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Steroid-Induced Hypertension in the Rat

A Microangiographic and Histologic Study on the Pathogenesis of Hypertensive Vascular and Glomerular Lesions

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THE VASCULAR and glomerular lesions that occur in experimental steroid hypertension have been described in a previous communication.[1] Evidence was adduced from that experiment and other studies [2-4] to show that the development of these lesions is closely related to elevated intravascular pressure. Particular attention was called to the work of Byrom and Dodson,[2] who produced acute vascular lesions in normal rats by the sudden forcible injection of saline into the aorta, and showed that obstructing one renal artery during injection protected that kidney from developing lesions. They thus demonstrated conclusively that increased pressure in and of itself may produce vascular lesions. However, their experimental model has not seemed entirely satisfactory because in most types of experimental hypertension [4-6] and in human malignant hypertension,[7] early and/or minimal hypertensive lesions predominantly involve the arterioles and glomeruli, rather than the arteries as in Byrom and Dodson's model.

A microangiographic and histologic study of steroid hypertension has revealed some vascular phenomena which may help to clarify Byrom and Dodson's results. Observations from the current study support the

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evidence from our previous communication[1] that development of vascular hypertensive lesions is dependent on elevated intravascular pressure. They augment this concept by providing evidence that, although increased intravascular pressure is a prerequisite for the formation of hypertensive lesions, it may not be pressure per se which determines the development of lesions, but rather the ability of the vessel to resist distention by this pressure. They suggest also that there may be alterations in this ability during the course of hypertension.

Materials and Methods

Two groups of rats were used in this experiment. All were Holtzman females, weighing 200–225 gm.

The first group consisted of 11 animals used to study the early changes in steroid hypertension. One kidney was removed from each animal and 2 weeks later the steroid-saline regimen which was used in Group I of our previous communication was started.[1] This consisted of twice-weekly injections of 0.5 cc. of Percorten trimethylacetate (CIBA) containing in each milliliter 25 mg. of deoxycorticosterone trimethylacetate, 10.5 mg. of methylcellulose, 3 mg. of sodium carboxymethyl cellulose, and 1 mg. of polysorbate 80, with a solution of 0.9% NaCl and 0.49% KCl for drinking water. The rats were killed and perfused for microangiography as follows: 4 at 10 days, 4 at 15 days, and 3 at 20 days. Blood pressures were recorded twice weekly. One rat in the 10-day group and one in the 15-day group demonstrated pressure rises of 15 mm. Hg; the other rats in the 10- and 15-day groups showed no increase in blood pressure. Two animals in the 20-day group showed a 30-mm. rise in pressure, while the third animal showed no rise in pressure.

The second group of animals consisted of 11 rats used to study the long term effects of steroid hypertension. One kidney was removed from each rat 3 weeks before commencement of the steroid-saline regimen. The rats were given 1.0 cc. of Percorten trimethylacetate at 5-day intervals and were killed 2 months after injections were begun. Weekly blood pressures were recorded. A mean pressure elevation of 71 $\pm$ 28 mm. was reached in this group by the time of death.

The kidneys in all animals were perfused in the living anesthetized state with an 8% aqueous suspension of barium sulfate (Micropaque, Damancey). Perfusion was performed via the abdominal aorta at 180 mm. of pressure. The renal vessels were ligated and the kidneys removed and placed in 10% formol saline. After fixation thick (400 μ) sections were cut on a freezing microtome and exposed to X-rays at low kilovoltage on high-resolution photographic plates by techniques described elsewhere.[8] Following exposure these sections were paraffin-embedded for routine histologic sectioning and staining with hematoxylin and eosin, periodic acid-Schiff (PAS), Gomori's aldehyde-fuchsin, and van Gieson's connective tissue stain.

Results

Glomeruli and Postglomerular Vasculature

The alterations in the glomeruli and postglomerular vessels are so intimately related that they are described together rather than separately. In this description the term glomerular obsolescence will be used to denote the progressive functional and morphologic obliteration of glomeruli by hypertensive and methylcellulose lesions.

In the normal kidney the glomeruli are small, with a compact vascular pattern and postglomerular vasculature of uniform caliber (Fig. 1). By contrast, the glomeruli of kidneys in the experimental animals were invariably hypertrophic, as expected in an animal with one kidney removed. Our studies have shown that there is a steady accumulation of methylcellulose in the glomeruli, with minimal vacuolar lesions evident as early as the fifth day after the start of injection, and widespread well-developed lesions by the fifteenth day.[1] By this time there may be very occasional eosinophilic lesions of hypertension as well. The combination of these lesions leads to gradual obsolescence of the glomerulus, leaving behind only a puffy, spongy, largely avascular structure bearing little resemblance to a normal glomerulus (Fig. 2).

Microangiographs show glomerular obsolescence as a process of increasing vascular simplification, owing to blockage of the capillary loops by obstructive lesions (Fig. 3–6). Typically the glomeruli show a gradual transition in appearance from a tight, knobby ball, so complex that the vascular pattern cannot be made out (Fig. 3), to a glomerulus with a less tightly-knit appearance but a still indistinct vascular pattern (Fig. 4). This gradually becomes transformed to a glomerulus in which the vascular pattern can be readily made out as a group of large circling loops (Fig. 5). These may be thin and wire-like or of normal or enlarged caliber. At this stage it becomes apparent that flow has ceased in a great many capillaries, particularly the smaller side branches, probably because of obstructive lesions. This simplification continues, with vessel after vessel disappearing from the angiographic picture until only one or two long loops traverse the glomerulus (Fig. 6). Again, depending on the underlying morphologic changes (see below), these loops may be quite thin and delicate, or large and dilated. Occasionally the pattern of obstruction is such that a large segment of the glomerulus may be obstructed early, leaving the remainder to perfuse in fairly normal fashion.

Comparison of the microangiographic appearance of these glomeruli with their appearance in histologic section reveals that moderate simplification may be found in some glomeruli having only the vacuolar methylcellulose lesion (Fig. 4B), with no supervention of eosinophilic hypertensive lesions. Indeed, occasional large puffy glomeruli appear to have become obsolescent almost solely on the basis of the methylcellulose vacuolar lesions with little evidence of hypertensive lesions (Fig. 2). Generally, however, the lesions of hypertension appear, and the severity of the hypertensive lesions and the degree of simplification roughly parallel one another. One of the most striking features of the glomeruli showing hypertensive lesions is the frequent appearance of widely dilated capillary channels, invariably with deposits of fibrinoid material in their

walls (Fig. 2). In the glomeruli which have become obsolescent solely because of methylcellulose lesions such wide channels are not found.

However, the first recognizable microangiographic alteration is not glomerular simplification but a striking dilatation and expansion of the postglomerular vasculature derived from individual glomeruli (Fig. 4A, 7, and 8). We have named this the "sunburst effect" because of the dramatic and often raylike appearance of the dilated efferent arteriole and peritubular capillary plexus. This sunburst effect may be seen to a limited extent in normal kidneys, affecting perhaps 2–5% of glomerular units (by which term we mean the glomerulus with its associated afferent arteriole and efferent vasculature.) It becomes quite prominent in kidneys subjected to hypertensive stimuli and may be seen in up to 20–30% of the glomerular units at any given time. In no case, however, were all glomeruli affected and even in the most severely damaged kidneys some glomeruli appeared relatively intact and their postglomerular filling was normal, without evidence of dilatation. (Mildly affected kidneys often show increased perfusion of the medullary vessels as well, usually via efferent arterioles of wide caliber. It may be that this represents a specialized instance of the sunburst effect. This appearance is not seen in the more severely involved kidneys, probably owing to widespread glomerular obliteration at the corticomedullary junction.)

The sunburst effect was seen in the animals in Group I as early as the tenth day after commencement of the steroid-saline regimen, in the absence of any rise in blood pressure or of any evidence of hypertensive lesions, although early methylcellulose lesions were present in the glomeruli. This efferent dilatation occurs equally at all levels of the cortex and affects glomerular units individually and randomly rather than in any recognizable pattern, such as affecting all the glomeruli supplied by a given interlobular artery. It is most frequent and spectacular in animals which have had a hypertensive stimulus for a long period of time but in which, for one reason or another, hypertensive lesions have not supervened (see *Discussion*). This study does show, however, that significant capillary obstruction by methylcellulose or hypertensive lesions leads to disappearance of the sunburst effect (Fig. 9–11). On occasion, postglomerular filling is approximately normal. More usually it disappears almost entirely, particularly if glomerular simplification is advanced. In a moderate number of cases, however, some flow is maintained even through a greatly simplified glomerulus to the efferent vessels beyond. This flow may be carried in one or two capillary loops through the glomerulus from afferent to efferent arteriole, in a pattern somewhat like the Greek letter omega (Fig. 12), or it may pass directly from the afferent

to the efferent arteriole. This latter occurs most frequently in the juxtamedullary glomeruli, resulting in the formation of arteriolae rectae verae, as classically described by MacCallum,[9] but may occasionally occur in mid- and peripheral cortex as well. Often, in severely affected cases, some vasa recta are greatly dilated and tortuous, with extensive deposits of fibrinoid material in their walls as far down as the inner zone of the medulla (Fig. 13). Because of the limitations of this technique it has not been possible in all instances to trace these vasa recta back to their origin. Where this has been possible, an arteriola recta vera has invariably been found, either fully formed or in the process of developing, permitting flow to be maintained past the severely damaged and obsolescent glomerulus (Fig. 14–17). Similarly, in the mid- and peripheral cortex it has been possible to find dilated capillaries with fibrinoid deposits in their walls. It has not, of course, been possible to trace any of these directly back to the parent glomerulus, but it has been noted that these capillaries were almost always in the vicinity of glomeruli with hypertensive damage but some persistent channels.

In all cases examined the glomerular hypertensive lesions have assumed a regular pattern (Table 1). The incidence of severely damaged glomeruli is greatest at the corticomedullary junction and decreases peripherally (Fig. 9–11). This disparity in degree of involvement between different levels of the cortex is greatest in the moderately affected cases and becomes less conspicuous as the degree of involvement becomes severe. Similarly, glomerular damage tends to parallel that in the attached afferent arteriole (Table 2), and if there is a disparity between the two, the tendency is toward more severe glomerular damage than arteriolar damage (Table 3). However, unlike the glomerular hypertensive lesions, the methylcellulose lesions, although varying somewhat in extent from glomerulus to glomerulus, are equally severe at all levels of the cortex.

Arterial and Arteriolar Lesions

The first vessels to show hypertensive lesions are the afferent arterioles. The mildest alteration is simply an accumulation of fibrinoid material in the inner portion of the wall with little or no compromise of the lumen; consequently there is no change in the microangiographic appearance. With increasing severity, there may be very considerable compromise of the arteriolar lumen by fibrinoid material and marked granulomatous reaction in the adventitia and surrounding interstitium. However, quite frequently one may see severely damaged afferent arterioles with both large fibrinoid deposits and lumens of normal or increased caliber (Fig. 2, and 6B).

