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Unilateral Renal Hypoplasia with Associated Venous Anomaly and Hypertension

A Study of the Juxtaglomerular Cells

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Summary. A child with unilateral renal hypoplasia, high plasma renin levels and hypertension was found to have large numbers of juxtaglomerular granular cells in the affected kidney. They were seen adjacent to and sometimes in the interior of hyalinized glomeruli or, in loose nests scattered in the interstitium. Ultrastructurally they contained large numbers of crystalline protogranules in the Golgi region and also displayed other features suggestive of hyperactivity. Atrophic tubules, smooth muscle and mast cells were present in considerable numbers. Well-preserved renal cortex remained in the affected kidney with no demonstrable juxtaglomerular granularity. After unilateral nephrectomy the patient became normotensive and plasma renin levels became normal. Thus it appears that the juxtaglomerular cells are able to produce and release renin independent of the structural integrity of the juxtaglomerular apparatus and renal glomerulus.

Key words: Juxtaglomerular apparatus – Renin – Kidney – Congenital abnormalities – Ultrastructure – Hypertension – Renal hypoplasia.

Introduction

Unilateral renal hypoplasia is a well-recognized cause of childhood hypertension. In this condition the renin activity in the renal vein of the affected side is increased, indicating involvement of the juxtaglomerular (JG)[1] cells (Favre,

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[1] We use the terms juxtaglomerular cell, JG cell and juxtaglomerular granular cell to refer to the cells that contain the characteristic granules

1967; Fikri et al., 1973; Godard et al., 1973; Rosenfeld et al., 1973; Fay and Kaufman, 1974). We studied juxtaglomerular cells by light and electron microscopy in the hypoplastic kidney of a child with severe hypertension and elevated plasma renin activity. The contracted kidney in this patient drained into a venous plexus and the inferior vena cava was absent. There were large numbers of juxtaglomerular cells in the hypoplastic kidney. They displayed a unique distribution in the absence of anatomically distinguishable juxtaglomerular apparatuses, functioning glomeruli or tubules. Thus, juxtaglomerular cells appear able to produce and release renin independent of the structural integrity of the normal constituents of the juxtaglomerular apparatus and the renal glomerulus. This is a report of the first detailed study of the morphology of the JG cells in unilateral renal hypoplasia in childhood.

Clinical Studies

The patient was an eight year old girl noted to be hypertensive shortly before admission when her blood pressure was taken following a minor foot injury. Past history was unremarkable except for intermittent severe headaches and occasional episodes of epistaxis. There was no other history of renal disease, urinary tract infection or a family history of hypertension.

The patient was the product of a seven month gestation and weighed 1.76 kg at birth. The mother recalled having been severely ill during the first month of pregnancy. She was vague about her symptoms but remembered that the diagnosis of "viral infection" was made. She also had toxemia at the end of her pregnancy.

On admission to the hospital the weight was 36.9 kg and height was 133.4 cm. The blood pressure was 186/140 in the right arm and 290/180 in the right leg. Examination of the fundi revealed marked arterial spasm and narrowing of the arterioles without hemorrhages or exudates. A coloboma was present in the right eye. There were no palpable abdominal masses or abdominal bruits. The genitalia, extremities, and neurological examination were normal. A chest x-ray showed cardiomegaly and an electrocardiogram was normal. The BUN was 11 mg/dl, creatinine 0.5 mg/dl and serum electrolytes were normal. The peripheral plasma renin activity was elevated at 35 ng/h/ml (normal less than 3) (Boucher et al., 1967).

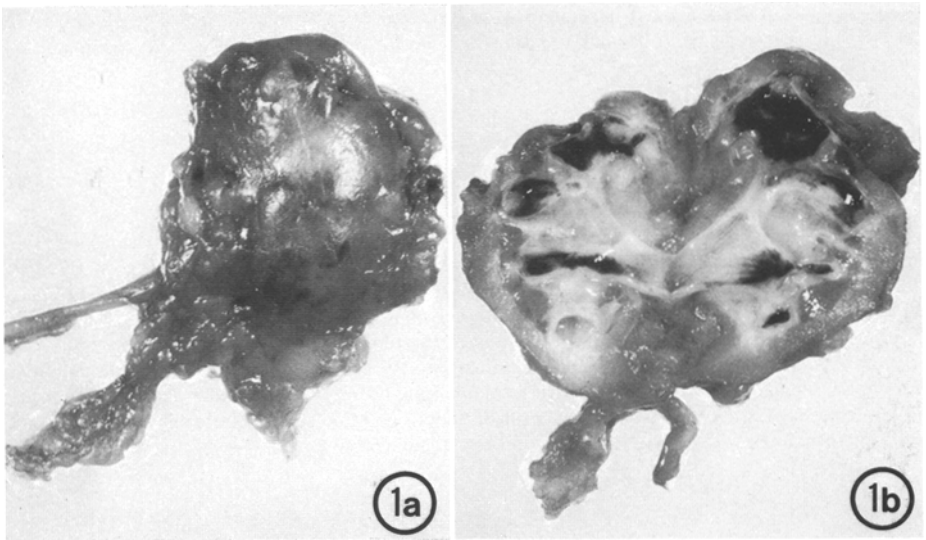
An intravenous pyelogram revealed a hypoplastic right kidney. Arteriogram confirmed the presence of a hypoplastic right kidney and showed no renal artery stenosis. When bilateral renal vein catheterization was attempted it was noted that the inferior vena cava was replaced by a venous plexus which drained the hypoplastic right kidney. The small kidney was visualized in the delayed films of the same study.

