PRODUCTION OF OCCLUSIVE VASCULAR LESIONS BY BACTERIAL ENDOTOXIN IN KIDNEYS OF RATS WITH DEOXYCORTICOSTERONE HYPERTENSION

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Deoxycorticosterone acetate (DOCA) produces a characteristic syndrome in partially nephrectomized rats kept on a high sodium diet, which in many ways resembles the morphologic and functional aspects of human hypertensive vascular disease.[1,2] The administration of renin-containing kidney extract to such rats, according to Masson, Corcoran and Page,[3] results in an eclampsia-like syndrome with renal vascular lesions primarily involving the glomeruli. In the course of our study of DOCA hypertension in the rat, an attempt was made by various means to alter the course of the disease. This report describes the morphologic alterations noted after the administration of 5-hydroxytryptamine (5HT), bacterial endotoxins, and renin-containing kidney extracts (renin) to DOCA-hypertensive rats.

The effects of renin previously observed [3] are confirmed in this report. 5HT was given in view of its reported nephrotoxicity [4] and its suggested role in the etiology of essential hypertension [5] and eclampsia.[6] Bacterial endotoxins are known to be vasculotoxic. Their administration in various species results in renal cortical necrosis and also intravascular deposition of fibrinoid,[7] features which are at times encountered in different forms of hypertensive vascular disease. Our observations show some histologic similarities between the renal lesions caused by renin and endotoxin. Moreover, demonstrating that the renal vasculature in DOCA-hypertensive rats is unusually reactive to bacterial endotoxin, the present study may have implications in relation to the pathogenesis of human eclampsia and malignant nephrosclerosis.

MATERIAL AND METHODS

Carworth Farm Nelson rats of both sexes, weighing approximately 150 gm., were used. Hypertension was produced by unilateral nephrectomy, subcutaneous implantation of two 25-mg. pellets of DOCA, and the substitution of 1 per cent sodium

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chloride for drinking water. Within 3 weeks all of the animals were hypertensive, with systolic blood pressures in excess of 150 mm. of Hg. Systolic blood pressures were measured at regular intervals by the microphonic method of Friedman and Freed,[8] with the animals under light ether anesthesia.

The renal extract, containing 0.55 dog units of renin per mg., was prepared from hog kidneys by Dr. Oscar Helmer (Lilly Research Laboratories) and purified *Escherichia coli* endotoxin was prepared by the method of Webster, Sagin, Landy and Johnson.[9] 5-Hydroxytryptamine was used as the creatinine sulfate.

The schedule of treatment in the different categories is summarized in Table I.

In the first series of experiments, animals with DOCA hypertension of short duration (30 days after implantation of DOCA pellets) were divided into 4 groups. Group I consisted of untreated controls. Rats in group II received 3 subcutaneous injections of renin, 0.25 ml. (15 dog units) each, 12 hours apart. The animals in group III were given 5HT twice subcutaneously in doses of 1 mg. and 2 mg. respectively, 12 hours apart. Those in group IV received injections of endotoxin intraperitoneally in 2 doses of 1 mg. and 2 mg., respectively, 12 hours apart. Group V consisted of normotensive controls. Members of this group received renin, or 5HT, or endotoxin, according to the above-mentioned dose schedule. All surviving animals were sacrificed with chloroform 26 to 28 hours after the first injections, and necropsy examinations were performed immediately. Blocks of kidney, heart, and liver were fixed in Zenker's solution, and sections were stained with hematoxylin and eosin, and by the periodic acid-Schiff (PAS) method.

In another series of experiments, the effects of "endotoxin tolerance" and the long-term administration of endotoxin to normotensive rats with uninephrectomy and to those with DOCA hypertension were investigated. All animals listed in groups VI to IX received 400 μg. of endotoxin, intraperitoneally, weekly for 6 months. These groups consisted of normal animals divided as follows: Group VI served as controls. In group VII, rats were given 1 per cent NaCl instead of water. In group VIII they were kept on an "endotoxin tolerance regime" for 5 days (injection of 50, 100, 150, 200, 250 μg. of endotoxin daily), a procedure which makes rats resistant to normally toxic doses of endotoxin. At the end of this time, DOCA pellets were implanted subcutaneously. In group IX, in addition to the endotoxin tolerance course, rats were given 1 per cent NaCl as a substitute for water.

