Spontaneously Occurring Renal Disease in the Guinea Pig

Toshio Takeda, MD* and Arthur Grollman, MD, PhD

DISORDERS OF THE KIDNEY occurring spontaneously in laboratory animals are of interest because they may shed light on comparable disorders in human beings and for their potential effects on other experimental studies. In an attempt to induce the adrenogenital syndrome by cross-breeding various strains of guinea pigs, a high incidence of renal lesions which resembled the nephrosclerosis observed in hypertensive human beings was noted. The present study describes the incidence and nature of these lesions and their correlation with the arterial blood pressure.

Materials and Methods

Highly inbred guinea pigs of the Abyssinian and Hartley strains either born and reared in the laboratory or purchased from different dealers were maintained on commercial guinea pig chow (Ralston Purina Company) and tapwater, to which ascorbic acid (0.1%) was added, and given access to alfalfa hay *ad libitum*. A total of 79 animals of either sex were examined.

Blood pressures were recorded on a Sanborn apparatus (Model 152-100B) connected to a Statham transducer (Model p23AA and Gb) through a pE-50 polyethylene catheter inserted into the femoral artery under light ether anesthesia. The animals were exsanguinated through the carotid artery; the kidneys and hearts were weighed and, along with the adrenals, liver, gonads and pancreas, were fixed in 10% formalin, embedded in paraffin and stained with hematoxylin and eosin, PAS, PTAH and Verhoeff's elastic tissue stains.

At 2 and 5 months of age some of the animals were subjected to unilateral nephrectomy. The kidney was weighed and fixed for histologic examination as described above. Pieces of renal tissue from kidneys removed aseptically from animals 1–2 months of age were also incubated on blood-agar plates and in thioglycolate and tryptophosphate broth, and the cultured materials stained and examined for bacterial contamination.

To exclude the possibility that the observed lesions were laboratory-acquired, 6 pairs of animals were maintained in an enclosed open area during the warm months of the year, and allowed to graze on grass with access to hay, food and water as described above. The offspring of animals raised under these conditions

From the Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.

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Address for reprint requests: Dr. Arthur Grollman, University of Texas Southwestern Medical School, 5323 Harry Hines Blvd, Dallas, Texas 75235.

* Present address: Department of Pathology, Chest Disease Research Institute, Kyoto University, Kyoto, Japan.

were examined as described. A group of 12 of these animals were also injected every 2 weeks for 2–3 months after weaning with either cyclosphosphamide in doses of 50 mg/kg body weight or cortisone acetate suspension in doses of 50 or 100 mg/kg body weight and examined as described above.

Immunofluorescence studies of the affected blood vessels, precipitin tests of the sera by the Ouchterlony technic with tissue extract as antigen, and serum globulin concentrations were determined by procedures described elsewhere.[1]