A right nephrectomy was performed. Blood pressure gradually became normal and at the time of discharge, seven days postoperatively, the blood pressure was 180/80. In the 18 months

Fig. 1. a Outer surface of the small contracted kidney displaying distortion of shape and extensive scarring. **b** Coronal section of the kidney. The cortex is narrow and of irregular thickness. The cortico-medullary junction is sharply demarcated in the center. The upper pole shows marked narrowing and the lower one is scarred throughout. The calyceal system is not dilated

Fig. 2. Low magnification view of the renal cortex. An outer rim of severely affected cortex is seen. The vascular channels and cast-containing tubules are seen. Below, the cortex is well-preserved. PAS stain. × 15

Fig. 3. Higher magnification from area boxed in Figure 2. Normal glomeruli and tubules in the well-preserved cortex are seen in an area adjacent to the affected renal parenchyma. × 53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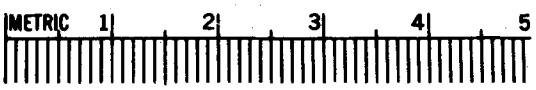
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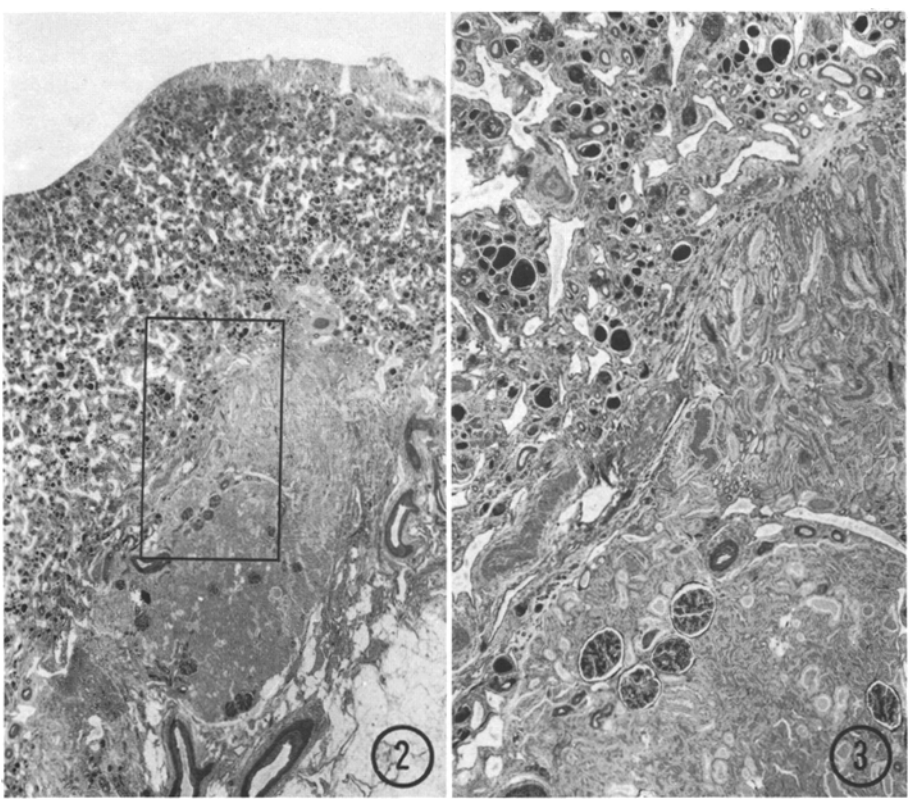
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since surgery she has remained normotensive (BP 120/80), without medication. The plasma renin activity has been repeatedly normal and the BUN and creatinine have remained within normal limits.