Table 1. Glomerular Hypertensive Lesions: Relative Severity of Lesions at Different Levels in the Cortex

Animal No.	Periphery					Midcortex					Juxtamedullary				
	Total glomeruli	Grade*				Total glomeruli	Grade*				Total glomeruli	Grade*			
		0	1	2	3		0	1	2	3		0	1	2	3
201	46	31	11	1	3	60	22	19	13	6	32	9	10	8	5
202	36	14	5	6	11	54	15	11	14	4	27	6	5	4	12
208	47	7	19	12	9	80	18	19	17	26	28	2	4	5	17
217	40	25	8	2	5	67	22	22	13	10	32	7	7	9	9
1771	52	32	18	2	0	101	33	32	24	12	45	11	14	8	12
1766	41	19	10	11	1	64	13	20	20	11	20	4	5	8	3
Total	262	128	71	34	29	426	123	123	101	79	184	39	45	42	58
Per Cent		48.9	27.1	13.0	11.0		28.9	28.9	23.7	18.5		21.2	24.4	22.8	31.6

Chi-square = 64.21; $p < 0.001$

* Only eosinophilic lesions were considered in grading glomerular hypertensive lesions: Lesions were graded on a scale of 0–3, as follows:
  0 — No hypertensive lesions.
  1 — Minimal hypertensive lesions affecting only a few capillaries, with majority of tuft unaffected.
  2 — Moderate hypertensive lesions involving numerous capillaries, but with much of tuft unaffected.
  3 — Severe hypertensive lesions involving entire glomerular tuft with widespread capillary damage and obstruction.

Table 2. Afferent Arteriolar Lesions: Relative Severity of Lesions at Different Levels in the Cortex

Animal No.	Periphery				Midcortex				Juxtamedullary			
	Total arterioles	Grade*			Total arterioles	Grade*			Total arterioles	Grade*		
		0	1	2		0	1	2		0	1	2
201	11	10	0	1	20	2	14	4	6	0	4	2
202	10	4	2	4	6	2	0	4	8	0	1	7
208	10	2	3	5	9	0	4	5	8	1	2	5
217	8	6	2	0	16	2	10	4	4	0	3	1
1771	12	10	2	0	16	3	6	7	6	1	2	3
1766	3	1	2	0	19	4	11	4	3	0	1	2
Total	54	33	11	10	86	13	45	28	35	2	13	20
Per cent		61.1	20.4		18.5	15.1	52.4	32.5		5.7	37.2	57.1

Only those afferent arterioles seen in definite relation to glomeruli were considered. Chi-square = 51.24; $p < 0.001$.

* Arteriolar lesions were graded on a scale of 0–2, as follows:
  0 — No lesions.
  1 — Minimal to moderate accumulation of fibrinoid material, little or no granulomatous response, and no compromise of arteriolar lumen.
  2 — Moderate to severe accumulation of fibrinoid material, usually with some granulomatous response, and often compromise of lumen.

Table 3. Comparison Between Glomeruli and Attached Afferent Arterioles with Respect to Severity of Lesions

Arteriolar lesions*	Glomerular hypertensive lesions*			
	0	1	2	3
0	**35**	11	2	0
1	3	**24**	**29**	13
2	0	3	**24**	**41**

Bold face numbers represent groups in which glomerular and arteriolar lesions are of approximately equal severity.
* See Table 1 for grading criteria of glomerular lesions and Table 2 for grading criteria of arteriolar lesions.

The pattern of afferent arteriolar involvement is quite characteristic (Table 2). The earliest lesions appear at the corticomedullary junction. This remains the region of severest involvement as lesions progress outward through the cortex. Arteriolar damage occurs randomly, and all degrees of damage from mild to severe may be seen at any level of the cortex. However, the percentage of severely altered arterioles is always greatest at the corticomedullary junction and least at the periphery. As with glomerular lesions, this feature is most prominent in cases of moderate severity and is less prominent in severe cases, where peripheral involvement may be very nearly as great as juxtamedullary. (Compare Rats 201 and 208, Table 2.)

As arteriolar and glomerular damage progresses, lesions begin to appear in the interlobular and larger arteries. It is difficult to evaluate adequately the pattern of large vessel alteration. However, as with afferent arterioles, the impression is gained that fibrinoid and granulomatous alteration is more marked near the corticomedullary junction than peripherally. Lesions are often more severe near the point of branching of a vessel than further down its length, as for example in the wall of an interlobular artery near its origin from an arcuate artery (Fig. 18).

The presence of arterial vasoconstriction at the time of perfusion is revealed in microangiographs by a characteristic appearance. The interlobular arteries may show varying degrees of constriction but the afferent arterioles are usually widely patent. This picture is brought about by postmortem contraction of the vascular smooth muscle which tends to cause some shifting of perfusate from the larger arteries with their thicker walls and greater contractile power into the thin-walled afferent arterioles. Thus, although the presence of vasoconstriction can be recognized, the precise level in the arterial tree at which it occurs cannot be identified. A similar constricted appearance may be obtained in animals perfused at low pressure. However this factor was eliminated in this study by per-

fusing at 180 mm., a pressure found in previous experiments to be adequate to completely distend all vessels in the absence of significant vasoconstriction.

Vasoconstriction is found only very occasionally in normal animals, but some degree of vasoconstriction was present in all but one of the animals in this study. The exception was an animal showing only minimal evidence of either microangiographic or histologic hypertensive alterations. (This does not necessarily indicate that vasoconstriction is present under basal conditions in the hypertensive animal, although there is abundant evidence that it is, but might simply reflect increased sensitivity to some aspect of the perfusion procedure.) In the mildly damaged kidneys constriction is uniform throughout the kidney and affects all vessels approximately equally (Fig. 7). As the degree of damage increases, however, there is considerable variation in the degree of constriction. Although the majority of arteries in the kidney are constricted, numerous interlobular arteries show dilatation rather than constriction. Frequently constricted and dilated segments alternate in the same vessel, producing a sausage-like effect (Fig. 14–17). This is similar in appearance to the vascular phenomena described in hypertensive encephalopathy by Byrom [10] and others [11,12] but may not be of similar origin. This is considered in *Discussion*. Histologically, some such dilated vessels show little or no evidence of damage. Others have an accumulation of fibrinoid material in the wall and lumen, with some adventitial and interstitial cellular reaction and often a necrotic or hyalinized muscularis, although the lumen may be as large or even larger than the lumen of undamaged segments of the same artery (Fig. 18). In addition many other interlobular arteries, although showing secondary constriction or obstruction of their lumens by fibrinoid material, have dilated walls as shown by stretching and loss of undulations in the internal elastic lamina. By contrast, constricted interlobular arteries are usually histologically normal, although occasional ones show a minimal accumulation of fibrinoid material and cellular reaction. In the more severely damaged kidneys, dilatation with accompanying hypertensive alteration is seen not only in the interlobular arteries but in occasional arcuate and interlobular arteries as well. This is exceptional, however. More usually the larger arteries exhibit fibrinoid deposits and cellular reaction in the absence of any gross dilatation. Even here, however, it is a characteristic feature that the internal elastic lamina underlying the fibrinoid deposits is distended and smooth whereas that in the remainder of the vessel has the crinkled corrugated appearance typical of a vessel in contraction (Fig. 19). This suggests there may be localized distention of the vessel wall in the absence of over-

all dilatation. Support for this notion comes from the observation that while the media underlying the contracted elastica usually appears relatively intact, that beneath the distended elastica frequently shows some degeneration and necrosis, often with inflammatory response (Fig. 19).

Discussion

Byrom and Dodson[2] were able to create renal arterial and arteriolar lesions acutely in the normal rat by means of forcible intra-arterial saline injections, thus demonstrating that elevated pressure may of itself produce lesions. However, there are numerous indications that factors other than simple elevation of pressure must be at work in the production of vascular lesions in spontaneous hypertension. The pattern of vascular lesions produced by high-pressure saline injection is the reverse of that in naturally occurring hypertension, with lesions being most prominent in the interlobular and larger arteries, less frequent in the afferent arterioles, and rare or absent in the glomeruli; in spontaneous hypertension, lesions appear only later in the larger vessels and are first seen in the afferent arterioles and glomeruli. Moreover, it is at the glomerular and arteriolar level that pressure in the normal kidney is most closely controlled by the autoregulatory process. It has been demonstrated that in normal kidneys, over a range of systemic pressure from 90 to 200 mm., renal blood flow (RBF)[13] and glomerular filtration rate (GFR)[14,15] are remarkably constant. Thurau and Weber[16] have shown that the peritubular capillary pressure also remains constant over this range of systemic pressure, demonstrating that the regulation occurs in the preglomerular vessels, probably primarily in the afferent arterioles since they contribute the major portion of the preglomerular resistance.[17] Finally, it has been observed that in certain situations—e.g., neurogenic hypertension in the dog[18] and rat[19]—hypertension of marked degree can persist for long periods of time with only minimal vascular lesions. By contrast, in other situations, particularly in steroid hypertension, it has been our impression and that of others[20,21] that significant lesions may occur in the face of only modest rises of blood pressure, once again suggesting that factors other than simple elevation of pressure must be at work in the production of vascular lesions. An approach to this issue from the opposite direction has come through the demonstration that rats pretreated with DOCA[22] or cortisone[23] develop severe vascular and glomerular lesions when renin is administered, compared with only minimal changes when renin is administered to controls, presumably because of sensitization of the vessels in some way. Similarly it has been shown that X-irradiation of mesenteric vessels sensitizes them in such manner that severe necrotizing lesions de-

velop in the irradiated segment of mesentery on induction of a moderate degree of hypertension, at a time when they are not present elsewhere in the mesentery or the body.[24]

Taken together, these observations suggest that the development of vascular hypertensive lesions must be a function not only of elevated intravascular pressure but also of some alteration in the functional capacity of the smooth muscle during the onset of hypertension. As will be seen, our observations indicate that such an alteration does occur, forming the functional substrate for the development of morphologic lesions.

Our observations are also in accord with those of Giese [20,25] indicating that morphologic lesions arise in dilated rather than constricted segments of vessels. Giese [20] studied the development of hypertensive lesions in the mesentery of the rat in acute drug-induced hypertension by a combination of vital microscopy and colloidal-tracer techniques. He found that angiotensin very often gave rise to a pattern of alternating segments of dilatation and constriction similar to that seen in chronic hypertension. Moreover, the deposition of particles from the bloodstream occurred only in the dilated segments of a vessel and never in the severely constricted portions. He concluded that the essential force allowing passage of particles—and by inference plasma proteins—into the arterial wall is a distention of the vessel wall. In addition he described diffuse deposits of colloidal particles in the mesentery, representing increased permeability of the small vessels. These deposits were often located in close proximity to dilated arteries. It was suggested that this represents a situation in which dilatation has permitted the high pressure to be transmitted distally, causing a rise in pressure and increased permeability in the small vessels. As will be seen, this is exactly analogous to the mechanism that we suggest is responsible for glomerular hypertensive lesions.