Groups X, XI and XII consisted of older DOCA-hypertensive animals. Group X served as controls. Group XI rats were given weekly injections of 400 μg. of endotoxin, and in group XII, in addition to the weekly injections of endotoxin, an endotoxin tolerance course was maintained before the implantation of DOCA pellets. All surviving animals in groups VI to XII were sacrificed with chloroform 6 months after the start of the experiments. Kidney, heart, liver and spleen were fixed in Zenker's solution, and sections were stained with hematoxylin and eosin and the PAS and azan-carmine stains.

Results

Short-term Experiments with Renin, 5HT and Endotoxin

Group I. The salient pathologic features of early DOCA hypertension, as described by various workers,[2,10] were reproduced (Figs. 1 and 2). Hematoxylin and eosin and PAS stained sections of kidneys revealed minimal thickening of small arteries and arterioles. In each midsagittal section of the entire kidney, one or two arterioles showed subintimal degeneration, which was PAS-positive; however, the lumens of such vessels were not compromised. The glomeruli exhibited little or no thicken-

TABLE I

EXPERIMENTAL PLAN

	No. and sex	Av. blood pressure on last day of experiment (mm. Hg)*	Av. wt. on last day of experiment (gm.)*	Duration of DOCA hypertension	Occurrence of occlusive glomerular lesion
Group I DOCA control	2 M 2 F	170	243	30 days	None
Group II DOCA + renin	3 M 3 F	172	254	30 days	4 of 6 †
Group III DOCA + 5HT	3 M 3 F	176	241	30 days	None
Group IV DOCA + endotoxin	3 M 3 F	177	235	30 days	4 of 6 ‡
Group V (normotensive) Renin or 5HT or endotoxin	2 F 2 F 2 F	115	262		None
Group VI Endotoxin control	4 F	110	290		None
Group VII Endotoxin + NaCl	4 F	116	283		None
Group VIII Endotoxin + endotoxin tolerance	4 F	116	289		None
Group IX Endotoxin + NaCl + endotoxin tolerance	4 F	122	279		None
Group X DOCA control	4 F	180	271	6 mo.	None
Group XI DOCA + endotoxin	10 F	199 §	267	6 mo.	8 of 8
Group XII DOCA + endotoxin + endotoxin tolerance	10 F	183	250	6 mo.	6 of 10

* In groups I to V data obtained refer to measurements made prior to injections.

† One animal died after first injection of renin.

‡ Two animals died after first injection of endotoxin.

§ Average in 8 animals; 2 died after 2 months of endotoxin treatment.

ing of the basement membrane. Occasional glomeruli were hyalinized, and a few showed focal necrosis of portions of their tufts. Scattered convoluted tubules were dilated and contained hyaline or red cell casts. The latter were most likely due to the focal necrosis in glomerular tufts. There was no evidence of inflammation.

Two of the 4 rats in this group exhibited small focal areas of necrosis

of myocardial fibers in the left ventricle. No lesions were noted in the livers.

Group II. The physiologic manifestations of the DOCA-renin syndrome were similar to those observed by Masson, Corcoran and Page.[11] Blood pressures measured one hour after the first injection of renin indicated an average rise of 30 mm. of Hg. The second injection induced convulsions, hematuria and anasarca in surviving animals.

Sections of kidneys (Fig. 5) revealed lesions characterized by fibrinoid degeneration of the capillary walls and basement membranes in the tufts of the majority of glomeruli in 4 of 6 rats. There was cytoplasmic degeneration of endothelial and epithelial cells especially in those portions bordering the basement membrane. This degeneration, evidenced by PAS-positive droplets in the cytoplasm, occasionally resulted in coalescence, leading to obliteration of capillary lumens. In a few of the glomeruli there were focal intraluminal deposits of homogeneous PAS-positive material with preservation of the related capillary wall. All 6 animals in this group had pathologic changes in arteries, arterioles and tubules, identical to those seen in the DOCA controls (group I).

Small foci of myocardial necrosis were seen in 2 of the 4 rats with glomerular occlusion and in 1 of the 2 rats that failed to develop this lesion. In the liver, no lesions were seen.

Group III. The only pathologic alterations in DOCA-hypertensive animals given 5HT were those seen in DOCA controls (group I). Blood pressures taken one hour after the first injection of 5HT showed an average reduction of 20 mm. of Hg.

