid latex "Neoprene".* This material overcame the disadvantage of shrinkage and the brittleness of the final cast seen in corrosion specimens made by any of the materials previously used. This material was capable of reaching vessels down to the size of capillaries. Neoprene colored with various acid-fast dyes can be obtained, and there is a variety containing a radio-opaque material. When a corrosion specimen is made the finer structures can be separated from one another and studied under the dissecting microscope. Histological section can be made from the injected kidney. Neoprene was selected for use in the present investigation as an injection mass for study of the renal arterial architecture of the kidney in corrosion specimens. The method of Lieb was used with slight modifications, the details of which are described under Methods in the next part of this thesis.

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*Neoprene obtained from the American Anode Inc., 60 Cherry St., Akron, Ohio.

Part III

ORIGINAL INVESTIGATIONS

Our present knowledge regarding the normal blood supply and the arterial and arteriolar changes in kidneys in hypertension shows in the former that there are still some points open to controversy, and in the latter that there is still confusion and lack of agreement as to the character, site and degree of the arterial and arteriolar changes in hypertension. Also the question is still open as to the significance of these changes, whether they are primary or secondary in hypertension. Following the production of experimental hypertension in dogs by constriction of the main renal arteries, papers have appeared purporting to show that there are marked constrictions of the main renal arteries in kidneys from cases of essential hypertension. But the suggestion that this is the cause of essential hypertension in man is not very convincing as it is not a consistent finding in kidneys from cases of essential hypertension. Others believe that the pathological changes occurring in the small arteries and arterioles of kidneys from hypertensive cases cause sufficient ischaemia of the kidney to produce essential hypertension by the Goldblatt mechanism. Here again the changes in small vessels of the kidney are not found in every case of hypertension and there is no convincing proof that during life there is any marked constriction of the lumina of the small vessels showing pathological changes in their walls. Some perfusion experiments tend to show that there is no reduction of the vascular bed in kidneys from cases of essential hypertension. The question still exists as to whether essential hypertension in man is a result of ischaemia of the kidneys, and if ischaemia of the kidneys is responsible for essential hypertension in hyman beings, there is still the question as to what exactly is the cause of this ischaemia.

There appeared to be a possibility that these questions could be clarified by use of neoprene as a new injection mass for preparation of corrosion specimens, which possesses certain advantages over materials previously employed as pointed out in the review of injection techniques. Lieb had pioneered in the use of this material but had merely worked out the technique and had not applied it to any systematic study of the arterial vasculature of either normal or abnormal kidneys. Therefore it seemed worthwhile to attempt a thorough-going investigation of both normal kidneys at various age periods and abnormal kidneys from cases of essential hypertension, in the hope that by means of this new technique it might be possible to gain new and pertinent information, not hitherto available by older methods. The present investigation was therefore undertaken.

Methods and Material

The kidneys to be injected were removed as soon after death as possible. In general the best results were obtained in kidneys removed five hours or less after death, although excellent results were obtained in some kidneys removed as long as fifteen hours after death. As much of the surrounding fat as possible was removed with the kidney and the main renal artery was cut close to the aorta and the vein left as long as possible. As large a cannula as possible was tied into the renal artery and this was attached to a cold water tap connected with a mercury manometer. The water tap was then turned on and the pressure regulated to 75 mm. of mercury for the first half hour and then raised to 150 mm. of mercury until the kidney was completely washed. As soon as the water was turned on, obviously leaking vessels were clamped and ligated. Any oozing from indefinite sources was controlled by ligating a mass of perirenal tissue. The discovery of these leaks was facilitated by tying a long glass cannula into the vein so that this bloody escaping fluid would not colour the whole kidney. The utmost care was taken not to twist the arteries or angulate the

cannula so that its orifice was not in any way pressed against the side of the vessel wall. The best injections were obtained when the washings coming through the renal vein were almost clear within the first half hour. Some kidneys appeared to wash clear much better than others but often for no known reason. The number of hours elapsing between death and the washing of the kidney was probably important especially when the time exceeded ten hours but there was no constant relationship between the elapsed time after death and the ease of achieving satisfactory washing of the kidney. If the washings came back almost clear in the first half hour the kidney would be pale within three hours. When the kidney was uniformly pale it was removed from the tap. If it did not become pale it generally did not inject well.

After washing by perfusion with water was completed, the kidney was kept at 4°C. for twelve hours to allow for the escape of as much of the fluid as possible that had accumulated in the tissues. It was then kept at room temperature for five hours in order to decrease the oedema still further, to remove any rigor mortis that might still remain and to make the whole kidney soft and pliable. The kidney was then ready for injection. Fig. 1 shows a histological section of a normal kidney at this stage in the technique. It is seen that while the histological detail is not well preserved there is still no great distortion due to oedema. Fig. 2 shows a histological section of the opposite kidney which has been washed with two litres of kerosene, which, according to Cox and Dock, does not cause oedema. The histological detail is better preserved but so far as oedema is concerned, there is no great difference between the two kidneys. Moreover, all of the glomeruli in Fig. 1 are washed free of any red blood cells while the peripheral glomeruli seen in Fig. 2 are stuffed with blood, indicating the greater efficiency of washing the vascular system with perfused water rather than with kerosene.

The neoprene was injected into the washed kidney from an apparatus possessing a mercury manometer and an escape valve so that the pressure could be kept constant. The injection was made through the main renal artery under a pressure of 150 mm. of mercury. Injection at this pressure was continued for 3½ minutes and then stopped. It was found important to have the full pressure on as soon as the neoprene entered the renal artery. Before the pressure was released, the main renal artery and vein were ligated and the kidney immediately immersed in commercial hydrochloric acid at 56° C. For the purpose of either injecting completely through the capillary system or of overcoming some obstruction to the flow caused by renal disease, 3 factors may be modified to obtain the desired injection. The kidney may be warmed up to 60° for half an hour, the injection pressure raised to 250 mm. of mercury and the injection time lengthened to five minutes. This higher injection pressure will not destroy the glomeruli if the washing has been carried out at a pressure of 150 mm. of mercury.

For corrosion specimens the injected kidney was then placed in commercial hydrochloric acid at 56° C. and agitated gently from time to time. At the end of 24 to 36 hours all of the macerated kidney tissue could be removed by gently washing in warm water. The pliable neoprene cast of the renal arterial tree floats in water like some delicate sea plant. Pieces of varying size can be removed, floated in water and carefully teased apart under the binocular dissecting microscope.

Studies of the finer structures were made from special mounts of such structures on glass slides under coverslips. The measurements recorded later in this paper and the photographs of the small structures from neoprene casts were made from sprigs of interlobular arteries mounted in this way. This

method consists of placing a drop of Farrant's* solution on a glass slide. This is a viscid transparent fluid. An interlobular artery with a few branches was then snipped from a neoprene cast and placed in this drop of fluid. The branches, afferent arterioles and glomeruli were then straightened out by gently teasing with fine needles. A coverslip was then applied. Sufficient Farrant's solution was used so that no pressure of the coverslip was made on the cast.

The injected kidneys may be studied in two other ways. If radio-opaque neoprene is used x-ray films may be made of the injected kidney. This method was not employed in the present study. Histological sections may be made of an injected kidney. This method has been described in detail by Lieb. To do this the injected kidney is immediately fixed in 4% formaldehyde and 4% acetic acid in dilute alcohol (50-70%). After 18-24 hours fixation, the block is prepared by the gelatin embedding technique. The sections are cut on the freezing microtome, stained with haematoxylin and eosin and mounted in glycerin jelly. A microphotograph of such a section is shown in Fig. 3. It shows well a vessel completely full of the neoprene indicating that no shrinkage takes place as the neoprene hardens and, therefore, any cast is an accurate reproduction of the vessel lumen.

From this description it is apparent that "Neoprene" as an injecting fluid for the study of blood vessels possesses all the advantages found in all of the materials previously used for injection of blood vessels. Serial sections can be cut and stained from which drawings and reconstructions can be made. Radiographs can be made of whole organs. In addition, there is a great

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*Glycerine 50 cc., H_2O 50 cc., Powdered Gum Arabic 50 gms., Arsenous acid 1 gm. Dissolve arsenous acid in water, place gum Arabic in glass mortar and mix in the water. Add glycerin and filter through muslin or wet filter paper.

advantage in the type of corrosion specimen produced. The two most important features of the corrosion specimens, not obtainable with the use of any other material, are that an accurate cast of the smallest structures is obtained, and that the cast is flexible and can therefore be studied minutely under the microscope.

Fifty-seven human kidneys in all were successfully injected (Table I). These were from patients varying in age from 6 months to 78 years. Of these, 36 were from patients with no antecedent history of kidney disease or of hypertension and in which at autopsy there was no cardiac hypertrophy and no gross or histological abnormality of the uninjected kidney. Of the remaining 21 kidneys injected, 18 were from cases of essential hypertension. The criteria used for the selection of these eighteen cases were those of Moritz and Oldt. In each case during life there had been 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 grams and no female if the heart weighed less than 350 grams. Other abnormal kidneys injected included one from a child 7 years of age who had died of renal amyloidosis secondary to Pott's disease of the spine; one from a girl 14 years of age who clinically presented the picture of lipoid nephrosis and in whom the kidneys at autopsy showed a pure lipoid nephrosis or "membranous glomerulonephritis" of Bell; and one from a case of marked chronic pyelonephritis. During life this latter patient had had persistent hypertension and at autopsy marked cardiac hypertrophy was found. The age and sex distribution of all the cases is shown in Table I.

Table I

Age in Years	Normal			Hypertensive			Miscellaneous	Total		
	M	F	Total	M	F	Total		M	F	Total
0 - 9	4	3	7				1 female amyloidosis	4	4	8
10 - 19	2	1	3				1 female lipoid nephrosis	2	2	4
20 - 29	5	1	6					5	1	6
30 - 39	3	2	5					3	2	5
40 - 49	6	2	8	2	3	5		8	5	13
50 - 59	3	1	4	1	4	5	1 male chronic pyelo-nephritis	5	5	10
60 - 69	1	1	2	5	2	7		6	3	9
70 - 79	1		1		1	1		1	1	2
	25	11	36	8	10	18		34	23	57

Observations

Normal Kidneys

General: The appearance of a complete neoprene cast of a normal kidney is shown in Figure 4. In such a cast, the main renal artery is seen to divide into four or five large branches which after a short distance are hidden from view by the luxuriant foliage of the small vessels loaded with their glomeruli which overhangs the hilum of the kidney. The glomeruli on the surface are shown in higher magnification in Figure 4A. When such a specimen is studied with a hand lens the glomeruli look like apples on a tree, each glomerulus being suspended from a small artery by the connecting afferent arteriole.

Main Renal Artery and its Primary Divisions: When a neoprene cast of the renal arterial vasculature is separated into anterior and posterior halves (Fig. 5) the main renal artery is seen to divide into branches running in two

main directions in order to supply the anterior and posterior portions of the kidney. More than half and usually about two-thirds to three-quarters of the renal vascular tree arises from the branches passing to the anterior surface of the kidney. The kidney falls easily into two halves indicating that no anastomoses exist between these two main divisions of the renal artery. This first division is usually in the form of one large branch to the anterior surface and one to the posterior surface of the kidney, or there may be more than two branches arising simultaneously with the greater number passing to the anterior surface. These two or more first large branches further divide so as to form usually three large divisions which pass around the anterior surface of the pelvis and two around the posterior surface of the pelvis. These five branches may be spoken of as the primary divisions of the renal artery and all of them lie between the pelvis and the overhanging lip of cortex which bounds the hilum of the kidney. The only side branches from the main renal artery and its primary divisions are small slender twigs which supply the capsular fat (Fig. 6) and occasional branches to the pelvis and peripelvic tissue (Fig. 7).

Interlobar Arteries: From the large primary divisions of the renal artery, eight to twelve large divisions arise corresponding approximately to the number of pyramids in the kidney. These arteries, which fan out towards the upper and lower poles of the kidney, may be called interlobar arteries.

Arcuate Arteries: The large interlobar arteries divide dichotomously into two directions at right angles to one another. Before examining portions of the neoprene cast it is well to study Fig. 8A, which is a photograph of the surface of a kidney exposed when a layer about half an inch in depth has been shaved from the convex surface of the kidney. This shows the medullary pyramids in cross section. Each medullary pyramid is surrounded by a rim of cortical tissue. Towards the surface of the kidney this layer of cortical

tissue is thick. Between adjacent medullary pyramids it is thin. In this cortico-medullary interval cross sections of intrarenal arteries are seen. The dichotomous division of an interlobar is seen well in Figure 8. These divisions spread out in two directions from the central interlobar artery like the veins of a leaf. All of these branches lie parallel to the surface of a medullary pyramid and when they lie on the side of the pyramid facing the surface of the kidney they are also almost parallel with the surface of the kidney. When an interlobar artery lies near the pole of the kidney the branches arise only from the side of the interlobar artery facing that pole (Fig. 9). The interlobar arteries also divide dichotomously into arteries which pass with a slight inclination towards the surface of the kidney and therefore these branches lie slightly superficial to the cortico-medullary interval. This is well shown in Figure 10. The arteries are seen passing with a slight inclination towards the surface of the kidney but still almost parallel to the arteries which lie in the cortico-medullary interval. The first of these branches which pass with a slight inclination towards the surface of the kidney arise from the interlobar arteries to supply cortex near the hilum, while the terminal ones supply cortex near the convex border of the kidney. These branches then supply areas of cortex situated along lines passing from the hilum to the convex border of the kidney. The divisions previously described spreading out in the cortico-medullary interval supply an area of cortex extending along lines joining the two poles. Thus the branches of the interlobar arteries which pass in two different directions, one set branching parallel to the surface of the kidney and the other branching at right angles to this surface, form a series of arteries which succeed in supplying an area of cortex which lies on either side of the interlobar artery and extends along the course of the interlobar artery from the hilum to the convex border of the kidney.

All of these branches of the interlobar arteries along with the continuation of the interlobar artery, when that remains as a continuous vessel, lie either in the interval between cortex and medulla or parallel to it but slightly towards the surface of the kidney. These branches vary a good deal in length, each forming a segment in the line from the hilum to the convex border of the kidney. They all end rather abruptly by breaking into a series of branches which run towards the surface of the kidney. All of these branches might quite properly be called arcuate arteries so long as the term does not convey the idea that such an artery must run an unbroken course from the hilum to the convex border of the kidney lying in the interval between the cortex and medulla and conforming to the arch of that interval. In other words, the term arcuate artery should be reserved for a series of branches of the interlobar arteries of varying length, site of origin and termination, which lie in or parallel to the interval between cortex and medulla. There is normally a marked constriction of the lumen of the arcuate arteries at their origin (Fig. 11). This constriction is in the portion of the vessel lumen which passes through the wall of the parent vessel and may possibly be accounted for by contraction of that vessel wall.

Near the hilum, arteries arise corresponding to the arcuates already described, but instead of passing towards the convex margin of the kidney they arch towards the margin of the hilum of the kidney but still parallel to the surface in order to supply the lip of cortex which closes in the hilum (Fig. 12).

Interlobular Arteries: From the convex surface and the terminations of the arcuate arteries there arise a series of rather uniform but small calibre arteries which run out from and perpendicular to the surfaces of the medullary pyramids. In the columns of Bertin lying between the pyramids these vessels

approach one another from their origins near adjacent pyramids. When these vessels arise from a surface of a pyramid facing the surface of the kidney the vessels are then also perpendicular to the surface of the kidney (Fig.14). These small arteries may be called interlobular arteries. From them arise the majority of the afferent arterioles to the glomeruli. It seems that in most instances the arteries do not give origin to afferent glomerular arterioles until they are of a fairly small size, so that all of these interlobular arteries at their origin are of a uniformly small bore. They are truly interlobular arteries since they are the arteries which lie between and surround the kidney lobule as described by Traut (Fig. 15), and it takes many of these interlobular arteries along with their afferent arterioles to supply the glomeruli of one of these lobules. They are true end-arteries and there is no arterial anastomosis between interlobular arteries supplying the same lobule or adjacent lobules. This is shown very well in Figures 16 and 17 where there are groups of interlobular arteries with no anastomoses whatsoever between them. The interlobular arteries arise in two ways. Some of them arise from the convex surface of the arcuate arteries (Figs. 14 & 16). Others arise from the abrupt termination of the arcuate arteries in a series of small vessels which spread out like the lash of a whip (Fig. 17). The interlobular arteries vary considerably in length within the same kidney (Figs. 18A & B). Even though they give off afferent arterioles they continue to divide giving rise to more interlobular arteries (Figs. 16 & 17). The contour of these vessels is smooth and they taper gradually to end in a series of afferent arterioles (Fig. 19).

Afferent Glomerular Arterioles: Most of the afferent glomerular arterioles arise from the interlobular arteries. They vary considerably in length. Sometimes they supply only one glomerulus, at other times two or more (Fig. 20). They arise either from the sides of the interlobular arteries, or the interlobular arteries may terminate in a series of long slender afferent

arterioles (Fig. 19). The afferent arteriole maintains a fairly uniform bore throughout its entire length except for a slight constriction at the origin (Fig. 21) and at its entrance to the glomerulus (Fig. 22). The constriction at the entrance to the glomerulus is often hidden from view by the capillary tuft. These constrictions vary a good deal but there is usually at least a suggestion of some constriction at the origin and termination of the afferent arteriole, most marked when they arise from the sides of interlobular arteries. Even when an afferent arteriole supplies more than one glomerulus the original arteriole is not a great deal larger than the two or more final divisions (Fig. 20), indicating that these are all of similar functional significance. The afferent glomerular arterioles arising close to the medulla, including a few originating from the arcuates and origins of the interlobular arteries, are often very or moderately long (Fig. 23). While the afferent arterioles with their glomeruli do not arise at regularly spaced intervals from the interlobular arteries, they have sufficient regularity in their spacing to prevent the appearance of any large gaps between adjacent glomeruli (Figs. 16 & 17).

Glomeruli: The glomeruli consisting in the cast of masses of capillaries present a fairly uniform rounded appearance with a slight flattening at the point of entrance of the afferent arteriole. In any one kidney they are of fairly uniform size, although there are usually a few large glomeruli seen most often near the cortico-medullary junction. Only rarely are the small glomeruli seen that Golubew described. No microdissection was carried out to determine the minute structure.

Efferent Arterioles and Capillary Plexuses: In the neoprene casts the efferent arterioles are definitely smaller than the afferent arterioles. They end in a capillary plexus after a rather short course. Adjacent capillary plexuses appear to anastomose (Fig. 25). The efferent arterioles of glomeruli

near the medulla, after a short course, break up into a series of long fine vessels which pass towards the pelvis. These are the so-called arteriolae rectae spuriae (Fig. 26).

Figure 27 is a photograph of a cast dissected and prepared in such a way as to show the course of the blood as it passes through the interlobar arteries, the arcuates, the interlobulars,the afferent arterioles and the glomeruli. A sufficient number of branches have been removed that the relation of these various divisions to one another can be seen. Figure 28 illustrates how the arcuate arteries divide at various levels into more arcuate arteries. The abrupt ending of a fairly large arcuate artery by breaking up into a large number of interlobular arteries is well seen in this picture.

Up to this point the description of the renal vascular architecture in the normal kidney indicates that all of the blood entering the main renal artery first passes through the glomerular capillaries before supplying the parenchymal capillary bed. This is a true statement of the facts as seen in a neoprene cast of the arterial vessels of a normal kidney. These observations agree with the views of those who followed Bowman in stating that the renal vascular architecture was formed on a primary glomerular blood supply, and that all blood passed through the glomeruli before supplying the intertubular capillary plexus of the cortex and medulla.