Materials and Methods

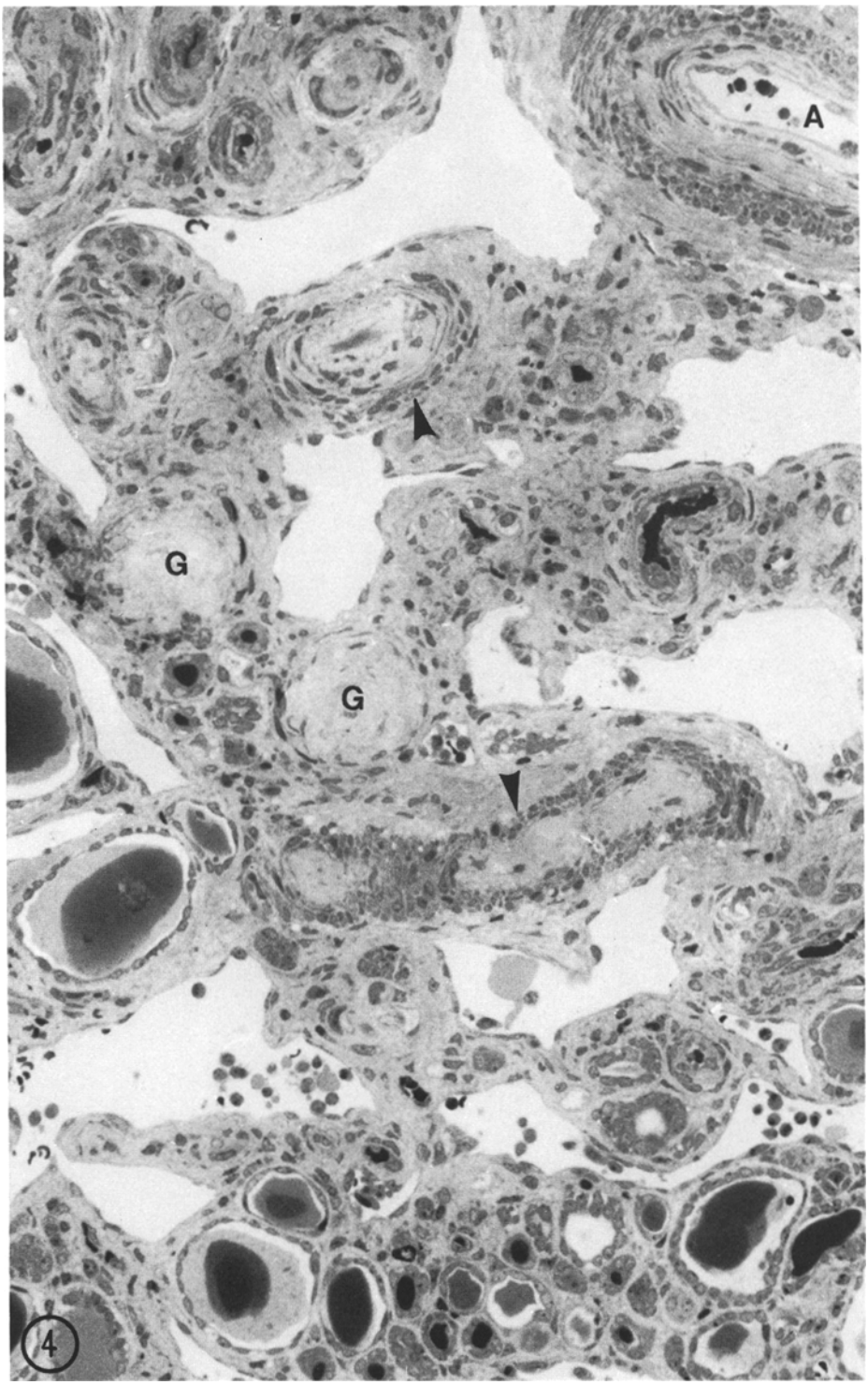
For *light microscopy* half the kidney was fixed in Helly's solution and embedded in paraffin. Four micron sections were cut and stained with hematoxylin and eosin, the Bowie (Hartroft, 1968) or PAS method. For *electron microscopy* small blocks were taken from the other half and fixed either directly in 1% osmium tetroxide in phosphate buffer or in 1% glutaraldehyde in phosphate buffer followed by immersion in 1% osmium tetroxide in the same buffer. After fixation the tissue was dehydrated in graded alcohols and embedded in Epon. One micron thick sections were cut from the plastic embedded blocks, stained with toluidine blue (Zamboni, 1972) and examined with the light microscope. Areas were selected from those sections and thin sections were cut with a diamond knife and examined with a Siemens Elmiskop I electron microscope.

Results

The excised kidney weighed 10 g and measured $3.5 \times 1.8 \times 5$ cm. The outer surface showed marked scarring (Fig. 1a). A frontal section displayed a cortex ranging in thickness from 0.1 cm to 0.4 cm (Fig. 1b). The thicker portions were of a tan color and presented a sharp corticomedullary junction and well-developed papillae. The cortex was whitish in the thinner areas where there was no associated pyramid. The calyceal system was lined by smooth, pearly-white epithelium. The artery, vein, and ureter were unremarkable except for their small size.