Group IV. Endotoxin administration resulted in diarrhea, prostration, and evidence of shock in all animals within this group. An average of 50 mm. of Hg drop in blood pressure was noted one hour after the first injection of endotoxin. Such a dose (1 to 2 mg.) is rarely fatal in normotensive controls and causes only mild malaise but no evidence of circulatory collapse.

Four of the 6 animals given endotoxin revealed intraluminal deposition of homogeneous PAS-positive material in most of the glomerular capillaries. The occluding deposit was dense and resembled fibrinoid (Fig. 6). In addition, the glomerular basement membranes in these 4 rats were moderately thickened by granular masses of PAS-positive substance, similar to, but less extensive than that observed following the administration of renin (group II). Although 2 of the animals in this group failed to exhibit these lesions, they showed arterial, arteriolar and tubular alterations identical to those in DOCA controls (group I). It is interesting to note that the occlusive glomerular lesion was most marked in animals with the highest blood pressures (Table II).

In 1 of the 4 rats with the occlusive glomerular lesion and in 1 without this lesion there were small focal areas of myocardial necrosis. The liver in 1 animal showed numerous areas of centrilobular necrosis with an early neutrophil infiltration. This animal lacked the occlusive glomerular lesion but had focal myocardial necrosis. The liver damage was probably secondary to shock induced by endotoxin.

Group V. Microscopic examination of the kidney, liver and heart in normal animals receiving renin, or 5HT, or endotoxin revealed no lesions.

TABLE II

INCIDENCE OF OCCLUSIVE RENAL LESIONS IN RATS TREATED WITH ENDOTOXIN

	Animal no.	Blood pressure before endotoxin injection (mm. Hg)	Blood pressure before sacrifice, 24 hr. after endotoxin (mm. Hg)	Occlusive glomerular lesion *
Group IV	1 †	202		+++
DOCA hypertension + 1 mg. and	2	190		++
2 mg. of endotoxin, 12 hr.	3	175		++
apart	4	162		o
	5	164		o
	6 †	170		++
Group XI	1		198	++
DOCA hypertension + 400 μg. of	2		220	++
endotoxin once weekly for	3		202	+++
6 mo.	4		196	++
	5		222	+++
	6		180	++
	7		190	++
	8		182	+
Group XII	1		202	++
DOCA hypertension + endotoxin	2		156	o
tolerance + 400 μg. of endo-	3		215	+++
toxin once weekly for 6 mo.	4		190	++
	5		194	++
	6		190	o
	7		158	o
	8		148	o
	9		186	+
	10		192	++

* Severity of lesions is graded by number of plus signs; o indicates absence of lesion.
† Died 10 hours after first injection of endotoxin.

Long-Term Experiments with Endotoxin

Groups VI, VII, VIII and IX. Since the histologic appearance of the organs in all these groups was essentially normal, it is unnecessary to describe each group in detail. Suffice it to say that the substitution of 1 per cent NaCl for water did not produce a significant rise in blood pressure and did not predispose the animals toward the development of renal lesions during the long-term treatment with endotoxin.

Group X. The pathologic features previously outlined as characteristic of DOCA hypertension were severe (hypertension of 6 months duration) and quite similar to those found in malignant nephrosclerosis (Figs. 3 and 4). Sections of kidney showed marked fibrous thickening of small arteries and arterioles with some concomitant narrowing of the lumens, subintimal fibrinoid degeneration of arteriolar walls, fibrous thickening of glomerular basement membranes and, occasionally, complete fibrous obliteration of glomerular tufts. There were varying degrees of tubular damage ranging from dilatation and hyaline cast formation to atrophy with the appearance of minute rings of cells.

Examination of the heart, liver and spleen showed no noticeable pathologic alterations.

Groups XI and XII. The two groups are considered together since "endotoxin tolerance" did not influence the development of the occlusive lesions and did not prevent the appearance of DOCA hypertension. The weekly administration of 400 μg. of endotoxin did not significantly alter the course of DOCA hypertensive disease. Systolic blood pressures reached hypertensive levels approximately 3 weeks after the implantation of DOCA pellets and remained at this high level throughout the experiment. The average weight of these animals was lower at the end of the experiment than that of uninephrectomized controls receiving endotoxin.

