HISTOLOGIC STUDIES OF KIDNEY BIOPSY SPECIMENS FROM PATIENTS WITH HYPERTENSION*

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In the past 20 years, since the study of Moritz and Oldt[1] concerning pathologic changes in arterioles and their relation to hypertension, the majority opinion has shifted. It was found in their necropsied cases that arterioles in hypertensive patients showed 3 chronic lesions: intimal hyalinization; medial hypertrophy and degeneration; and intimal proliferation. Taking into account clinical and experimental evidence, including that of Goldblatt,[2] Moritz and Oldt concluded that arteriolar sclerosis was more likely the cause than the effect of high blood pressure. To the contrary, necropsy studies in this period by Kimmelstiel and Wilson,[3] and Williams and Harrison[4] were thought to favor the concept of hypertension as a cause of arteriolar sclerosis. Since that time most investigators have supported the latter theory.

Ellis[5] and later Wilson[6] considered that human and animal hypertension of the Goldblatt type constituted a vicious cycle, beginning with hypertension, and through renal ischemic damage resulting in further hypertension. The reviews of renal biopsy specimens from patients with hypertension by Castleman and Smithwick[7,8] indicated that 4.2 to 7 per cent of cases had no evidence of arteriolar disease. Their material appeared to show that in some cases the hypertensive state might precede the development of renal vascular lesions; the latter could not, therefore, be considered the cause of essential hypertension. Heptinstall's renal biopsy studies[9] supported this belief, and J. P. Smith[10] from an analysis of renal arterioles at necropsy concluded that arteriolar sclerosis was aggravated by, but was not the cause of, benign essential hypertension. Findley[11] reflected that in hypertension all roads somehow returned to the kidney. He thought that a tubular enzymatic defect might be responsible for essential hypertension. In an editorial, Wakerlin[12] pointed out that in the development of human hypertension, physiologic disorders, either nervous, humoral, or both, were considered at present to be the most significant factors.

The availability of a relatively large number of kidney biopsy speci-

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mens removed during sympathectomy operations at the Massachusetts Memorial Hospitals in the 10-year period 1946 to 1955 has stimulated a review study of the morphologic and histochemical alterations of renal tissue removed from living persons with high blood pressure.

Surgical Materials and Methods

All microscopic sections of surgical kidney specimens filed in the Pathology Laboratory, Massachusetts Memorial Hospitals, during the 10-year period 1946 through 1955 were re-examined as unknowns. The material included 1,882 renal biopsy sections and 271 nephrectomy specimens. The histologic data recorded included descriptions of the glomeruli, juxtaglomerular apparatuses, tubules, stroma and blood vessels. Among the 30 or 40 glomeruli usually available in each section, 15 were individually assayed for hyalinization or other alterations. The tissues later found to have been removed for conditions unrelated to sympathectomy or other operations performed for hypertension were excluded from the study.

There remained available for further analysis 1,766 renal biopsy sections from 1,350 patients. In 940 cases single specimens had been removed, and in 410, renal biopsy had been bilateral. Six persons had had 3 biopsy procedures. Most operations had been performed by one of us (RHS) or his associates. A biconvex piece of kidney cortex, approximately 0.6 to 1.0 by 0.5 by 0.4 cm. was removed and fixed immediately in Zenker's solution in the operating room. During the last 18 months some specimens were divided, and portions were frozen-dried and embedded in paraffin or carbowax for special studies.

Slides already available had been stained with hematoxylin and eosin, Mallory's aniline blue, Lee-Brown connective tissue, silver reticulin, and Verhoeff's elastic tissue stains. Slides were also stained with the periodic acid-Schiff (PAS), PAS-Alcian blue and aldehyde fuchsin-PAS methods. Histochemical and ultraviolet microscopic studies are to be reported elsewhere.

A grade reflecting the degree of thickening or sclerosis of the small arterioles, chiefly those afferent to glomeruli, was established for each specimen. The grade represented the average severity of arteriolosclerosis for the specimen, an approximation, in view of the focal nature of the milder blood vessel changes. A grading of "negative" (grade 0) indicated unaltered arterioles; "grade I" represented arterioles with minor localized thickenings; "grade II," vessels, the thickened walls of which approximately equalled the lumen diameters; and "grade III" designated arterioles with wall thickness exceeding the diameter of the lumen. The presence of focal or diffuse vascular necrosis was separate-

ly noted. The classification used was comparable to that of Castleman and Smithwick,[7] except that their "grade IV" was included in the present "grade III."

When the biopsy gradings were indexed in relation to the patients from whom the specimens had been procured, some cases with specimens from both kidneys were found to have different grades of arteriolosclerosis in each. In 60 per cent of the cases the same grade was found bilaterally. The cases with dissimilar grades were tabulated in intermediate groups. To test the reproducibility of the grading method, 200 consecutive specimens were re-examined as unknowns. The grade was identical in 87 per cent of these. In 200 instances, grades assigned in the present study were compared with the original diagnoses made by other pathologists, and agreement was found in 80 per cent, indicating a reasonable degree of objectivity.

Results

For convenience, the various microscopic observations are considered and tabulated in relation to the grades of vascular alteration. It appears to be generally accepted that more severe and advanced examples of clinical hypertension are accompanied by more pronounced arteriolar nephrosclerosis.[10,12] Bearing in mind that the renal biopsy samples consisted of cortex, usually without any medulla or any medium-sized arteries, the changes found would necessarily be those that were both diffuse and located in the outer renal cortical zone. The grading for the entire group is shown in Table I.

Table I

Grades of Arteriolar Sclerosis in 1,350 Persons with Hypertension Based on Kidney Biopsy Specimens

Grades	Cases*
Negative	14
Negative–Grade I	7
Grade I	274
Grade I–II	118
Grade II	849
Grade II–III	34
Grade III†	50
Total	1,346

*Also 1 case with both negative and grade II, and 3 cases with both grade I and III arteriolar sclerosis.

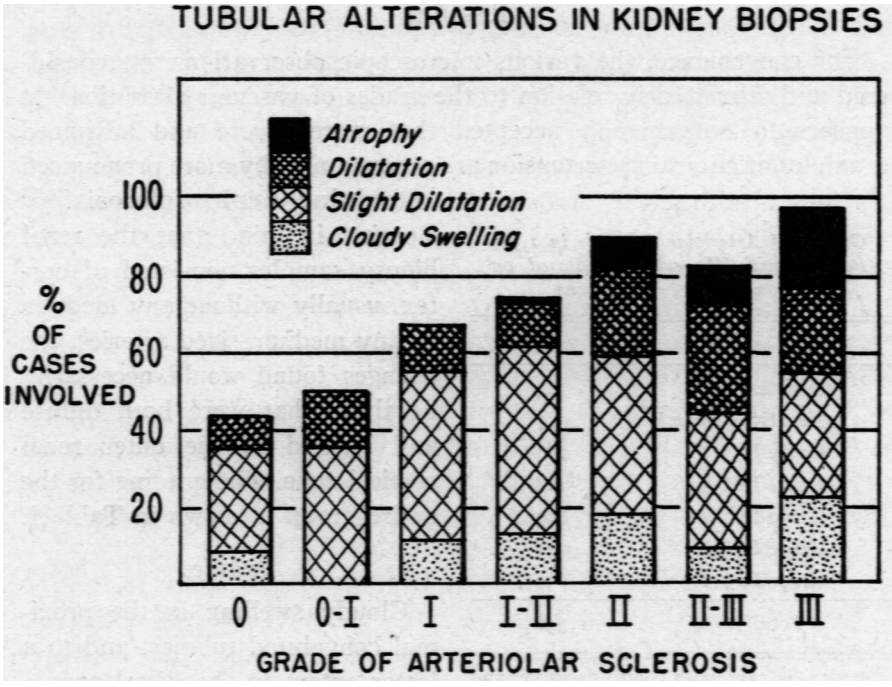
†Includes 9 cases with diffuse vascular necrosis.

Tubules

Cloudy swelling in the proximal convoluted tubules, and to a lesser extent in the distal convoluted tubules, occurred in from 7 to 22 per cent of the cases, more frequently with the higher grades of arteriolar sclerosis. The convoluted tubular epithelial cytoplasm bulged irregularly and excessively, and contained numerous, fine, distinct, or blurred basophilic granules.[7] In view of the practice of immediate fixation and the excellent histologic detail otherwise present, this

relatively minor variation was thought to be worthy of attention. It was analogous to, and could be equated with, the reversible mitochondrial fragmentation reported by Emmel[14] to occur in cells of the convoluted renal tubules of rats after 6 minutes or more of renal ischemia (Fig. 1).