Direct Blood Supply to Cortical and Medullary Capillary Plexuses: That the controversial direct vessels to the cortical and medullary plexuses exist in what would be considered a normal kidney cannot be denied. Nevertheless, these direct vessels arise most likely as the result of some damage to this part of the kidney. Figure 29 shows a direct vessel from an interlobular artery to the cortical capillary plexus. Occasionally a similar vessel is seen to arise from the afferent arteriole before it enters the glomerulus. Figure 30 shows a straight vessel arising directly from an interlobular artery and

breaking up into fine straight vessels as it passes towards the pelvis. This is the so-called arteriola recta vera. No capillary communications are seen in the normal kidney between such arteries and the intertubular capillary plexus. If capillary communications were present they should be injected by this method which completely injects the delicate coils of the glomerular capillaries. The two forms of direct vessels described represent examples of the vessels over which there has been much controversy. Some authors have claimed that they are numerous in the normal kidney and form a large part of the supply to the intertubular capillary plexus. MacCallum has given an excellent description of the various kinds of direct vessels and how they are formed. Most of these are extremely rare and sometimes none of them can be found in neoprene casts of normal kidneys and must be considered exceptions to the fundamental plan of the renal arterial blood supply, resulting from adaptation to age and disease, even though they occur in kidneys which for practical purposes would be considered normal. That these direct vessels are a result of damage, and not just an anomaly, seems clear because of the fact that it is very difficult to find them in kidneys from young individuals while they are found more readily in kidneys from older people and in kidneys damaged extensively by disease.

A more common departure from the typical pattern of blood supply is the continuation of an interlobular artery through the capsule of the kidney into the capillaries of the perirenal fat (Fig. 31).

Age Changes: All of the parts of the renal arterial tree already described are present at birth except for direct vessels to the cortical and medullary capillary plexuses. A neoprene cast of the arteries of an infant's kidney is a miniature replica of that from the injection of an adult kidney. All of the vessels are smaller in diameter and length and the glomeruli are smaller in size (Figs. 32 & 33). The various components of the arterial bed

gradually increase in size until the middle of the second decade or a little later. Growth then of the renal vasculature after birth is only an increase in size of the structures already present. There is no development of new structures. After middle life the larger vessels become notched and the constrictions at their origins more marked (Fig. 31). The contour of interlobular arteries becomes uneven and tortuous and the origins of many of the interlobular arteries show marked constriction (Figs. 34A & B). The glomeruli lose their delicate structure and become more simplified and coarse (Fig. 35). A sprig of interlobular arteries shows a loss of many of the glomeruli and presents a "blighted appearance" like the branches of a tree from which most of the leaves have fallen (Fig. 36). The number of direct vessels to the capillary plexuses of the cortex and medulla increases with age. All of these changes occur in kidneys from elderly individuals who have not had hypertension. A comparison of these changes with those seen in neoprene casts of kidneys from hypertensive cases will be made later.

Observations

Abnormal Kidneys

Kidneys from Cases of Essential Hypertension: The most striking features revealed by an examination of renal arterial casts from patients with essential hypertension is the lack of any uniform or characteristic change in the renal vascular architecture. Neoprene casts from individuals who have had definite hypertension for a year or more may fail to show any abnormality while others show an extreme degree of change in the arterial pattern. In this respect they follow closely the degree of abnormality seen grossly and in the histological sections in the opposite kidney.

Sometimes the cast may show nothing more than a slight tortuosity of the interlobular arteries and arterioles. All of the glomeruli may be well injected. There may be nothing to suggest even the slightest abnormality of the renal

vasculature. This is well illustrated in Figures 37A & B which, respectively, represent photographs of a paraffin section stained with haematoxylin and eosin, and an arterial cast of the opposite kidney from a 49 year old female who was known to have had persistent hypertension for the four years preceding death. There is some intimal proliferation of arteries corresponding to the arcuates in size. At no place do these show any severe constriction. The interlobular arteries and arterioles are free of any recognizable change. There are a few scattered fibrosed glomeruli. The neoprene cast shows a slight tortuosity of the interlobular arteries. The afferent arterioles and glomeruli are normal in appearance. While there is apparently some change in the small arteries in the histological section, the complete injection cast indicates that none of these changes has seriously constricted any of the arteries in the injected kidney.

More pronounced, but still slight degrees of change are often seen. Figure 38 shows the arterial architecture of the kidneys from a 68 year old female known to have had persistent hypertension for some months. Histologically the kidney is normal in spite of the patient's age and the authentic history of hypertension. The neoprene cast, on the other hand, presents a blighted appearance with tortuosity of the interlobular arteries and arterioles and loss of glomeruli. Other glomeruli show what appears to be only a partial injection ending in three or four of the primary capillary divisions of the afferent arteriole.

In casts showing more marked alterations in the arterial architecture, a variety of changes may occur. Sometimes the constrictions appear to be limited to the arterioles and there is loss of glomeruli without any other significant abnormality. Figure 39B shows the appearance in such a case. In the histological sections of the opposite kidney there is seen definite hyaline thickening of arterioles and thickening of the basement membranes of the

glomeruli. There are a few scattered fibrosed glomeruli surrounded by atrophied tubules (Fig. 39A). There is a marked reduction in the number of glomeruli in the cast but since those near the end of the interlobular arteries are injected this loss must be real and not due to technical reasons. The injected glomeruli are simple and coarse in their structure compared to the intricate and delicate structure of the normal glomerulus (Fig. 39C). The interlobular arteries are quite smooth in their outline. These kidneys were from a 50 year old woman who was said to have had hypertension for twenty-seven years before death. At autopsy the heart was found to weigh 600 grams. The restriction of severe changes to the afferent arterioles in this case appears to refute the opinion of those who claim that hypertension is an important factor in the development of organic changes seen so often in the small arteries as well as arterioles of the kidney in cases of hypertension. Changes for the most part limited to the arterioles are well shown in Figure 46. Here the afferent arterioles are long and tortuous. The interlobular arteries are fairly smooth in outline and there is some loss of afferent arterioles from the proximal parts of the interlobular arteries.

Severe changes of the renal arterial architecture in cases of essential hypertension may present a different picture. There may be marked tortuosity and constriction of the interlobular arteries. Some of these constrictions may almost completely cut off the vessels. There may be very great accentuation of the normally slight constriction present at the origins of the interlobular arteries (Fig. 40). In these cases there is also a loss of glomeruli due to constriction of the afferent vessels sufficient to prevent the injection of glomeruli. These extreme constrictions of afferent arterioles appear most often in those arising from the interlobular arteries close to their origin, suggesting the possibility that these afferent vessels, more exposed to the full force of the elevated blood pressure, suffer more severely than those arising from the terminations of the interlobular arteries, which remain well preserved.

All of this is well seen in Figure 41 in which is illustrated the renal vasculature of one kidney from a male patient 47 years of age who had a persistent blood pressure of 210/120. The capsule of the opposite kidney stripped with difficulty revealing a fine granular surface. The kidney weighed 140 grams.

One further and important change occurring in the blood supply of kidneys from patients with hypertension is the development of many new direct vessels to the intertubular capillary plexus. These are more numerous than in normal kidneys from normal subjects of the same age. Sometimes a simplified glomerular structure, as described by MacCallum, may be seen among these direct vessels. Figures 42A, B and C, show a histological section and injection from such a case. In the section, marked intimal proliferation of the interlobular arteries is seen and there is a marked hyaline thickening of arterioles. Many of the glomeruli are fibrosed and there is atrophy and dilatation of the tubules in many areas of the cortex. In the injection only an occasional glomerulus was injected. It is unlikely that this means that all of the uninjected glomeruli were completely removed from the circulation. It only indicates a severe degree of constriction present in the afferent arterioles sufficient to have prevented injection of such glomerular capillaries as remained open. Arising from the interlobular arteries are many long slender vessels which end in capillaries. While it is impossible to say precisely what these capillaries represent, it seems safe to conclude that these small vessels arising from the interlobular arteries have passed into a capillary plexus without the interposition of any glomeruli.

Kidneys of Other Chronic Renal Diseases: These changes of interlobular arteries, afferent arterioles and glomeruli are not limited to, or necessarily characteristic of kidneys from cases of essential hypertension., Tortuosity or constriction of interlobular arteries and loss of glomeruli are seen in other cases of chronic renal disease. Such changes, illustrated in Figures 43A and B,

were observed in the neoprene cast of a kidney of chronic pyelonephritis, associated with hypertension.

Broadly speaking, severe changes of the interlobular arteries, afferent arterioles and glomeruli occurring as a result of old age are of a similar kind to the changes occurring in kidneys from hypertensive cases, but the severity and location of these changes show some differences between the kidneys of old age and those of hypertension. The constrictions and tortuosity of the interlobular arteries and afferent arterioles,and the loss and coarseness of glomeruli of the kidneys from elderly individuals, are scattered evenly along the course of the interlobular arteries. In kidneys from cases of hypertension, sometimes the interlobular arteries show marked irregularities, while the afferent arterioles and glomeruli show no very marked departure from the normal. Sometimes the interlobular arteries are smooth and the irregularities are confined to the afferent arterioles. This particular appearance is peculiar to kidneys from cases of hypertension and is seen in many such kidneys. The interlobular arteries are smooth and from the proximal parts of the interlobular arteries there arise only little stubs of afferent arterioles, while the ends of these interlobular arteries are surrounded by a brush of long tortuous afferent arterioles and fairly normal appearing glomeruli.

Figure 44 is a photograph of a kidney from a fourteen year old girl who clinically presented the features of lipoid nephrosis and who at autopsy showed the findings in the kidney of a pure lipoid nephrosis or "membranous glomerulonephritis of Bell." This was not a completely successful injection but it can be noted that the interlobular arteries and afferent arterioles are normal while the glomerular capillaries have lost some of their usual delicacy. Figure 45 represents an injection of a kidney from a boy 7 years of age suffering from amyloidosis secondary to Pott's disease. In a histological section all of the glomeruli were filled with amyloid deposit. The injection shows a

complete absence of glomeruli. While this does not indicate complete obstruction of blood flow through the glomeruli during life, it certainly indicates a marked reduction in the dimensions and perhaps in the numbers of capillary loops in the glomeruli.

Measurements

General: If it is assumed that a widespread narrowing of the lumina of the small arteries and arterioles of the kidneys in patients with essential hypertension is sufficient to produce a renal ischaemia of a degree capable of producing hypertension, it would be of value to have an accurate quantitative estimation of this narrowing. The sprigs of interlobular arteries mounted on glass slides by the technique described above seemed to offer material upon which such a study could be made. The measurements adopted to determine the degree of narrowing and other changes of the small vessels of the renal cortex were measurements of the length and width of the afferent arterioles and the width of the interlobular arteries at the point of origin of these same afferents. It was hoped that such measurements would render it possible to follow accurately the changes that occur with the development of the kidney from childhood to adult age, and the changes that occur in the adult kidney with the advance of age. In order to determine whether significant changes occurred in these structures in kidneys from cases of hypertension, it seemed desirable to make similar measurements of the kidneys in hypertensive cases and to compare these with measurements of the same structures from normal kidneys of the same age period. In the hope of discovering the nature of any such changes, the measurements of kidneys from hypertensive patients were also compared with measurements of the so-called normal kidneys of advanced age groups showing changes due to degenerative processes of the vascular tree.

The mounted samples of interlobular arteries and their afferent arterioles

were usually spread out sufficiently that under the microscope the majority of afferent arterioles were in a fairly straight line capable of measurement. There were in some instances slight angulations that rendered accurate measurement of these vessels impossible but in order to compensate as much as possible for error, all measurements were done by the same individual. The narrowest points in the width of afferent arterioles and the width of the interlobular artery at the origin of the afferent arteriole are susceptible of accurate measurement. All measurements were carried out with a Zeiss micrometer, kompens-okular No. 755.

In the measurements of the lengths of the afferent arterioles a magnification was used such that one unit of the ocular scale was equal to .08 mm. In measuring the widths of the afferent arterioles and interlobular arteries another magnification was used in which one unit was equal to .03 mm. The means and standard deviations are given in terms of units and their equivalent given with each table.

Preliminary measurements were carried out to ensure the accuracy of the observations and of the sampling. The accuracy of the measurements was determined by measuring the length and width of one arteriole and the width of one interlobular artery one hundred times. The mean values and standard deviations of these 100 measurements are seen in Table II.

Table II

		Mean	S.D.*
Length of afferent arteriole	1 unit = .08 mm.	1.68	.17
Width of afferent arteriole	1 unit = .03 mm.	.97	.07
Width of interlobular artery	1 unit = .03 mm.	1.93	.10

* S.D. = Standard Deviation.

The standard deviations of these measurements is obviously small enough, especially in the measurements of width, to indicate that the error of measurement is insignificant when making one hundred measurements on these structures.

To test the accuracy of sampling, six sample sprigs or sprays of interlobular arteries were picked from a normal adult kidney and 50 measurements in each sample were made of the lengths and widths of different afferent arterioles and the widths of the interlobular arteries. Samples A & A′ are from the opposite poles, B & B′ from opposite sides of the hilum, and C & C′ from two points on the convex surface of the kidney. The mean and S.D. of these groups of fifty are shown in Table III.

Table III

		A		A′		B		B′		C		C′	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Length of afferent arteriole	1 unit=.08 mm.	2.02	.75	2.08	.65	1.89	.43	2.08	.80	2.02	.60	2.14	.75
Width of afferent arteriole	1 unit=.03 mm.	.91	.14	.92	.14	.88	.20	.94	.17	.86	.24	.94	.33
Width of inter-lobular artery	1 unit=.03 mm.	2.65	1.32	2.71	1.16	2.68	1.12	2.74	1.09	2.58	1.33	2.89	1.44

The mean and S.D. of the length of the afferent arterioles show no great differences except for those obtained in sample B. The mean and S.D. of the width of the afferent arterioles show no significant variation. The means of the width of interlobular arteries show no significant variation. The S.D. of the width of the interlobular artery is quite large and places the validity of this measurement open to question. When the A A′ samples, the B B′ samples, and C C′ Samples are placed in three groups of one hundred measurements in each sample, the mean and S.D. of these measurements are as shown in Table IV.

Table IV

	A & A′		B & B′		C & C′	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Length of afferent arteriole 1 unit=.08 mm.	2.04	.70	1.95	.69	2.08	.59
Width of afferent arteriole 1 unit=.03 mm.	.92	.14	.91	.19	.91	.29
Width of interlobular artery 1 unit=.03 mm.	2.67	1.24	2.71	1.06	2.59	1.40

When the means and S.D. are calculated for the six samples together amounting to 300 measurements for each structure, the results are as shown in Table V.

Table V

		Mean of 300 Meas.	S.D. of 300 Meas.
Length of afferent arteriole	1 unit = .08 mm.	2.04	.79
Width of afferent arteriole	1 unit = .03 mm.	.91	.03
Width of interlobular artery	1 unit = .03 mm.	2.66	1.22

Samples were taken and measurements made in exactly the same way from a neoprene cast of a kidney from a definite case of hypertension. The results are set forth in Tables VI, VII, and VIII, in the same way as for the preceding kidney.

Table VI

		A		A′		B		B′		C		C′	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Length of afferent arteriole	1 unit=.08 mm.	2.12	.93	2.04	.32	2.35	.80	2.03	.60	2.12	.97	2.14	.93
Width of afferent arteriole	1 unit=.03 mm.	1.09	.66	1.10	.17	1.06	.14	1.01	.20	.94	.14	.99	.10
Width of inter-lobular artery	1 unit=.03 mm.	1.89	.41	1.74	.52	1.81	.51	1.70	1.27	2.01	1.18	1.77	.60

Table VII

		A & A′		B & B′		C & C′	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Length of afferent arteriole	1 unit=.08 mm.	2.07	.74	2.18	.86	2.13	.87
Width of afferent arteriole	1 unit=.03 mm.	1.10	.42	1.04	.14	.98	.06
Width of interlobular artery	1 unit=.03 mm.	1.82	.54	1.76	.43	1.89	.79

Table VIII

		Mean of 300 Meas.	S.D. of 300 Meas.
Length of afferent arteriole	1 unit=.08 mm.	2.13	.81
Width of afferent arteriole	1 unit=.03 mm.	1.05	.35
Width of interlobular artery	1 unit=.03 mm.	1.83	.58

In these measurements of a normal kidney and a kidney from a case of hypertension there are slight variations between the mean and S.D. from sample to sample of the same kidney. These variations are largest in the length of the afferent arteriole and in the width of the interlobular artery. They are sufficiently close, however, to be of value in determining, on the basis of 50 measurements, whether there is a significant difference between similar measurements in different kidneys. This is particularly true regarding the measurements of the width of the afferent arterioles where the variations of the mean and S.D. in groups of 50 measurements are sufficiently close to allow calculation of any statistical difference that might occur in 50 measurements of different kidneys.

Normal Kidneys: For these reasons it seemed justifiable to make one hundred measurements of any one structure in each of the kidneys measured from which to determine any significant differences in the measurements of similar structures from one kidney to the other. Two samples of fifty measurements each were used from each kidney. The samples were arbitrarily chosen, one from the

convex surface of the kidney and one from around the hilum.

In order to determine the changes that occur in the measurements of the length and width of the afferent arteriole and the width of interlobular arteries as the kidney develops from childhood to adult age and the changes that occur with the advance of age, measurements were made in a series of normal kidneys from autopsy cases ranging in age from three years to seventy-eight years. The mean and S.D. of these measurements are recorded in Table IX and these figures are graphically represented in Graphs I, II & III with the various measurements plotted against age.

Table IX

Measurements of Normal Kidneys								
			*L. of Aff. 1 unit=.08 mm.		#W. of Aff. 1 unit=.03 mm.		+W. of Inter. 1 unit=.03 mm.	
Decade	Age	Sex	Mean	S.D.	Mean	S.D.	Mean	S.D.
0-10	3	F	1.35	.35	.90	.01	1.60	.46
10-20	20	M	2.04	.79	.91	.03	2.66	1.22
20-30	27	M	1.84	.51	.99	.20	1.85	.82
30-40	39	F	2.29	.84	.86	.29	1.82	.83
40-50	43	M	2.14	.85	1.01	.14	1.59	.73
	45	M	2.11	1.00	1.13	.14	2.03	.80
50-60	52	M	1.97	1.01	.94	.26	1.94	.91
	54	M	2.14	.48	1.04	.41	2.21	1.12
60-70	61	F	2.47	.14	1.11	.24	2.38	1.07
70-80	78	M	1.82	.48	.95	.35	1.76	.51

* L = Length of afferent arteriole

W = Width of afferent arteriole

+ W = Width of interlobular artery

The trend of any differences in the measurements from different kidneys is best seen in the graphs. It is apparent at once that there is no straight-line relationship between the length of the afferent arterioles and age. There is a tendency for the afferent arterioles to increase in length up to forty years of age. But at any given age, normality in regard to the length of the afferent arterioles is represented by a broad band. Similarly the width of afferent arterioles seems to remain about the same up to twenty-five years. Then there appears to be a wide scatter in the widths of afferent arterioles during middle and old age. There is a tremendous variation between the widths of interlobular arteries for any one age. It is doubtful if any conclusion whatsoever can be drawn about differences in the width of interlobular arteries. Since these measurements are made at the point of origin of the afferent arterioles the figure will vary according to whether the afferent arterioles arise evenly along the course of the interlobular arteries or whether they arise mainly from the proximal or distal parts of the interlobular arteries.

The number of normal and abnormal glomeruli were counted in each sample. Two hundred were counted altogether from each kidney. The glomeruli were considered normal when two or more capillary loops were completely injected. When an afferent arteriole ended without entering a glomerulus this was considered to represent only one abnormal glomerulus, even though in many instances this may have represented the loss of two or more glomeruli. Uninjected glomeruli were counted as abnormal only when other glomeruli supplied by the same interlobular artery at a more distal point were properly injected.

The percentage of normal glomeruli for normal kidneys of different ages is seen in Table X and these are arranged graphically in Graph IV.

Table X

Percentage of Normal Glomeruli in Normal Kidneys

Decade	Age	Sex	Percentage of Normal Glomeruli
0-10	3	F	93.5
10-20	20	M	98
20-30	27	M	96
30-40	39	F	91
40-50	43	M	80
	45	M	83.5
50-60	52	M	67.5
	54	M	80
60-70	61	F	60
70-80	78	M	50

Graph IV shows well a fairly regular loss in the number of normally injected glomeruli with a marked decrease in the number of normal glomeruli after the age of fifty.