Microscopic examination of the kidneys revealed a striking homogeneous, intraluminal deposit, resulting in occlusion of glomerular vessels, afferent arterioles and small arteries; these changes were similar to those found in group IV. In addition, the pathologic features due to long-standing DOCA hypertension (see group X) were also present.

Small, scattered focal collections of chronic inflammatory cells were found in the renal cortex in most of these rats, but they lay in relation to vascular scars and were not the result of any infectious process. The sub-epithelial tissues of the renal calyces were free of any inflammatory cells in all but 3 rats. The azan-carmine stain was used to distinguish the generalized basement membrane thickening and fibrosis from the intraluminal deposit of fibrinoid which occluded glomerular vessels. The latter stained bright red; the fibrous tissue thickening the glomerular basement membranes and the walls of small arteries and arterioles stained blue.

Review of the lesions disclosed that the most marked deposition of fibrinoid occurred in animals having the highest blood pressure recordings (Table II). Four of 18 rats failed to develop this lesion.

Three animals showed small focal areas of myocardial fibrosis in the

left ventricle. Examination of livers and spleens revealed no significant pathologic alterations.

Discussion

DOCA and other sodium-retaining adrenal cortical steroids are believed to play a role in the pathogenesis of hypertension. The substitution of 1.75 per cent NaCl for water may, in itself, cause hypertension in adrenalectomized rats.[12] The long-term administration of DOCA and salt together in experimental animals seem to act synergistically to produce a hypertensive syndrome with concomitant renal alterations and to sensitize such animals to vasoactive agents.

Renin injections to early DOCA-hypertensive animals elicited degenerative changes in glomeruli which bore a resemblance to renal lesions found in malignant nephrosclerosis. Attention has been brought to the fact that the existence of DOCA hypertensive disease is a prerequisite to the syndrome elicited by renin since the concurrent injections of DOCA and renin do not produce glomerular lesions.[11]

The renal cortical necrosis reported by Fiore-Donati and Erspamer[4] and Waugh and Pearl,[13] and the thrombotic lesions observed by Page and Glendening[6] following 5HT administration were not observed in the present study. It should be pointed out, however, that the doses and route of administration of 5HT by these investigators were quite different from ours.

The foregoing observations afforded definite evidence that the intraperitoneal administration of endotoxin to rats with early DOCA hypertension produced a characteristic glomerular lesion reminiscent of some of the lesions found in eclampsia and malignant nephrosclerosis. The findings seemed to indicate that DOCA hypertensive disease was prerequisite to the appearance of endotoxin-induced renal lesions in the rat since in the absence of DOCA hypertension, neither endotoxin nor the substitution of 1 per cent NaCl for drinking water brought about lesions in the kidney. Some of the degenerative glomerular changes elicited by renin or long-standing DOCA hypertension were found to a lesser extent after endotoxin administration to rats with early DOCA hypertension. In the latter case, however, the presence of intracapillary fibrinoid thrombi was the most impressive observation.

The rat generally is quite resistant to the effects of bacterial endotoxin, while man, the rabbit and the dog are much more susceptible. In the rabbit, for example, two intravenous injections, spaced 24 hours apart, produce the familiar generalized Shwartzman reaction, characterized by the intracapillary deposition of fibrinoid material in glomeruli and by bilateral renal cortical necrosis.[7] Gronvall and Brunson[14] pro-

duced this phenomenon in rats by the intraperitoneal administration of endotoxin in conjunction with the high molecular weight acidic polymer, sodium polyanethanol sulfonate (Liquoid). The lesions produced by the injection of endotoxin to DOCA-hypertensive animals described in this paper have a resemblance to the renal vascular lesions seen in the generalized Shwartzman reaction, in that the intraluminal deposit of fibrinoid was a prominent finding in both cases.