It is perhaps best at the outset of discussion of our observations to comment on the microangiographic technique, its limitations, and the conclusions which may be drawn from it. The microangiograph represents a combination of three sets of factors: (1) the natural or basal state of the vasculature prior to perfusion, including those alterations brought about by the disease process under study; (2) alterations and artifacts created by the perfusion procedure; and (3) postmortem alterations, including contraction of vessels and shifting of perfusate (see also *Results*). Variation in any of these factors may have a profound effect on the final picture. But if these factors are kept in mind, much useful information regarding morphologic alterations in vessels can be derived from microangiographic material. Limited conclusions may be drawn concerning vascular functional status as well, but the limitations of these conclusions should be

clarified where they bear on the present study. First, postmortem alterations prohibit any statement about the degree of constriction in the afferent arterioles. Barring obstructive lesions, almost all afferent arterioles are dilated in section, whereas in life most or all of them may have been contracted. The presence of arteriolar dilatation in a given vessel can only be inferred from other morphologic changes, it cannot be concluded from direct examination. Second, the appearance of constriction in the arteries does not necessarily mean that they were severely, or even partially, constricted at the time of perfusion. Even the microangiographic picture of segmental, alternating constriction and dilatation, although exactly similar in appearance to that described by Byrom [10] and others [11,12,20] must not necessarily be regarded as its exact equivalent. All that can be said with certainty is that the constricted segments were capable of contracting post mortem and the dilated segments were incapable of doing so. That these appearances reflect similar capabilities in the living animal seems probable. In particular, it seems likely that the dilated segments would demonstrate reduction or absence of contractile power in vivo, but no statement can be made as to whether the arterial segments contracted post mortem were contracted in life.

Indirect evidence in favor of Giese's contention that vascular lesions occur in dilated segments of vessels comes from our observations on the sunburst effect—the marked dilatation of efferent vasculature derived from individual glomeruli. The sunburst phenomenon appears to reflect primarily some failure in individual afferent arterioles, leading to relative arteriolar dilatation (although this cannot be directly observed with this technique for the reasons stated above). This permits the glomerulus and peritubular capillaries beyond to perfuse at increased pressure. This opinion is based on two considerations. The efferent arteriole does not seem to be responsible. Smith [26] has demonstrated in the human kidney that up to 40% of the efferent arterioles may be "endothelial" in character, without any smooth muscle component. Our own work indicates that this percentage may be even higher in the rat; obviously muscular efferent arterioles are found mainly in the juxtamedullary cortex and in the most peripheral cortex, those in the remainder of the cortex being primarily endothelial in type. Yet in the normal kidney no difference can be distinguished in the caliber of the peritubular capillaries supplied by each type. If there is a change in the caliber of the peritubular capillaries due to change in pressure it must come primarily from alterations in the preglomerular vessels. Also, the highly individual and random nature of the process, with some glomeruli deriving from a given interlobular artery affected and others not, points to the afferent arteriolar segment being the site of failure.

At this point certain other characteristics of the sunburst effect, from the material in this study and from comparison with other experimental models, should be described.

1. This effect occurs to a limited extent in apparently normal animals, affecting no more than 5% of the glomeruli, and usually considerably less.

2. It occurs in all the hypertensive models studied to date, including: (*a*) steroid hypertension, most prominently in animals with one kidney removed, but also in animals with both kidneys present; (*b*) silver-clip hypertension, in both the clipped and the nonclipped kidneys; (*c*) the hypertension produced by a clip on a solitary kidney; and (*d*) hypertension following unilateral pyelonephritis.

3. It bears no relation to the perfusion pressure used in the injection because perfusions in all animals were made at identical pressures. It is not a function of renal hypertrophy, as shown by its occurrence in the clipped kidney of silver-clip hypertension. Nor is it in compensation for loss of arteriologlomerular units, as suggested by Ljungqvist[27] who observed this phenomenon in a microangiographic study of the human hypertensive kidney, for it may occur bilaterally in steroid hypertension in kidneys showing no histologic evidence of nephron loss.

4. It is not related to the ambient pressure in the kidney, as demonstrated by its presence at an early stage in animals treated with DOCA, before the blood pressure rises, and in clipped kidneys where blood pressure is low-to-normal.

5. It appears not to be directly related to the renin-angiotensin system. It appears equally in the DOCA-treated and unclipped kidneys where renin is low,[28,29] in the solitary clipped kidney where renin is approximately normal,[30] and in the clipped kidney where renin is high.

Numerous observations indicate an association between the sunburst phenomenon and the development of glomerular hypertensive lesions; most striking is the timing of the two events. Sunbursting appears before there is any rise of blood pressure or glomerular lesions, reaches its height at the time when hypertensive lesions are becoming well-established, and gradually becomes less prominent as glomerular lesions become more severe. (It is of interest that sunbursting reaches perhaps its greatest prominence in the solitary clipped kidney where a strong hypertensive stimulus is present over a period of time but the arterioles and glomeruli are protected by the clip so that lesions do not supervene.) Although it would be gratifying to be able to state that sunbursting is an invariable precursor of glomerular hypertensive lesions, the present data do not permit this conclusion because of the problem of interference by methylcellulose capillary-obstructive lesions. It was demonstrated on the one hand that sunbursting could appear before any overt hypertensive lesions,

and on the other hand that moderate-to-marked methylcellulose and eosinophilic lesions usually caused enough glomerular capillary obstruction to result in the disappearance of sunbursting. Thus, to study the question of association only those glomeruli showing recognizable hypertensive lesions, but with only minimal methylcellulose lesions, could be taken into consideration. And, while the vast majority of such glomeruli did indeed show evidence of sunbursting, a few did not. Even here, however, the possibility of methylcellulose obstructive lesions could not be ruled out. The definite answer to this question must await study in a model such as silver-clip hypertension where obstructive capillary lesions are not a problem. Nonetheless, the interpretation most consistent with our observations is that the sunburst effect is the usual, if not the invariable, antecedent of morphologic hypertensive lesions, and that it represents a functional abnormality in the afferent arteriolar smooth muscle which, while giving rise to no morphologic manifestations, renders the arteriole and glomerulus vulnerable to dilatation and hyperdistention by rising blood pressure with resultant vascular lesions, in line with Giese's concept.

Further indirect evidence supporting Giese's views comes from observations of the interlobular and larger arteries, particularly during the later stages of hypertension. Arteries were frequently seen showing alternating segments of constriction and dilatation, similar to those described by Byrom [10] in hypertensive encephalopathy and by Giese [20] in acute drug-induced hypertension. Except in the larger arteries where the possibility of localized dilatation of a portion of the circumference could not be ruled out (Fig. 19), the segments of arteries which were constricted in microangiographic and histologic section showed no sign of fibrinoid or granulomatous lesions, whereas the dilated segments frequently showed severe involvement. Certainly one might anticipate that a vessel with a markedly damaged muscle layer would show dilatation secondary to this damage, so the observation that dilated vessels may show hypertensive lesions is not by itself helpful. However, the observation that, for practical purposes, all morphologic lesions occur in dilated vessels (Fig. 2, 6B, 11, 13, 16, and 18), whereas *some* dilated vessels (Fig. 17) and *all* constricted vessels appear histologically normal suggests strongly that vascular dilatation preceeds morphologic lesions. If the reverse were true, i.e., if vascular lesions preceeded and led to dilatation, one would expect that *some* constricted vessels and *all* dilated vessels would show lesions. Owing to the difficulties in interpreting the state of vascular constriction in microangiographic and histologic sections discussed above, these observations cannot be put forward as direct evidence supporting Giese's concept, but they are entirely compatible with it.

More direct evidence for the role of vascular hyperdistention in the development of hypertensive lesions is the occasional finding of widely distended vasa recta showing marked fibrinoid deposits in their walls. Where traceable, they are seen to originate from glomeruli which have suffered severe hypertensive lesions but in which there remains a large through-channel to the vasa recta. This permits the elevated pressure in the afferent arteriole to be transmitted, unchecked, to the efferent arteriole and vasa recta rather than being throttled down by passage through the glomerular capillaries. Lacking smooth muscle, the vasa recta become hyperdistended and rapidly show accumulation of fibrinoid material. By contrast, those vasa recta protected from increased pressure by an intact glomerulus do not show fibrinoid deposits even in the face of severe lesions elsewhere in the kidney.

The nature of the alteration which we believe occurs in the vascular smooth muscle must now be considered. Three characteristics are immediately clear—it is focal, random, and first detectable in the afferent arterioles and only later in the larger arteries. In combination, these characteristics suggest a process which affects isolated smooth muscle cells or groups of cells in a progressive manner. In such a situation whether or not a vessel showed evidence of involvement would depend on the percentage of fibers which were altered in that vessel. The afferent arterioles would thus be more likely to show evidence of involvement than would a larger artery where surrounding muscle cells could compensate for localized alteration. Compatible with this notion is the early afferent arteriole involvement and also the eccentric location and pattern so often seen in the early stages of large artery lesions. An alternative possibility might be that this smooth muscle "alteration" is not an alteration at all, but a reflection of intrinsic differences in contractile capacity among smooth muscle cells which come to light only as these capacities are exceeded. In line with this suggestion is Giese's demonstration[20] that segmental constriction and dilatation occur not only in chronic hypertension, but also in acute experiments using angiotensin infusion, and that the same segments are consistently dilated on repeated stimulation. Nonetheless, it appears that even if this alteration is only an exaggeration of the factors giving rise to consistent acute segmentation, there must indeed be some alteration because sunbursting is seen only in rare glomeruli in the normal animal but is spread throughout the kidney in prehypertensive DOCA-treated animals and in the clipped kidney of silver-clip hypertension where the pressure is presumably normal.

On the basis of the above considerations we can begin to formulate a working hypothesis to explain the pattern of development of renal hypertensive lesions and the mechanisms immediately underlying this

development. With the onset of the hypertensive stimulus, (i.e., renal artery stenosis, steroid administration, etc.) some functional alteration begins to occur in the vascular smooth muscle leading to partial or complete loss of contractile ability. The pattern of involvement indicates that this is probably a progressive process affecting smooth muscle cells individually and randomly so that the afferent arterioles are the first to show evidence of involvement, giving rise to the sunburst phenomenon. Although this process betrays itself by no recognizable histologic change, it predisposes the arteriole and glomerulus, lacking smooth muscle, to hyperdistention and development of lesions with rising blood pressure. The role of increasing pressure is illustrated by the fact that although sunbursting occurs randomly at every level of the cortex, morphologic lesions appear earliest at the corticomedullary junction and spread centrifugally outward, probably in relation to a gradient of diminishing pressure in this direction. (This pressure gradient has not been directly demonstrated, but Brown *et al.*[31] have shown that the renin content of individual glomeruli, presumably related inversely to the pressure reaching the afferent arteriole, is lowest at the corticomedullary junction and increases steadily toward the periphery.) With increasing smooth muscle alteration more and more afferent arterioles and glomeruli develop lesions. Also, the interlobular and larger arteries gradually become unable to compensate in the face of progressive muscle alteration and increasing blood pressure, so that the typical picture of alternating constriction and dilatation appears, followed by the formation of fibrinoid and granulomatous lesions in the dilated segments. The effects of hyperdistention are also manifest in the vasa recta which, if not protected against increased pressure by an intact glomerulus, may become widely distended and lined by fibrinoid deposits.