Results

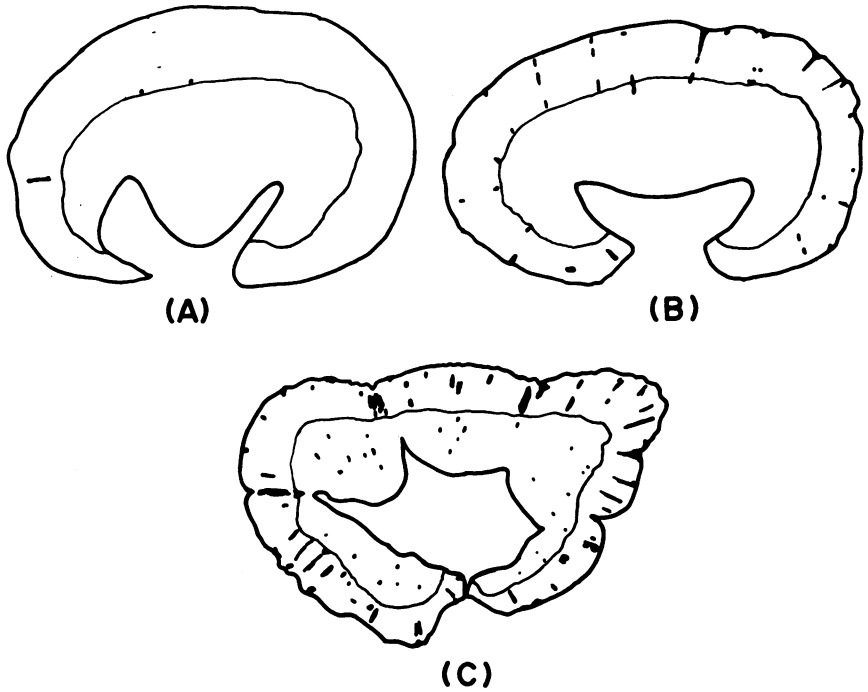
When examined at 1 month of age, none of the animals showed gross lesions of the kidney (Fig 1). At 2 months of age, small pitting lesions were noted on the surface of the kidneys of the Abyssinian strain (Fig 2) but were not apparent in the Hartley strain. Microscopically, the initial lesions appeared in the kidney of the Abyssinian strain at 1 month of age and in the Hartley strain at 2 months of age. By 5 months of age, lesions were noted in all animals (Fig 3) but were more pronounced in the Abyssinian than in the Hartley strain. No difference in the severity of the lesions was noted between male or female animals of either strain. By the eighth month of age the kidney surface was distinctly pitted and now showed uniform granularity with faint areas of pallor.

The lesions progressed gradually with age and at 15–17 months of age the surface of the kidney was pale and granular with irregularly infarcted areas and a narrowed cortex as shown in Fig 3. The lesions in both kidneys were essentially of the same severity. No pathologic changes were seen in the pelvis of the kidney at any age in either strain.

Microscopically, the first lesions appeared in the cortex as small foci (Text-fig 1A) which gradually spread toward the surface of the kidney (Text-fig 1B), ultimately involving the medulla at 17 months of age (Text-fig 1C). The earliest lesions consisted of arteriolar thickening and narrowing caused by the proliferation of smooth muscle and endothelial cells. As the lesion progressed, there was proliferation of connective tissue with gradual replacement of the smooth muscle and endothelial elements. The most advanced lesions presented hyalinized connective tissue which replaced normal smooth muscle, intercellularly and throughout much of the endothelial structure of the blood vessel.

The lesions were devoid of any arteriolar or periarteriolar infiltration of mononuclear cells (Fig 4–6) and there was no evidence of an inflammatory process suggesting pyelonephritis or interstitial nephritis (Fig 7). Most of the glomeruli were normal; only a few showed thickening of Bowman's capsule and fibrosis of the glomerular tuft (Fig 8).

At 2 months of age, the kidneys showed proliferation of interstitial connective tissue as well as distortion and irregularity of the tubular



TEXT-FIG 1. Schematic illustration of renal lesions, in sagittal section, of male guinea pigs (Abyssinian strain) at (*A*) 2 months of age; (*B*) 10 months of age; and (*C*) 17 months of age. Note linear spread of lesion, which appears first as a spot in cortex, along nephron with ultimate involvement of medulla at the older age.

lumen under the areas of pitting (Fig 9). These changes progressed with age. Only one animal of the Hartley strain at 17 months of age showed moderate lymphocytic infiltration of the cortical lesion (Fig 10) with scarring of the medullary tissue. Kidneys obtained at 15–17 months of age showed progression of the sclerotic lesions of the glomeruli, with proliferation of the interstitial connective tissues, and atrophy of the tubules (Fig 10). The small arteries as well as the arterioles in these kidneys showed some sclerosis.

Examination of other organs revealed no striking changes except for thickening of the arterioles in the testis and the small arteries of Glisson's capsule (Fig 11). There was no evidence suggestive of fibrinoid necrosis in the arterial or arteriolar walls or in other collagenous tissues.

Animals born and reared in the open revealed the same lesions as those reared in the laboratory. Accordingly, confinement and diet could not be responsible for the observed lesions. Animals treated with immunosuppressant drugs (cyclophosphamide and cortisone) also dis-

played the same lesions, indicating that these were not autoimmune in origin. Consistent with this finding was the failure to demonstrate γ globulin in the kidney by the fluorescent antibody technic and the absence of lymphadenitis.