It is important to emphasize that there was a direct relation between the severity of the occlusive phenomena and the height of blood pressure in our experiments. Animals that failed to develop these lesions were generally those with near normal blood pressures. The indication is that high blood pressure alone or increased circulating DOCA with concomitant sodium retention, or both, can "prepare" the glomerular vessels for the "provocative" effects of endotoxin as does the "preparatory" dose of endotoxin in the production of the generalized Shwartzman reaction. In the same manner pregnancy seems to be able to take the place of the "preparatory" dose of endotoxin since in the pregnant rabbit a single injection of toxin will induce the renal lesions.[15]

Opinions differ as to the pathogenetic interpretation of renal lesions in human eclampsia. Recent publications by McKay and his associates [16,17] indicated that eclampsia was primarily a disorder characterized by intravascular thrombosis brought about by a mechanism similar to that of the generalized Shwartzman reaction. They postulated that pregnancy "prepared" the blood vessels for the provoking action of toxin which could originate either in the placenta or from a bacterial infection. The reduced fibrinolytic activity and the fibrinogenemia during pregnancy,[18] together with the increase in fibrinogen due to one endotoxin injection,[19] may facilitate the development of thrombosis. The reproduction of the renal features of human eclampsia in the experiments reported in this paper provide indirect evidence for the participation of endotoxin (or bacterial infection) in the pathogenesis of the disease. Mention should be made of a recent publication by Stamler [20] in which it was reported that pregnant rats kept on vitamin E deficient diet containing polyunsaturated fatty acids manifested the physiologic and histologic changes seen in eclampsia.

The observations in the present work have additional interest in that animals with early DOCA hypertension treated with endotoxin showed some degenerative changes in the glomerular basement membranes resembling those seen in malignant nephrosclerosis. It is thus conceivable that the human counterpart to this syndrome may be induced by bacterial infection, especially since it has been shown that hypertensive humans [21] and animals [22,23] are much more prone to succumb to pyelone-

phritis than normotensive subjects, and that a considerable proportion of patients with pyelonephritis develop malignant nephrosclerosis.[24]

Summary

Rats with DOCA hypertensive disease of short duration were subjected to various regimes of injections with renin, 5-hydroxytryptamine, and endotoxin. Rats with prolonged DOCA hypertension were also investigated with respect to long-term administration of endotoxin.

Four of 6 rats given renin exhibited an eclampsia-like syndrome accompanied by a degenerative glomerular lesion. 5HT treatment did not produce any noticeable pathologic alterations.

Endotoxin administered in various dose schedules to rats with early as well as long-standing DOCA hypertension produced a striking occlusive glomerular lesion associated with fibrinoid degeneration of glomerular basement membranes in 18 of 24 animals. The histologic lesion seen in these kidneys had the salient features of human eclampsia and reproduced some of the changes seen in the generalized Shwartzman phenomenon. Severity of renal involvement was related to the height of blood pressure.

It is suggested that DOCA hypertension as well as pregnancy may manifest increased renal vascular reactivity to endotoxin, resulting in the development of renal lesions.

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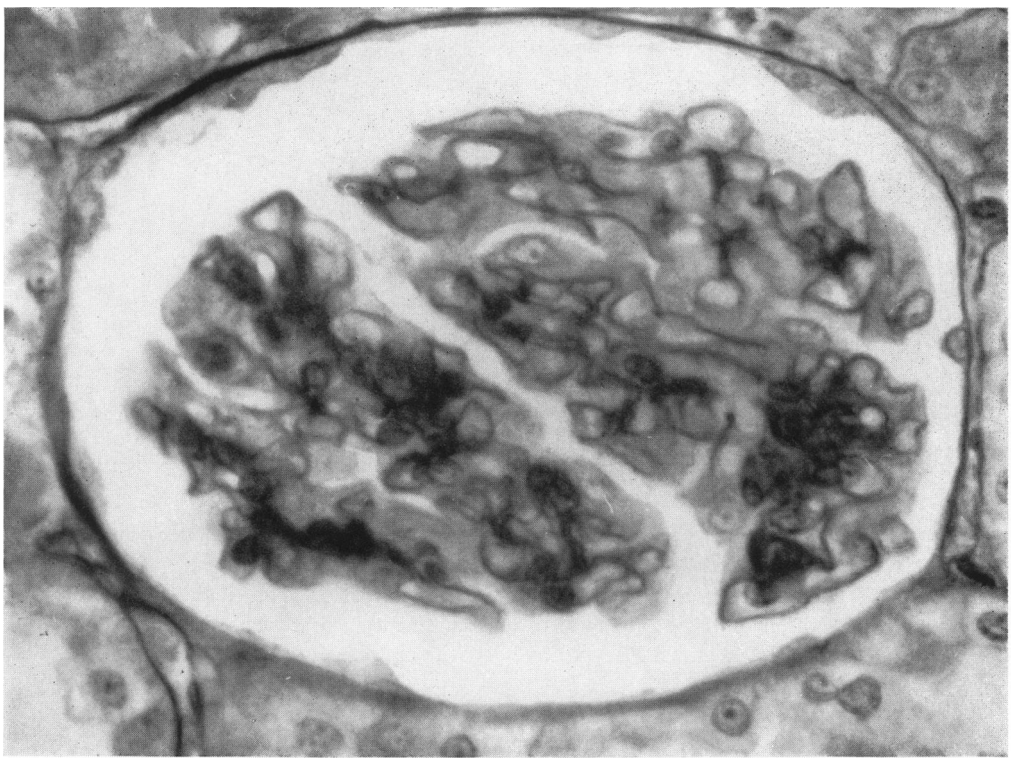
[*Illustrations follow*]