The cortex microscopically showed two sharply different areas (Figs. 2, 3). The outer cortex of most of the kidney and in some areas the whole thickness of the cortex, appeared to be replaced by a brocade of vascular channels with an interstitium which at low magnification showed tubules containing casts. At higher magnification (Fig. 4), in addition to the cast containing tubules, hyalinized glomeruli, markedly atrophic tubules, and dense interstitial fibrosis were seen. The larger blood vessels showed marked intimal thickening. In the smaller arteries and arterioles, the extreme intimal thickening was associated with very narrow or absent lumina. Large numbers of juxtaglomerular granular cells were seen arranged in loose nests often adjacent to a totally hyalinized glomerulus at sites corresponding to that of the juxtaglomerular apparatus (Fig. 5). In many areas the loose nests of juxtaglomerular granular cells appeared in the interstitium close to the vascular channels and in no apparent association with a glomerulus (Figs. 6, 7). In others, granular juxtaglomerular cells appeared in the interior of a hyalinized glomerulus (Fig. 7). Scattered in the interstitium were the remnants of atrophic tubules composed of one, two, or just a few cells (Figs. 5–8). Also present in considerable numbers were smooth muscle (Figs. 5–8) and mast cells

Fig. 4. The affected area showing hyalinized glomeruli, vascular channels and atrophic tubules. Occluded arterioles are present (arrows). In the upper right corner there is an artery (*A*) displaying intimal proliferation. Glomerulus (*G*). Epon embedded, toluidine blue stain. ×280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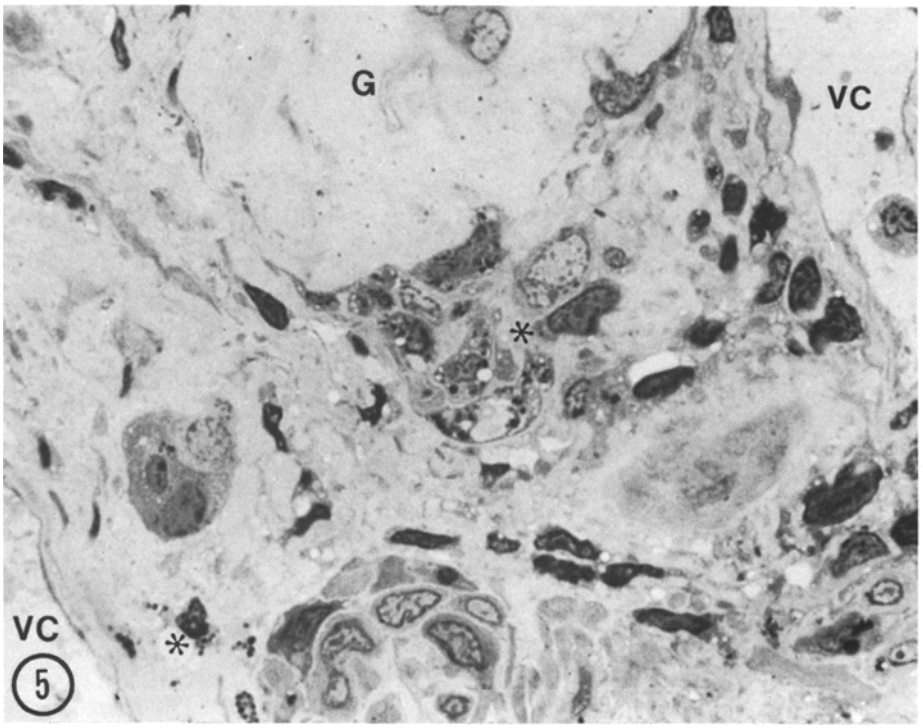