Bacterial cultures of kidneys removed from 1- and 2-month-old animals revealed no evidence of bacterial infection.

Blood pressure gradually rose from an average of 55/40 mmHg at 1 month of age to 80/55 at 3 months of age, and 115/80 at 15 months of age, reflecting the spontaneous development of a mild degree of hypertension with age.

Discussion

The spontaneous lesions observed in the guinea pig, in the present study, resemble nephrosclerosis of the human being. As in the latter, the pathogenesis of the lesions in the guinea pig is conjectural. The results of the present study indicate that an autoimmune reaction or bacterial infection is not a likely cause of the disorder. The fact that narrowing of arterioles and small arteries was noted in parenchymatous organs other than the kidney suggests that some general vascular disturbance gives rise to focal areas of ischemia and scarring, with or without cell infiltration, which ultimately lead to granular contracted kidneys in the older animals.

The observed vascular changes differ from the periarteritis-like lesion accompanying hypertension and infection in the rat; [2] the spontaneously occurring nephritis observed in the mouse; [3] the chronic glomerular nephritis induced in mice by viral infection; [4] and the genetically controlled hereditary renal disease observed in a mutant strain of rats.[5] The results of the present study suggest that the renal lesion observed in the guinea pig is a consequence of narrowing of arterioles and small arteries (endarteritis obliterans), the pathogenesis of which is not apparent. The vascular lesion leads to local ischemia with the development of small areas of scarring, sometimes accompanied by cellular infiltration, and leading ultimately to a granular contracted kidney and at times infarction.

The observed rise in arterial blood pressure of our animals with age may be attributed to the spontaneously developing structural changes in the kidney aggravated by the loss of renal tissue in animals subjected also to unilateral nephrectomy.[6]

Summary

Lesions appear spontaneously in guinea pigs of the Abyssinian and Hartley strains which resemble those of nephrosclerosis in the human

being and differ from the spontaneously occurring and virus-induced nephritis previously observed in the mouse and rat. The lesions are not inhibited by immunosuppressant drugs (cyclophosphamide or cortisone) nor are they accompanied by bacterial infection of the kidney. The lesions progress with age and are apparently responsible for the gradual increase in systolic and diastolic blood pressure noted with increasing age.

References

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[Illustrations follow]

Legends for Figures

Fig 1. *(Top left)* Normal external appearance of kidney of a female guinea pig (Hartley strain) at 1 month of age. × 2.

Fig 2. *(Top right)* Kidney of a male guinea pig (Abyssinian strain) at 3 months of age showing pitting scattered over surface. × 2.

Fig 3. *(Bottom)* External and cross-sectional views of kidneys of female guinea pig (Hartley strain) at 17 months of age *(left)* and of male (Abyssinian strain) at 16 months of age *(right)*. Former shows uniform pitting of surface; latter shows uniform granularity of surface, with scattered areas of infarction and pale narrowed cortex. × 2.