Slight dilatation of the proximal convoluted tubules, characterized by both an enlargement of the lumen and a decreased height of the epithelium, was described by Shorr[15] in renal tissue procured from persons with hypertension. In the present series it occurred in over one third of the cases, with relatively equal frequency in all vascular grades (Fig. 2). Histochemical study of the tubular epithelial cytoplasm also has been reported to show an abnormally coarse staining reaction for succinic dehydrogenase, an oxidation-reduction enzyme.[15] Fajers[16] encountered a comparable microscopic lesion in the proximal



Text-figure 1. Relations between the degenerative changes of convoluted kidney tubules and the grades of arteriolar sclerosis are indicated. The percentages refer to the patients with hypertension affected, not to the number of individual biopsy specimens.

convoluted tubular epithelium of rabbits after 10 minutes of renal ischemia produced by ligature. A mild dilatation of the proximal convoluted tubules appeared to be a more extreme stage of the same general nature as cloudy swelling; the summation of these changes is shown in Text-figure 1. Strikingly dilated tubules with more rounded contours and definitely flattened epithelium, particularly of the proxi-

mal convoluted segments, were present in some of the cases. Atrophy of tubules represented further evidence of tubular retrogression.

As noted in Text-figure 1, these degenerative tubular lesions appeared in 50 per cent of the cases in the "negative-grade I group," and in 97 per cent of the grade III group. In all degrees of arteriolar sclerosis, tubular degeneration was the most frequent parenchymal lesion observed. This also constituted the earliest recognizable renal abnormality accompanying hypertension. The tubular lesions accompanying pyelonephritis were distinguished by the presence of ordinary inflammatory and reparative processes.

Interstitial Tissue

The normally inconspicuous renal stroma was infiltrated by collections of lymphocytes in approximately 20 per cent of the renal biopsy specimens obtained from "negative" and grade I groups, and in over half the specimens from the more advanced grades of vascular disease (Fig. 3). Unaccompanied as they were by plasma cells or other stigmas of inflammation, the lymphocytic foci were regarded as concomitants of renal atrophy and degeneration. In the kidney as well as in other organs, lymphocytes have been found collected at sites of basement membrane dissolution.[17] Oliver[18] and numerous other authors have emphasized the damaging effect of ischemia upon renal tubular basement membranes (Fig. 4).

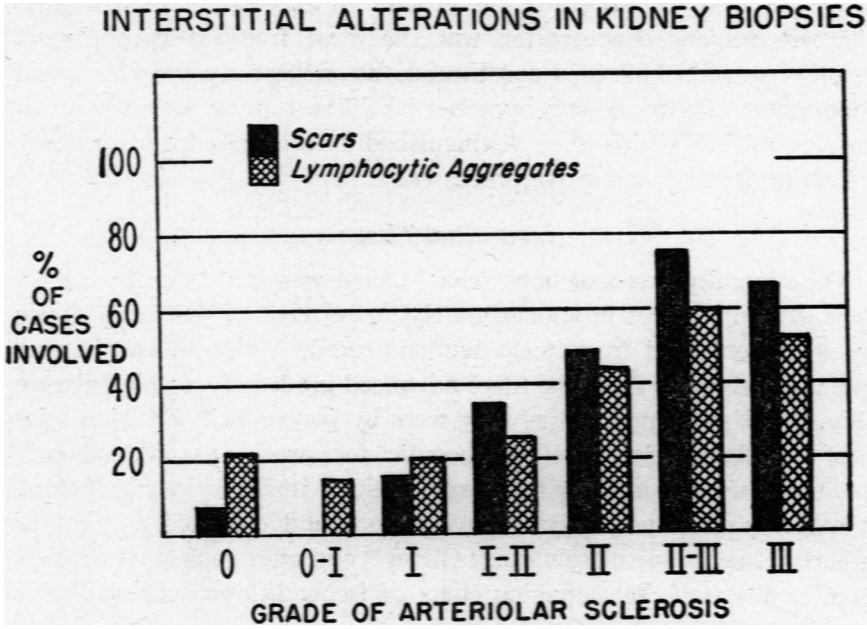
Finely pitted cortical surfaces reflect the scarring of kidneys in individuals with hypertension. Microscopically, scars with or without lymphocytic infiltration were observed in up to 74 per cent of cases with the higher grades of vascular alteration (Fig. 5). The majority of microscopic scars occurred in kidneys without other indications of inflammation; these were thought to represent reparative reactions at sites of localized atrophy and disappearance of cortical tubules[5,19] (Text-fig. 2).

Glomeruli

Most sections from the cases with less severe grades of arteriolosclerosis showed no obvious alterations of glomeruli. The earliest structural alteration identified consisted of a slight irregular stiffening of the glomerular capillary walls, due to focal thickening of the basement membrane by fibrillar acidophilic material. The glomerular loops became more obvious than normal, with an apparent simplification of the usual capillary tortuosities. Some loops sagged slightly, and in more advanced examples the entire glomerulus appeared wilted (Fig. 6). McGregor[20] and McManus[21] and others[22] have described this change in both necropsy and biopsy material.

Specimens from the group of kidneys without arteriolar sclerosis

were submitted to Dr. J. F. A. McManus for histochemical study. He found histochemical indications of glomerular ischemia even in such cases.[23] The more obvious glomerular changes have long been regarded as secondary to the establishment of arteriolar sclerosis and to



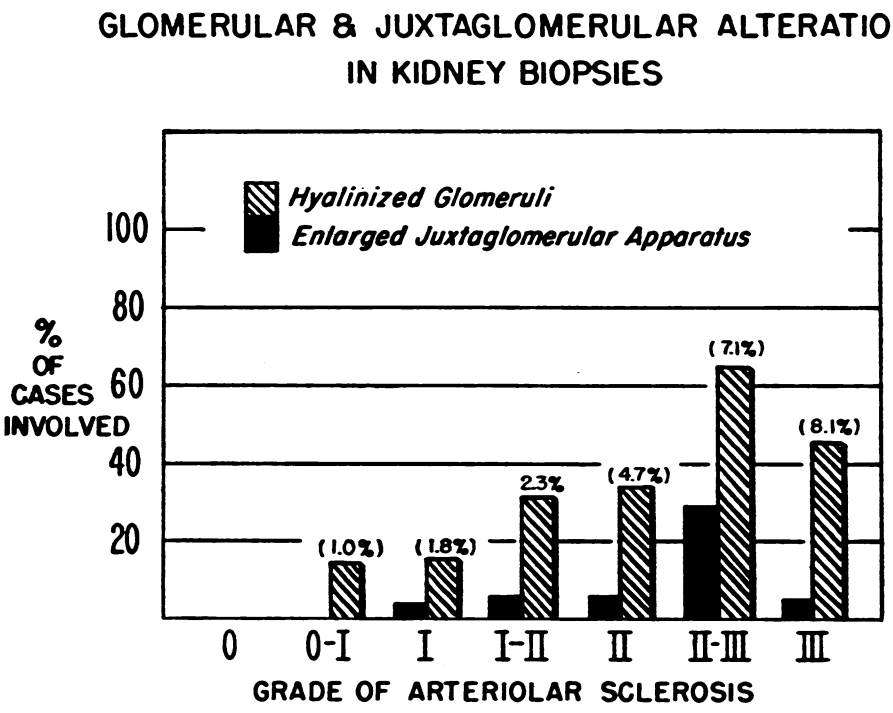
Text-figure 2. Percentages of patients with hypertension who had renal scarring or lymphocytic infiltrations in kidney biopsy specimens. Arranged according to the grades of arteriolar nephrosclerosis.

attendant mild local ischemic atrophy.[20,24,25] Hyalinized glomeruli, the end result of such regressive changes, were found more frequently in association with advanced arteriolar sclerosis. In two thirds of the patients with severe arteriolar sclerosis, there were hyalinized glomeruli, but it was estimated that only about 8 per cent of the glomeruli counted were completely hyalinized (Text-fig. 3).

Enlargement of cells with cytoplasmic vacuolization was the only alteration recognized in the juxtaglomerular apparatuses of Goormaghtigh. This occurred in from 3 to 29 per cent of cases, most commonly in the transitional grade II-III group.[26] Vacuolization was not so common in less advanced cases, and was regarded as a likely secondary manifestation of the more extreme degrees of local ischemia (Fig. 7).

Becher cells appeared as rounded groups of clear cuboidal epithelium, forming small tubules which seemed to sprout as diverticula from degenerated distal convoluted segments.[27] They were not observed except in scarred regions. These cells have been considered to

be related functionally to the juxtaglomerular apparatus. However, their presence was uncommon in the biopsy material examined. *Becher cells* occurred in 0, 0, 1.1, 2.5, 2.4, 3, and 0 per cent of cases respectively in the 7 groups of arteriolar sclerosis analyzed. The tubular buds in



Text-figure 3. The percentages of patients whose renal specimens included some completely hyalinized glomeruli and the presence of juxtaglomerular cell enlargements are shown. These are grouped according to the different grades of arteriolar sclerosis. The figures in parentheses are the percentages of completely hyalinized glomeruli in the total number of glomeruli counted.

scars were thought to represent merely localized epithelial regenerations in the distal nephrons, infrequent and of doubtful functional importance (Fig. 8).

Arterioles

Spasm of morphologically unaltered afferent arterioles, found in all but one specimen of the grade 0 group, was inferred from an abnormal concentric overlapping of the otherwise normal appearing smooth muscle cells that composed their walls (Fig. 9). Spasm was observed only once in a control series of 12 kidney biopsy specimens removed for diagnostic purposes from normotensive individuals. Artifact could not be excluded; on the other hand, spasm has not been seen commonly in the arterioles of other rapidly fixed human tissue, such as that removed for cervical biopsy.