Kidneys from Cases of Hypertension: To determine if there were any significant differences in corresponding measurements between kidneys from cases of hypertension and normal kidneys of the same age period, measurements were made on the neoprene casts of the kidneys from 4 cases of hypertension. Glomerular counts were also done. The measurements and glomerular counts are seen in Table XI. The results are also recorded on Graphs I, II, III & IV by a cross. The four cases were selected cases of hypertension. This was necessary because the technique adopted for a desired injection of normal kidneys was maintained when injecting abnormal kidneys. This failed to inject a sufficient number of glomeruli in some cases to make proper measurements on a small sprig of interlobular arteries. Therefore, the results of these four cases must be considered in their proper perspective and probably represent the least possible changes that occur in the small vessels of kidneys from cases of definite hyper-

Table XI

Measurements of Kidneys from Cases of Hypertension

Age	Sex	Heart Wt.	B.P.	Length of afferent arteriole 1 unit=.08 mm. Mean	S.D.	Width of afferent arteriole 1 unit=.03 mm. Mean	S.D.	Width of interlobular 1 unit=.03 mm. Mean	S.D.	Percentage of Normal Glomeruli
47	M	615 g.	210/120 many years	2.13	.81	1.05	.35	1.83	.58	55
60	M	475 g.	190/100 unknown duration	1.98	.77	1.02	.14	1.49	1.40	60
68	F	315 g.	160/120 unknown duration	2.11	.59	1.04	.24	1.91	.73	58
73	M	635 g.	200/90 some years	2.41	.56	.95	.17	1.83	.48	50

It is obvious that the length and width of the afferent arterioles of kidneys from hypertensive cases lie within the normal ranges for these measurements in corresponding age groups. While it would be necessary to study many more hypertensive kidneys before definite conclusions could be drawn regarding this problem, it can at least be stated that the injected afferent glomerular arterioles in these cases of hypertension did not show any significant reduction in the size of their lumina. These measurements of width are for the narrowest points in the glomerular arteriole. However, this is not the whole picture for it is noted in the glomerular counts that the percentage of normal glomeruli in these cases of hypertension lies between 60 and 50 percent. This does not mean that during life there was complete occlusion of afferent arterioles to 50 percent of the glomeruli, but it does indicate a severe degree of obstruction. Because of the loss of glomeruli from the proximal parts of the interlobular arteries, the afferent arterioles measured are a select group from the distal parts of

the interlobular arteries and this may modify the value of the measurement. It is interesting to note that the percent of normally injected glomeruli for the kidneys from the hypertensive and the elderly non-hypertensive cases are both on the lower margin of the normal range. The values for the width of the interlobular arteries from kidneys of cases of hypertension all lie along the lowest limit for normal and one is definitely below this. As pointed out above, this has no significance since the afferent arterioles measured in these cases, and so the points of the interlobular arteries measured, may lie along the distal parts of the interlobular arteries. Also, it is impossible to give a normal figure that can be considered valid.

The variable factors, the error of measurement and the S.D. in the measurement of the length of the afferent arterioles and the width of the interlobular arteries are of such a magnitude that a true value for these measurements cannot be obtained. The slight error of measurement and the small S.D. for measurements of the width of the afferent arteriole in the normal kidney make this the only measurement which is statistically valid. The error of measurement and S.D. for this measurement in kidneys from cases of hypertension is also small enough that this mean width of the afferent arteriole of these kidneys should be an accurate mean for the afferent arterioles measured. From the results of the measurements on kidneys from cases of hypertension, it is impossible to generalize about the width of afferent arterioles in all kidneys from cases of hypertension as compared to the same measurement in normal kidneys because the measurement represents the width of a select group of afferent arterioles in these kidneys from cases of hypertension. In order to have a true measurement for the width of the afferent arterioles of kidneys from cases of hypertension it would require a neoprene cast resulting from an injection in which every afferent arteriole was injected to the point of complete occlusion. This result cannot be claimed for the casts used in this study as they were the result of injecting kidneys by

exactly the same method as was used for injection of the normal kidneys. The only just conclusion that can be drawn from the measurements obtained in this study for the width of the afferent arterioles of kidneys from cases of hypertension is that the mean width of the afferent arterioles measured in these kidneys lies within the range for this measurement in normal kidneys.

Part IV

DISCUSSION

Kolliker in 1860 described fairly accurately the main divisions of the renal artery in man. He recognized that the main renal artery divided into several large arteries in the hilum of the kidney and these were continued on in the cortico-medullary interval where there was repeated branching of these vessels without anastomoses. He did not note, as Huber did and as confirmed in this present work, that rather large branches arise from the arteries in the cortico-medullary interval and pass with a slight inclination towards the surface of the kidney but almost parallel to the branches in the cortico-medullary interval. Von Ebner in 1893 and Golubew in 1899 stated that the main renal artery divided into a few large branches which ran in the cortico-medullary interval and arched over the base of the pyramid, forming a continuous arched vessel running from the hilum of the kidney to the convex surface of the kidney. From these large arteries with an arched course there arose at right angles and at regular intervals a series of small vessels which ran directly towards the surface of the kidney giving off afferent arterioles in their course. The long arched vessels they called arcuate arteries. Lee-Brown's description as late as 1924 leaves a similar impression with the reader. The observations of the neoprene casts of the renal arteries from the kidneys of man in general are in agreement with Kolliker and more particularly Huber, and may be summed up by stating that the main renal artery divides usually into two primary divisions, one for the supply of the anterior surface of the kidney, and one for the posterior surface of the kidney. The branches to the anterior surface of the kidney supply more than half of the kidney. These two main divisions form about five branches in the hilum of the kidney between the kidney pelvis and cortex in this region, and these primary divisions in turn divide into a series of interlobar arteries equal in number to the number

of medullary pyramids which usually total between nine and twelve in number. These interlobar arteries gain the interval between the cortex and medulla and then by repeated division without anastomoses form a series of branches which lie in the cortico-medullary interval. In accord with Huber but not noted by Kolliker, a series of branches arise from the arteries in the cortico-medullary interval and pass with a slight inclination towards the surface of the kidney almost parallel to the arteries in the cortico-medullary interval. All of these vessels in and close to the cortico-medullary interval should be called arcuate arteries. Small arteries of uniform bore arise from the convex surface and from the ends of these arcuate arteries and pass out from the surfaces of the medullary pyramids. These small arteries divide repeatedly, do not anastomose, and give origin to the afferent arterioles. These small arteries are the interlobular arteries. They are not, as Von Ebner and Golubew thought, vessels which run a direct course without division from the cortico-medullary interval to the surface of the kidney, nor are they intralobular arteries as Gross called them. They are truly interlobular arteries, many of them lying between the adjacent renal lobules of Traut. The arteries Huber described running directly outwards between the arcuate arteries and the interlobular arteries but not giving origin to afferent arterioles are not present in the neoprene casts of the renal vasculature of normal human kidneys. There are, however, lateral divisions from the main renal artery and its primary divisions to the capsule, pelves and peripelvic tissues. These were described by Kolliker, Bowman and others.

Most authors agree that the majority of afferent arterioles arise from the interlobular arteries. The observations of the neoprene casts confirm the opinion of Huber, Traut, Morrison and others who stated that some afferent arterioles supplying glomeruli near the cortico-medullary junction arise from the arcuate arteries.

Bowman was the first to describe clearly the efferent arterioles joining the glomeruli and peritubular capillary plexus and he called this series of efferent arterioles the "renal portal system." These efferent arterioles are seen well in the neoprene casts and as stated by Kolliker and Lee-Brown, vary in their appearance depending on their position in the cortex. Those efferent arterioles arising from the peripheral glomeruli continue towards the surface of the kidney in the same direction as the corresponding arteriole to end in the subcapsular capillary plexus. Those efferent arterioles arising from the glomeruli in the central portions of the cortex often run at right angles to the corresponding afferent arteriole and after a short course end in the peritubular capillary plexus. The efferent arterioles taking origin from glomeruli near the cortico-medullary zone end in a series of long vessels which run as a sheath of long straight parallel vessels between the medullary tubules. These are the so-called "arteriolae rectae spuriae." Bowman observed these vessels and thought that they supplied all the blood to the medullary capillary plexus. Huschke thought that the medulla received its blood supply from the cortical capillary plexus.

Bowman believed that all of the blood to both the cortical and medullary capillary plexuses passed through glomeruli and then reached the capillary plexuses by way of the efferent arterioles. Since that time there has been a good deal of controversy regarding the truth of this statement. Ludwig, Kolliker, Morrison and others described various direct arterial connections between the arteries and the parenchymal capillary plexus of mammalian kidneys. The argument has resolved itself into the question of whether these direct vessels are found in normal mammalian kidneys and, if so, whether they are of importance.

In the cortico-medullary region these direct vessels were described as arising either from the proximal parts of interlobular arteries or from arcuate arteries, and were called the "arteriolae rectae verae." In the cortex these

direct vessels were described as arising from the terminations of the interlobular arteries, from the sides of the interlobular arteries and from the afferent arterioles just as these entered the glomeruli. Steinach stated that there were direct communications between arteries and veins, and Golubew claimed to have confirmed this. Huber did not believe any such direct connections existed in the normal mammalian kidneys which he studied. MacCallum in 1926 denied that any such direct communications existed although he thought that there might possibly be a few such vessels. In 1939 he had formed the opinion that in the normal mammalian kidneys which he studied there were direct communications both in the cortex and medulla. He showed by a series of drawings how these various direct communications developed as a result of degeneration of the glomeruli. He pointed out in conclusion that these direct vessels should not be considered to be entirely normal but were formed as the result of degeneration of a glomerulus and its associated afferent and efferent arterioles.

The present study deals only with the kidneys of man and except for the work of Morrison and Lee-Brown pfesents the only photographs of isolated small structures in the renal blood vessels of man, that the writer has been able to find. From the results of this study it is clear that in kidneys of man, which for practical purposes must be considered normal, there are no arterioles arising from large arteries and passing to the parenchymal capillary plexus of the kidney, and there are no direct communications between arteries and veins as described by Steinach and Golubew. There are, however, occasional direct vessels arising from the smaller arteries and passing to the capillary plexuses of the cortex and medulla. Close to the medulla these direct vessels arise either from the proximal ends of interlobular arteries or from arcuate arteries, and after passing towards the medulla they end in a series of long straight vessels which supply the medullary capillary plexus. These are the

"arteriolae rectae verae." In the cortex there are direct vessels arising from the sides and terminations of the interlobular arteries and from afferent arterioles which pass to the cortical capillary plexus.

Long search of neoprene casts of kidneys from individuals in the first two decades of life often fails to reveal any of these direct vessels. They are found more often in normal kidneys of adults in the later decades of life but in such normal kidneys a prolonged search reveals only a few. Previously it has been claimed by some that injection methods do not penetrate the finer structures sufficiently in corrosion casts of kidney blood vessels to warrant the conclusion that these direct vessels are not common in normal kidneys. The neoprene casts present a complete injection of glomeruli, efferent arterioles, a portion of the peritubular capillary plexus and in the medullary region reach as far as the normal "arteriolae rectae spuriae." There can be no doubt that this method would show any direct vessels that exist in the cortex and medulla. It can then be concluded from this study that in normal kidneys of man the fundamental plan of the renal vasculature is designed to carry all of the blood that enters the main renal artery through the glomeruli before any of this blood reaches the cortical or medullary capillary plexuses. As Huber pointed out, Bowman should be given full credit for being the first to discover the truth of this aspect of the kidney circulation. Occasional direct vessels to the peritubular capillary plexus do exist. But, as Huber, Lee-Brown and Morrison have pointed out, these are insignificant in their effect on renal physiology, and as MacCallum has shown they probably develop as a result of damage to glomeruli and their associated afferent and efferent arterioles. It seems reasonable to assume this origin for these vessels since they are very rarely seen in the kidneys of young individuals; they do occur more frequently in the kidneys from elderly individuals, and they may become quite common in kidneys the site of chronic renal disease.

It would seem, as MacCallum has pointed out, that whenever these direct vessels are mentioned in text-books of histology it should be specifically stated that they arise as the result of adaptation to some damage in the kidney cortex. As Oliver and his co-workers have shown, these direct vessels have a real significance in the physiology of the kidney of chronic Bright's disease.

The development of our present knowledge regarding the changes in the renal arteries and arterioles in hypertension has already been traced in the review of the literature. Thickening and narrowing of the arteries in contracted kidneys has been recognized for almost one hundred years. It is true that speculations as to the association of arterial hypertension could not be confirmed until a clinical method was available for measuring the blood pressure accurately, and the problem could not be properly appreciated until the differentiation had been made between the contracted kidney of chronic glomerulonephritis and that of nephrosclerosis. After this differentiation had been made, a sharp distinction was drawn between the hypertension associated with chronic glomerulonephritis and the so-called "essential" hypertension associated with nephrosclerosis. The former was, and still is, generally regarded as hypertension of renal origin. Essential hypertension, on the other hand, was at first thought of as having a non-renal origin and the associated renal vascular and parenchymal changes were regarded as the result of this hypertension. Indeed, the opposite view, that primary renal vascular disease is the cause of essential hypertension, has come into prominence only within very recent years, due largely to Goldblatt's experimental demonstration that renal ischemia is capable of producing hypertension without detectable impairment of renal excretory function.

Moritz and Oldt (1937) have brought forward anatomical evidence which they interpreted as supporting the conclusion that primary renal vascular disease by producing renal ischemia caused essential hypertension. However, in their

series of cases of hypertension, as in the series of Fishberg (1925) and Bell and Clawson (1929), there were a few cases in which no disease of the intrarenal arteries or arterioles could be discovered. Such cases provided one of the principal arguments supporting the conclusion of Fishberg, and Bell and Clawson, that the renal vascular lesions were not the cause of essential hypertension but secondary to it. Moritz and Oldt pointed out that in the cases in their series which lacked intrarenal vascular disease there were constricting arteriosclerotic plaques in the large renal arteries and they concluded that these were sufficient to account for renal ischemia and renal hypertension in those exceptional instances. This facile explanation, however, seems open to challenge for it has been pointed out by Christian and Schlesinger (1939) and Cox and Dock (1941) that anything but the most extreme constriction of the main renal artery does not affect the perfusion rate of the kidney post mortem. Indeed, Cox and Dock, contrary to Christian and Schlesinger, found no significant decrease in the perfusion rate of the kidney in cases of essential hypertension, unless the patient had died with signs of renal insufficiency. They concluded, therefore, that hypertension at its onset is usually not associated with a reduction of the renal vascular bed.

It need scarcely be pointed out that no definite conclusion can be drawn regarding the degree of renal ischemia produced during life by thickening and narrowing of renal arteries and arterioles observed in histological sections. Nor is the observation of post mortem renal perfusion rates a method beyond criticism, for it is obvious that the development of direct arterial connections to the capillary plexuses could well compensate for the closing off of vascular channels elsewhere. Thus, a normal perfusion rate cannot by any means be safely interpreted as indicating a normal flow through a normal renal vascular bed. From all of this, it seems clear that the possible rôle of renal arterial and arteriolar changes in producing renal ischemia and hence hypertension is still an open question.

It seems doubtful that this question can be definitely and finally settled by the application of any single method of study. It is clear that the study of neoprene casts of the renal vasculature cannot give a measure of renal blood flow any more than can the study of histological sections. However, the neoprene casts offer a definite advantage over histological methods in that the arteries and arterioles can be traced in continuity down to their finest ramifications. Moreover, the neoprene casts are accurate reproductions of the lumina of the renal arterial vessels distended under a pressure within a physiological range. Since the pressure used in the injection of the kidneys from cases of hypertension was the same as the pressure used in injecting the renal arteries of normal kidneys, and since all other factors were kept constant during the injection of normal and abnormal kidneys, it is reasonable to conclude that any differences noted between the casts of normal and abnormal kidneys represent changes due to organic lesions in the arterial walls. While it cannot be said that the width of the lumina of small arteries and arterioles as judged by the neoprene casts is an accurate measure of the width of these same lumina during life, it is safe to conclude that the diameters represented in the casts are in any case the maximum that could be found for a corresponding point during life. For these reasons, one can gain from a study of the neoprene casts a much more accurate idea of the all-important lumina of the renal arteries and arterioles in essential hypertension than is possible in histological studies which deal with the state of the normal or diseased vessel walls or with the supposed functional capacity of their more or less collapsed lumina.

Study of neoprene casts of the renal arterial vasculature in cases of essential hypertension shows that there are no constant severe constrictions of the main renal artery. In some kidneys there are no observable constrictions in the smaller arteries and arterioles. In other kidneys there are

constrictions and angulations of the interlobular arteries and arterioles, sometimes confined to the interlobular arteries, sometimes confined to the afferent arteriole and sometimes found in both types of vessel in the same kidney. These changes are often so slight that it would be difficult to believe that they are capable of producing an appreciable reduction of blood flow, much less an ischemia of the renal cortex sufficient to cause hypertension by the Goldblatt mechanism.

On the other hand, there are severe constrictions of the small renal arteries and arterioles in some of the hypertensive kidneys, especially when the kidneys are markedly contracted. In these cases the afferent arterioles and associated glomeruli are often missing from the proximal parts of the interlobular arteries and direct vessels to the cortical and medullary capillary plexuses may be very numerous. There may be a loss of as many as fifty percent of the glomeruli. Measurement of the width of the afferent arterioles which remain in these cases reveals no significant narrowing of the lumina of these vessels on the average. However, as has been already pointed out, the value for this measurement is only an average of the measurements of the injected afferent arterioles, and until it is certain that every afferent arteriole which is not completely occluded has been completely injected, no conclusion can be drawn regarding the average width of the afferent arterioles for the whole kidney. Nevertheless, the loss of 50 percent of the glomeruli in some of these kidneys from cases of hypertension indicates that the afferent arterioles to these glomeruli are severely constricted and in some instances completely occluded. It seems reasonable, therefore, to believe that in these cases there would be sufficient ischemia of the renal cortex to cause elevation of the blood pressure.

The lack of any observable change in the lumina of the small renal arteries and arterioles in the kidneys from some cases of definite and persist-

ent hypertension, and such slight changes in other kidneys that they could not be considered adequate to produce ischemia of the kidney cortex capable of causing hypertension, suggests that in the early stages of essential hypertension there is no widespread and severe organic constriction of the small renal vessels producing ischemia of the kidney cortex, and that if ischemia of the kidney is responsible for the hypertension then there must be a widespread functional vasoconstriction of the small renal arteries and arterioles. The normal constrictions of the afferent arteriole at its origin and termination may indicate some physiological mechanism capable of producing marked narrowing of these segments of the renal afferent arterioles under certain conditions resulting in a sufficient degree of ischemia of the kidney cortex to produce persistent high blood pressure.

The marked changes described in the small renal vessels in some cases of hypertension undoubtedly do produce ischemia of the kidneys, and may aggravate the mechanism already causing the hypertension; or when these changes are so severe as to be no longer reversible, they may be entirely responsible for the maintenance of high blood pressure. But it seems reasonable, on the basis of these facts, to believe that the organic changes noted in these vessels arise from damage to these small vessels, either as a result of severe vasoconstriction or the wear and tear of high blood pressure, or both.

SUMMARY & CONCLUSIONS

1. The literature on the blood supply of normal and abnormal mammalian kidneys is reviewed.

2. Injection methods for the study of blood vessels, more particularly of the kidney, are discussed and compared.

3. The injection technique using "Neoprene", a liquid latex, as the injection mass, is described in detail.

4. The advantages of this material, which produces an accurate mold of blood vessels, are pointed out.

5. A study is reported of fifty-seven kidneys injected by this method. Of these, 36 were normal, 18 were from cases of hypertension, one was from a case of amyloidosis, one from a case of lipoid nephrosis and one from a case of chronic pyelonephritis.

6. It is shown that the main renal artery divides into five main divisions, which then form about twelve interlobar arteries. These divide into a series of large vessels running parallel and close to the cortico-medullary interval and called arcuate arteries. From these arise the interlobular arteries which divide and give off the afferent glomerular arterioles.

7. Three types of efferent arterioles are noted: the subcapsular type, the cortical type, and the cortico-medullary type which end in the "arteriolae rectae spuriae".

8. Direct vessels to the cortex and medulla are described in essentially normal kidneys, but were considered to be unimportant in renal physiology and were considered to have developed as a result of damage to glomeruli.

9. Age changes of the renal blood vessels are described.

10. In kidneys from cases of essential hypertension there are no observable changes in the arterial lumina in some instances, while in others there are marked changes of the small arteries, arterioles and glomeruli.