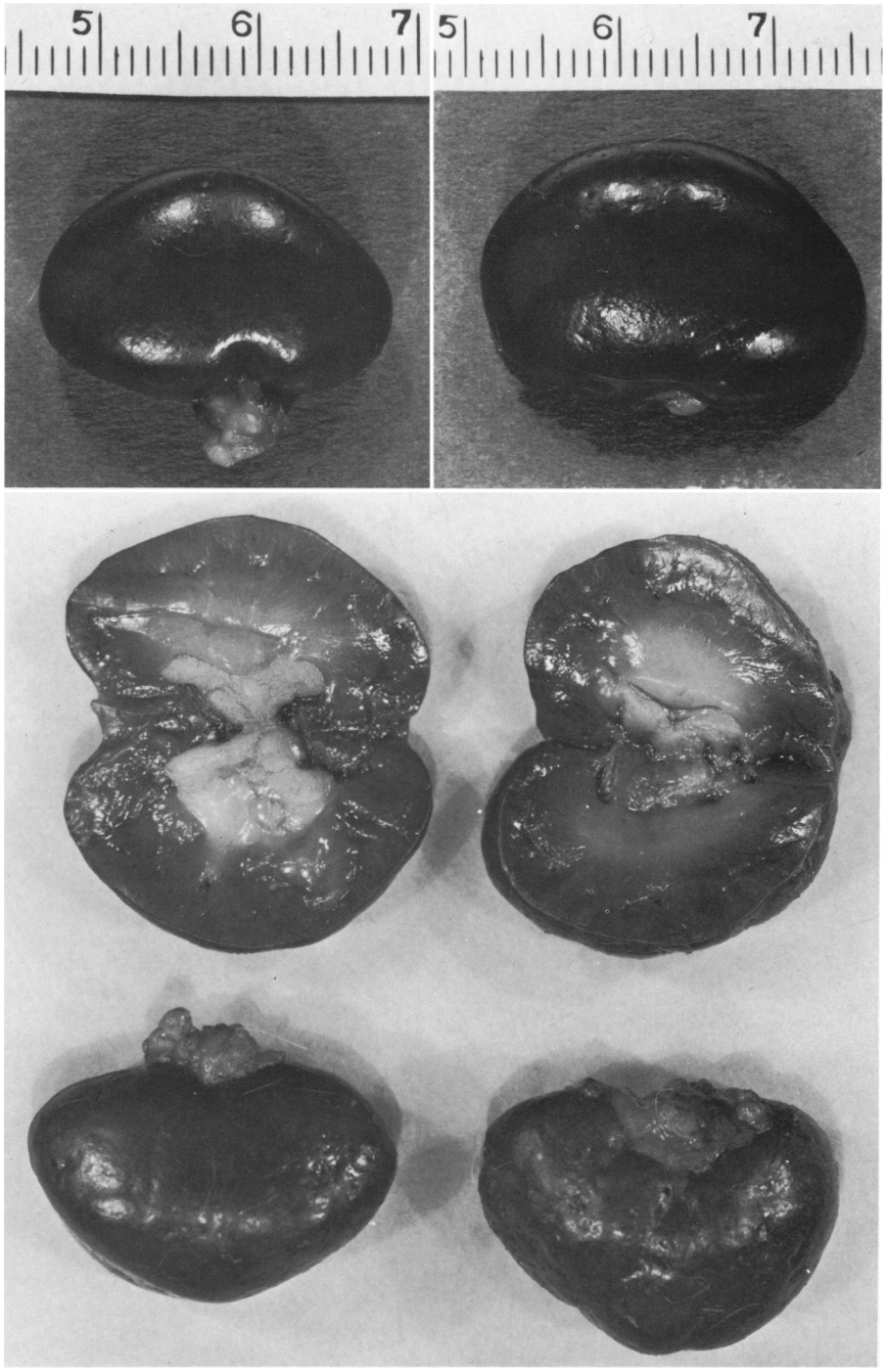
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Fig 4. (*Top*) Kidney of 1-month-old female guinea pig (Hartley strain) showing thickening of arterioles in cortex and narrowing of their lumens without inflammatory reaction and normal glomeruli. H&E. × 200.

Fig 5. (*Bottom*) Kidney of 2-month-old male guinea pig (Hartley strain) showing progression of arterial lesion. H&E. × 525.