Structural change in the afferent arterioles was first evident as a thickening of the wall due to swelling of the muscle cytoplasm; this stained very little with any method except for scattered PAS-positive granules. The hydropic alteration, or intracellular edema, of the smallest arterioles was diffuse, uniform, and characteristic of the degree of vascular thickening termed grade I. There was also a bulging of endothelial nuclei into the narrowed lumen and an irregular swelling or thickening of the PAS-positive component of the internal elastic membranes of afferent arterioles (Figs. 10 and 11).

Larger arterioles in grade I tissues were usually rather dilated, with a stretching of the elastic tissue into a smooth circle, and without the uniform hydropic change of muscle cells seen regularly in the smaller arterioles (Fig. 12). Focal thickening of the PAS-positive component of the elastica was found, apparently as a result of swelling of the elastic network and an increase in its matrix. True hypertrophy or proliferation of the elastic fibers[1] was not clearly demonstrable at any stage of arteriolar sclerosis.

With moderate thickening of small arterioles, grade II arteriolar sclerosis, a hydropic change was not prominent, while an overgrowth of smooth muscle cells became evident (Figs. 13 and 14). This hypertrophy was characterized by an excessively thick layering of individual muscle cells in concentric laminar manner, with an abundant cytoplasm stained red with the Masson-Goldner trichrome stain. Between muscle cells a prominent network of PAS-positive material often appeared. The internal elastic membrane was irregularly widened, sometimes with homogeneous nodules of PAS-positive material bulging outward. At this stage the vascular alterations in different cases, or in different microscopic fields in the same case, or along the same vessel, were much less uniform than in grade I arteriolar sclerosis. Hypertrophy of small arterioles characterized occasional specimens, while in others a swelling, nodularity and irregular PAS-staining of the internal elastic membranes and a deposition of PAS-positive material between muscle cells prevailed. In still other cases hydropic swelling, pooling of ground substance, and early indications of collagen formation were more evident in arterioles (Figs. 15 and 16).

Larger arterioles more closely mirrored the small arteriole changes in grade II sclerosis. There was an irregular but generalized thickening of the elastica by PAS-positive material, with focal nodules bulging outward. Hypertrophy of muscle cells was asymmetrical and rather irregular in location and extent. The lumens were irregularly and eccentrically narrowed.

In the grade III group the alterations became still less uniform, both

in smaller and larger arterioles. Degenerative changes predominated. The elastic tissue was no longer so clearly manifest, and, focally, a major component of the vessel wall appeared to be a pooled ground substance inundating an irregular feltwork composed of the fibrillar remnants of elastic tissue and muscle (Figs. 17 and 18). Fibrin seemed to penetrate into some vessel walls in small amounts. Collagen fibers were rarely detected in small arterioles stained by the Masson-Goldner technique. Lumens were irregularly and focally narrowed to a marked degree or were completely closed by relatively amorphous material largely composed of pooled ground substance mixed with autolyzed tissue and intercellular fluid or plasma components.

Changes were more varied in the larger arterioles. Extreme degeneration of the elastica was evident. This was characterized by thick lumps or heavy strands of an irregularly stained PAS-positive material which bulged into the lumen or outward. There was localized splitting of the elastic membrane with lacuna formation or apparent reduplication. A coarse, intercellular, PAS-positive network was usually present through the entire thickness of the affected arteriole. Endothelial and subendothelial proliferation of the type seen in endarteritis obliterans or organized thrombosis was only occasionally present in a very localized form. The large arteriolar lumens varied markedly in diameter along their courses; there were both dilatation and extreme narrowing (Figs. 19 and 20). The formation of subendothelial foam cell aggregates (atheromas) and the presence of excessive lipid[1,28] did not characterize the material studied and, in fact, were uncommon at any stage. Vascular calcification was also quite rare.

Collagen deposition in larger arterioles was found regularly in the grade III group. It was evident with the Masson-Goldner trichrome stain as a faint green network surrounded by the excessive PAS-stained ground substance. When more abundant collagen was present, it formed a layer in the midportion of the arteriolar wall, or was irregularly disposed and constituted most of the wall at some points, or made up the periphery of a vessel wall composed internally of mixed ground substance, degenerated muscle and elastic tissue. The participation of fibroblastic ingrowth was not apparent. Ultimately the collagen lost its fibrillar appearance and underwent hyaline degeneration.

Fibrinoid necrosis at any stage of arteriolar sclerosis was marked by a smudging of arteriolar wall outline and a replacement of living tissue by a fibrillar material, staining much like the fibrin in intravascular clots. The walls of affected vessels were composed chiefly of pooled ground substance, degenerated elastic tissue, and shrunken or compressed muscle cells. The fibrinoid lay in irregular intramural

masses, merging with the PAS-positive lumps and networks of pooled ground substance without regard to cell boundaries (Figs. 21 and 22). Deposition of fibrin was believed to have followed imbibition of plasma into the vessel wall, with subsequent degeneration.[29]

Venous dilatation of stellate and small interlobular venules was a regular finding in earlier stages of arteriolar sclerosis during which the efferent arterioles showed no abnormality. The explanation for the venous congestion was not evident in the cortical biopsy material, but the appearance suggested some factor encouraging splanchnic venous engorgement or possible interference with venous return deeper in the kidney. Sphincter-like activity of muscular veins at the kidney hilus appeared to be one possible explanation.[30]

Pyelonephritis

Evidences of chronic inflammation, in the form of plasma cell infiltration of interstitial tissue, dilated tubules containing colloid casts, and scars compressing atrophic tubules, were present in a minority of the specimens (13.5 per cent). Occasionally neutrophils within tubules indicated an acute exacerbation, or eosinophils mixed with other leukocytes in interstitial connective tissue pointed to a subacute inflammation accompanying chronic pyelonephritis. Healed pyelonephritis was characterized by the presence of typical dilated tubules with colloid

TABLE II

Diagnosis of Pyelonephritis in Renal Biopsy Specimens from Patients with Hypertension

Vascular grade	Percentages of cases in which pyelonephritis was observed		
	Single specimen	One of bilateral specimens	Both of bilateral specimens
Negative	14%		
Negative–Grade I		0%	0%
Grade I	5.3%	2%	2%
Grade I–II		11%	1%
Grade II	15.5%	14%	4%
Grade II–III		12%	9%
Grade III	12%	0%	0%
Totals	12.9%	11.8%	3.2%

casts simulating thyroid follicles, and scars containing atrophic tubules but without plasma cells among the interstitial lymphocytic aggregates (Figs. 23 and 24).[31,32]

As noted by Heptinstall,[9] small fragments of kidney cortex are not reliable means of recognizing pyelonephritis. In Table II are listed the percentages of cases in the various groups which were diagnosed as

pyelonephritis. Kimmelstiel and Wilson,[33] and Weiss and Parker,[34] using necropsy material, have shown that hypertension is associated with pyelonephritis in only 15 to 20 per cent of cases; these figures are comparable to the 13.5 per cent overall incidence found in the present series. Neither these necropsy studies nor the present biopsy investigations provide sufficient data to establish an accurate estimate of the real incidence of pyelonephritis in hypertension.

Unusual Observations

Unilateral renal ischemia, and a disproportionate development of arteriolar sclerosis, associated with a hypertension of the Goldblatt type, was rarely encountered. In only 2 of the 4 cases with differences of 2 grades between the degrees of arteriolar sclerosis found in bilateral renal biopsy specimens were the clinical records at least consistent with the existence of the Goldblatt phenomenon.[35] Review of the clinical records of all patients from whom negative kidney biopsy specimens were procured revealed no evidence of unilateral renal disease.[36] As a group, their hypertension was characterized clinically by a reversion to normal levels after bed rest.

A pheochromocytoma was removed at operation for hypertension in each of 13 cases during the period 1946 to 1955. Renal biopsy specimens were available from 9 cases, and in 2 there were serial biopsies. A 22-year-old man had grade I arteriolar sclerosis at the time the adrenal tumor was removed. Blood pressure preoperatively ranged between 180/115 and 240/150. There were focal thickenings of glomerular basement membranes and capillary endothelial hyperplasia; elsewhere glomerular capillaries were dilated in a focal manner. Pooled PAS-positive material of hyaline type was found in arteriolar walls and adventitia; basement membrane thickenings appeared in neighboring renal tubules (Fig. 25). Postoperatively the patient became normotensive and remained so. Six years later, at the time of cholecystectomy, a second biopsy showed that the irregular thickening of glomerular basement membranes was more pronounced. No definite arteriolar sclerosis was identified (Fig. 26). Two of 72 glomeruli counted were hyalinized. No other abnormalities were seen.