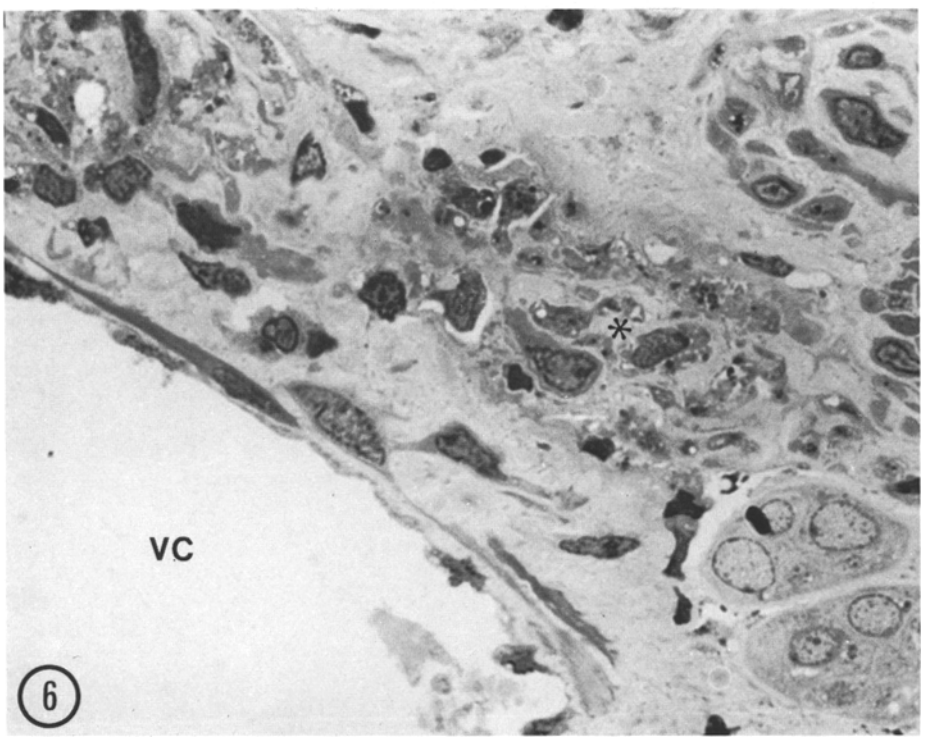
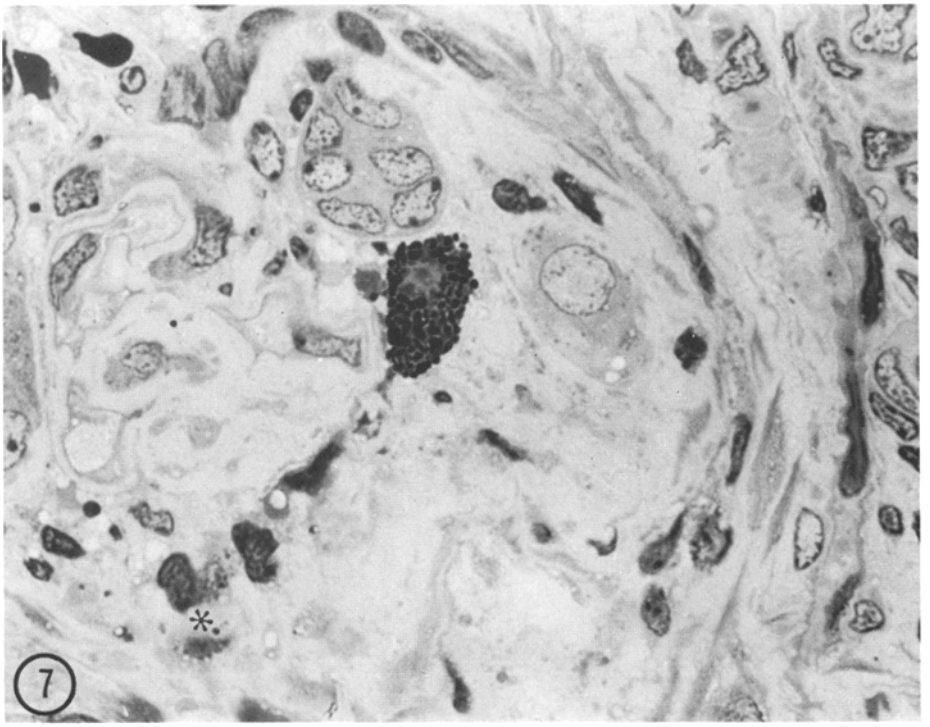


Fig. 5. Hyalinized glomerulus (*G*) with associated cluster of juxtaglomerular cells (*) containing granules. Scattered granular juxtaglomerular cells are seen at the lower left next to a vascular channel (*VC*). Epon embedded, toluidine blue stain. × 1100

Fig. 6. Cluster of juxtaglomerular cells (*) near a vascular channel (*VC*). Scattered smooth muscle cells and atrophic tubules are seen. Epon embedded, toluidine blue stain. × 1100