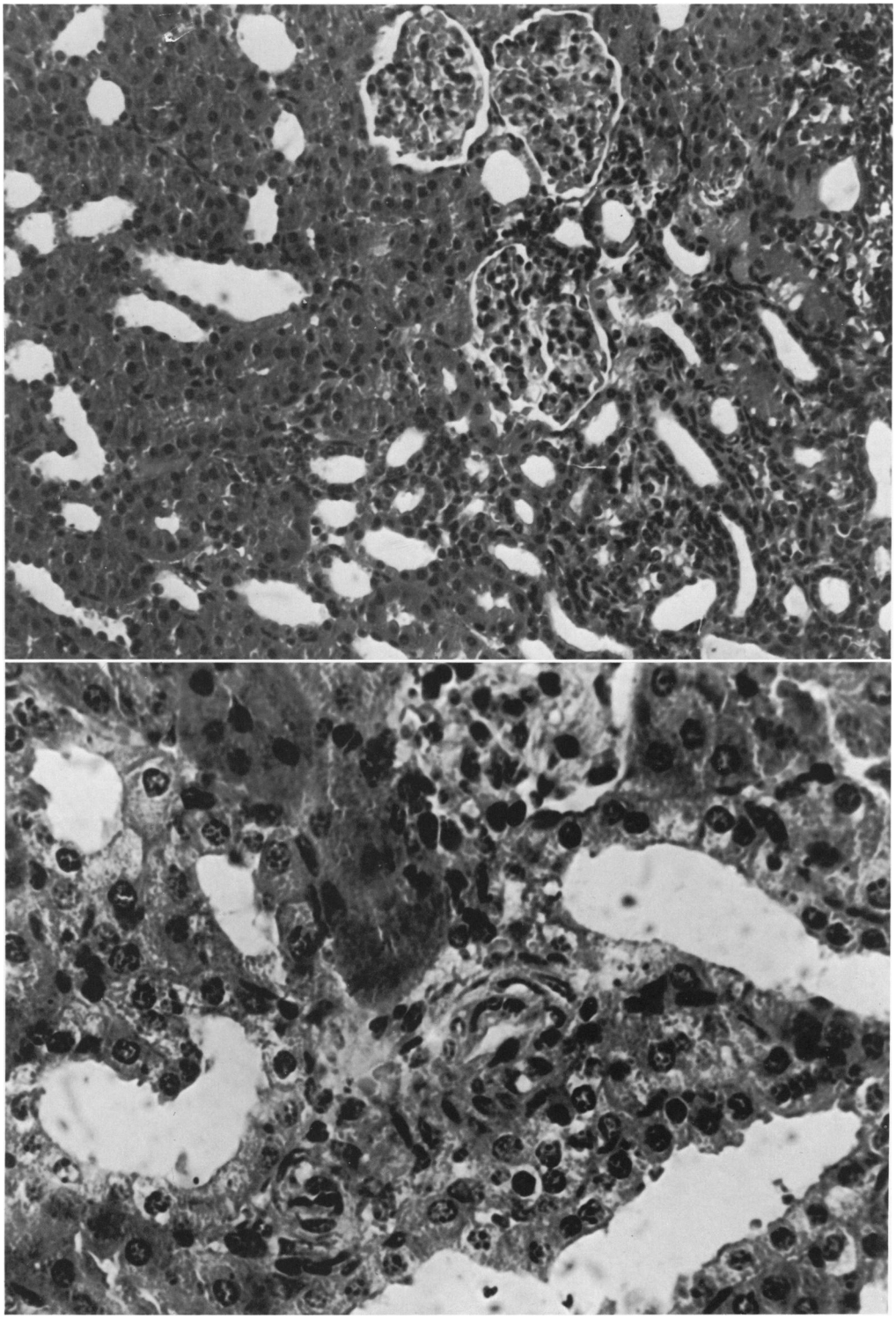


Fig 6. (*Top*) Kidney of 2-month-old male guinea pig (Abyssinian strain) showing arteriolar sclerosis of vasa afferentia. H&E. × 425.

Fig 7. (*Bottom*) Kidney of 2-month-old male guinea pig (Abyssinian strain) showing absence of inflammatory changes in pyramids and pelvic mucosa. H&E. × 170.