A man 21 years old had a sympathectomy, which revealed neurofibromatous malformations of the nerves and ganglia.[37] Severe hypertension persisted until almost 8 years later, when a pheochromocytoma was removed. Kidney biopsy at sympathectomy demonstrated multifocal thickenings of the glomerular basement membranes. This was associated with localized endothelial hyperplasia and dilatation of the capillaries near the glomerular roots. Arterioles exhibited grade I

sclerosis with some increase in PAS-positive material in the adventitia. The biopsy specimen taken at the time of the operation for pheochromocytoma showed grade II arteriolar nephrosclerosis, with increased amounts of PAS-positive hyalin in both arterioles and arteries. Glomeruli manifested more extensive ischemic alteration, and there were interstitial scars with compression of some tubules.

Four specimens, which on retrospective review showed some convoluted tubular vacuolization of the type since recognized as accompanying potassium depletion,[38] might possibly have resulted from primary aldosteronism. In one case a 1 cm. adrenal cortical adenoma was removed at operation. No data on potassium balance were available, but preoperatively this patient had a dilute, persistently alkaline urine which might have been due to aldosteronism. Postoperatively her condition was greatly improved. No evidence suggestive of aldosteronism was noted in the other 3 patients. Another patient, proved to have aldosteronism but encountered since this study was completed, had been treated preoperatively to restore the potassium balance. In this case no unusual renal tubular changes were found microscopically in biopsy tissue. Absence of tubular vacuolization indicative of the hypokalemic state naturally does not exclude aldosteronism; hence no conclusions can be drawn from the present material concerning the incidence of this condition in hypertensive patients.

Glomerulonephritis was found in 7 cases; these included 4 with healed lesions, 2 of the membranous type, and one with focal lesions. One case of membranous glomerulonephritis with biopsy specimens from both kidneys also showed lesions of chronic pyelonephritis with grade I arteriolar sclerosis. The other patients all had grade II arteriolar sclerosis, suggesting that two separate disease processes had affected the kidney (Fig. 27). No instance of typical chronic proliferative glomerulonephritis was encountered. Nodular intercapillary glomerulosclerosis was observed once.

Hyaline droplet nephrosis[39] occurred occasionally as an incidental finding in 10 of the cases (0.25 per cent) with bilateral biopsy specimens. Interstitial collections of large foam cells, resembling in miniature the so-called xanthogranuloma of the kidney accompanying pyelonephritis, were observed in 2 cases (Fig. 28).[40] One other section showed nodular inflammatory infiltrations resembling the lesions of interstitial nephritis which accompanies some infections or allergic diseases.

Arteriosclerosis was recognized in 4 cases from the presence of small arteries with intimal degeneration and sclerosis. Their inclusion in the specimen indicated a chance occurrence or reflected atrophy of the renal cortex.

Discussion

Less than 2 per cent of patients with hypertension were found at sympathectomy to have either insignificant or no arteriolar abnormalities in kidney biopsy specimens. Although two thirds of the cases revealed advanced renal arteriolar sclerosis, the presence of even a few individuals with apparently normal renal vessels is consistent with the view that hypertension precedes structural changes in the kidney vasculature.[7,8] The present material is probably not representative of patients in the initial stages of hypertensive disease, and there is reason to believe that the incidence of normal renal biopsy material would be higher in earlier or milder hypertension.

This finding does not, of course, exonerate the kidney from a role in the pathogenesis of essential hypertension. Under resting conditions renal blood flow may be either normal or only slightly reduced,[41,42] but it is not unlikely that the postural and emotional stresses of daily life produce significant though transient periods of ischemia in patients with hypertension. Certainly, there is adequate experimental evidence to implicate alterations in renal blood supply in the pathogenesis of hypertension.

In the present study, the existence of what appears to be spasm in otherwise normal afferent arterioles, sometimes associated with cloudy swelling of the convoluted tubules, provides evidence suggestive of the role of renal ischemia in essential hypertension. Tubular cloudy swelling and dilatation of convoluted tubules as evidences of ischemia were found antecedent to any visible alterations of arterioles. Indications of the pernicious effects of more prolonged and persistent ischemia were found in the form of lymphocytic aggregations collected about irreversibly damaged tubular segments. Ultimately, collagenization and extensive glomerular hyalinization appeared.

Vascular abnormalities were at first characteristically localized and lacked uniformity. It was inferred that the sequence of events was: spastic arteriolar contraction, intramural vascular edema, muscular overgrowth, replacement of the degenerated muscle by pooled ground substance, and, ultimately, collagenization and hyalinization.

Elastic tissue is normally probably more important in the maintenance of a steady tone in arterioles than smooth muscle.[43] Changes observed in the subendothelial elastica were thought to indicate a spreading apart of its fiber network, resulting in an increased prominence of the mucoprotein PAS-positive matrix. Degeneration and disappearance of elastic tissue were accompanied by pooling of the ground substance and its permeation of adjacent intercellular spaces. Mechanical effects of local tissue pressure may account for the localization of this PAS-

material in certain zones of arteriole walls.[17] It was not clear that any hyperplasia of elastic fibers occurred. Collagen in arteriolosclerosis was rather sluggishly formed and focal in its deposition.

Fibrinoid was found either focally or diffusely in arteriolar walls. Since it was identifiable in all grades of arteriolar sclerosis from I through III, it appeared to be a fairly commonplace event accompanying hypertension. Accelerated arteriolar degeneration appeared to account best for the presence of this substance.[44-46] No special investigation of fibrinoid was made, but an imbibition of plasma into the arteriolar wall, precipitation of fibrin and its subsequent degeneration or eventual transformation into hyalin were thought to reflect exacerbations of the elevated blood pressure. The conclusions of Gitlin, Craig and Janeway[47] from studies of fibrinoid in other diseases were believed to have likely applicability to hypertension. Experimentally induced necrosis of arteriolar muscle may also apparently result in the appearance of fibrinoid.[48,49]

Except for arteriolar spastic contraction, and the subsequent chain of degenerative changes, there was no morphologic explanation for the renal ischemia found; larger blood vessels were not available for study. It is of interest that pathologists have concluded that ischemia rather than vascular occlusion is the central factor in the production of both the cerebral[50] and the myocardial damage[51] which constitute the two other major complications of hypertension. Indications point to the afferent arterioles as the sites of narrowings which are at first functional and later structural, but other mechanisms for renal ischemia must be considered. Whether venous stasis produced by muscular sphincters near the hilus or by other means may contribute to renal ischemia is beyond the scope of this study. Anatomic structures resembling sphincters exist; these become prominent after sympathomimetic stimulation and in certain instances of unilateral renal atrophy.[30] Further attention should be paid to venous stasis in hypertension, and to the role of renal phlebitis in perpetuating or exaggerating damage to nephrons in chronic pyelonephritis.

Some of the clinicopathologic correlations derived from this series of cases are reported elsewhere.[52,53] Statistically significantly elevated diastolic blood pressures were found in association with the more advanced grades of arteriolar sclerosis. The basis of this correlation is debatable. On the one hand, it is possible that the diastolic blood pressure level contributed to the degree of vascular thickening. On the other hand, it is conceivable that secondary vascular changes might tend to intensify pre-existing hypertension further. In the kidney such vascular changes may lead to the production of a pressor substance or

substances which could then initiate a vicious circle. Whatever the nature of the relationship between renal vascular lesions and the severity of hypertension, it is obviously not a precise one, since there were wide variations in local kidney alterations at most levels of blood pressure.

Arteriolar necrosis was not found to require any specific diastolic pressure level for its development. Nor did the presence of fibrinoid, either focal or diffuse, indicate a terminal state or an inevitably poor prognosis.[54,55] In the present material it was found that no correlation could be made between diffuse vascular necrosis and postoperative survival time.[52] Fibrinoid necrosis was judged to be simply an evidence of accelerated renal damage and was reasonably reversible after sympathectomy. The clinical state of malignant hypertension and the pathologic demonstration of arteriolar fibrinoid necrosis appeared related, but not equivalent.

Summary

Kidney biopsy specimens from 1,350 patients with hypertension who underwent sympathectomy were re-examined microscopically. The earliest parenchymal alterations observed were cloudy swelling, dilatation and atrophy of some convoluted tubules, and accompanying spasm of afferent arterioles. Significant arteriolosclerotic lesions characterized over two thirds of the cases. Subsequent to spastic arteriolar contraction, intramural edema and muscular hypertrophy were thought to occur. These, in time, were followed by arteriolar elastic tissue degeneration with pooling of its ground substance and, eventually, irregular collagen deposition and hyalinization in the afferent arterioles. Scars, lymphocytic aggregates in interstitial tissue, and slight or obvious glomerular alterations commonly accompanied the more advanced grades of arteriolosclerosis. Fibrinoid necrosis was observed in arterioles in all grades of arteriolosclerosis.

It is concluded that renal ischemia probably precedes detectable vascular abnormalities in essential hypertension. When structural alterations have developed in the arteriolar walls, secondary renal changes may serve to maintain or accelerate the hypertensive process.