The diminished autoregulatory capacity implied in afferent arteriolar alteration may serve to explain the difference between the lesions created by Byrom and Dodson's high-pressure saline injections and those in naturally occurring hypertension. It seems likely that in normal animals with an intact autoregulatory mechanism, Byrom and Dodson were unable to raise pressure in the afferent arterioles and glomeruli sufficiently to create lesions (although Wolfgarten and Magarey,[32] using higher pressures, were able to create some few glomerular lesions by this technique). By contrast, in animals with afferent arteriolar alteration, and presumable loss of autoregulatory capacity, glomerular lesions readily develop with modest rises in pressure.

It is paradoxical that this alteration, which would tend to diminish peripheral vascular resistance, occurs in the face of the well-known over-

all increase in resistance characteristic of almost all forms of hypertension. At first this is somewhat disturbing, but perhaps need not be when it is considered that only a fairly small proportion of vessels are involved at any one time, and that the lesions which follow are of an obstructive nature, tending to raise the resistance in affected vessels to former levels.

It is beyond the scope of this discussion to speculate on the possible nature of the proposed alteration in smooth muscle in hypertension. Several authors[33–36] have suggested that cellular electrolyte imbalance may lead to smooth muscle necrosis, but the evidence for this is inconclusive at present, and numerous other possibilities present themselves. It is worth while to point out in conclusion that, in stressing the role of vascular hyperdistention and smooth muscle alteration in the pathogenesis of hypertensive lesions, we do not ignore or exclude the possibility that other factors may play a role in their development. These possibilities have been considered at length in the preceeding communication.[1] Finally, a note of caution must be sounded. Steroid hypertension is of relatively acute onset, reaching very high levels in a few weeks. It might be anticipated that in hypertension of slow onset, where there is time for muscular hypertrophy and vascular compensation, a totally different picture might be obtained and different mechanisms invoked to explain the production of vascular and glomerular lesions. Indeed, Byrom[37] has demonstrated that under certain circumstances arterial muscular hypertrophy may protect against vascular fibrinoid and necrotic lesions.

Summary

A microangiographic and histologic study has been made of the vascular and glomerular lesions occurring in steroid hypertension. One of the earliest and most dramatic alterations is marked dilatation of the efferent vasculature associated with individual glomeruli, an appearance we have named the "sunburst effect." This appears before there is any rise in the systemic blood pressure or any evident histologic alteration and tends to disappear as lesions appear in the affected glomerulus, although in some cases it may persist. This dilatation is felt to be the result primarily of some failure of the afferent arteriole which permits the glomerulus and postglomerular vasculature to be perfused at increased pressure. It is noted also that glomerular and arteriolar hypertensive lesions appear earliest and most severely at the corticomedullary junction and diminish in severity toward the capsular surface. This is probably related to a gradient of diminishing pressure in this direction. Finally, it is noted that arterial lesions are frequently if not invariably preceded by dilatation of the vessel wall, either localized or generalized.

These observations suggest that some alteration in the vascular smooth muscle occurs, leading to partial or complete failure of ability to contract. This alteration occurs randomly and is first detectable in the afferent arterioles (as the so-called sunburst effect), suggesting that only single muscle cells or small groups of cells are affected. This alteration in itself gives rise to no detectable histologic change but predisposes to the development of hypertensive lesions. It appears that, although increased pressure is prerequisite for the development of hypertensive lesions, it is not pressure per se which is the cause immediately underlying the development of hypertensive lesions, but the inability of the vessel to withstand overdistention by this pressure. Ironically it is not too-vigorous contraction, but inability to contract adequately, that leads to vascular lesions. According to this concept, when vascular pressure is raised sufficiently hypertensive lesions occur in those vessels in which there has been sufficient alteration of smooth muscle and in those glomeruli left unprotected by alteration in their afferent arterioles.

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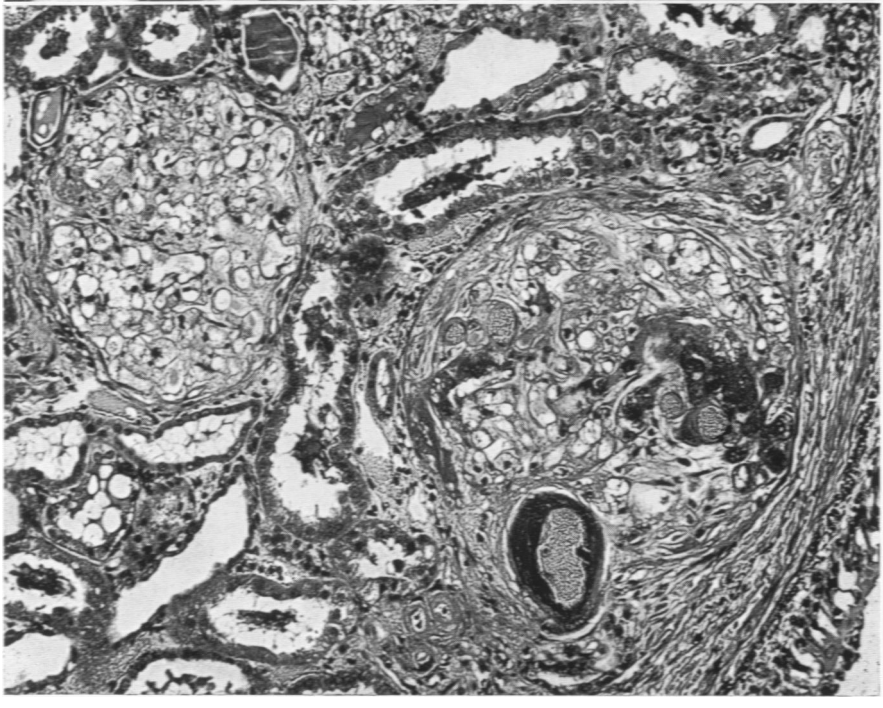
Legends for Figures

Fig. 1. Microangiograph showing cortex of normal rat kidney. Note straight arteries and afferent arterioles with their uniform and wide diameter, and abundant peritubular capillary plexus of uniformly fine caliber. × 40.

Fig. 2. At left, Glomerulus which has become obsolescent almost exclusively on basis of methylcellulose vacuolar lesions, with no patent glomerular loops remaining yet showing little evidence of hypertensive alterations. At right, Glomerulus has suffered severe hypertensive alterations. Those capillaries still patent show marked deposition of fibrinoid, eosinophilic material in their walls. Note that afferent arteriole, though severely damaged and showing marked fibrinoid change, is widely patent, with larger-than-normal lumen. Hematoxylin and eosin. × 175.

1



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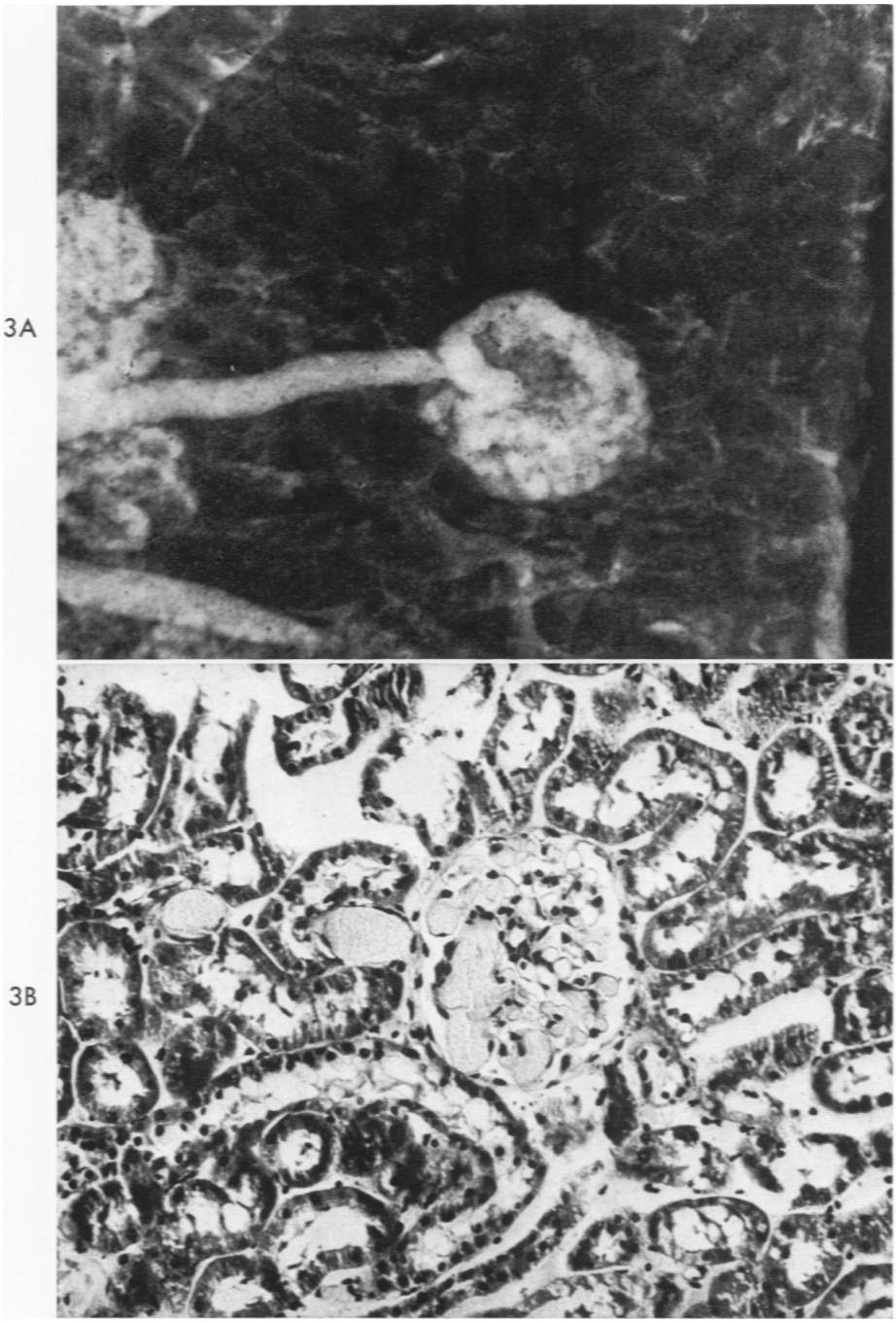
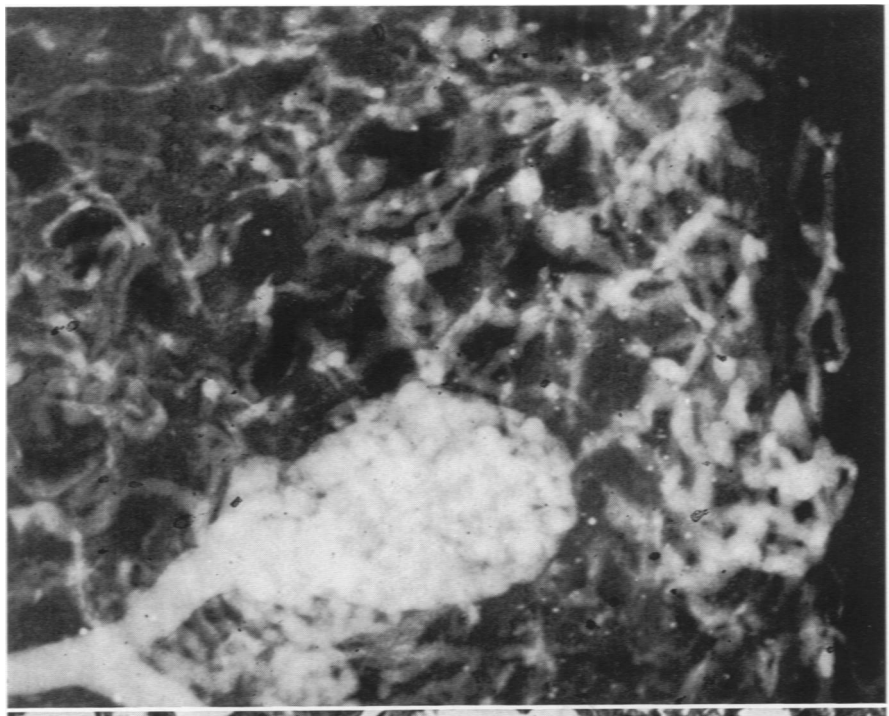