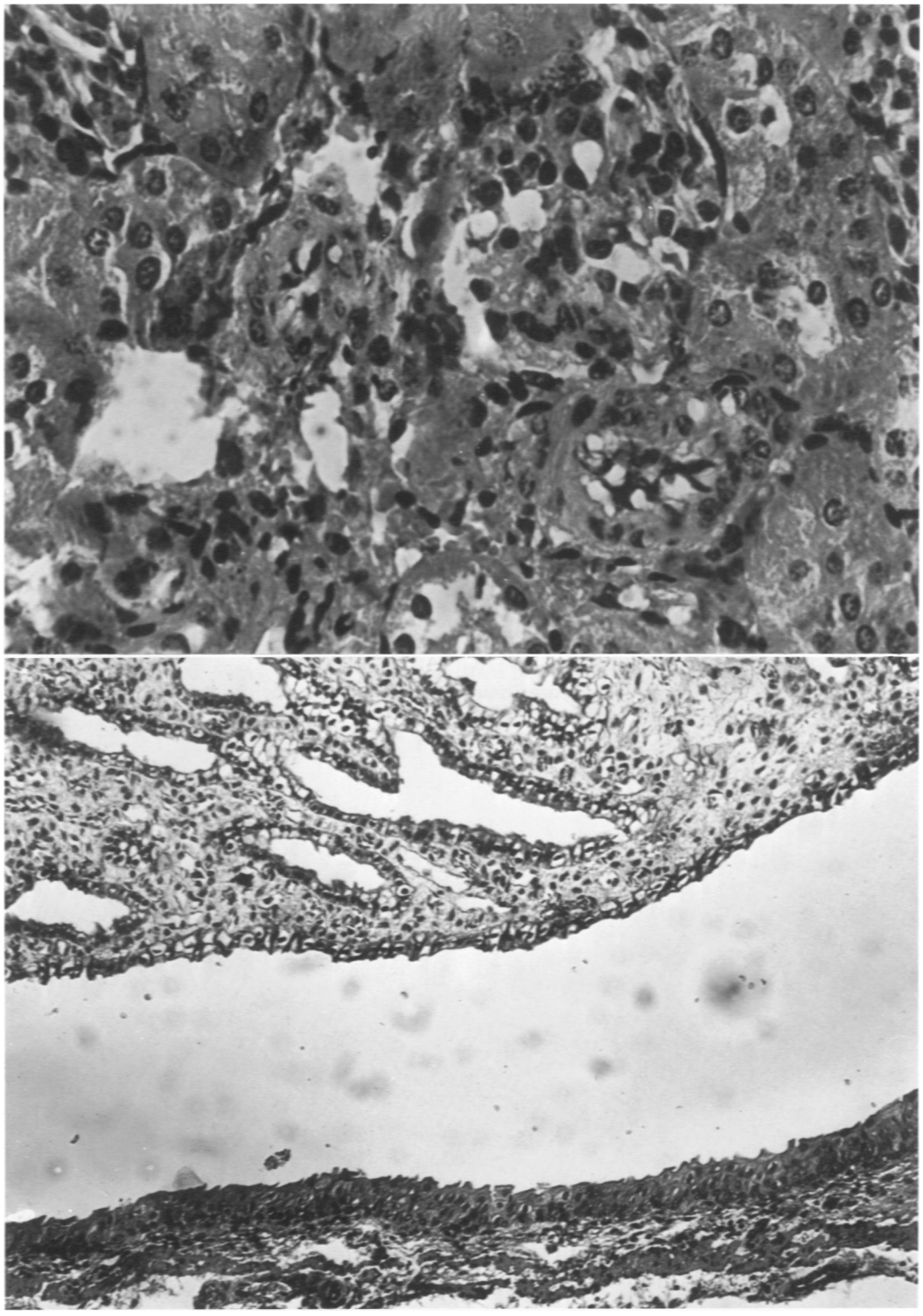


Fig 8. (*Top*) Kidney of 1-month-old male guinea pig (Abyssinian strain) showing marked thickening and hyalinization of Bowman's capsule and nodularity of glomerular tufts. H&E. × 800.

Fig 9. (*Bottom*) Kidney of 2-month-old male guinea pig (Hartley strain) showing slight proliferation of interstitial connective tissue and arteriolar sclerosis, but no inflammatory changes. H&E. × 170.