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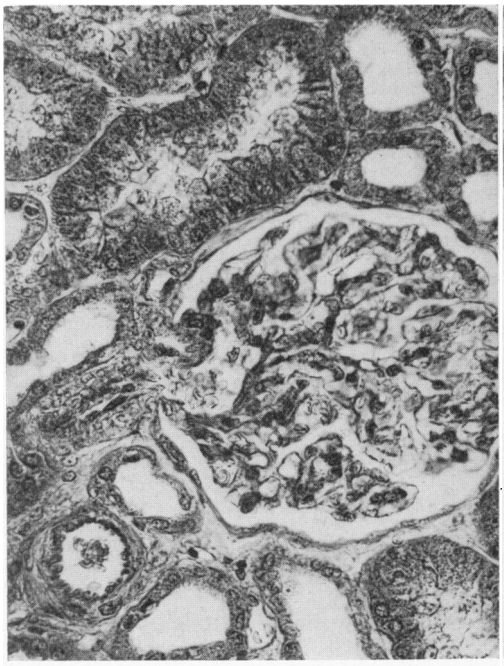
LEGENDS FOR FIGURES

FIG. 1. Renal biopsy with grade II arteriolosclerosis. There is cloudy swelling of convoluted tubular epithelium with cytoplasmic granularity. Of note is the dilated larger arteriole at lower left. Hematoxylin and eosin stain. × 225.

FIG. 2. Dilated convoluted tubules with cloudy swelling in a kidney with grade II arteriolosclerosis and diffuse fibrinoid necrosis. Tubular changes appear to represent a more severe degeneration of the same general type shown in Figure 1. Hematoxylin and eosin stain. × 180.

FIG. 3. Collections of lymphocytes in interstitial tissue from a case with moderate renal arteriolosclerosis (grade II). Thickened arterioles and slightly dilated convoluted tubules are also shown. Hematoxylin and eosin stain. × 120.

FIG. 4. Dissolution of renal tubular basement membranes, associated with an accumulation of lymphocytes, from a case with grade II arteriolosclerosis. Sulfuric acid hematoxylin stain. × 850.



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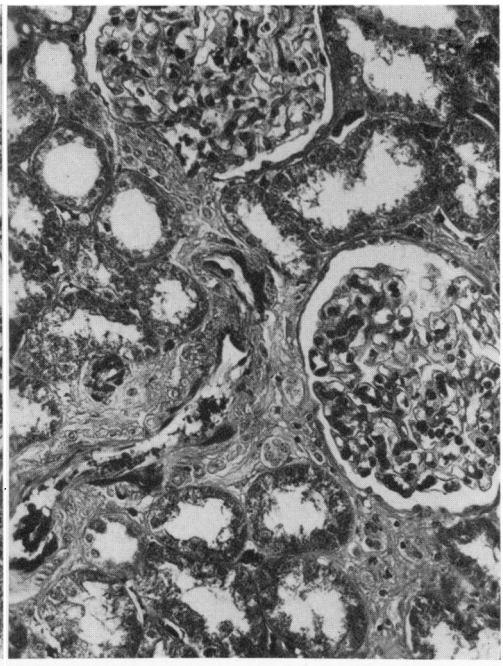

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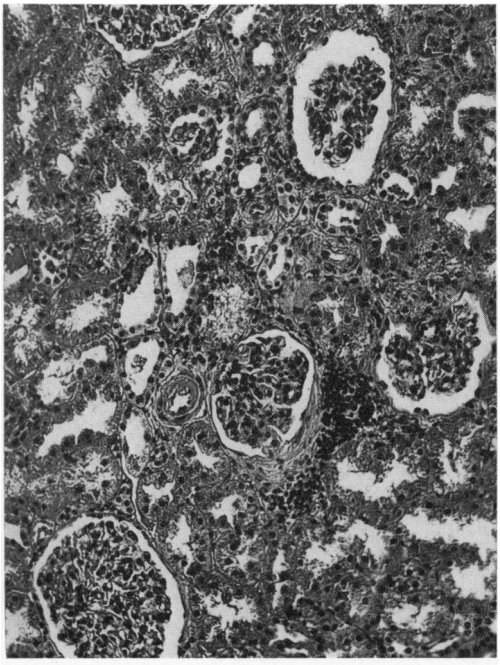

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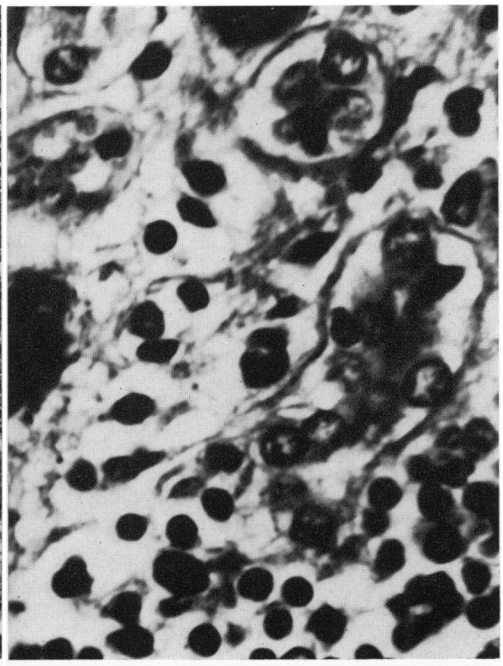

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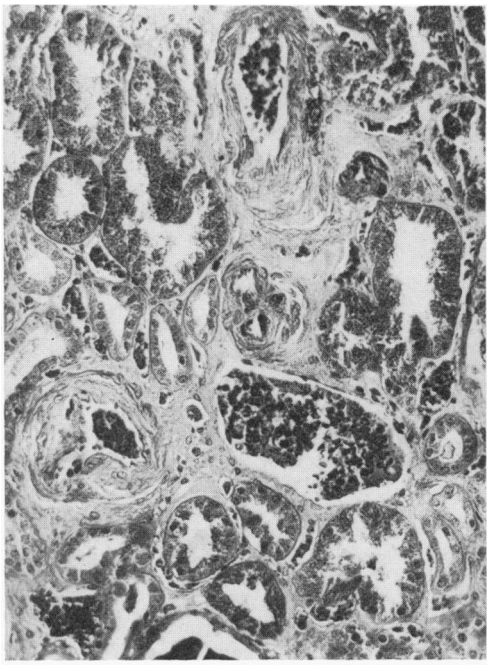
FIG. 5. Perivascular scars in a kidney biopsy with grade II arteriolosclerosis, showing moderate arteriolar thickening. Of note is the venous congestion. Hematoxylin and eosin stain. × 150.

FIG. 6. Slightly stiffened and thickened glomerular capillary walls, from a case with grade II arteriolosclerosis. Dilatation of a larger arteriole and vein are also shown. Verhoeff stain. × 180.

FIG. 7. Enlarged cells of the juxtaglomerular apparatus, with hydropic cytoplasm, in a kidney with grade I arteriolosclerosis. Verhoeff stain. × 300.

FIG. 8. Small groups of pale stained tubular cells, the so-called *Becher cells,* in a kidney with scars, cloudy swelling of convoluted tubules and grade II arteriolosclerosis. Phosphotungstic acid hematoxylin stain. × 150.



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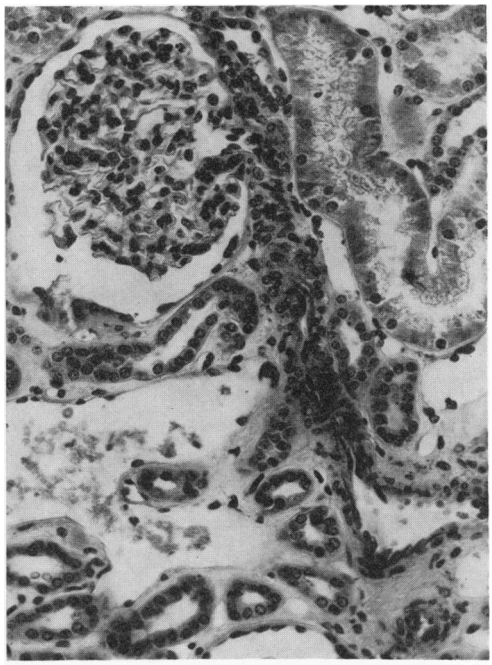

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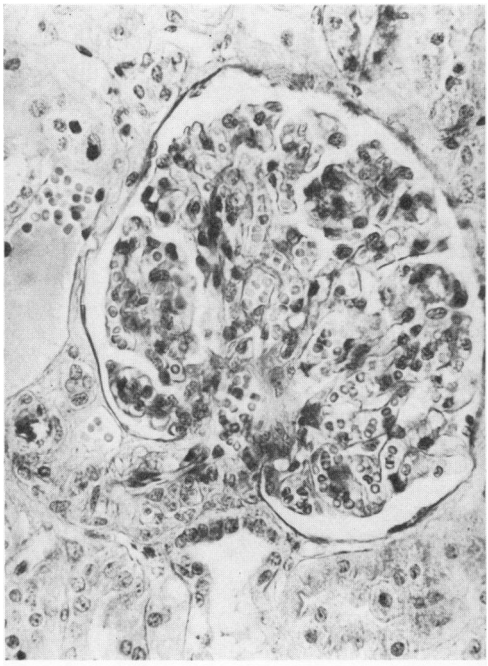