Legends for Figures

Illustrations were prepared from sections stained by the periodic acid-Schiff method.

Fig. 1. Normal glomerulus. × 600.

Fig. 2. Glomerular tufts in a rat with DOCA hypertension of short duration, showing minimal basement membrane thickening. × 800.



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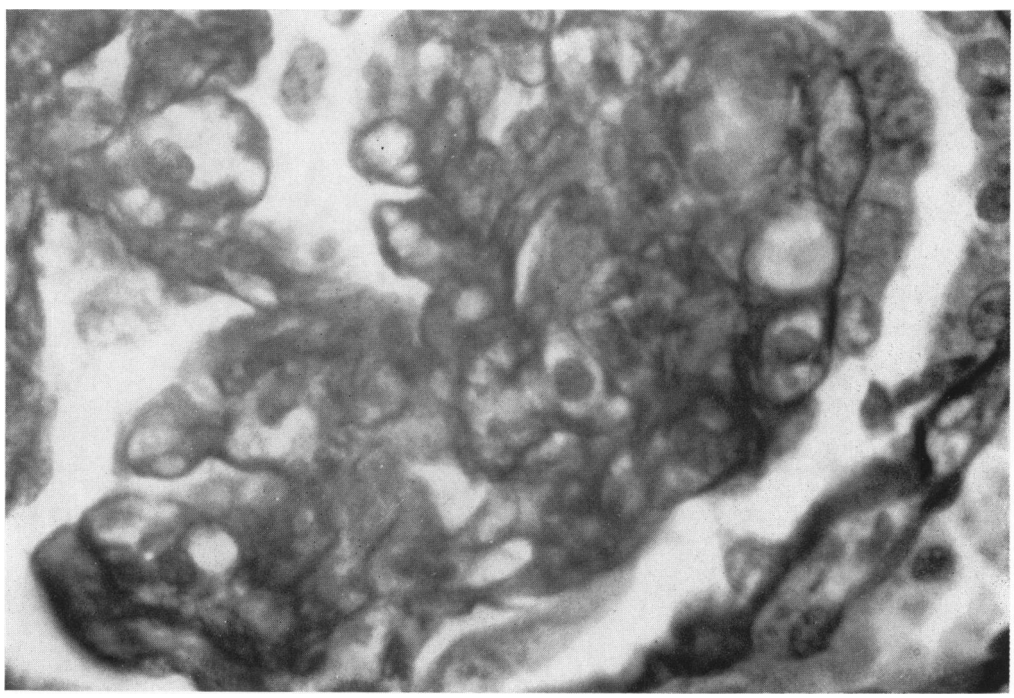