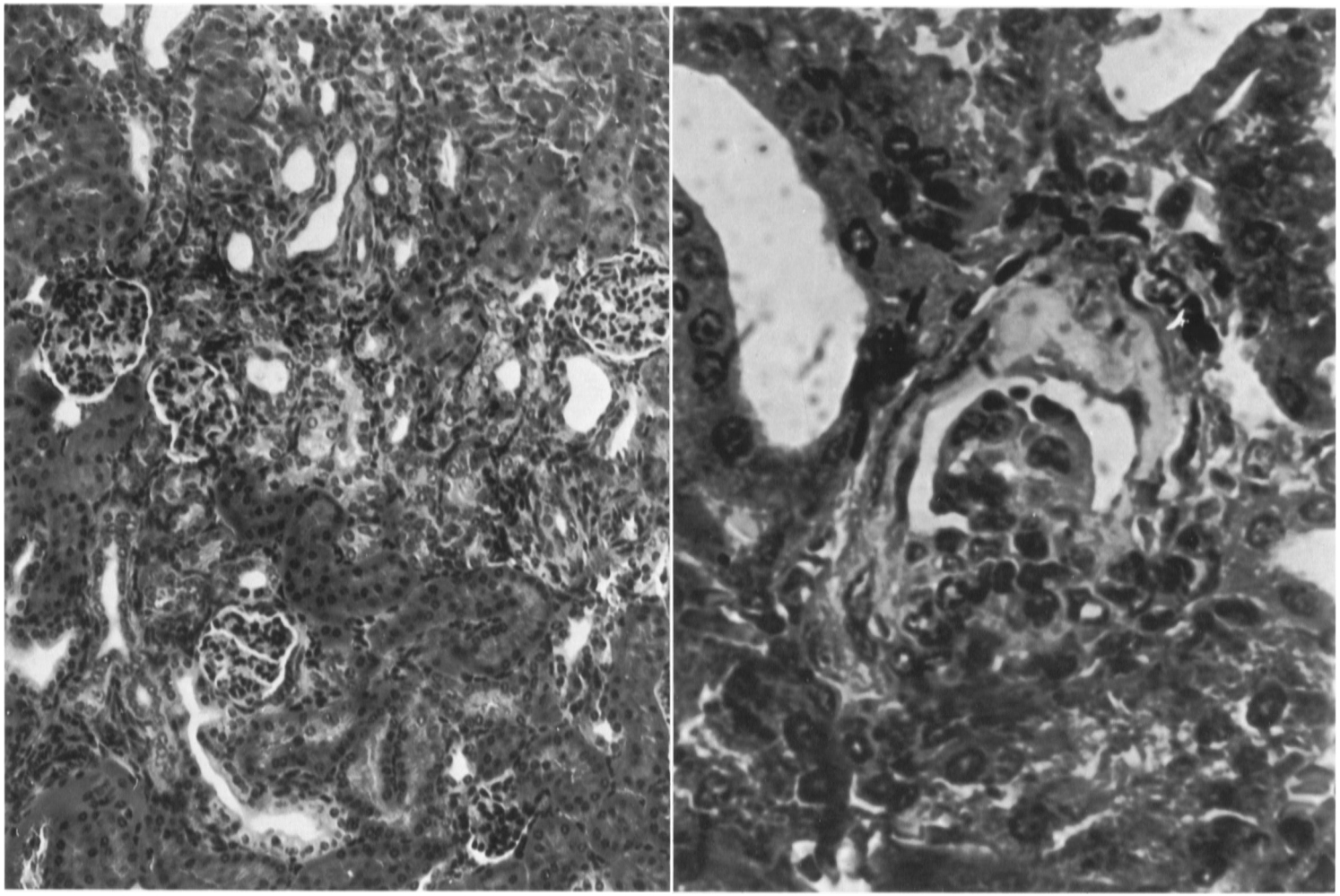
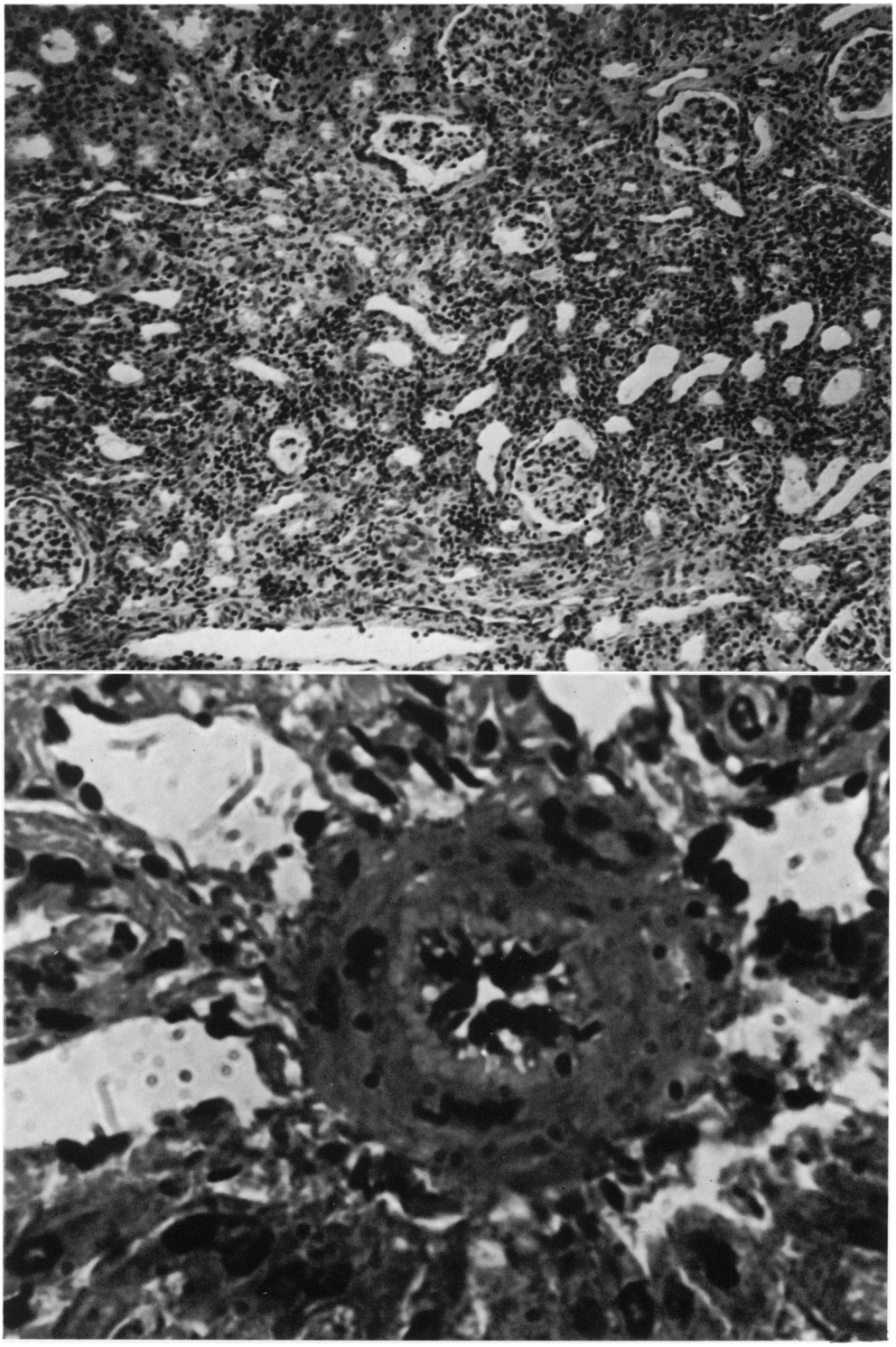


Fig 10. (*Top*) Kidney of 17-month-old female guinea pig (Hartley strain) showing marked degree of connective tissue proliferation with lymphocytic cell infiltration of cortex, atrophic tubules and some sclerotic glomeruli. H&E. × 125.

Fig 11. (*Bottom*) Liver of 15-month-old male guinea pig (Abyssinian strain) showing intimal and medial thickening of small artery in Glisson's capsule. H&E. × 800.



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