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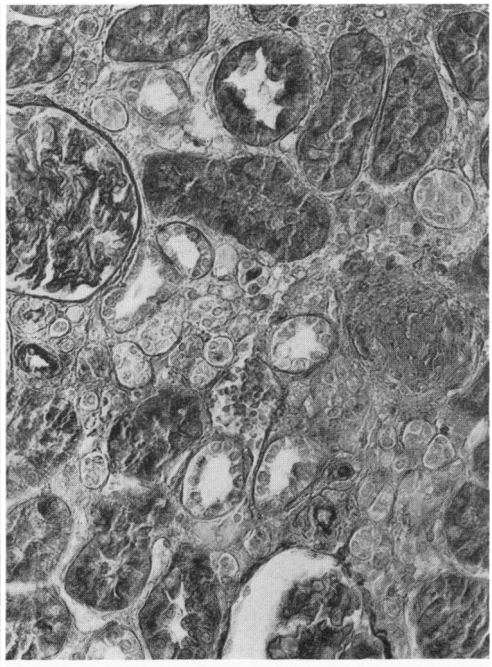

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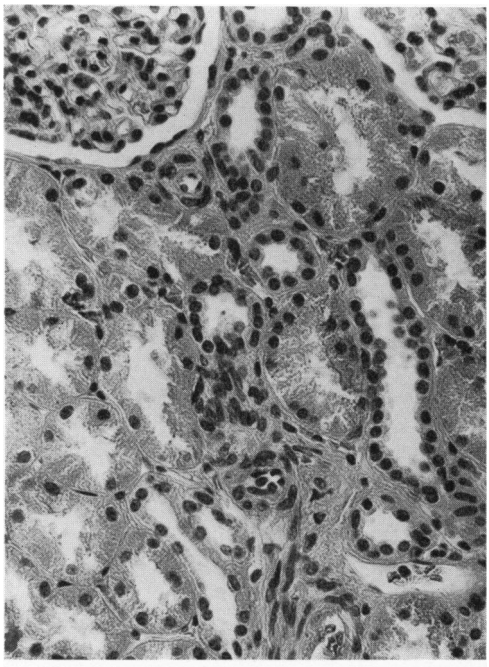
FIG. 9. Concentric overlapping of the arteriolar muscle cells indicative of spasm in otherwise normal arterioles from a kidney in hypertension. Hematoxylin and eosin stain. × 200.

FIG. 10. Hydropic change in the cytoplasm of muscle cells of an arteriole. There are prominent endothelium and enlargement of juxtaglomerular apparatus. Fine PAS-stained granules are present in some cells. Case with grade I-II arteriolosclerosis. Periodic acid-Schiff stain. × 200.

FIG. 11. Pooled PAS-positive material, partly shown as black subendothelial nodules in an arteriole. Grade I-II group. PAS stain. × 225.

FIG. 12. Stretched larger arteriole with a slightly thickened elastic membrane, and grade I arteriolosclerosis of a small arteriole. Tubular cloudy swelling is present. Aldehyde-fuchsin-PAS-orange-G stain. × 200.



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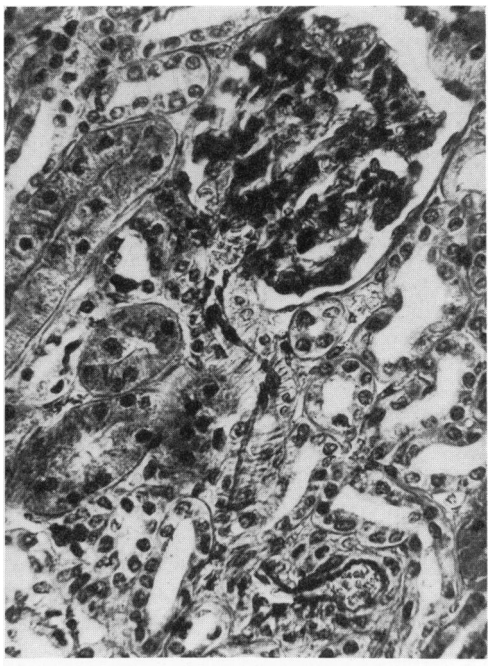

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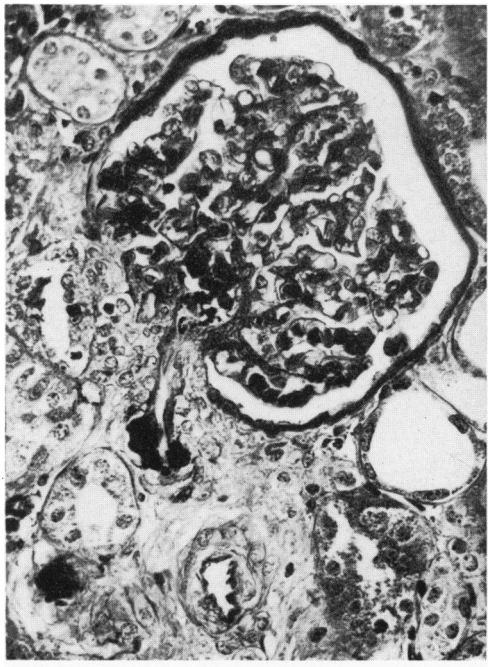

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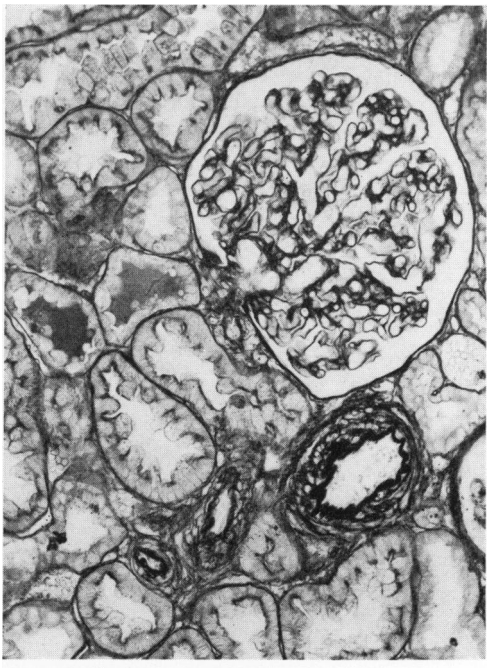

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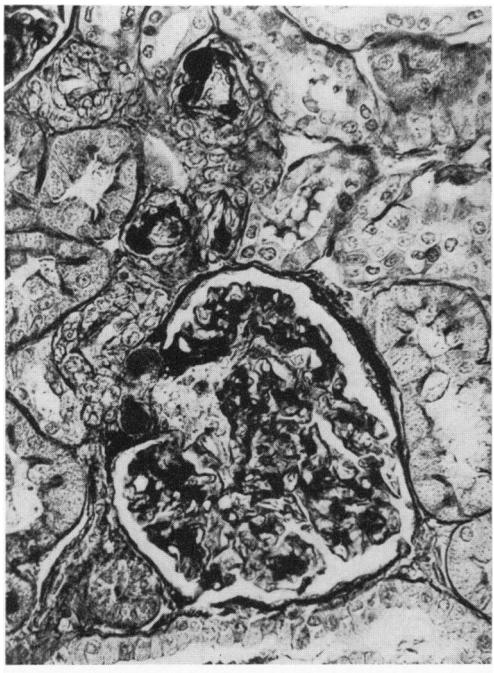
FIG. 13. Hypertrophy of an afferent arteriole, with prominent PAS-stained intercellular material shown in black. Case with grade II arteriolosclerosis. Glomerular ischemic changes are prominent. PAS stain. × 200.

FIG. 14. Another instance of arteriolar muscular hypertrophy, with prominent elastic tissue shown in black. Grade II arteriolar nephrosclerosis. Aldehyde-fuchsin-PAS-orange-G stain. × 150.

FIG. 15. More extreme hydropic changes and pooled PAS-positive material, shown in black, in renal arterioles with moderate arteriolosclerosis (grade II). PAS stain. × 150.

FIG. 16. Local collagen deposition, shown as the gray fibrillar portions of renal arteriolar walls which elsewhere have a moderate sclerosis (grade II) with pooled ground substance. PAS stain. × 200.