Stages in glomerular obsolescence as seen microangiographically and histologically. Differences in magnification between microangiographs and histologic sections are because of tissue shrinkage during paraffin-embedding.

Fig. 3. A and **B.** Normal glomerulus. Glomerular capillaries form tightly knit, knobby ball, and postglomerular capillaries are of uniformly fine caliber. Finely stippled material in glomerular capillaries in histologic section is barium sulfate. **A,** × 200. **B,** Hematoxylin and eosin. × 250.



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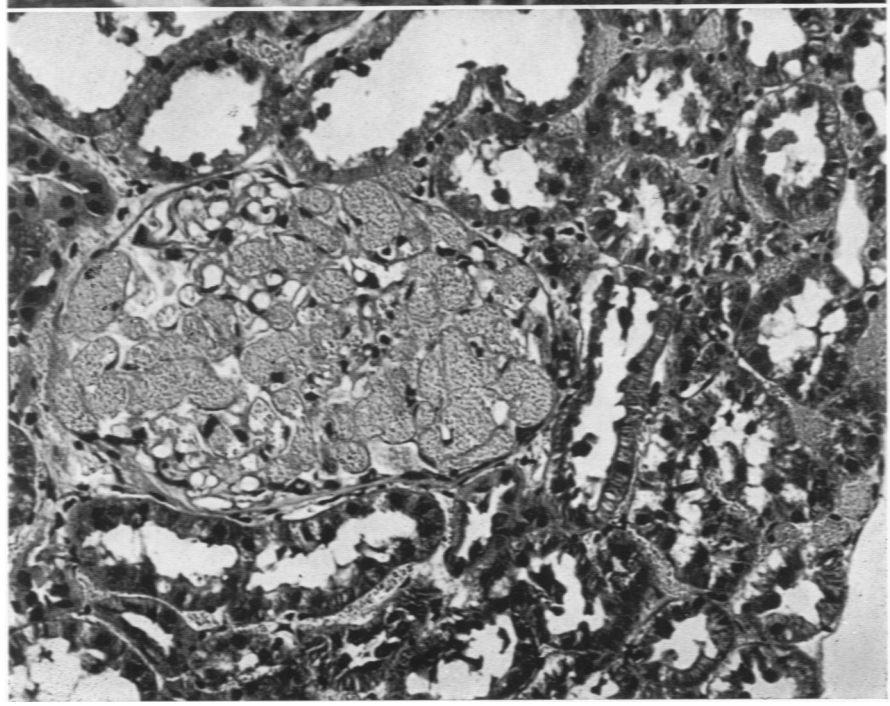


4B

Fig. 4. A and B. Glomerulus with "sunbursting" in postglomerular capillaries, but no angiographic evidence of glomerular simplification or histologic evidence of hypertensive lesions. Minimal methylcellulose vacuolar lesions are present, appearing as small empty spaces in the glomerular tuft, unfilled with barium sulfate. A, × 200. B, Hematoxylin and eosin. × 300.

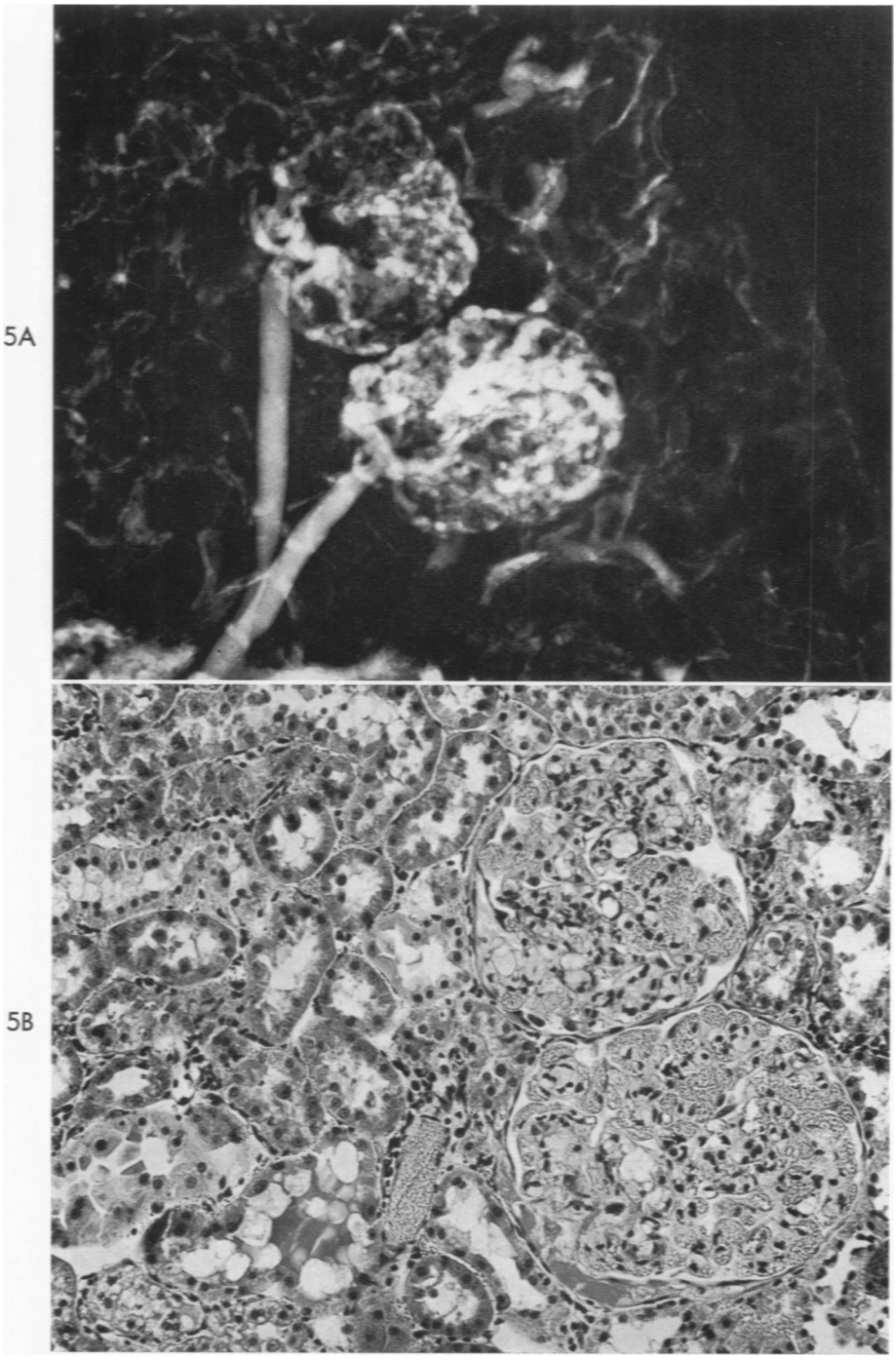


Fig. 5. A and B. Glomeruli in which there is early evidence of glomerular simplification, as evidenced by "looser" appearance of glomerular capillary pattern. Histologically there is evidence of methylcellulose vacuolar lesions and of early eosinophilic hypertensive alterations. These are associated with disappearance of "sunbursting" in the post-glomerular vasculature. A, × 150. B, Hematoxylin and eosin. × 200.