11. It is concluded that in the early stages of essential hypertension, there are no organic constrictions of small vessels capable of producing an ischemia of the kidney cortex sufficient to cause hypertension. The severe changes seen in small arteries and arterioles in the kidneys from some cases of hypertension are considered to be the result of damage caused by severe functional constriction of these vessels or by the wear and tear of high blood pressure, or both.

Part V

ILLUSTRATIONS AND GRAPHS

Illustrations: These include some photomicrographs of kidneys of the opposite side to the one injected. The majority of illustrations are of neoprene casts mounted according to the method described previously.

It should be remembered that in these photographs of neoprene casts it is a cast of the lumen that is seen. Therefore, any changes noted are indications of the effect on the lumen of the vessel observed. No conclusions can be drawn regarding the state of the vascular tree beyond the last point of injection. When the injection stops short of a glomerulus it does not indicate complete obstruction at that point but merely a severe degree of obstruction to the injected neoprene.

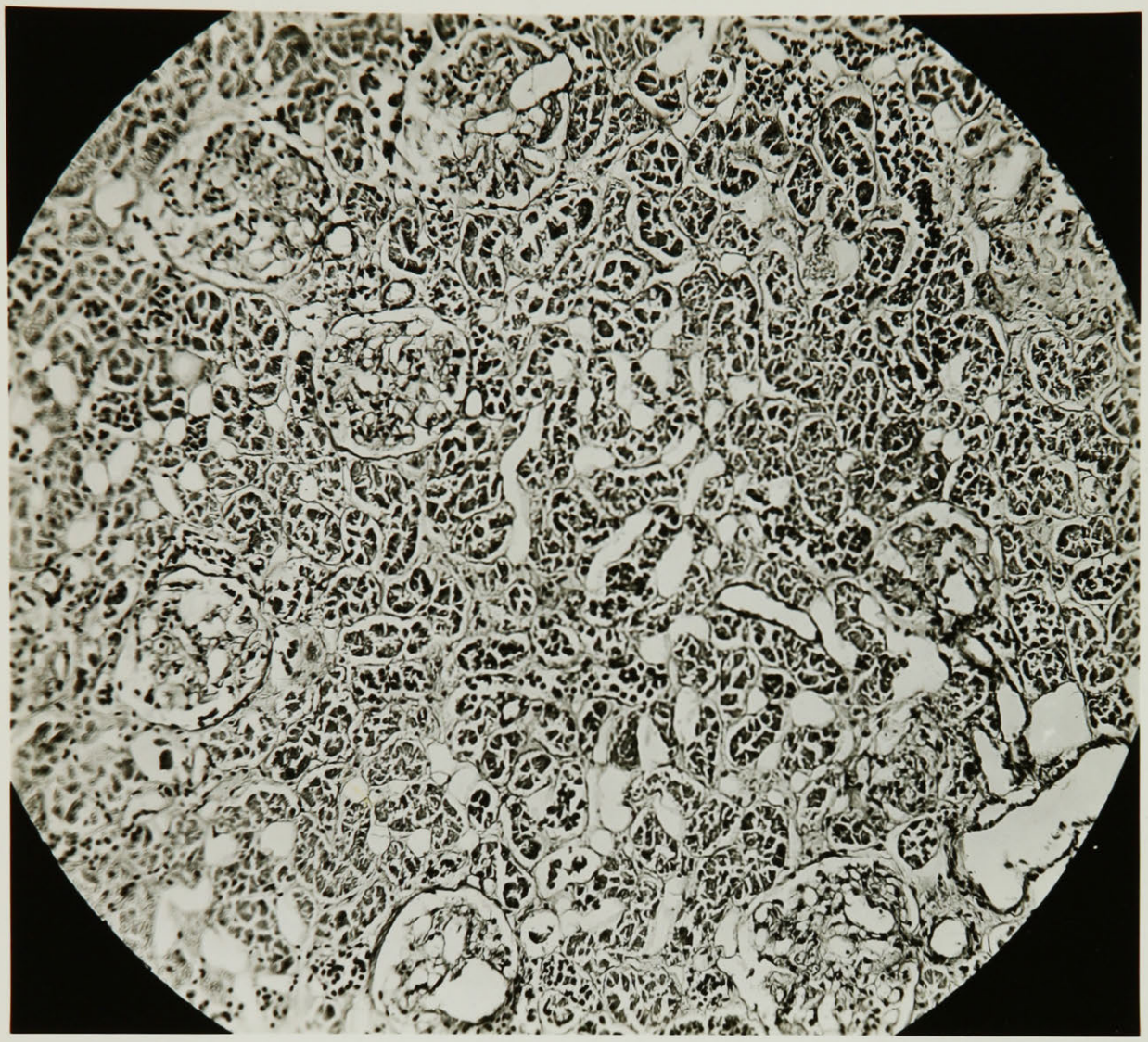


Fig. 1 (A-11369). Photomicrograph of a histological section of a normal kidney, man age 45. This is the appearance of a kidney ready for injection. The kidney was perfused with tap water for eight hours, left at 4° C. for 18 hours then at room temperature for 4 hours. A block of the kidney was then fixed in formalin and stained with haematoxylin and eosin. Note that while histological detail is not well preserved there is not much distortion of architecture due to oedema.

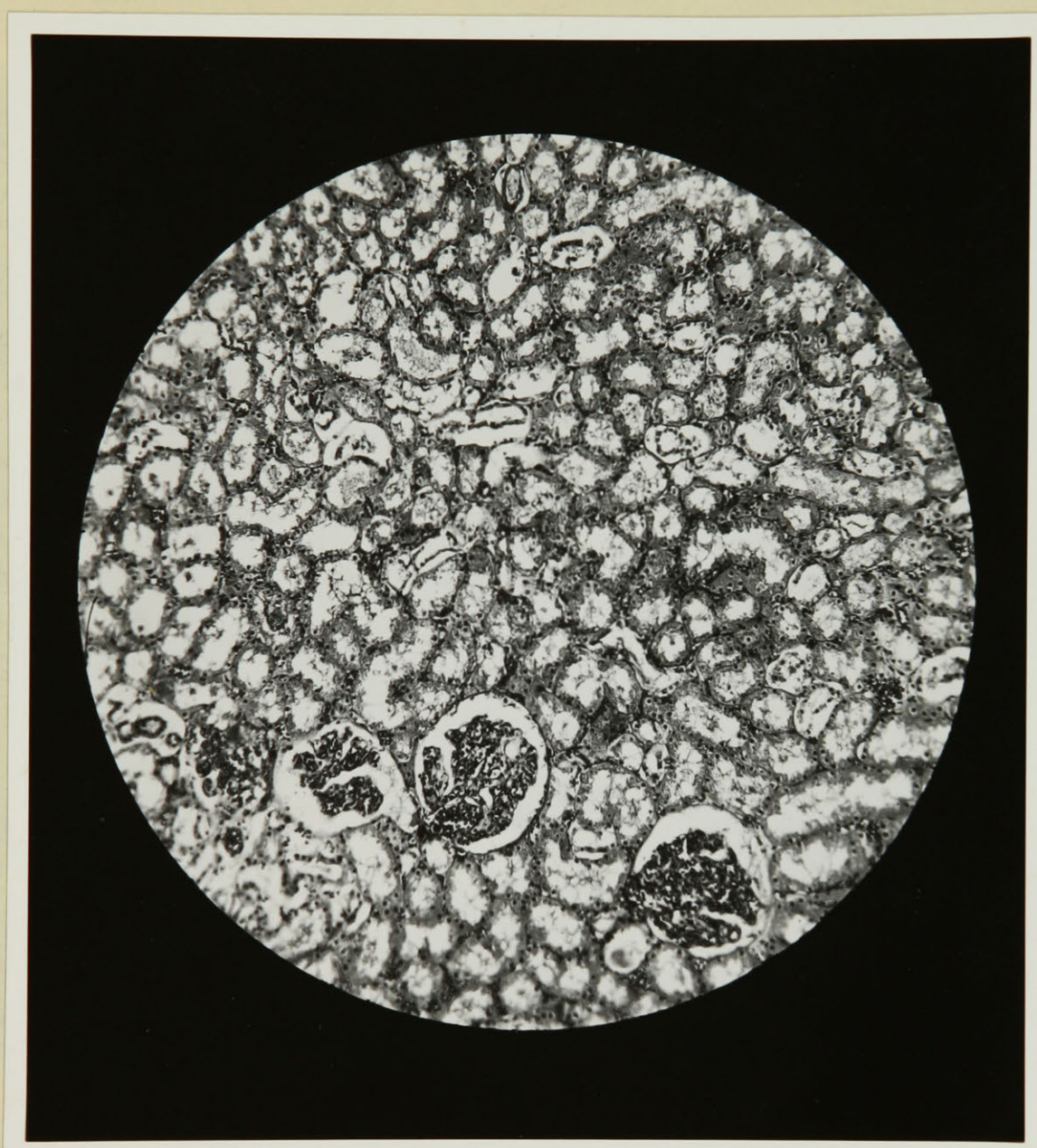


Fig. 2 (A-11369). Photomicrograph of histological section of a normal kidney from the same case as used in Fig. 1. This kidney was perfused with 2 litres of kerosene at 200 mm. of mercury, and then fixed in formalin and stained with haematoxylin & eosin. Compare with Fig. 1 which was taken at the same magnification. Note in Fig. 2 that the glomeruli are stuffed with blood. These are from the periphery of the cortex. The structures do not show any great variation in size between the two kidneys.

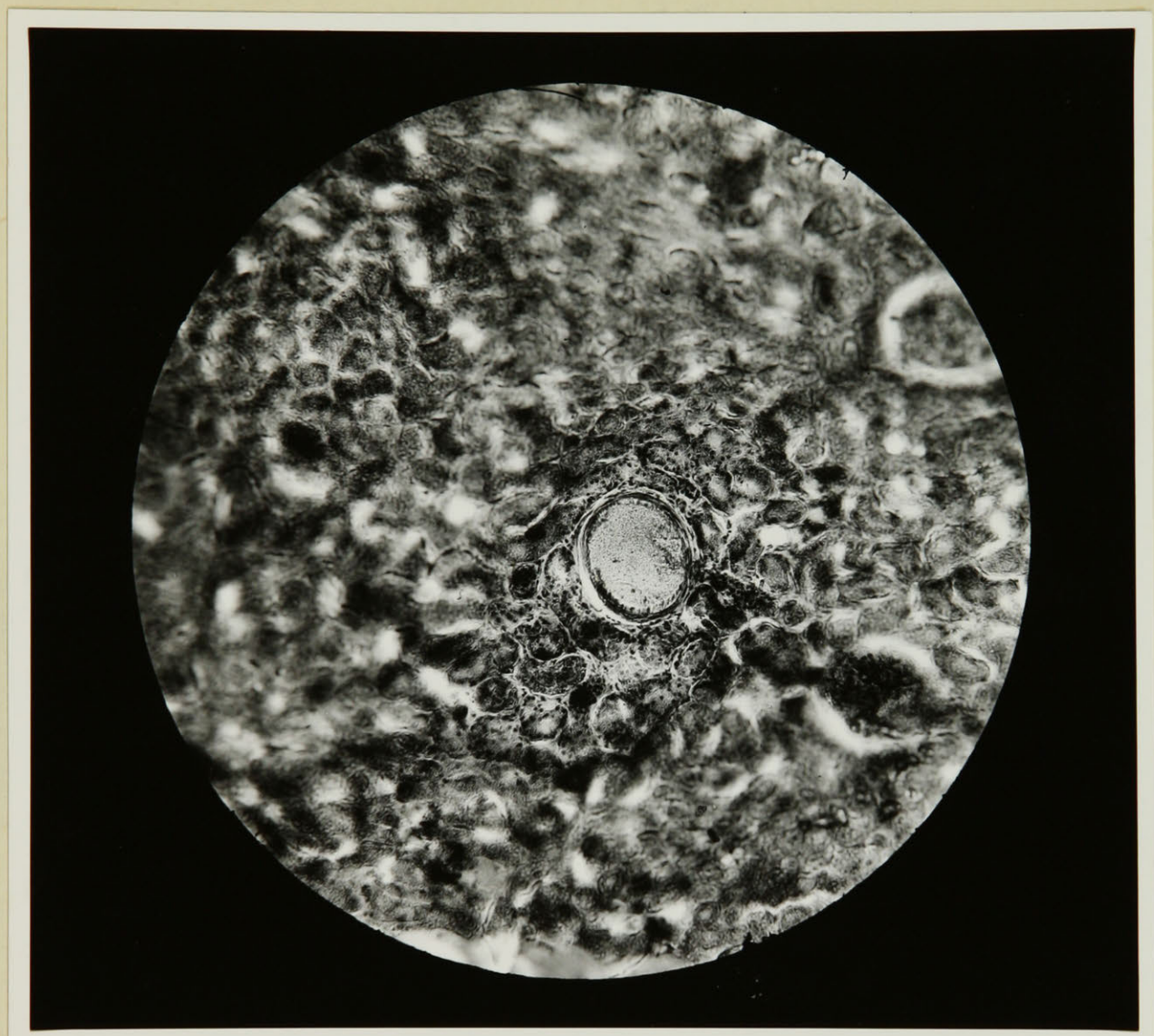


Fig. 3 . Photomicrograph of a histological section of a normal kidney. This kidney was injected and prepared for histological section by the method described in the text. Note the neoprene completely filling one of the arteries indicating that no shrinkage occurs as the neoprene hardens.

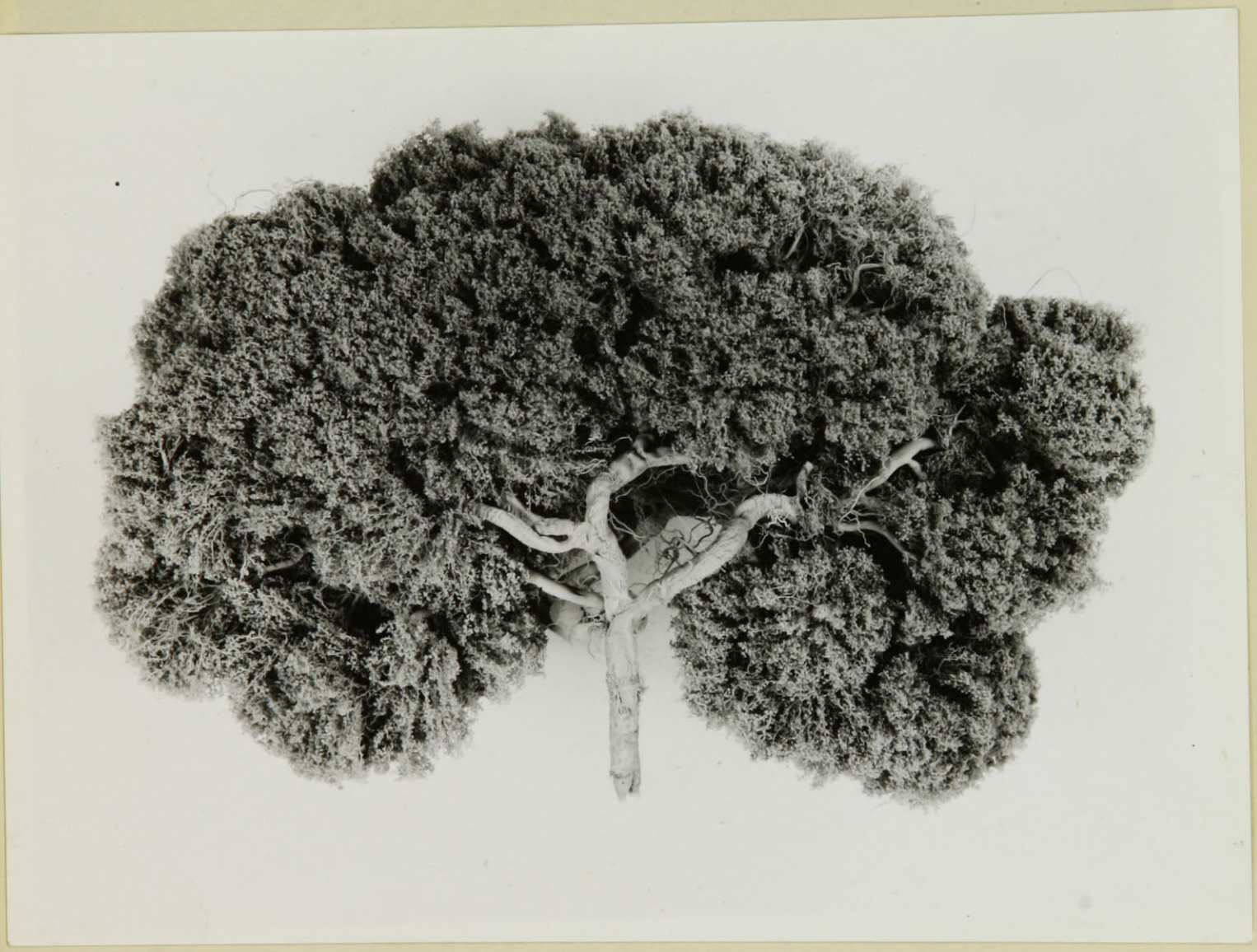


Fig. 4 (A-484-40). Photograph of a neoprene cast under water of a normal kidney from a woman, age 41. This shows the large branches dividing and then as they pass into the kidney they are soon covered by the overhanging mass of glomeruli around the hilum. The glomeruli form a dense thick covering giving the whole the appearance of some luxuriant tropical bush.

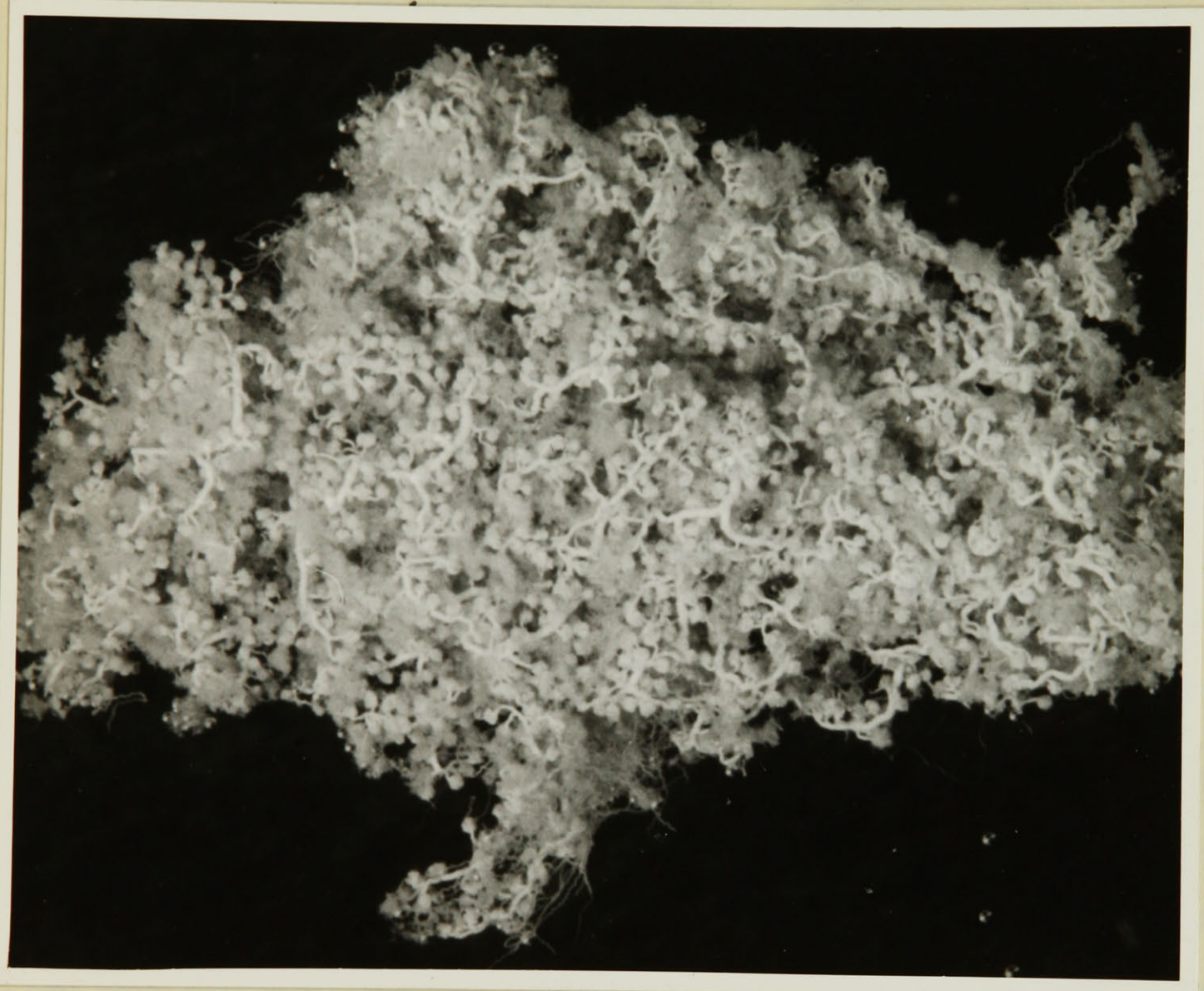


Fig. 4A (A-10955). Photograph of a neoprene cast under water. From a normal kidney, male age 20. Note how thickly the glomeruli cover the whole surface of the cast.