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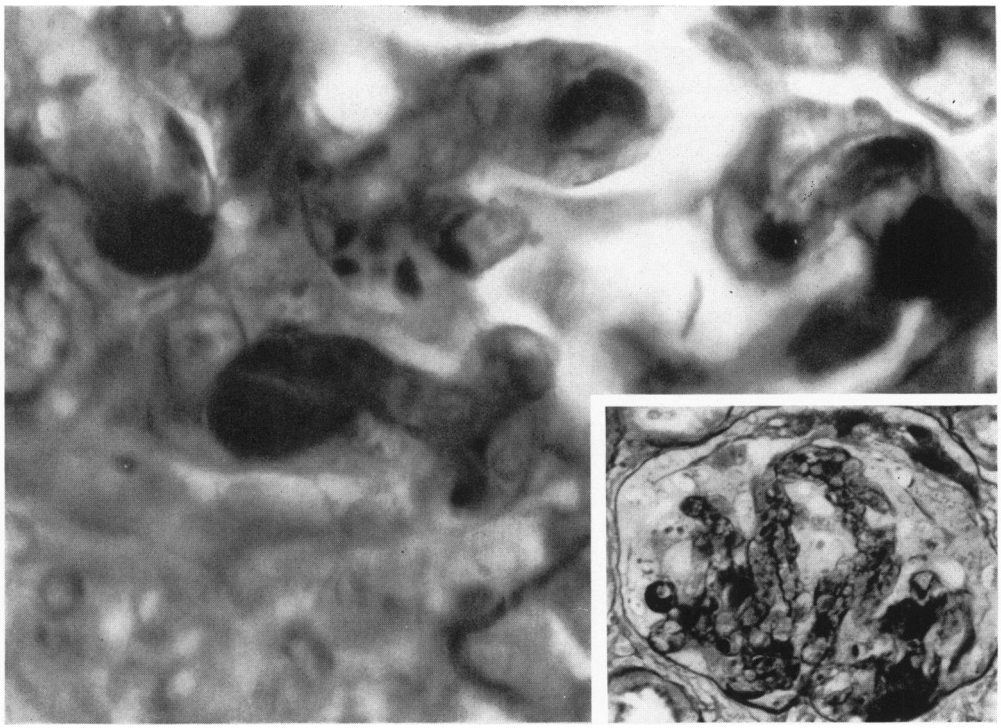
FIG. 3. Glomerulus in a rat with DOCA hypertension of long duration, demonstrating adhesions and fibrinoid degeneration of glomerular tufts. × 200.

FIG. 4. Higher magnification of a glomerulus in a rat with DOCA hypertension of long duration. Fibrinoid degeneration of tufts and adhesions are seen. × 800.

FIG. 5. Glomerulus in a rat with early DOCA hypertension given renin. Fibrinoid degeneration of the capillary walls and basement membrane is demonstrated. Occasional intraluminal PAS-positive deposits are seen focally. × 600.



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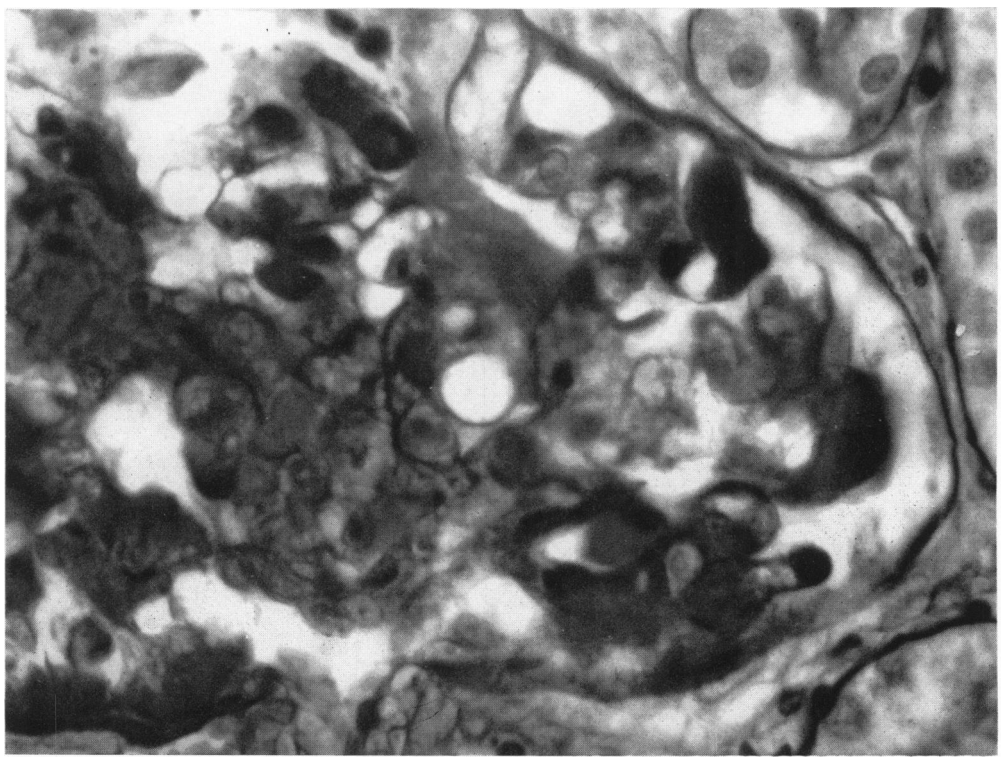