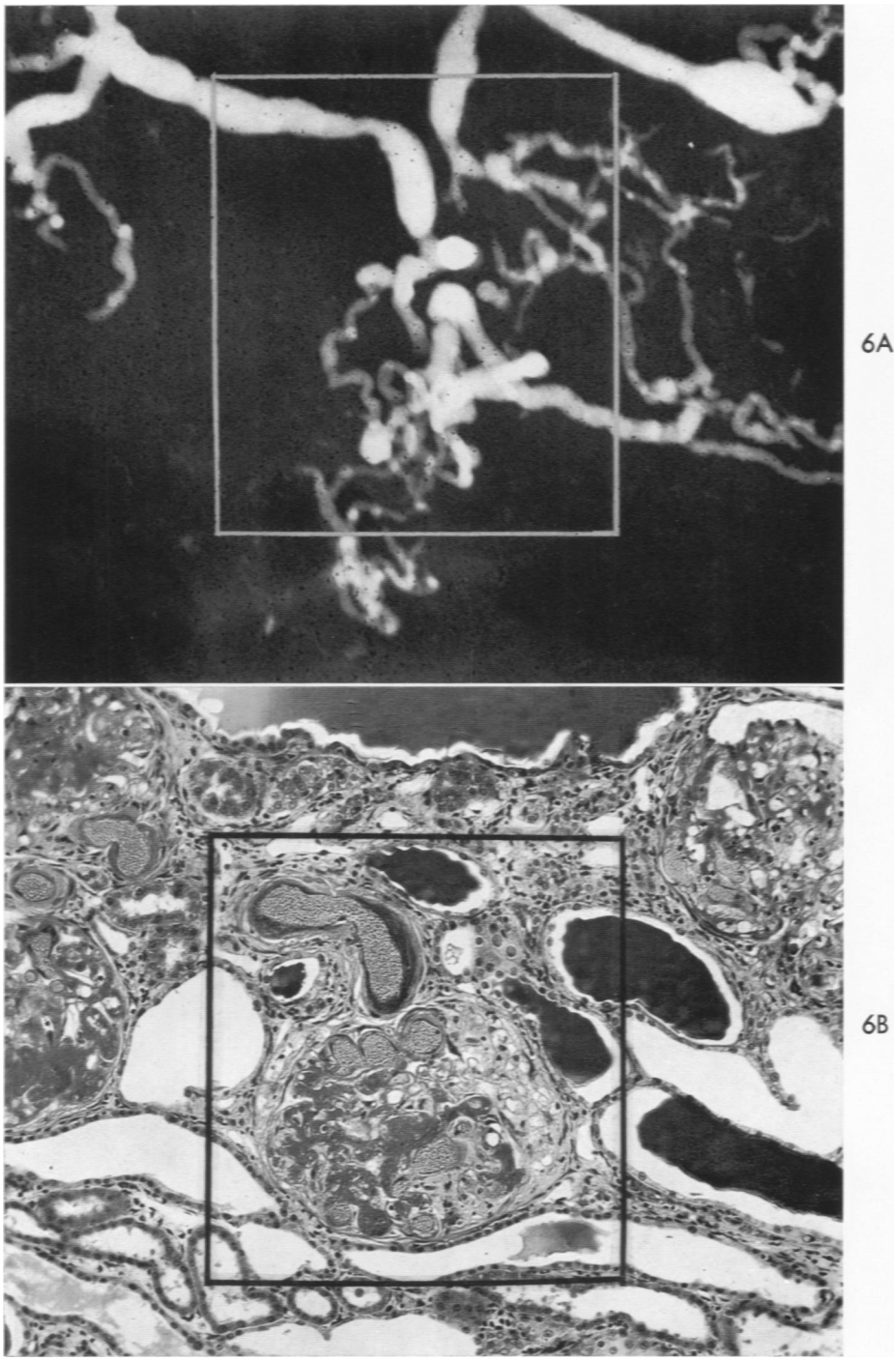
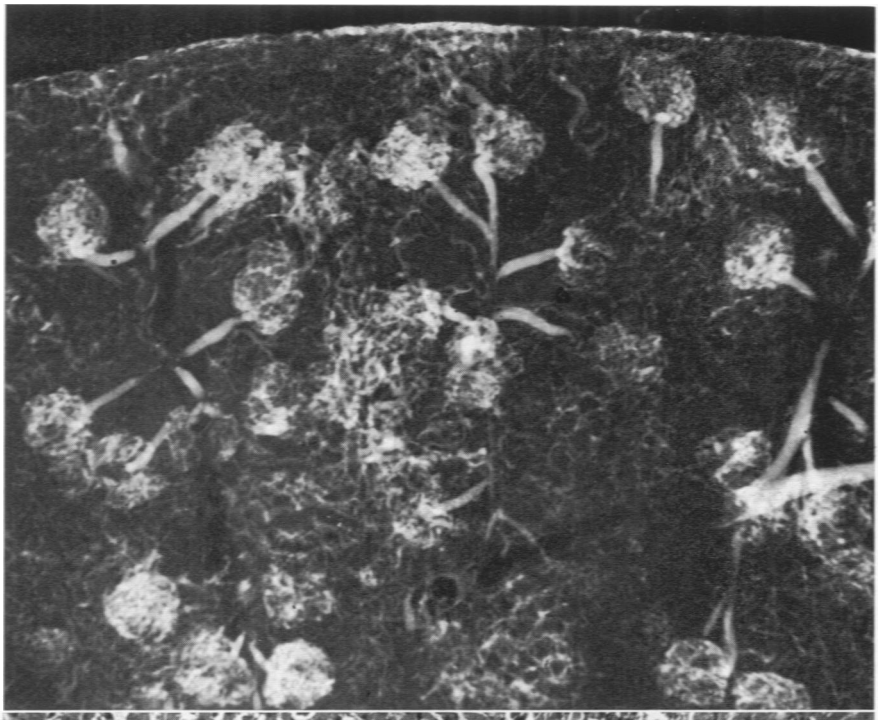


Fig. 6. A and B. Glomerulus (in box) showing marked capillary simplification owing to methylcellulose and hypertensive lesions seen histologically. (Portion of second glomerulus and its afferent arteriole, lying out of plane of histologic section, are visible in upper right corner of box in microangiograph.) Despite severe fibrinoid changes, afferent arteriole is widely dilated. In this glomerulus there has been persistence of the "sunburst" phenomenon in postglomerular capillaries. **A,** × 150. **B,** Hematoxylin and eosin. × 150.

Fig. 7. Microangiograph demonstrating early evidence of hypertensive alterations. Although afferent arterioles are widely patent interlobular arteries are not well visualized, indicating probable vasoconstriction at some level in preglomerular vasculature. In many places the peritubular capillary plexus around individual glomeruli is widely dilated, giving distinctive "sunburst" appearance. (Compare with Fig. 1.) × 60.

Fig. 8. Histologic section from region depicted in Fig. 7. No evidence of hypertensive alteration is visible in glomeruli or vessels, although some vacuolar methylcellulose lesions are present. Peritubular capillaries are widely distended. Hematoxylin and eosin. × 150.



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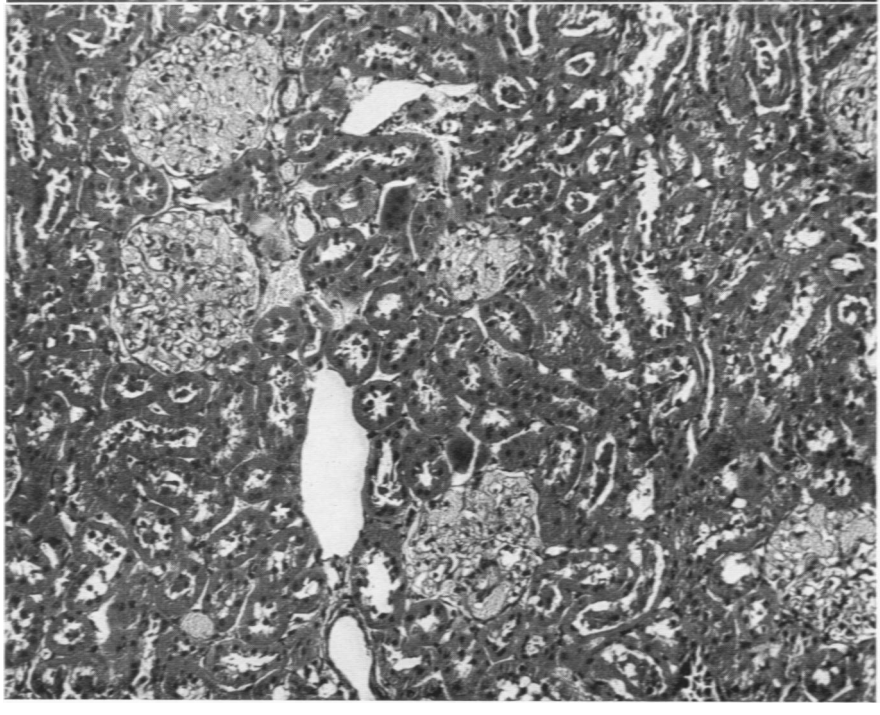

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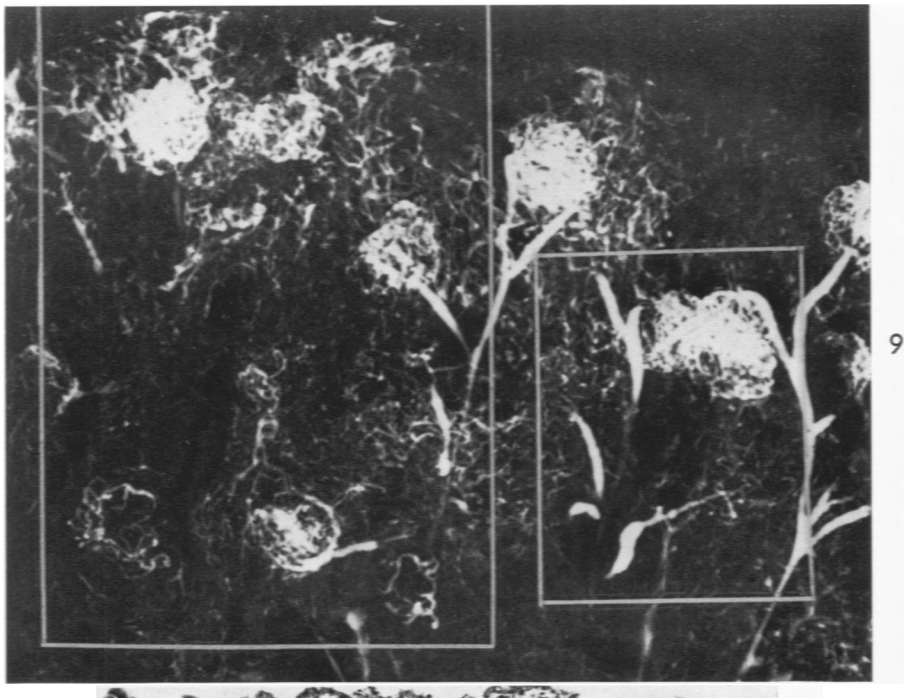
Fig. 9. Microangiograph from kidney showing moderately severe hypertensive lesions. In peripheral cortex most of glomeruli appear relatively intact and many show "sunburst effect." Near corticomedullary junction, however, numerous glomeruli are in various stages of obsolescence (note particularly lower portion of left box). Peritubular capillary filling is poor or absent in vicinity of these glomeruli. Although most afferent arterioles are well visualized, interlobular arteries are slender and threadlike, indicating vasoconstriction at some level in arterial tree. At this stage constriction is fairly uniform; however, 1 afferent arteriole (lower portion of right box) shows localized area of dilatation (See Fig. 10 and 11). × 70.

Fig. 10. Histologic section from left portion of Fig. 9 (see box). Glomeruli tend to show less evidence of hypertensive alterations toward periphery. One glomerulus (left) has filled so poorly owing to capillary obstructive lesions that it is only faintly visible in microangiograph. Hematoxylin and eosin. × 90.