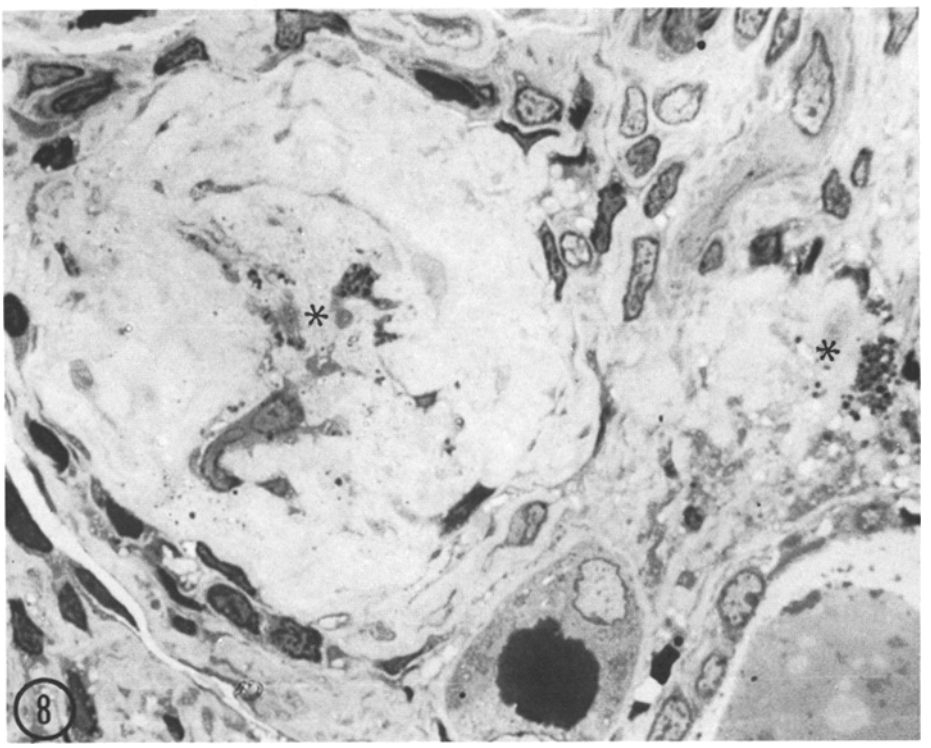
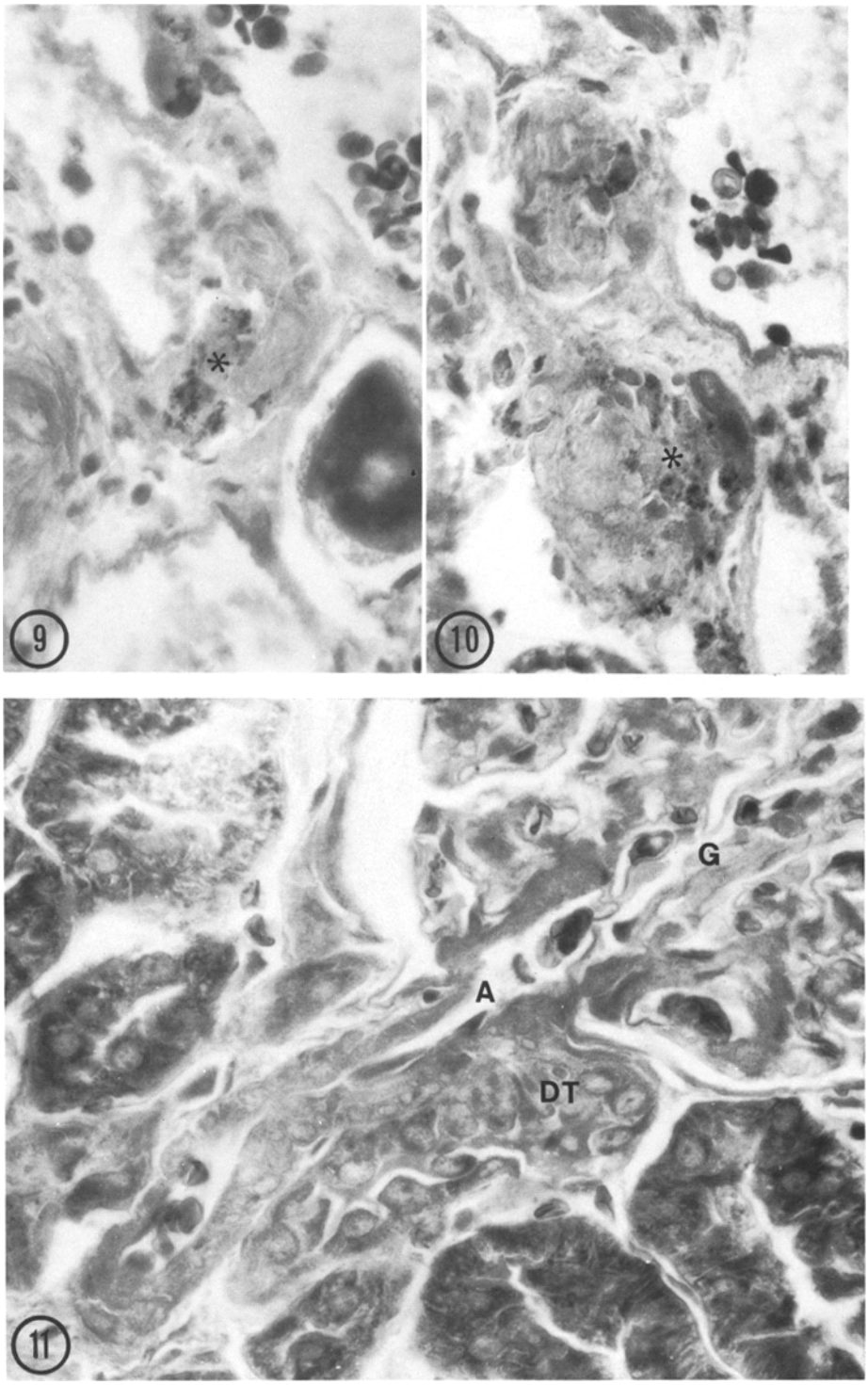