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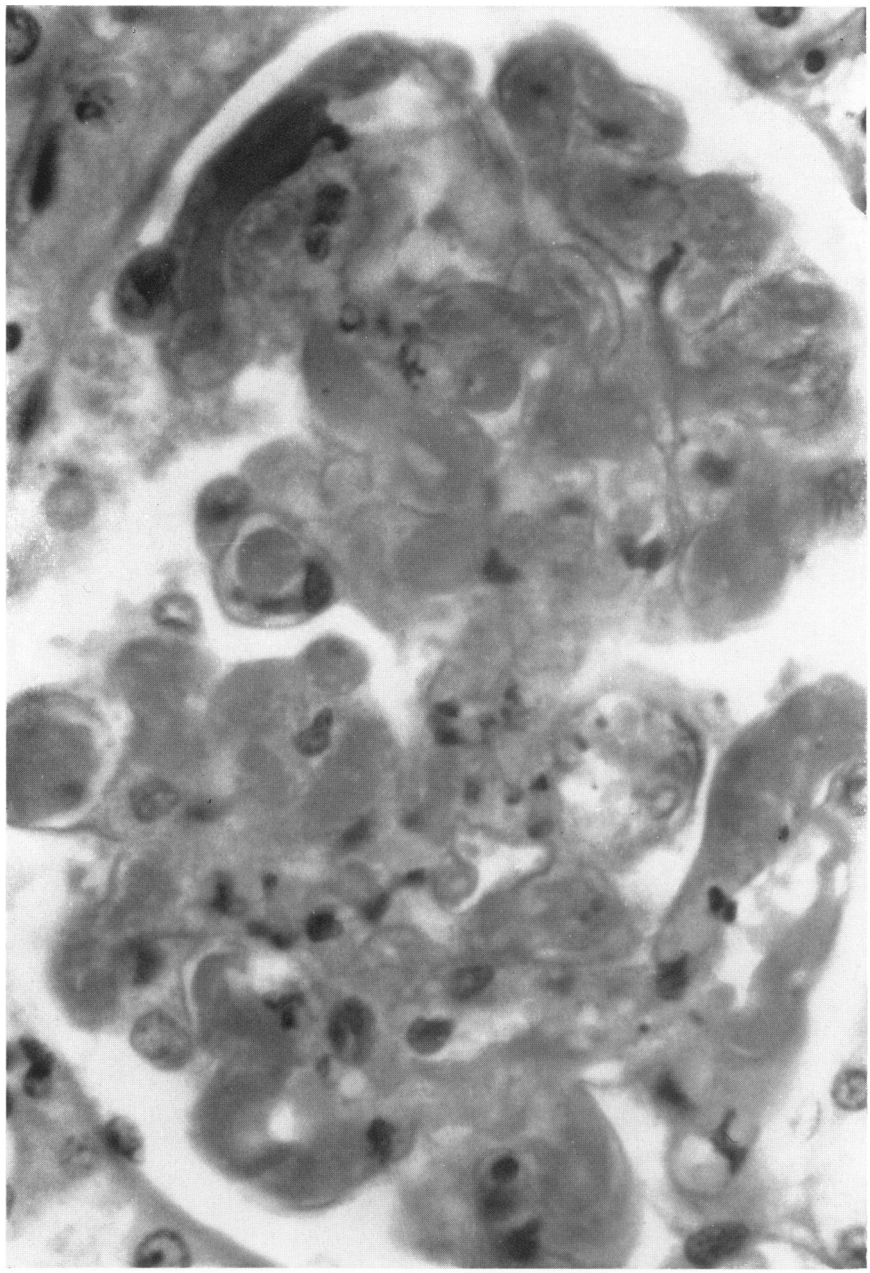
FIG. 6. Glomerulus in a rat with DOCA hypertension of short duration, given endotoxin. Note the striking deposition of intraluminal PAS-positive substance occluding glomerular capillaries. × 600.



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