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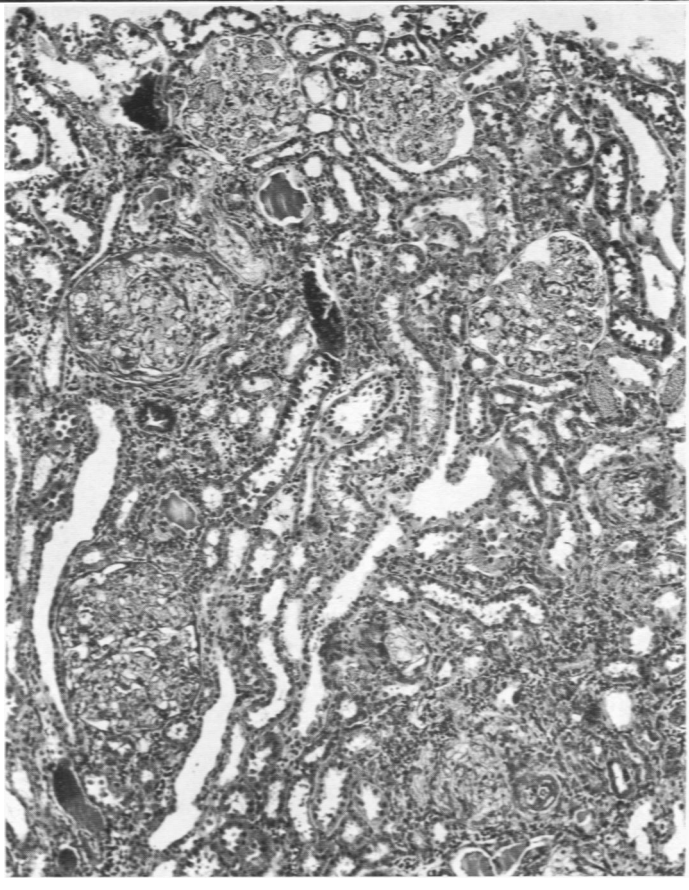

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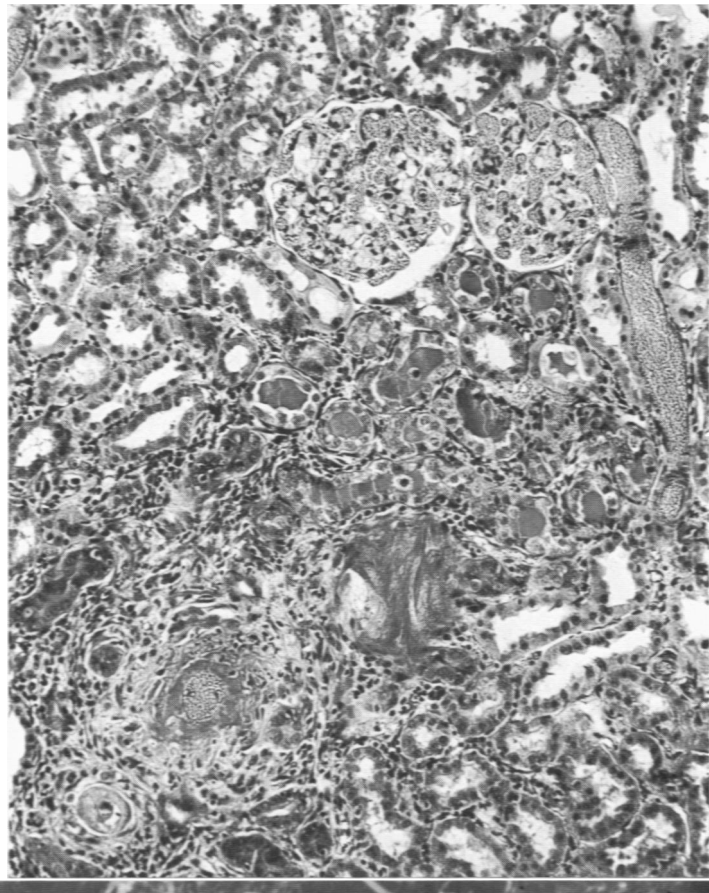
Fig. 11. Histologic section from right portion of region depicted in Fig. 9 (see box). Dilated segment of afferent arteriole seen in Fig. 9 is seen to have severe fibrinoid deposits in its wall with marked granulomatous reaction. Two glomeruli show little hypertensive alteration although there are methylcellulose lesions present. Hematoxylin and eosin. × 150.

Fig. 12. Glomerulus (center) showing great simplification. Blood enters from below through afferent arteriole, is carried through capillary loops and out through efferent arteriole on opposite side, after manner of Greek letter Ω. On right is another similar glomerulus with widely dilated efferent arteriole, showing an aneurysmal dilatation at one point. × 60.



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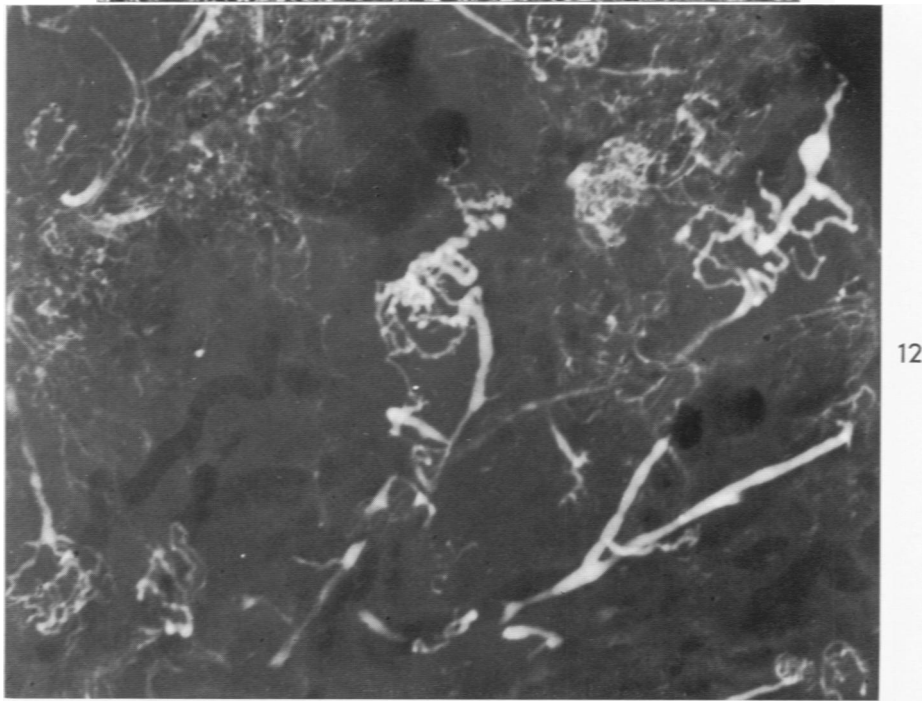

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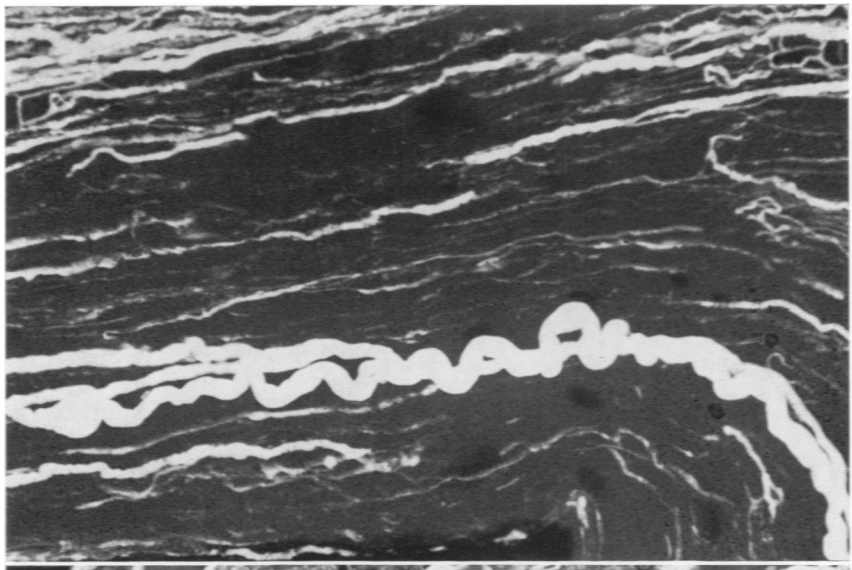
Fig. 13. A. Microangiograph of medulla in rat with moderately severe hypertensive lesions. Note extremely dilated and corkscrewed vasa recta in center and compare with more normal vasa recta above. × 60. **B.** Histologic section of greatly dilated vasa recta seen in Fig. 13A. Arrows point to accumulation of fibrinoid material in vessel wall. Hematoxylin and eosin. × 300.



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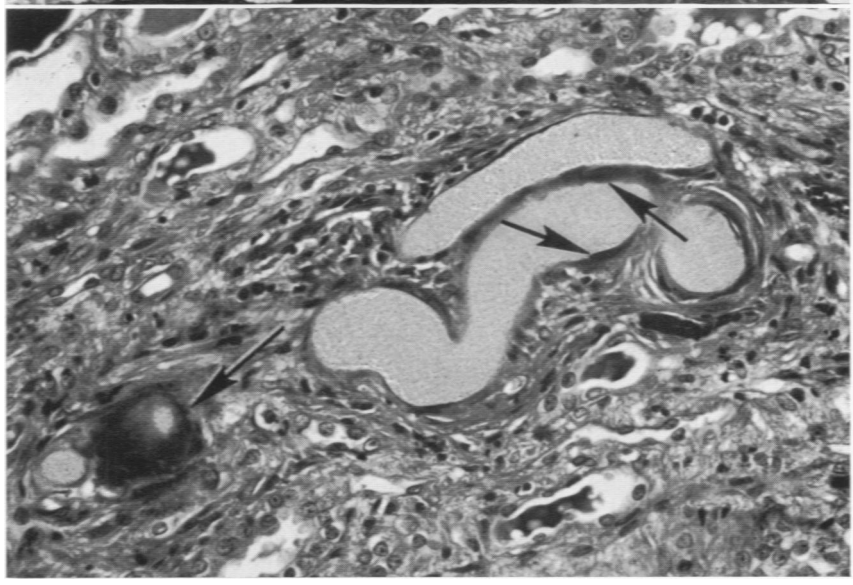

13B

Fig. 14. Microangiograph from kidney suffering severe hypertensive damage. (Arrows locate prominent landmarks for comparison with histologic section in Fig. 15.) Note areas of segmental dilatation and constriction, particularly in interlobular artery and afferent arteriole on far left but present in numerous other vessels as well. At lower right is arteriola recta vera (arrow points to glomerular portion) with widely dilated efferent limb. × 70.

Fig. 15. Histologic section of region shown in Fig. 14. Note segmental constriction and dilatation in interlobular artery passing diagonally upward to right and also in interlobular artery and afferent arteriole on the far left (see Fig. 14). Toward lower right is glomerulus (arrow) seen in preceding picture to have been converted into an arteriola recta vera. (Not all vessels present in microangiograph can be identified in histologic section, because microangiograph is 400 μ thick; histologic section taken from it is 5 μ. Many structures in microangiograph, e.g., lower portion of large interlobular artery, may not be in plane of a given histologic section.) Hematoxylin and eosin. × 70.