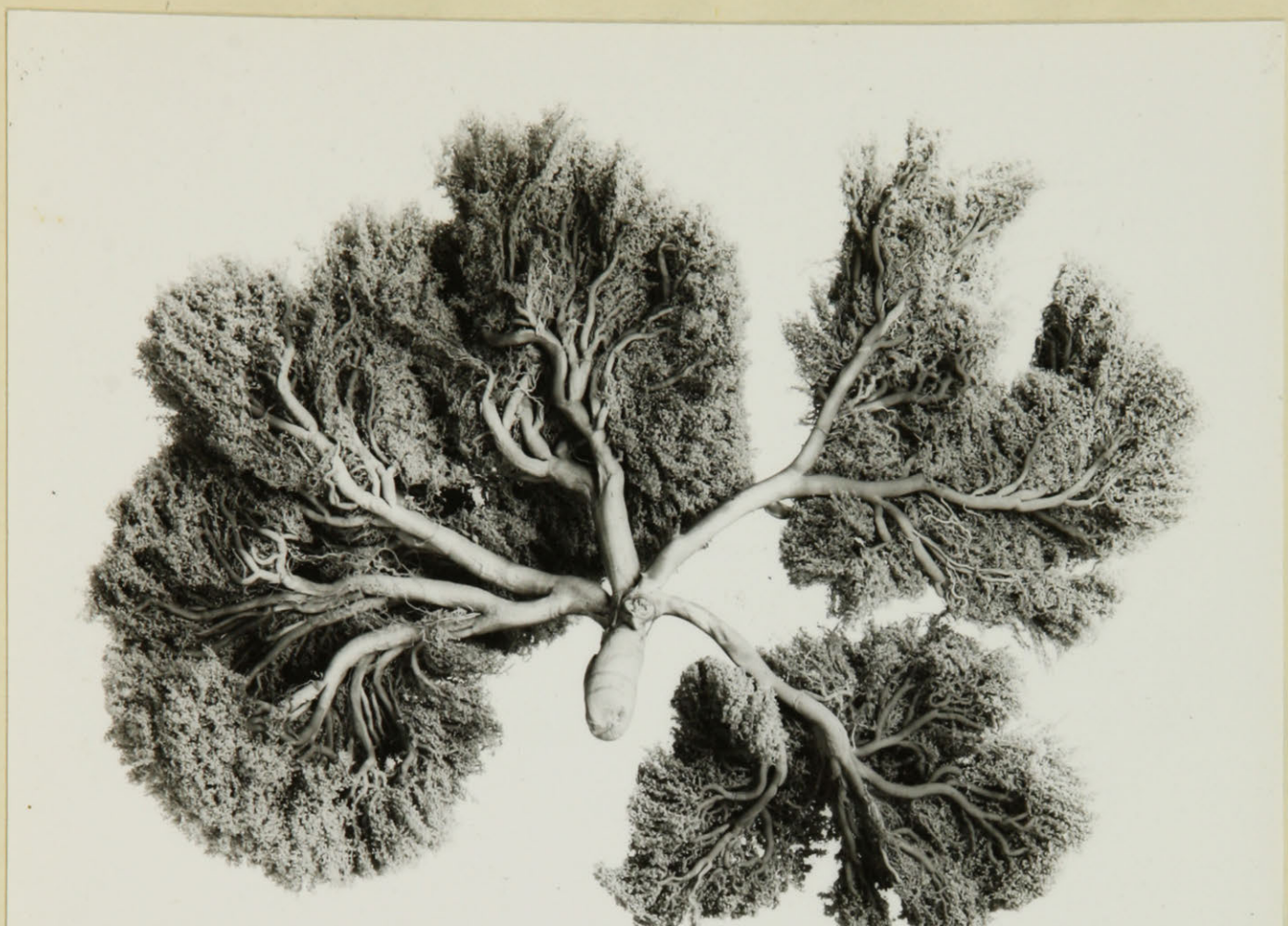


Fig. 5 (A-11412). Photograph of neoprene cast under water. From a normal kidney of a boy age 18. This is a cast separated into anterior and posterior sections. Note that the main renal artery divides into two main branches, one for supply of the anterior surface and one for the posterior surface. These both soon divide into further primary divisions. Almost two-thirds of the blood supply passes to the anterior portion.

Fig. 6 (A-11269). Photograph of neoprene cast under water. From a normal kidney of a man aged 52. Note the small vessels arising from the primary divisions of the renal artery to supply the capsule.

Fig. 7 (A-11333). Photograph of neoprene cast under water. From the kidney of a man age 43. Note a small vessel arising from one of the main divisions of the renal artery, for the supply of pelvic and peripelvic tissue.

Fig. 8 (A-11412). Photograph of neoprene cast under water. From the kidney of Fig. 5. This shows an interlobar artery dividing into arcuate arteries by repeated dichotomous division. Some of the larger branches lie parallel to the surface of the kidney. The smaller ones pass with a slight inclination towards the surface of the kidney.

Fig. 8A. Photograph of a cut surface of a normal kidney. A layer of cortex half an inch in thickness has been shaved from the convex surface of the kidney. The medullary pyramids are seen in cross section surrounded by a layer of cortical tissue which is thick towards the surface of the kidney and thin between adjacent pyramids. Cross sections of arcuate arteries are seen in the cortico-medullary interval.

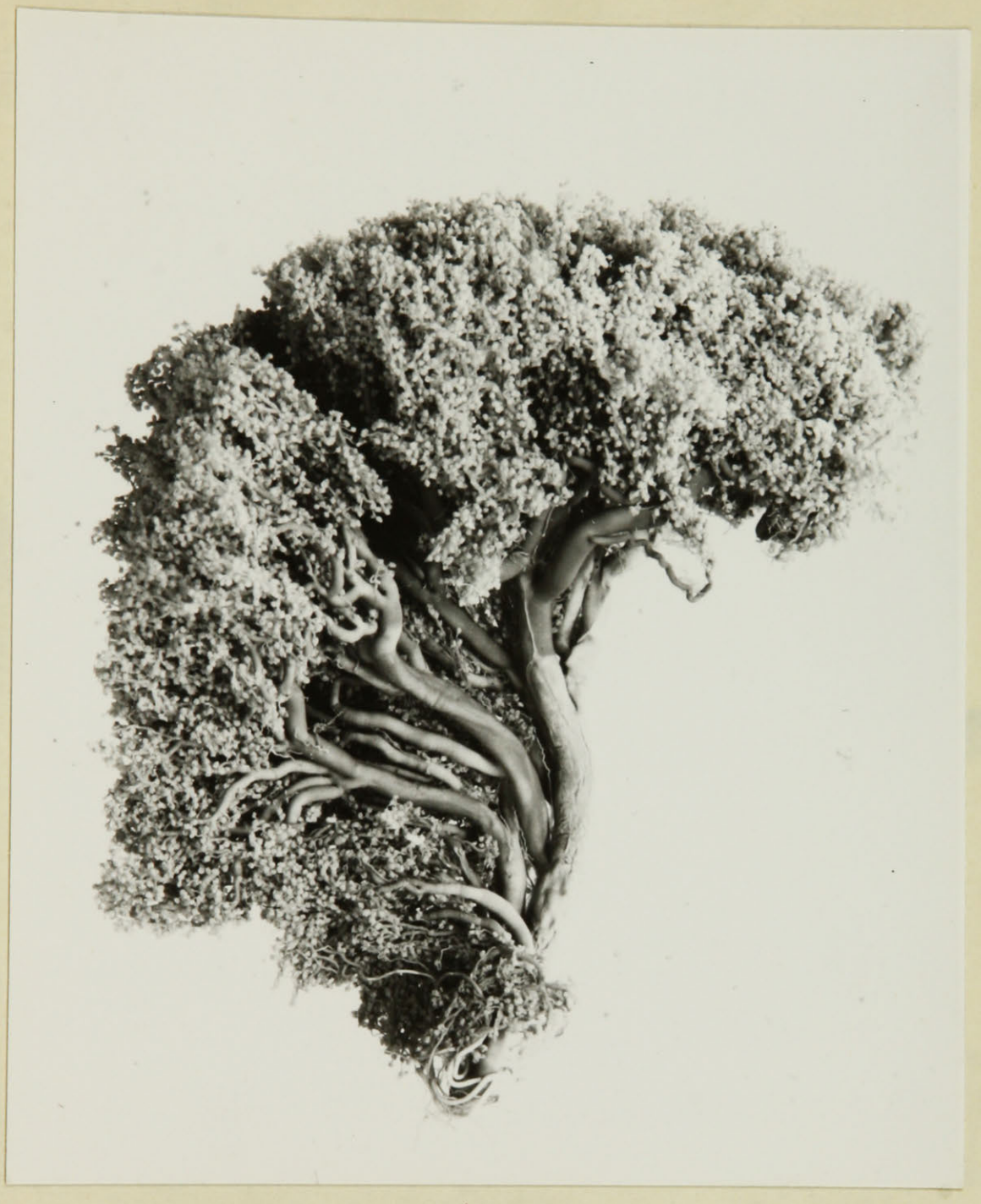


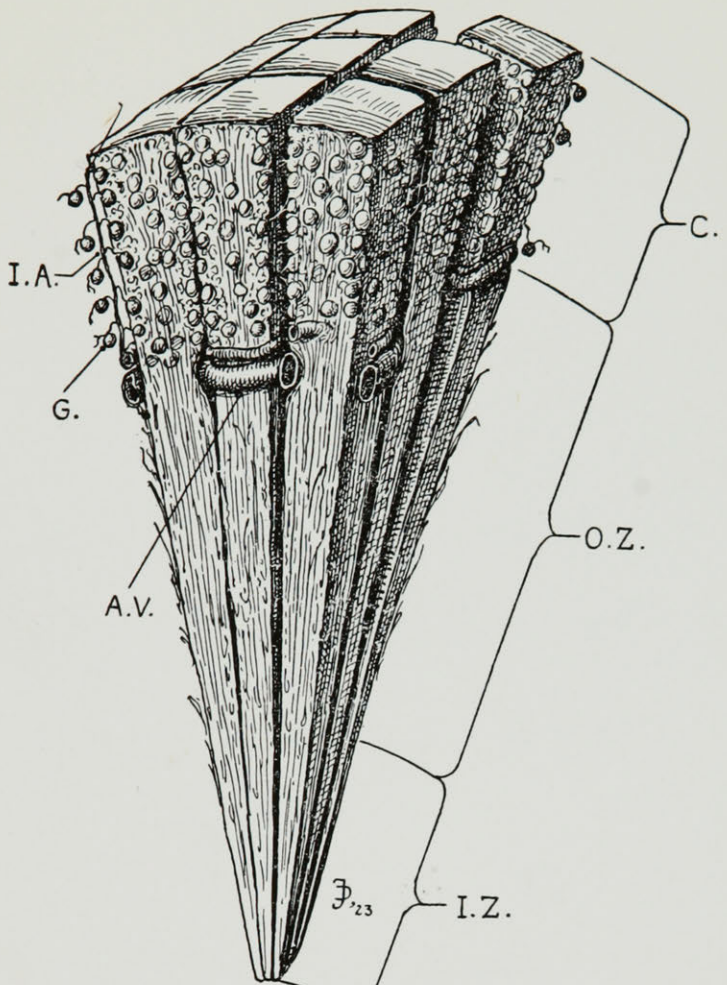
Fig. 9 (A-11412). Photograph of neoprene cast under water. From the kidney of Fig. 5. This shows an interlobar artery near the lower pole giving off arcuates only on the side towards the pole.

Fig. 10 (A-11412). Photograph of neoprene cast of a normal kidney. From the kidney of Fig. 5. This surface is at a right angle to the surface seen in Fig. 5. Note the interlobar artery dividing dichotomously into arcuates which pass with a slight inclination towards the surface of the kidney.

Fig. 11 (A-11412). Photograph of neoprene cast under water. From the kidney of Fig. 5. A primary division is seen dividing into two interlobar arteries. Note the marked constrictions occurring at the take-off of the arcuate arteries as they divide.

Fig. 12 (A-11412). Photograph of neoprene cast under water. From the kidney of Fig. 5. An interlobar artery dividing into arcuate arteries as seen in a plane at right angles to the surface of the kidney. Note that the proximal arcuates arch down to supply the glomeruli of the cortex overhanging the hilum of the kidney.

Fig. 14 (A-11412). Photograph of a neoprene cast from a normal kidney, male age 18 years. The interlobular arteries are arising in a fairly regular manner from the convex surface of an arcuate artery. These divide repeatedly but maintain a course almost parallel to one another with a slight radial arrangement.



semi-diagrammatic drawing of extensively macerated kidney tissue to illustrate the manner in which the kidney resolves itself into similar units of renal substance. The units are pyramids having their bases in the cortex and their apices in the inner zone of the medulla. *C.*, cortex; *O. Z.*, outer zone; *I. Z.*, inner zone; *I. A.*, interlobular artery; *G.*, glomerulus; *A. V.*, arcuate vein.

Fig. 15. Reproduction from Traut. This shows the pyramidal lobules formed around central collecting tubules. In the cortex the four sides of the pyramid are covered with glomeruli. In the interval between these lobules run the interlobular arteries.

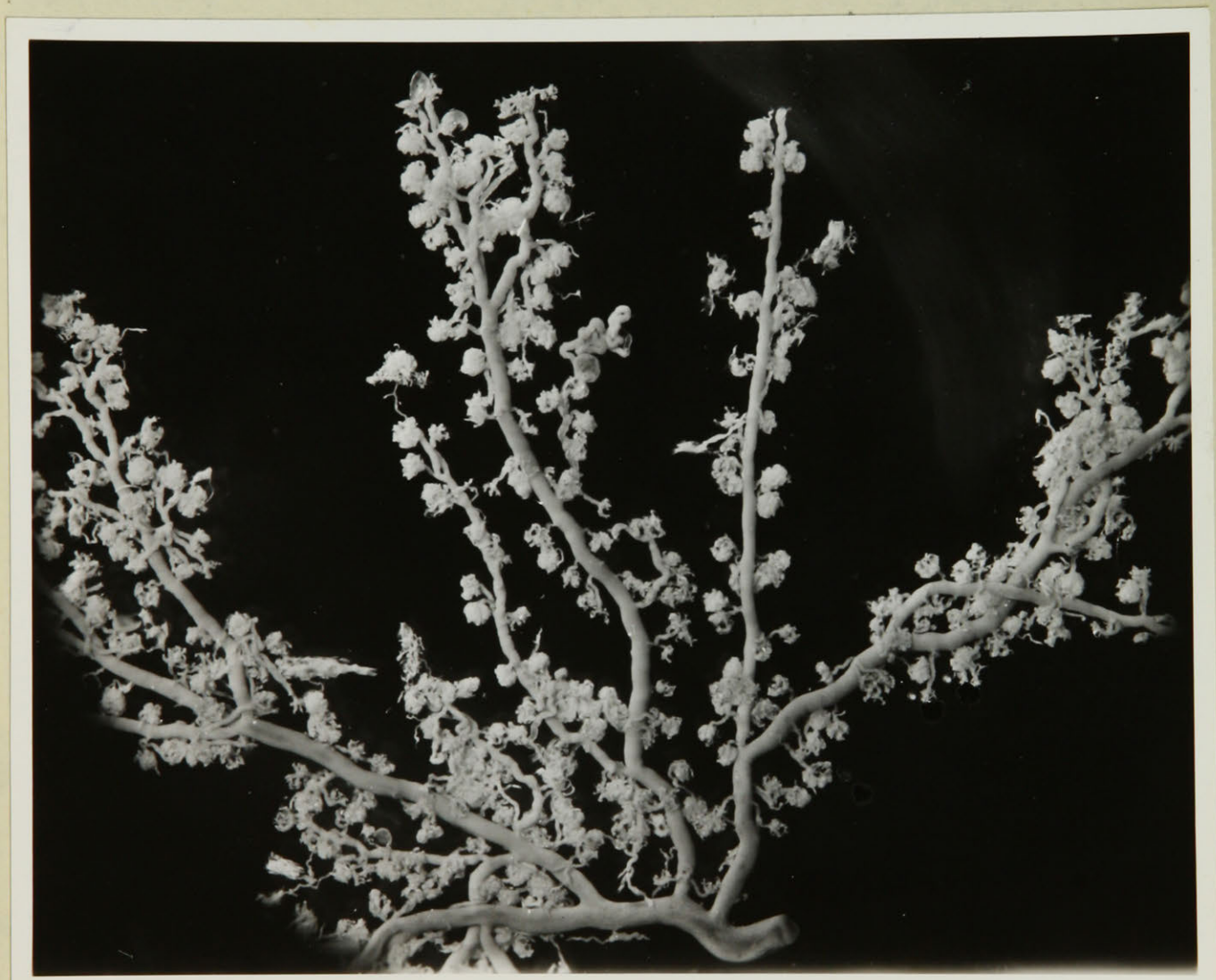


Fig. 16 (A-484-40). Photograph of a neoprene cast of a normal kidney. This shows a series of interlobular arteries arising from the convex margin of an arcuate artery. Note that the interlobular arteries divide after giving origin to afferent arterioles. No arterial anastomoses exist between any of these interlobular arteries.