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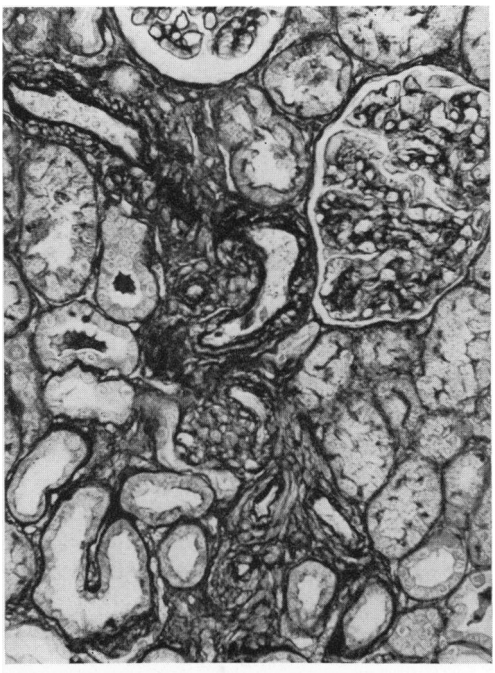

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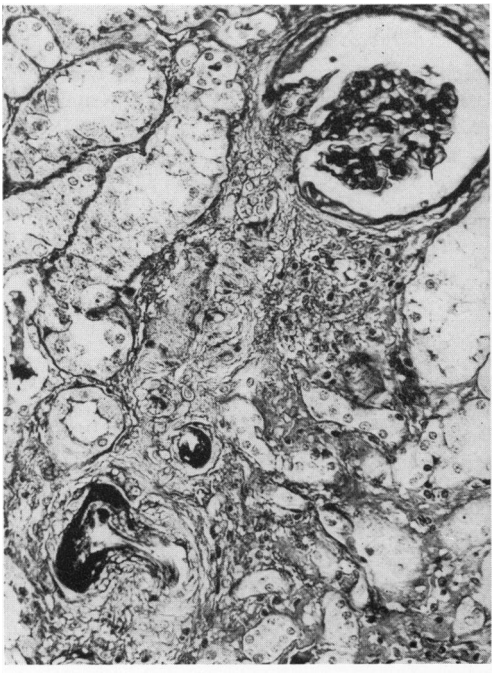

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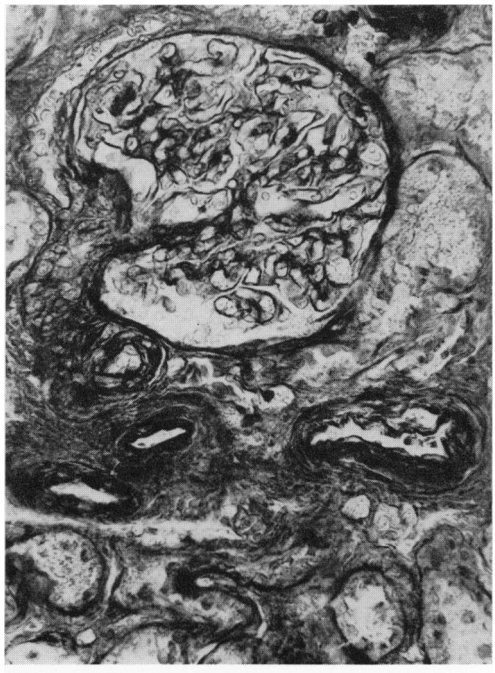

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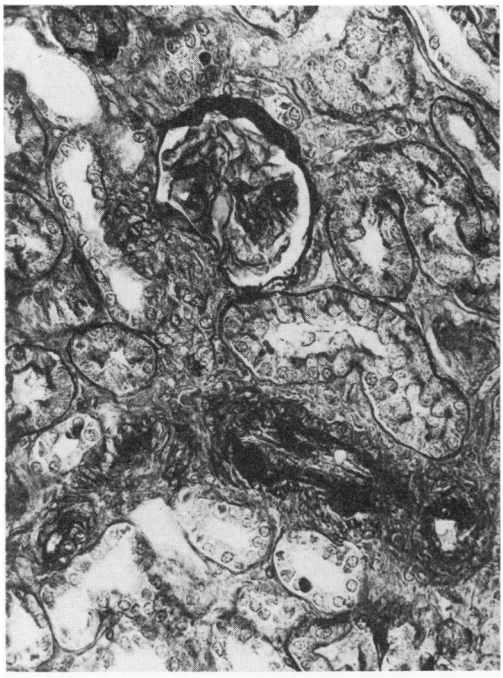
FIG. 17. Severe thickening and degeneration of arterioles from a kidney with grade III arteriolosclerosis. Abundant PAS-positive (black) material is present. PAS stain. × 150.

FIG. 18. Splitting of the arteriolar elastic tissue and exaggerated amounts of pooled ground substance in severe renal arteriolosclerosis (grade III). PAS stain. × 200.

FIG. 19. Irregular degeneration of the larger arterioles, involving all major tissue components. Grade III arteriolosclerosis and fibrinoid necrosis of smaller arterioles. Aldehyde-fuchsin-PAS-orange-G stain. × 150.

FIG. 20. Variation in the degree of local thickening of larger renal arterioles, with localized collagen deposits, shown as gray fibrillar material. Grade III renal arteriolosclerosis. Masson stain. × 150.



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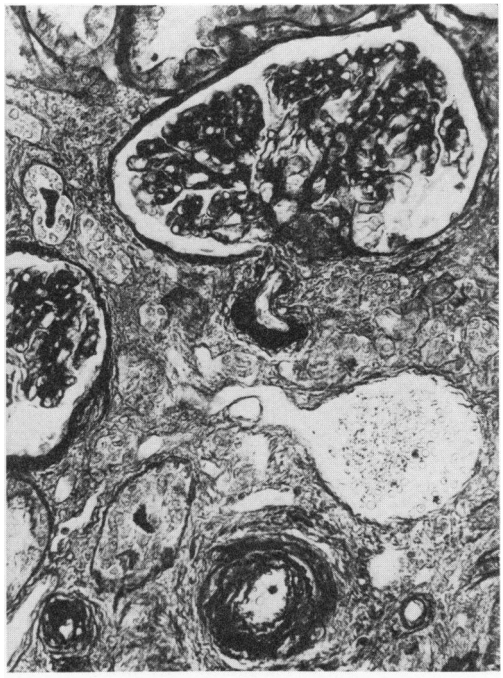

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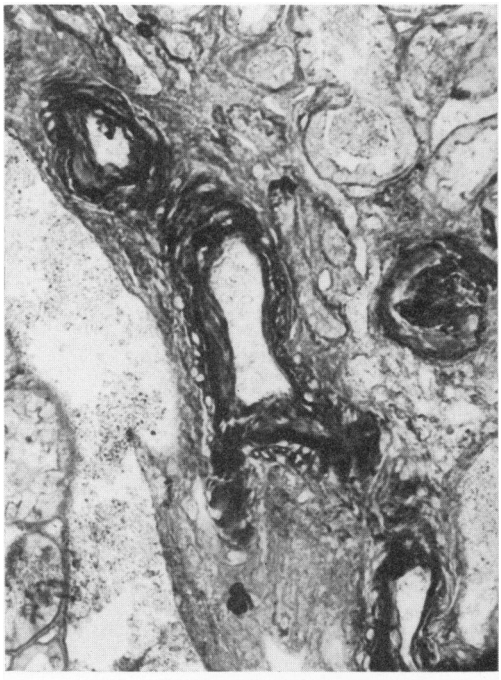

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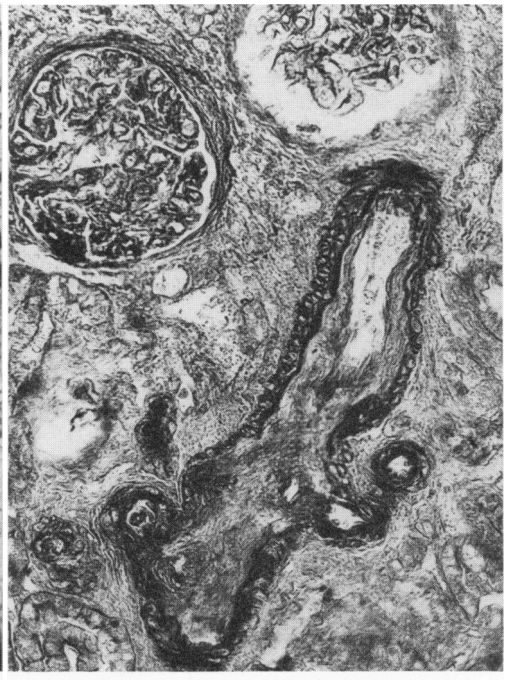

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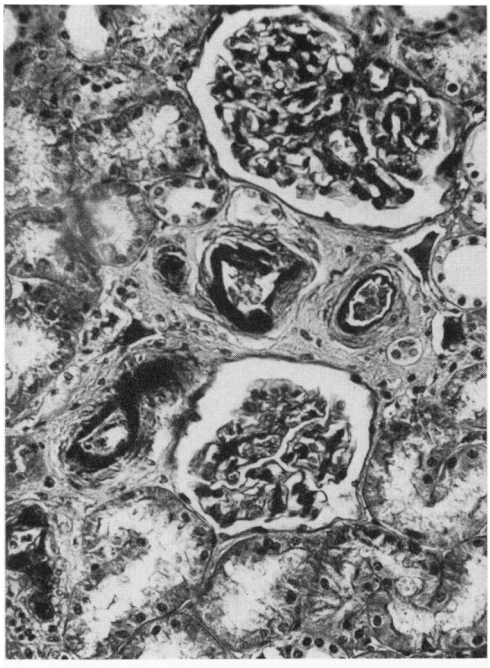
FIG. 21. Fibrinoid necrosis of small arterioles, with staining properties similar to the fibrin shown in a venule to left of center. The localization, irregular outlines, and staining characteristics favor its intramural deposition subsequent to imbibition of plasma. Grade II arteriolosclerosis, also shown in Figure 2. Hematoxylin and eosin stain. × 180.