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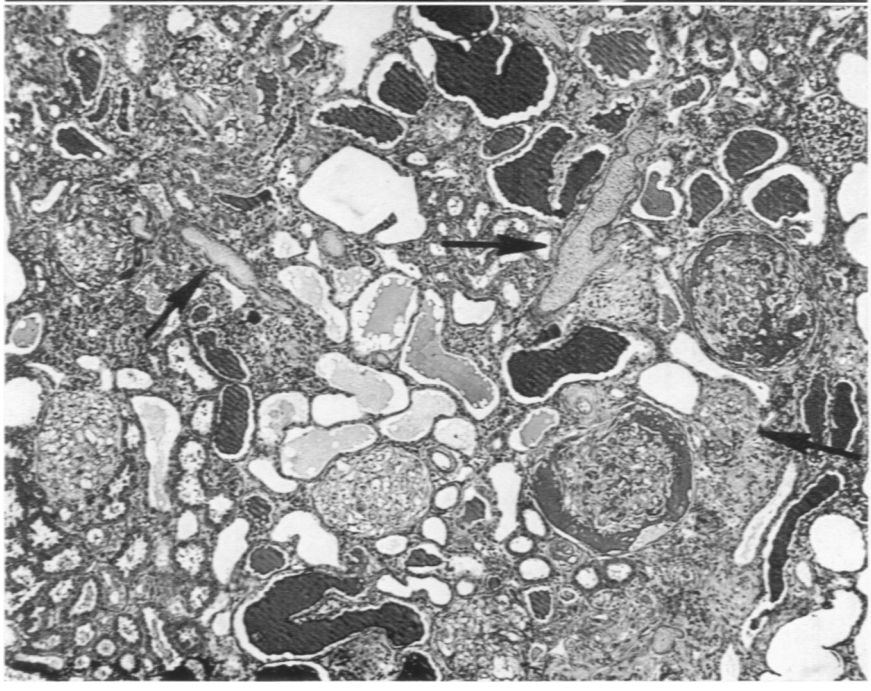

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Fig. 16. Higher-power view of interlobular artery shown by arrow on left in Fig. 15. Lower portion is contracted and appears quite normal. Remainder shows alternate dilatation and constriction. First two dilated segments show no obvious morphologic change, but 3rd (uppermost) segment displays fibrinoid necrosis. Afferent arteriole to glomerulus in upper left corner is out of plane of section. Hematoxylin and eosin. × 300.

Fig. 17. Higher-power view of interlobular artery on right in Fig. 15, showing alternating segments of dilatation and constriction. There is no obvious histologic alteration in either dilated or constricted segments of this vessel. Hematoxylin and eosin. × 300.

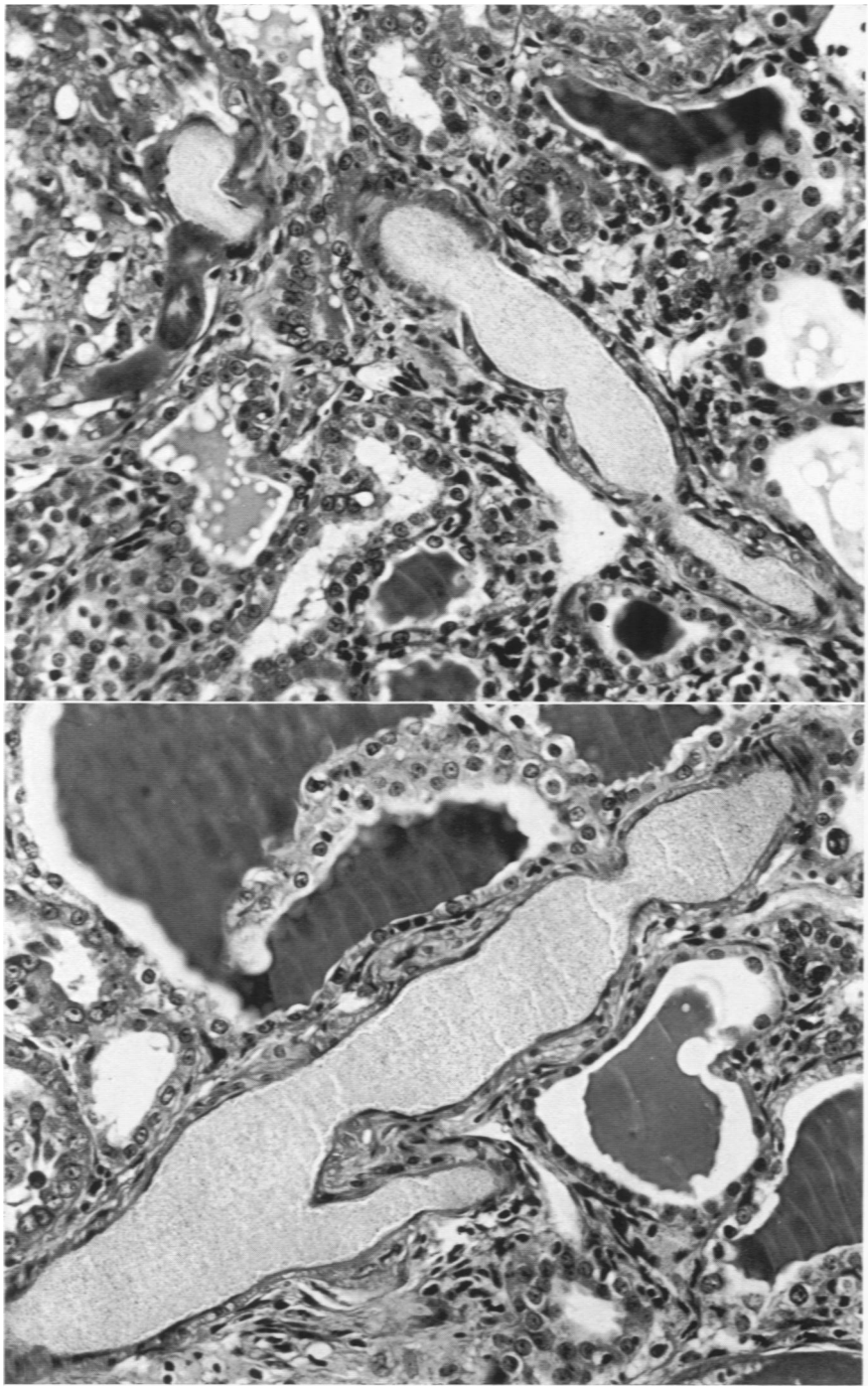

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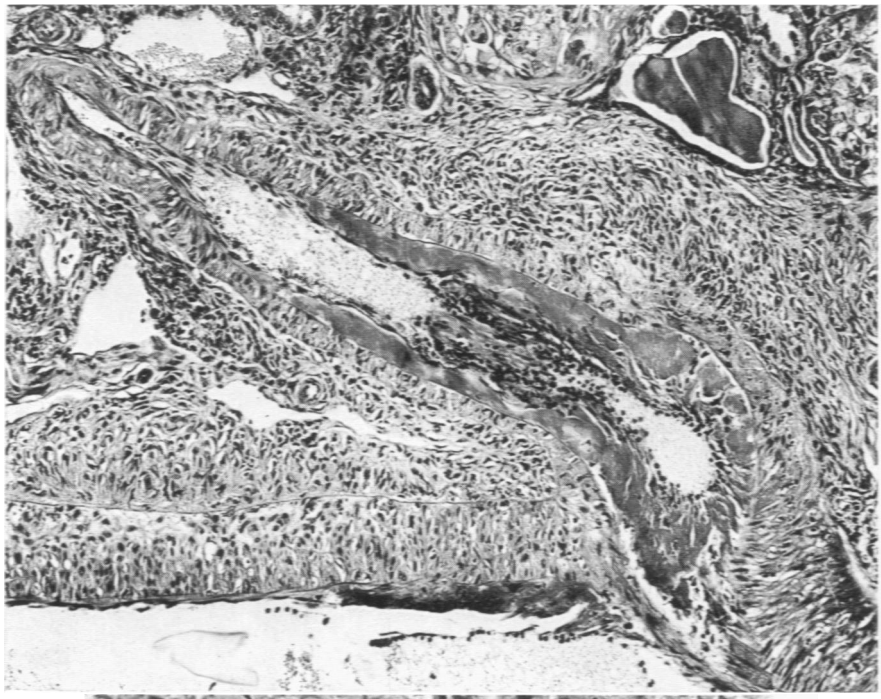
Fig. 18. Fibrinoid and granulomatous lesions in interlobular artery at and near point of branching from segmentary artery (only 1 wall shown). Only in contracted portion at upper left is smooth muscle layer reasonably intact; elsewhere it shows necrosis and inflammatory response. Lumen in damaged portion is even more widely patent, despite large accumulation of fibrinoid material, than in undamaged portion. Hematoxylin and eosin. × 125.

Fig. 19. Arcuate artery showing considerable accumulation of fibrinoid material and granulomatous response. Internal elastic lamina underlying fibrinoid deposits is distended and smooth, whereas in uninvolved areas it presents crinkled, corrugated appearance typical of vessel in contraction. Muscle layer beneath distended lamina shows varying degrees of necrosis and inflammatory cell infiltration, whereas beneath the crinkled lamina it appears relatively intact. Hematoxylin and eosin. × 300.



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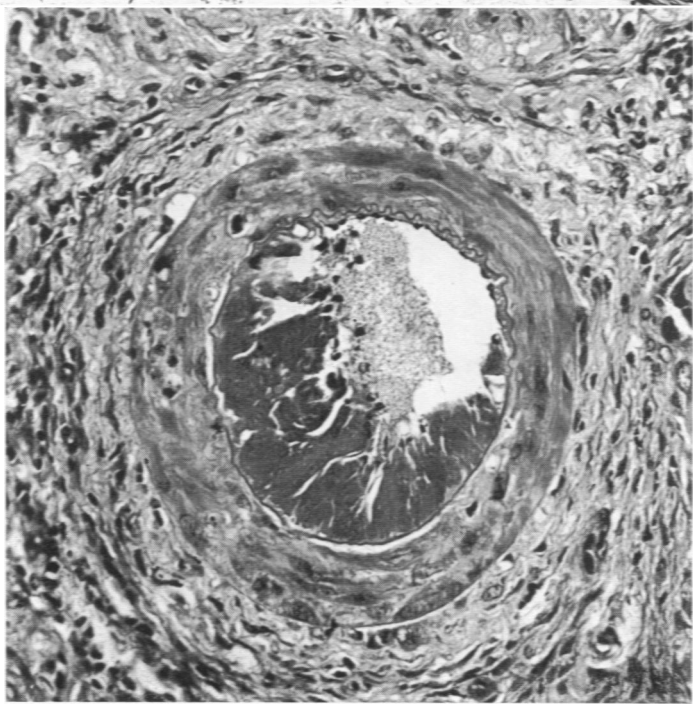

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