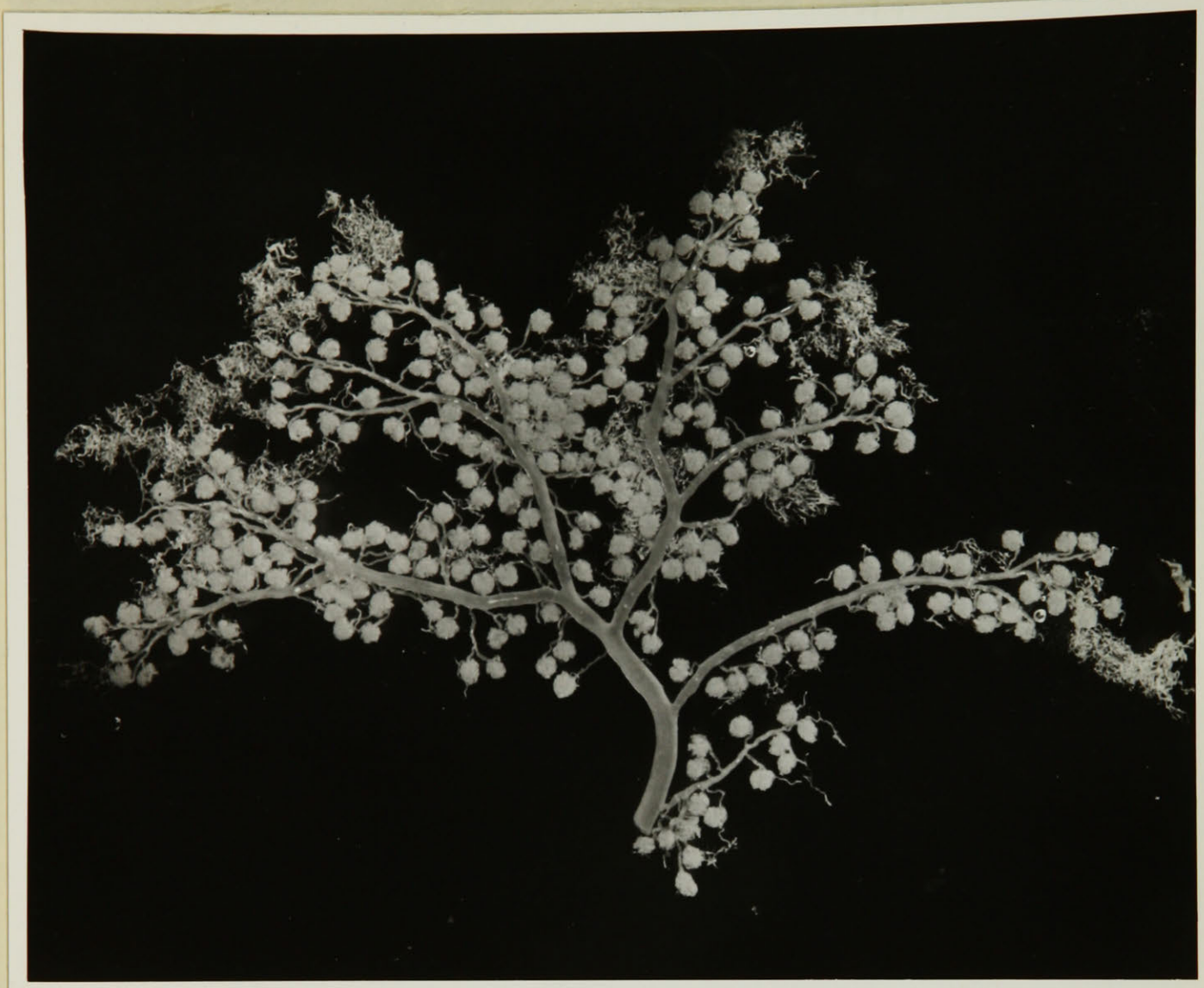
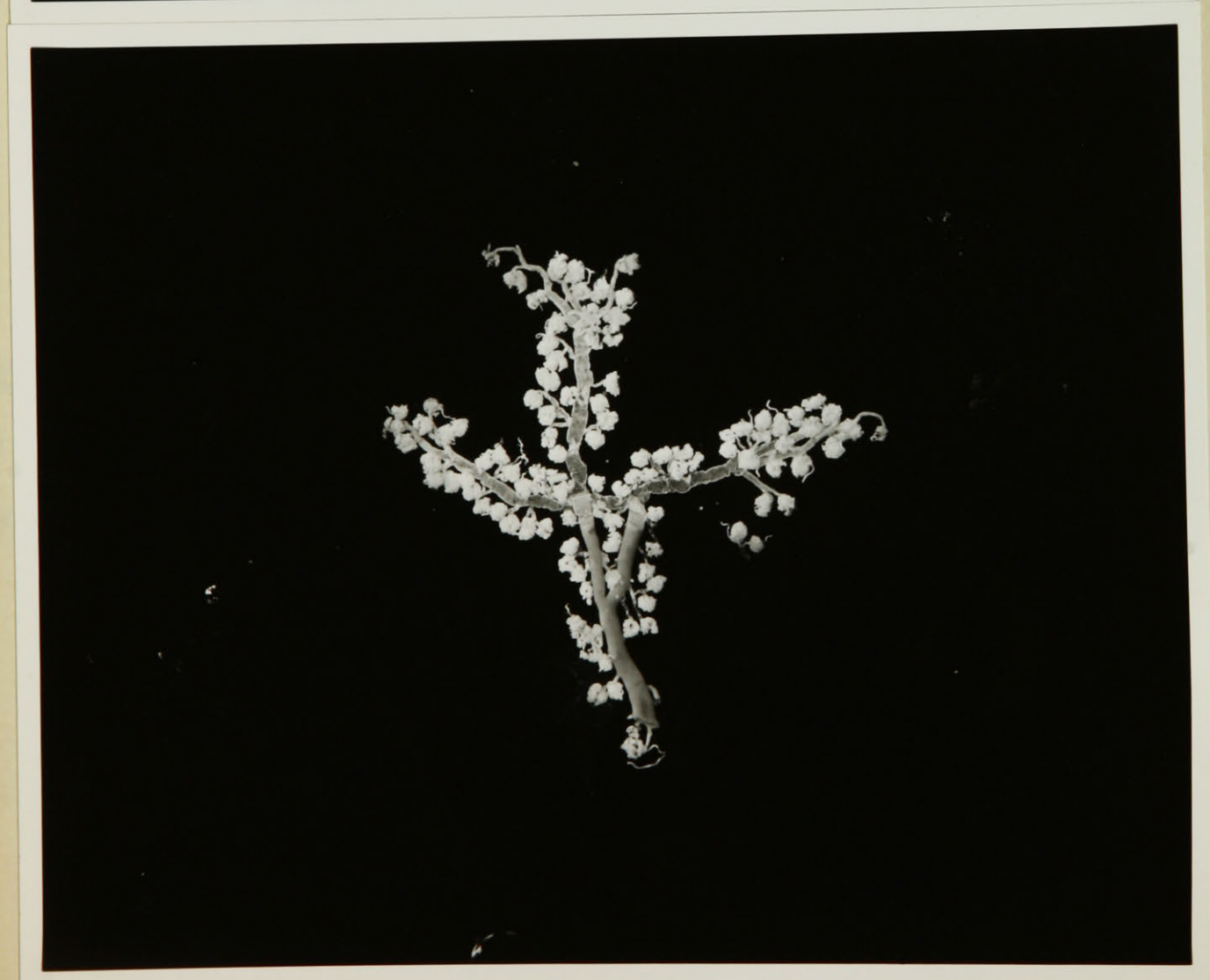


Fig. 17 (A-10958). Photograph of a neoprene cast of a normal kidney, man age 20. This shows the interlobular arteries arising from the termination of an arcuate artery. Note that no arterial anastomoses exist between the interlobular arteries.



Figs. 18A & B. Photographs of same neoprene cast as 14B. These are interlobular arteries taken at the same magnification showing the great variation in length between interlobular arteries from the same kidney.

Fig. 19 (A-10758). Neoprene cast of a normal kidney from a female, age 39. Note the way the interlobular artery terminates by breaking up into a series of long afferent arterioles ending in glomeruli.

Fig. 20. Photograph of a neoprene cast of a normal kidney from a female, age 50. Note the number of glomeruli arising from a structure the size of an arteriole. The size of this vessel is only slightly larger than any one of the afferent arterioles arising from it.

Fig. 21 (A-11376). Photograph of neoprene cast of a normal kidney from a man, age 23. Note the marked constriction of the afferent arteriole close to its origin from the interlobular artery.

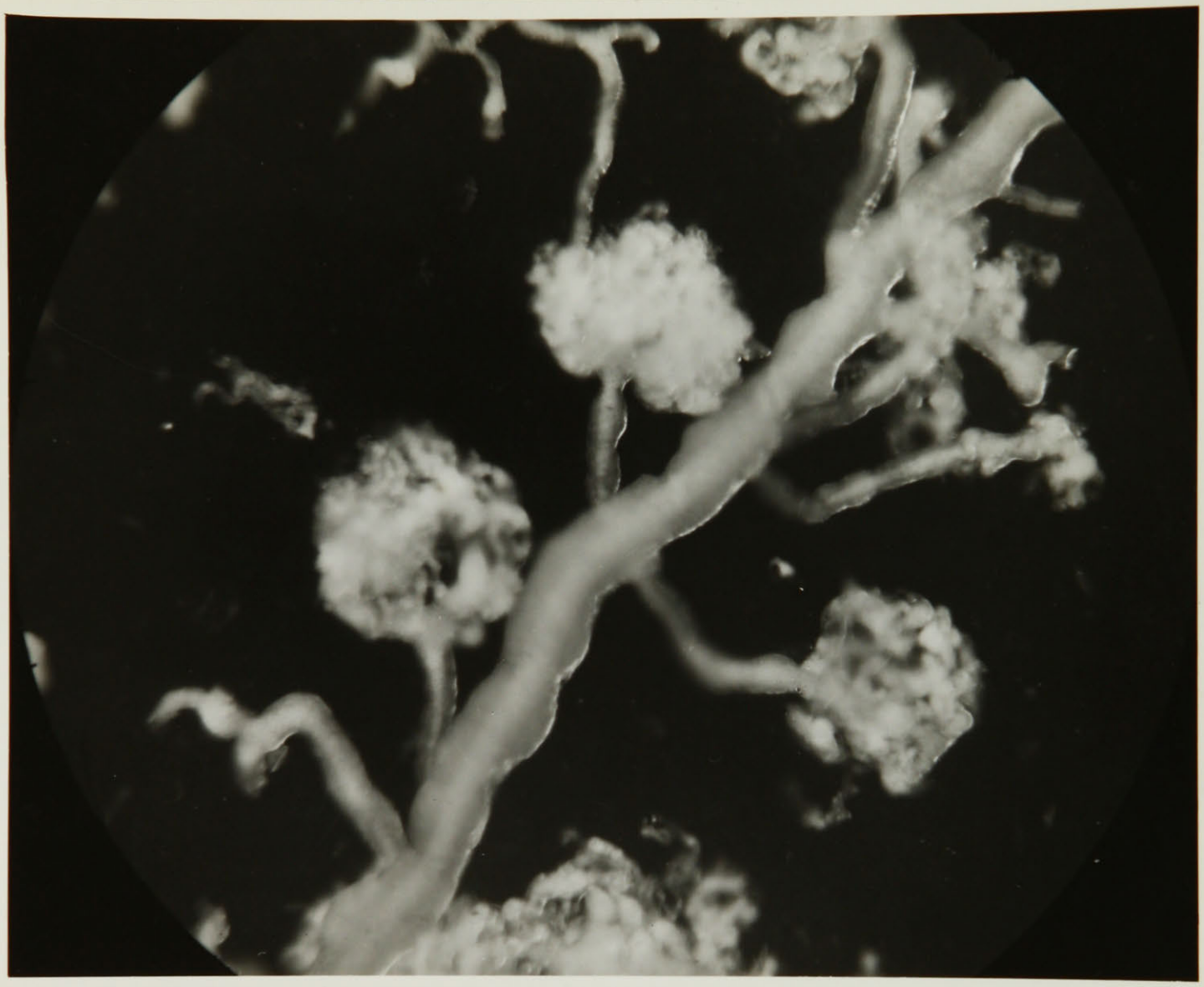


Fig. 22 (A-11269). Photograph of a neoprene cast of a normal kidney from a male, age 52. Some of the structures have been broken off in the preparation. This shows very well in two of the afferent arterioles the constriction that is commonly seen as the afferent arteriole enters the glomeruli.

Fig. 23. Photograph of a neoprene cast of a kidney from a man, age 50. Note the long afferent arterioles taking origin from the large proximal part of an interlobular artery.

Fig. 25 (A-10753). Photograph of neoprene cast of a normal kidney. Note the three subcortical glomeruli and their efferent arterioles which break up almost immediately into a peritubular capillary plexus. Apparently there is extensive anastomosis of capillaries from adjacent glomeruli.

Fig. 26 (A-11203). Photograph of neoprene cast of normal kidney. Note the groups of arteriolae rectae spuriae streaming out from the glomeruli close to the medulla and arising from very short efferent arterioles.

Fig. 27 (A-11412). Photograph of neoprene cast under water. From kidney of Fig. 5. This shows an interlobar artery dividing into arcuates and these in turn into interlobular arteries. Some of the branches have been removed. Some of the interlobular arteries arise from the terminations of arcuates while others arise from the trunks of the arcuates. All pass towards the surface at approximately the level of the origin of the interlobular arteries.

Fig. 28 (A-11412). Photograph of same neoprene cast as Fig. 14B. The large arcuate artery is dividing into further arcuate arteries which form acute angles at their origins. Some have been removed and the rest separated from one another. Ordinarily these lie almost parallel to one another. All of these arcuates give off interlobular arteries. A few direct vessels can be seen arising from the large arcuates and also a few afferent arterioles take origin from these.

Fig. 29 (A-11203). Photograph of neoprene cast from a normal kidney of a male, age 45 years. A direct vessel to the cortical capillary plexus is seen which appears to be the direct continuation of an afferent arteriole.

Fig. 30 (A-11197). Photograph of a neoprene cast of a normal kidney from a male, age 45. Among the arteriolae rectae spuriae one vessel can be seen arising directly from the interlobular artery and passing towards the medulla without passing through a glomerulus. This is one of the so-called "arteriolae rectae verae".

Fig. 31 (A-11276). Photograph of a kidney from a man aged 78. Note the marked gnarled appearance of the large branches. One interlobular artery is seen continued out and anastomosing with perirenal vessels.

Fig. 32(A-10955). Photograph of neoprene cast of a normal kidney from a man age 20. Compare size of structures with those in Fig. 33 from a child age 3. Both pictures taken at the same magnification. The glomeruli particularly vary in size.

Fig. 33 (A-11187). Neoprene cast of normal kidney, child age 3 years. Note the size of the various structures and compare with Fig. 32.

Fig. 34A (A-10737). Photograph of a neoprene cast of a normal kidney from a female, age 60. Note the marked constriction at the take-off of the lowermost interlobular artery.

Fig. 34B (A-11197). Photograph of a neoprene cast of a normal kidney from a male, age 45. The glomeruli are all well injected. Note irregularity of the interlobular arteries.

Fig. 35 (A-11276). Photograph of a neoprene cast of a normal kidney from a male, age 78. The interlobular arteries are irregular. Note particularly the coarse simplified appearance of many of the glomeruli.

Fig. 36 (A-10737). Photograph of a neoprene cast of a normal kidney from a female, age 60. Note the "blighted" appearance due to loss of glomeruli. Some glomeruli show only a coil or two injected and in some cases only the short primary divisions of the afferent arteriole. Note the marked constriction of the origin of the most proximal interlobular artery.

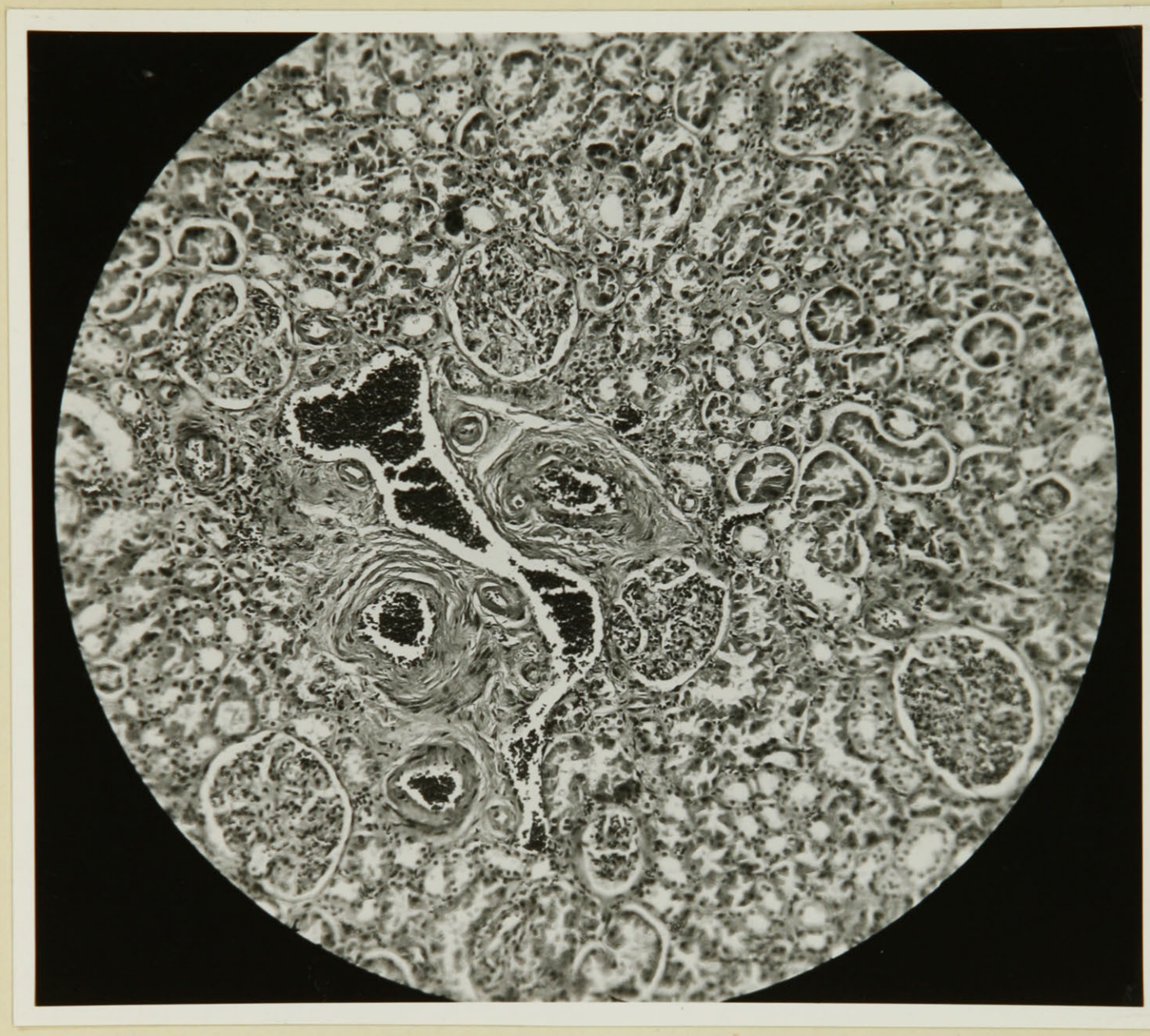


Fig. 37A (A-10873). Photomicrograph of a histological section from a kidney of a female, 49 years of age, blood pressure 196/126 for four years, heart weight 375 grams. There is marked hyaline thickening of the walls of some of the afferent arterioles with reduction in the size of their lumina. The glomeruli and tubules appear normal.

Fig. 37B (A-10873). Photograph of neoprene cast of opposite kidney from the same case as Fig. 37A. The interlobular arteries, afferent arterioles and glomeruli are all well injected. There are one or two small vessels that might be direct vessels to the peritubular capillary plexus.

Fig. 38 (A-512-40). Photograph of neoprene cast of kidney from a female, age 68. Blood pressure 160/120, heart weight 315 grams. Note the tortuosity of the interlobular arteries with some rather severe constrictions particularly at their bifurcations. Some glomeruli show only a few coils injected; some merely a few of the primary divisions, and in others the injection has not entered the glomerulus. There are a few convoluted tubules injected.