FIG. 22. Foci of fibrinoid necrosis in grade III renal arteriolosclerosis, with a fibrin thrombus in the vessel at lower right. Phosphotungstic acid-hematoxylin stain. × 180.

FIG. 23. Acute and chronic pyelonephritis exhibiting a pus cast at lower right and interstitial leukocytic infiltrations, including plasma cells. Grade II arteriolosclerosis. Hematoxylin and eosin stain. × 120.

FIG. 24. Healed pyelonephritis with a flat-based scar of the cortical surface. Beneath this are colloid casts, scars, and moderate arteriolosclerosis. No plasma cells are identified. PAS stain. × 120.



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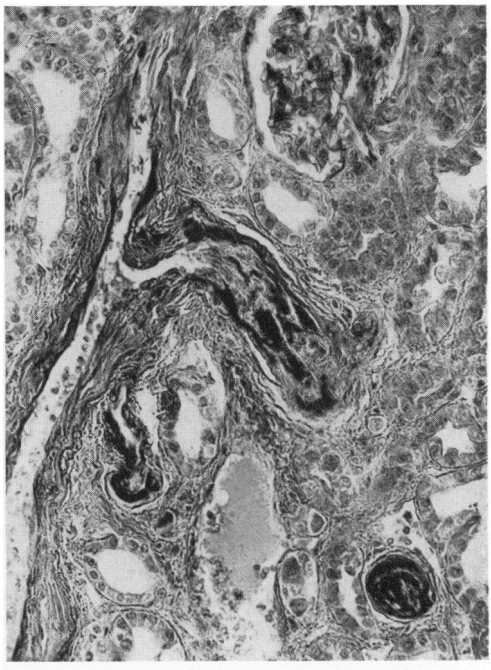

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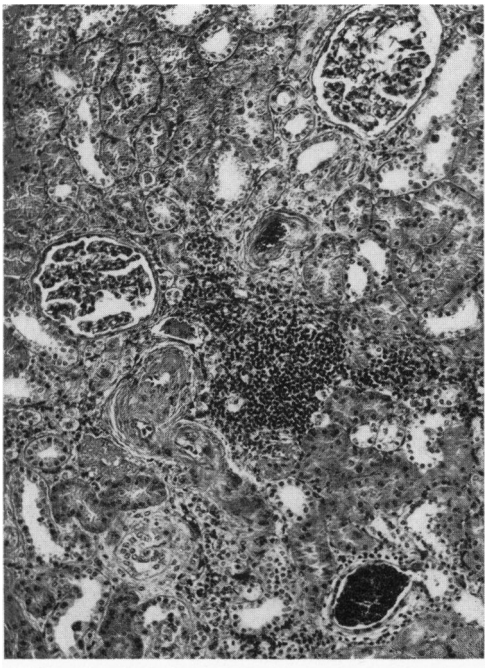

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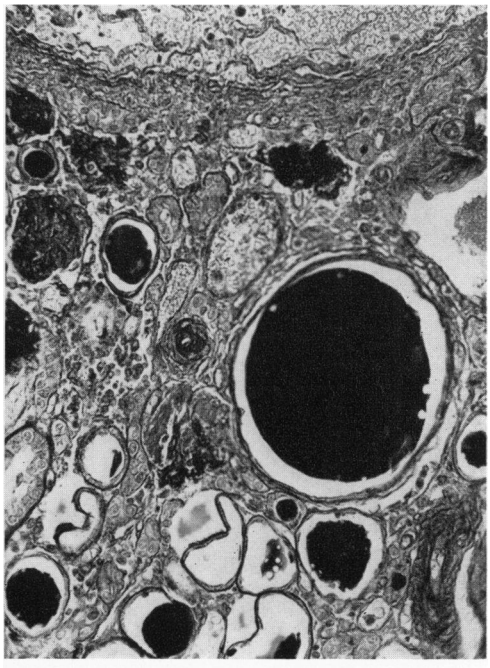

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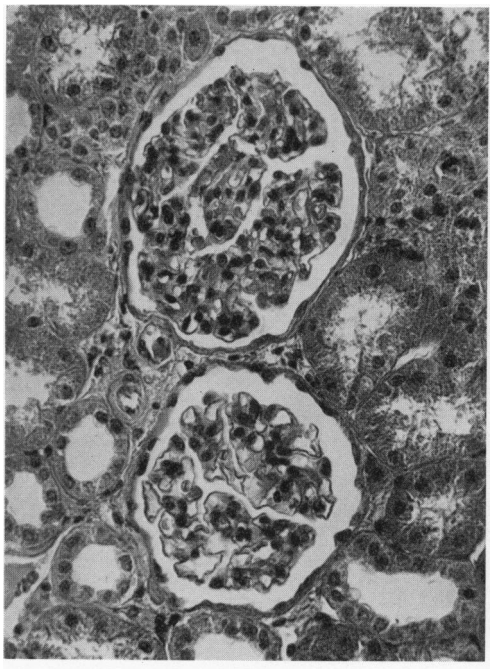
FIG. 25. Slight arteriolar sclerosis (grade I) in renal tissue procured at the time of removal of a pheochromocytoma accompanied by hypertension. Hematoxylin and eosin stain. × 180.

FIG. 26. Second kidney biopsy, from the same case shown in Figure 25, 6 years later. No arteriolar abnormality is evident. Hematoxylin and eosin stain. × 200.

FIG. 27. Membranous glomerulonephritis, with irregular and severe focal thickenings of basement membranes, as in the portion of glomerulus at lower right. This patient had grade I arteriolosclerosis. Hematoxylin and eosin stain. × 225.

FIG. 28. Interstitial collections of foam cells in a specimen with grade I arteriolosclerosis in one kidney and grade III sclerosis and severe pyelonephritis in the other. Case mentioned in the text as a possible example of the Goldblatt phenomenon. There is pyelonephritis in the area illustrated. Hematoxylin and eosin stain. × 150.



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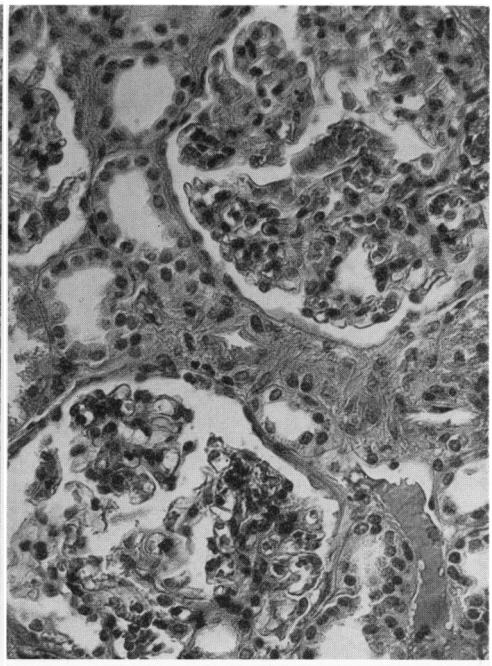

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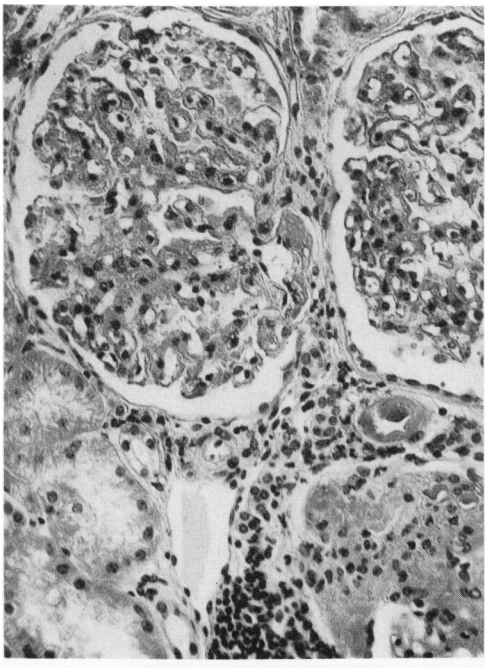

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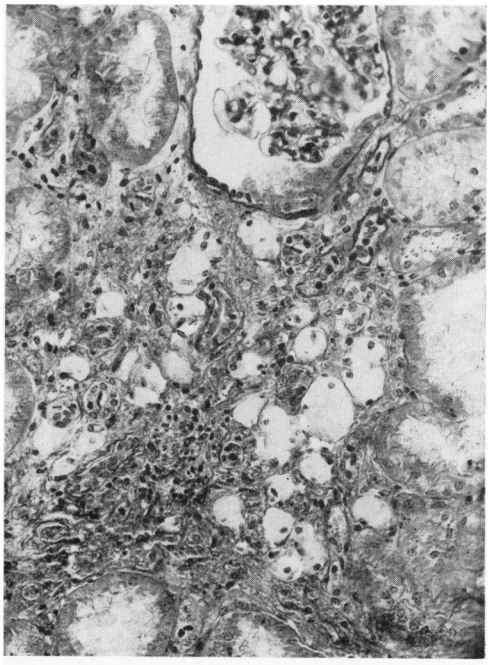

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