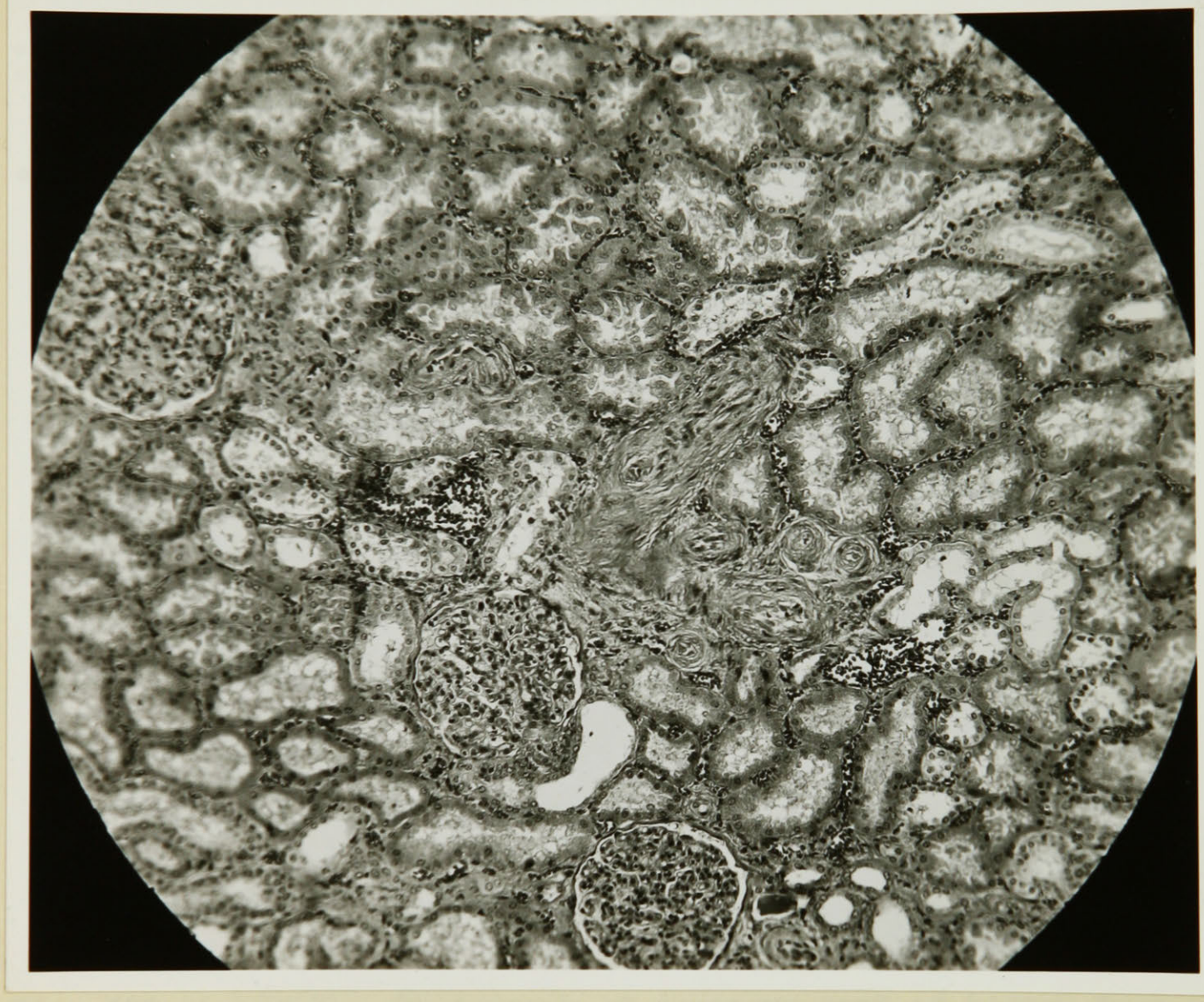


Fig. 39A (A-11178). Photomicrograph of a histological section of a kidney from a female, age 50. Blood pressure 270/130, heart weight 600 grams. The afferent arterioles show a marked hyaline thickening of their walls with extreme narrowing of their lumina. The basement membranes of the glomeruli are thickened.

Fig. 39B (A-11178). Photograph of neoprene cast of kidney from a female, age 50. Blood pressure 210/130, heart weight 600 grams. Note the rather even contour of the interlobular arteries. The short stems of afferent arterioles are seen arising along the course of the interlobular arteries but fail to end in glomeruli.

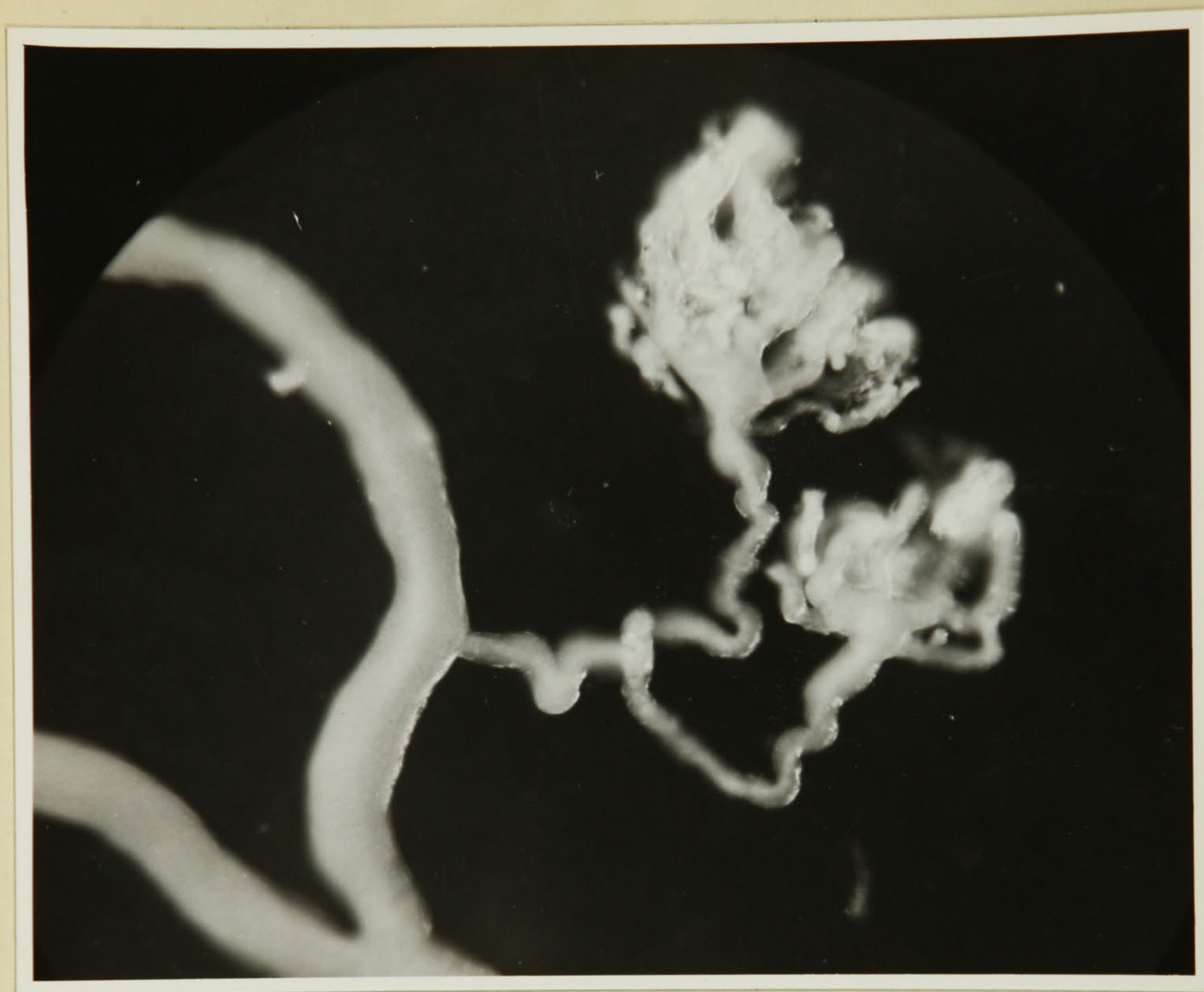


Fig. 39C (A-11178). Photograph of neoprene cast of a kidney from a female, age 50. Blood pressure 270/130, heart weight 600 grams. The interlobular arteries appear relatively normal. Note the marked tortuosity and constrictions of the afferent arteriole and the coarse pattern of the glomeruli.

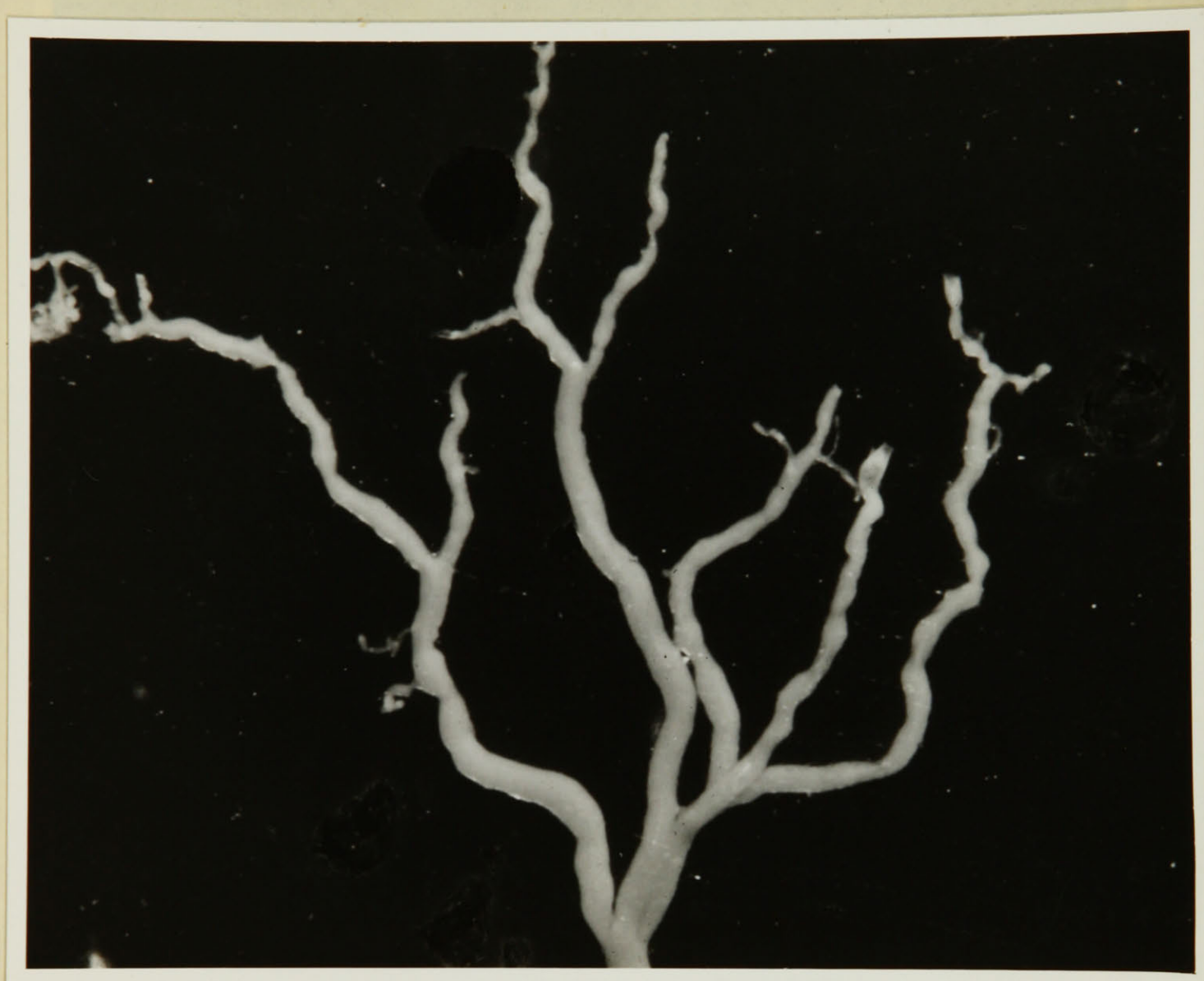


Fig. 40 (A-10776). Photograph of neoprene cast of a kidney from a female, age 59. Blood pressure 230/130, heart weight 430 grams. This injection was not complete but it shows well the beaded appearance of the interlobular arteries. Some of the angulations and constrictions almost completely occlude the lumen.

Fig. 41 (A-11194). Photograph of a neoprene cast of a kidney from a man age 47, B.P. 210/120, heart weight 615 gms. The proximal parts of the interlobular arteries are normal. There is slight notching and angulation of the terminal portion. Note the extreme lack of glomeruli from the proximal parts of the interlobular arteries. Only little spikes representing the afferent arterioles can be seen. The glomeruli around the terminal portions of the interlobular arteries are coarse.

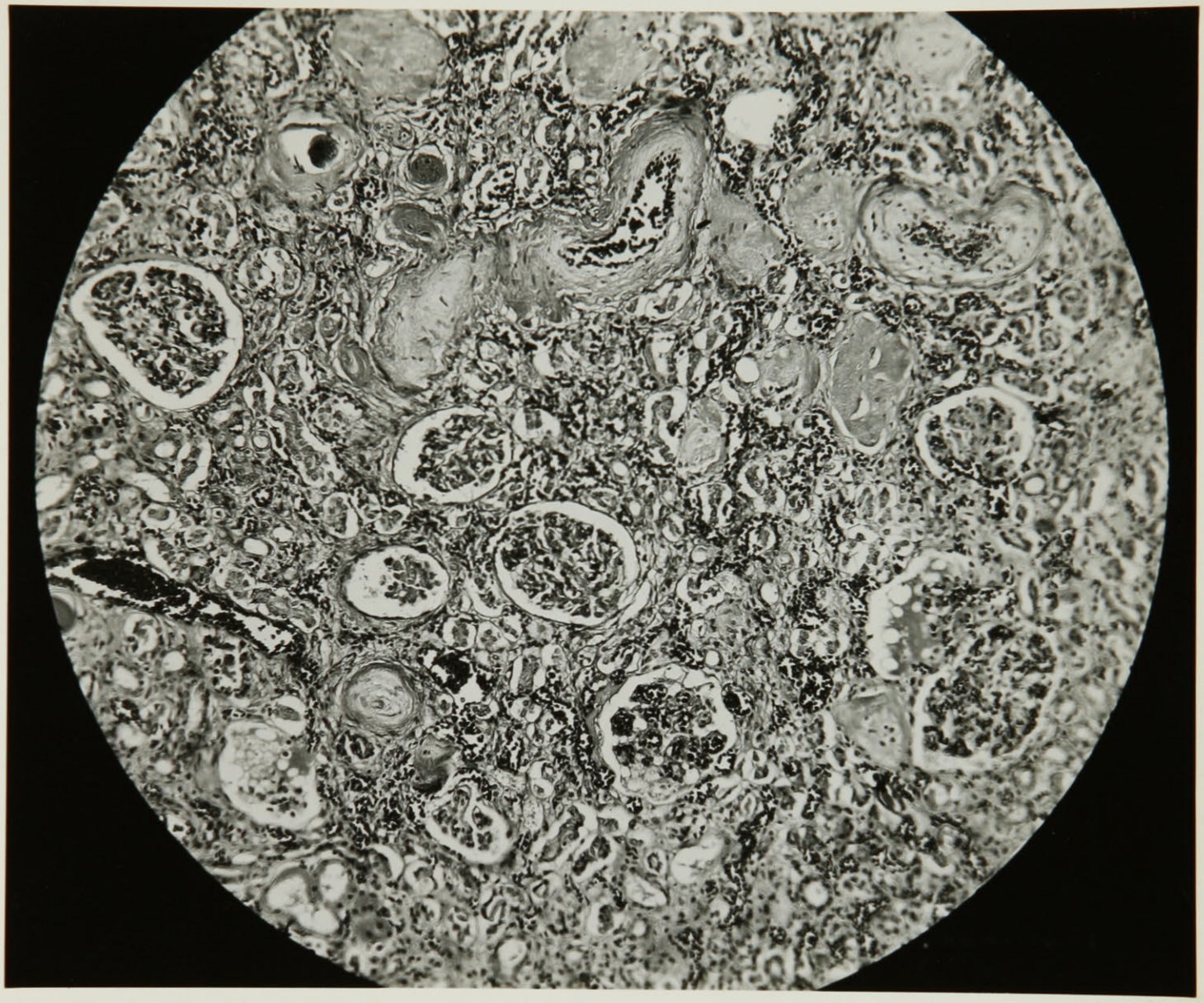


Fig. 42A (A-10857). This is a photomicrograph of a histological section from the kidney of a male, age 49, blood pressure 200/140, heart weight 680 grams. There is a marked intimal proliferation of the interlobular arteries which appear almost completely occluded at some points. The arterioles show a marked hyaline thickening of their walls. Some glomeruli are fibrosed and there is a good deal of tubular atrophy and interstitial accumulation of round cells.

Fig. 42B (A-10857). This is a photograph of a neoprene cast from the opposite kidney of the case shown in Fig. 42A. Many fine vessels arise from all portions of the interlobular arteries and end in a capillary plexus without the interposition of glomeruli. There are some simplified loops along the course of some of these which may represent degenerating glomeruli. The terminal portions of the interlobular arteries are notched.

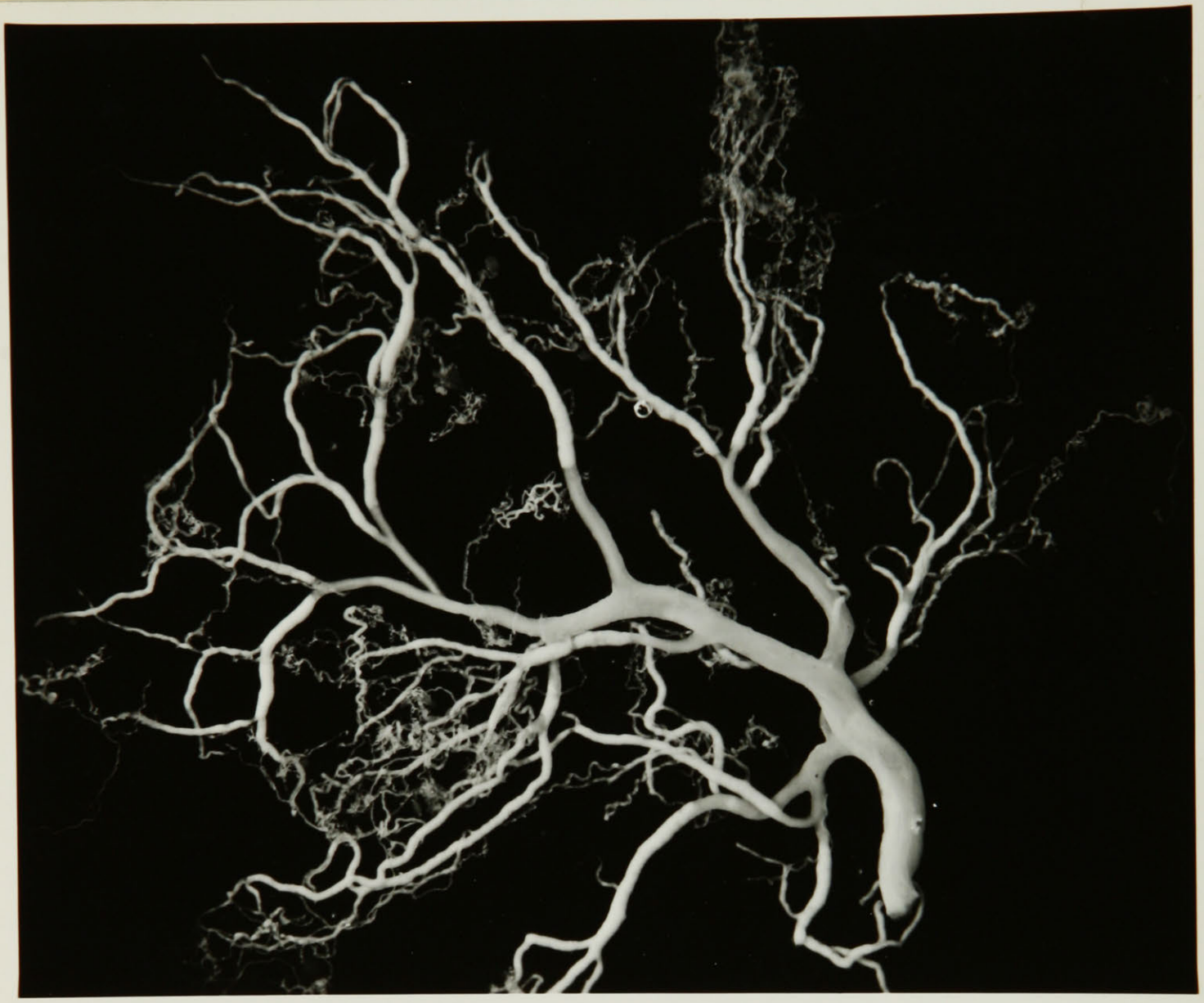


Fig. 42C (A-10857). This is a photograph of a neoprene cast from the opposite kidney of the case shown in Fig. 42A . This shows particularly well direct vessels to the cortical capillary plexus arising from all levels of the interlobular arteries. The lack of injection of more glomeruli does not mean that these arterioles were cut off completely from their blood supply. It only admits of severe obstruction of their afferent arterioles.

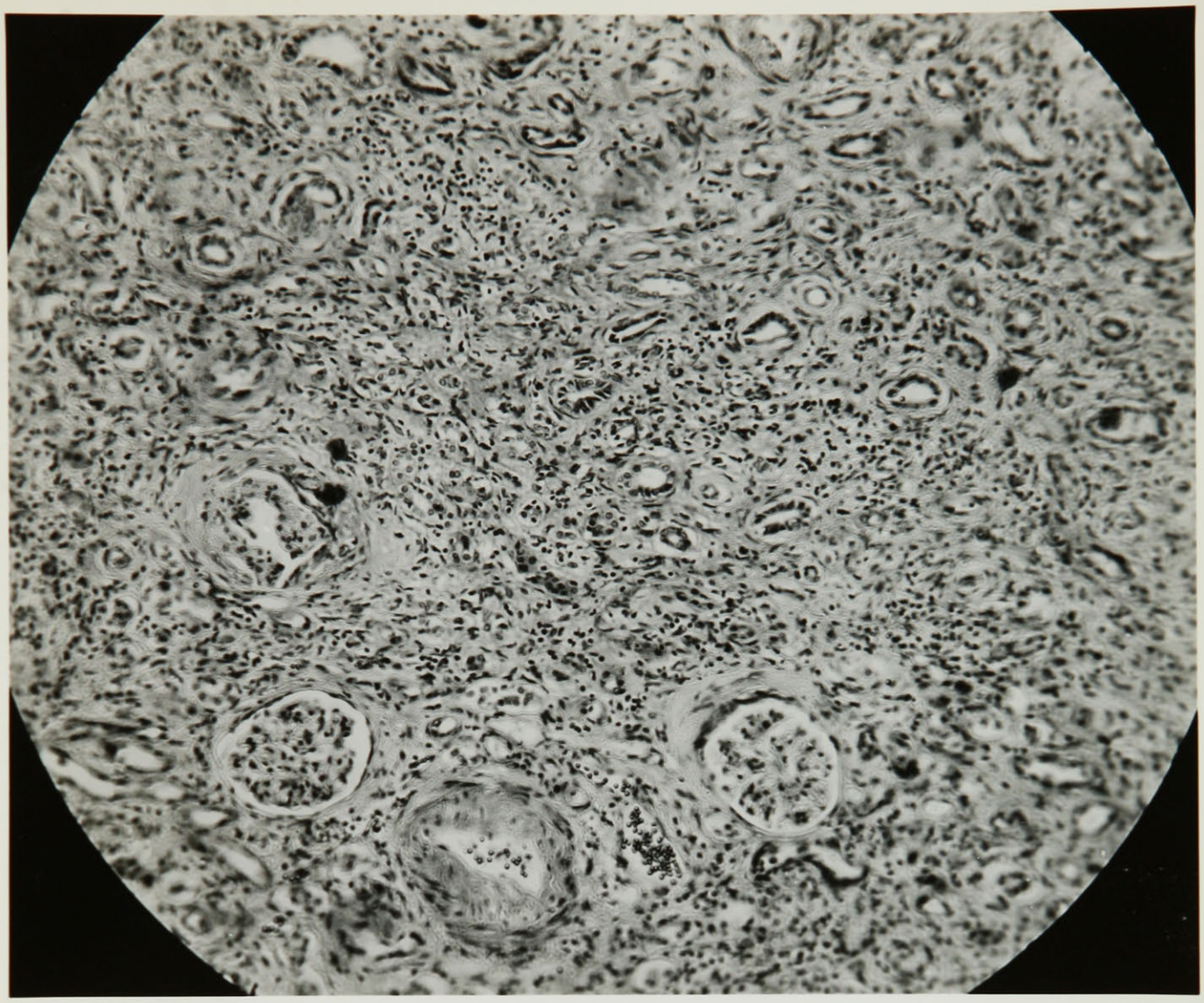


Fig. 43A (A-11239). Photomicrograph of a kidney from a man age 52, suffering from chronic pyelonephritis confirmed at autopsy. Note the loss of glomeruli, tubular atrophy and the marked interstitial proliferation.

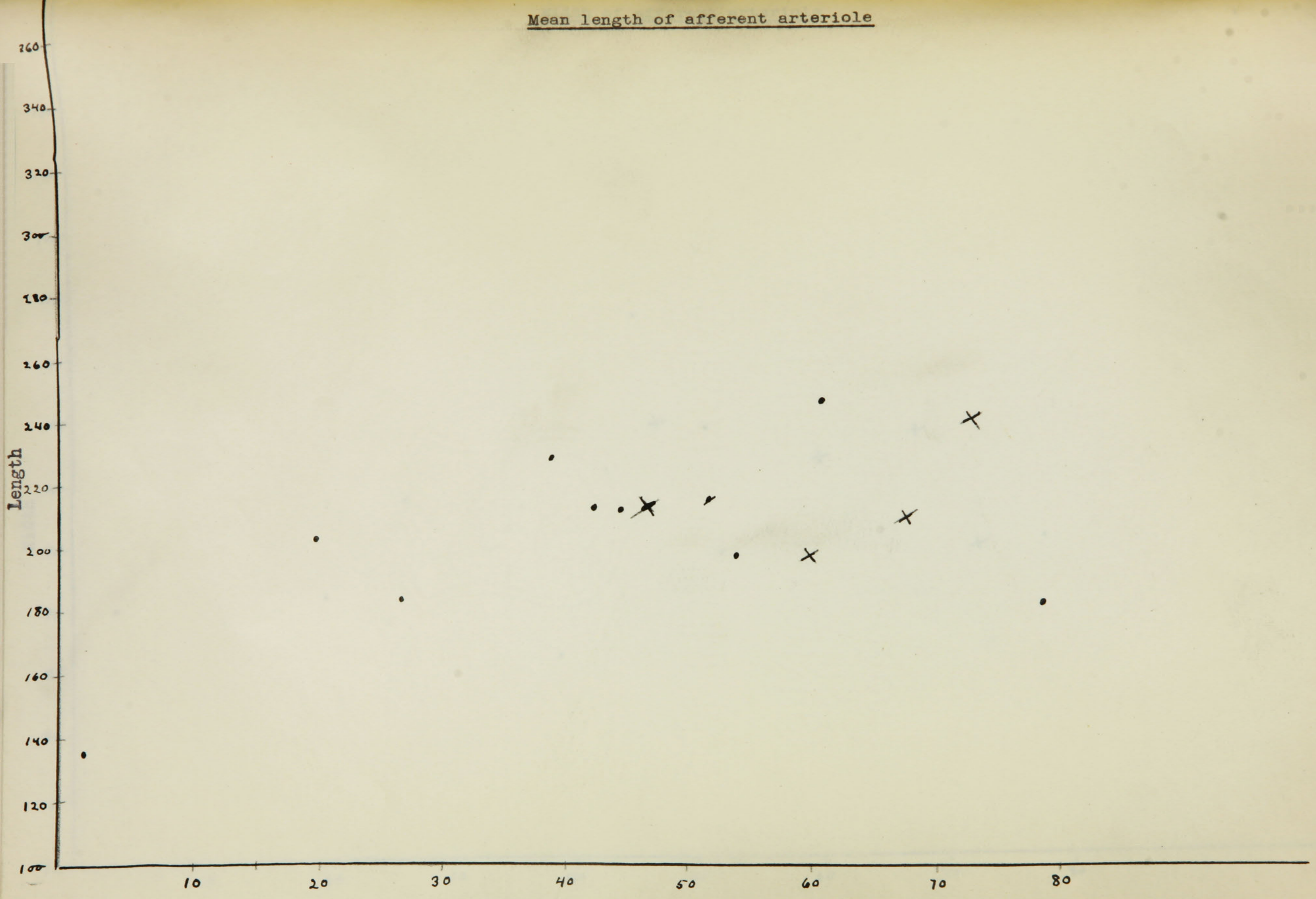
Fig. 43B (A-11239). Photograph of a neoprene cast of a kidney from a man, age 52, blood pressure 220/95. At autopsy there was found prostatic obstruction, chronic pyelonephritis; heart weight 450 grams. There is a beaded and tortuous appearance to the interlobular arteries. Some afferent arterioles are injected which fail to end in glomeruli. Many glomeruli are lost and those present simplified to a few coarse loops or stems.

Fig. 44 (A-11330). Photograph of neoprene cast of a kidney from a female, age 14. Clinical lipoid nephrosis confirmed at autopsy. Note the interlobular arteries and afferent arterioles are fairly even in contour. The glomeruli injected are coarse and decreased in number.

Fig. 45. Photograph of a neoprene cast from a boy age 7 suffering from amyloidosis. The histological section shows all of the glomeruli nearly filled with amyloid deposit. Note the normal contour of the interlobular arteries. Many afferent arterioles are injected but fail in almost every instance to reach the glomeruli.

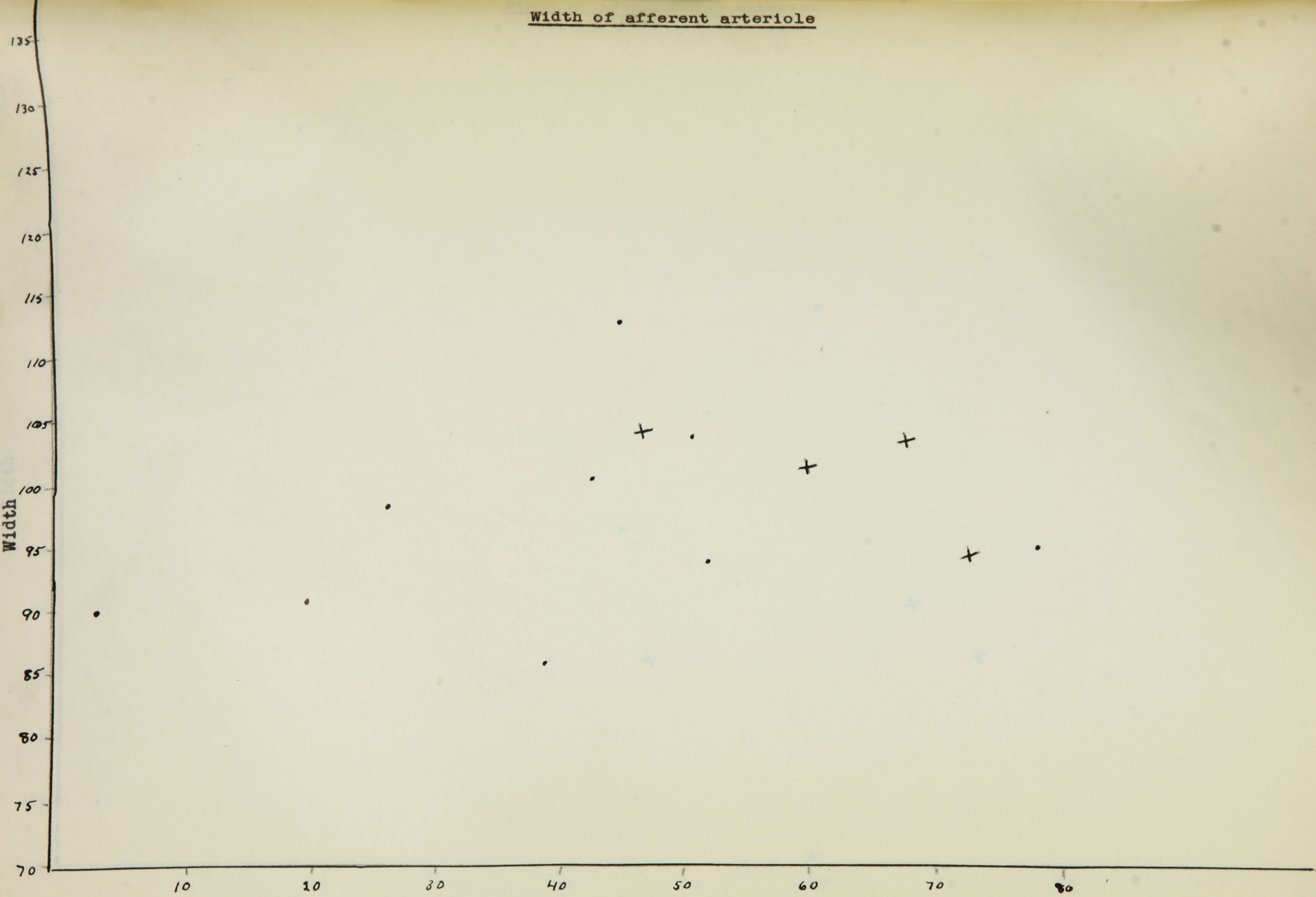
Fig. 46 (A-11388). Photograph of neoprene cast of a kidney from a male, age 73, B.P. 200/90, heart weight 635 grams. The interlobular arteries appear normal and present a smooth contour. There is a loss of glomeruli from the larger parts of the interlobular arteries, but occasionally a short stem of an afferent arteriole can be seen arising in these areas. The afferent arterioles situated near the ends of the interlobular arteries are long and tortuous. Many of the glomeruli are simplified in appearance.

Mean length of afferent arteriole



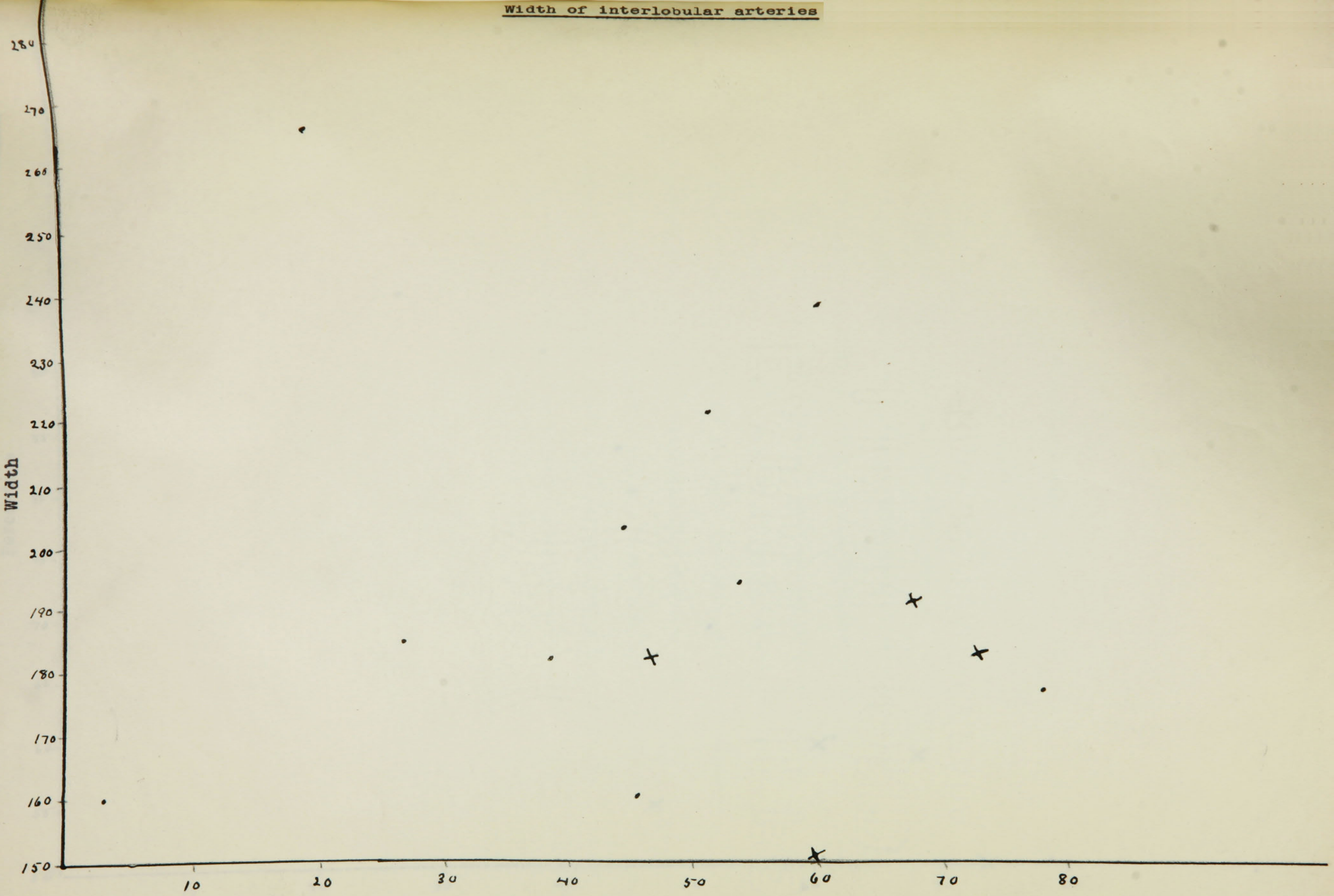
. Normal kidney
x Hypertensive kidney

Width of afferent arteriole



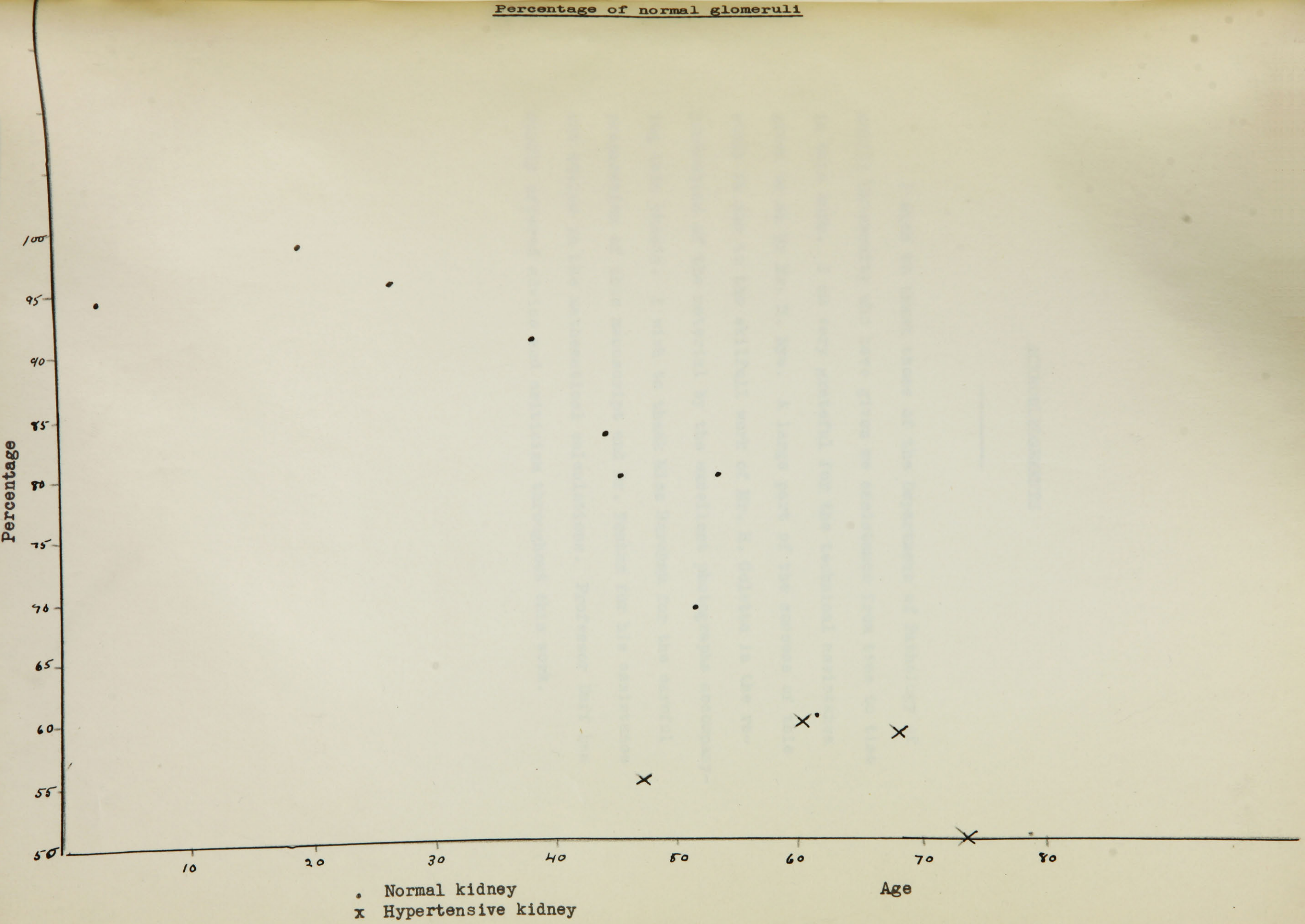
. Normal kidney
x Hypertensive kidney

Width of interlobular arteries



• Normal kidney
x Hypertensive kidney

Percentage of normal glomeruli



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Part VI

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