Fig. 7. Mast cell in the affected area is seen in the center of the photograph. A group of granular cells appear in the lower left (*). Note the much smaller size of the juxtaglomerular granules. Smooth muscle cells and tubular cells are dispersed in the connective tissue. Epon embedded, toluidine blue stain. × 1100

Fig. 8. Hyalinized glomerulus with granulated juxtaglomerular cells (*) in its interior. A group of granular juxtaglomerular cells (*) is present in the right side of the picture. Epon embedded, toluidine blue stain. × 1200



Figs. 9 and 10. The granules as observed with the Bowie stain. **Fig. 9:** Group of juxtaglomerular granular cells (*) near a vascular channel. **Fig. 10:** Juxtaglomerular granular cells (*) associated with hyalinized glomerulus. Bowie stain. ×750

Fig. 11. The juxtaglomerular apparatus of the non-affected area. No granules are seen in the vascular component of the juxtaglomerular apparatus. Arteriole (*A*), glomerulus (*G*), distal tubule (*DT*). Bowie stain. ×800

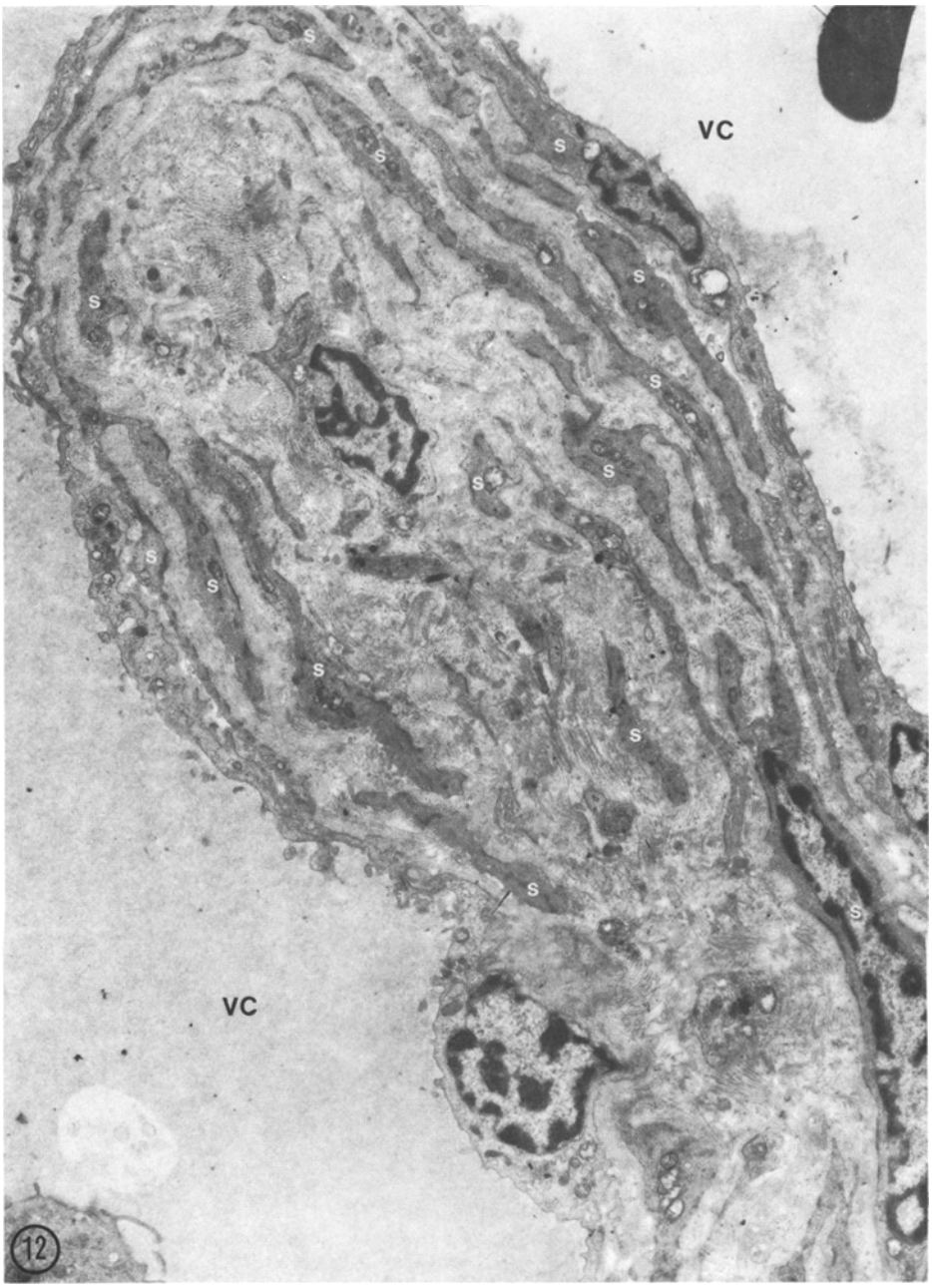


Fig. 12. Wall of vascular channels (*VC*). Smooth muscle cells (*S*) appear in the interstitium embedded in fibrillar and structureless material and arranged in rows parallel to the endothelial lining of the channel. Electron micrograph. ×7200

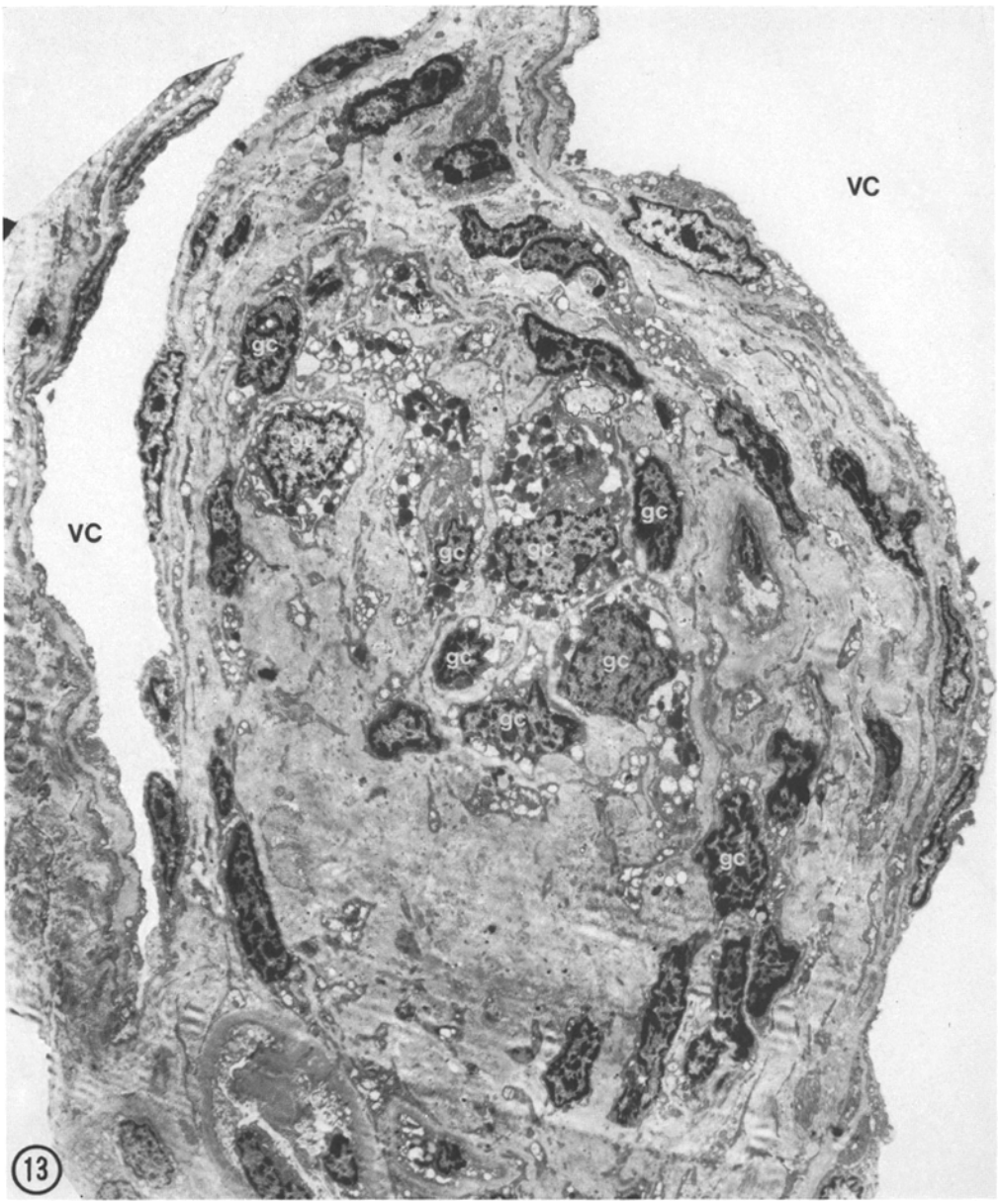


Fig. 13. Clumps of granular juxtaglomerular cells (*gc*) in the interstitium between two vascular channels (*VC*). There is no defined arrangement among granular cells. Electron micrograph. ×2400

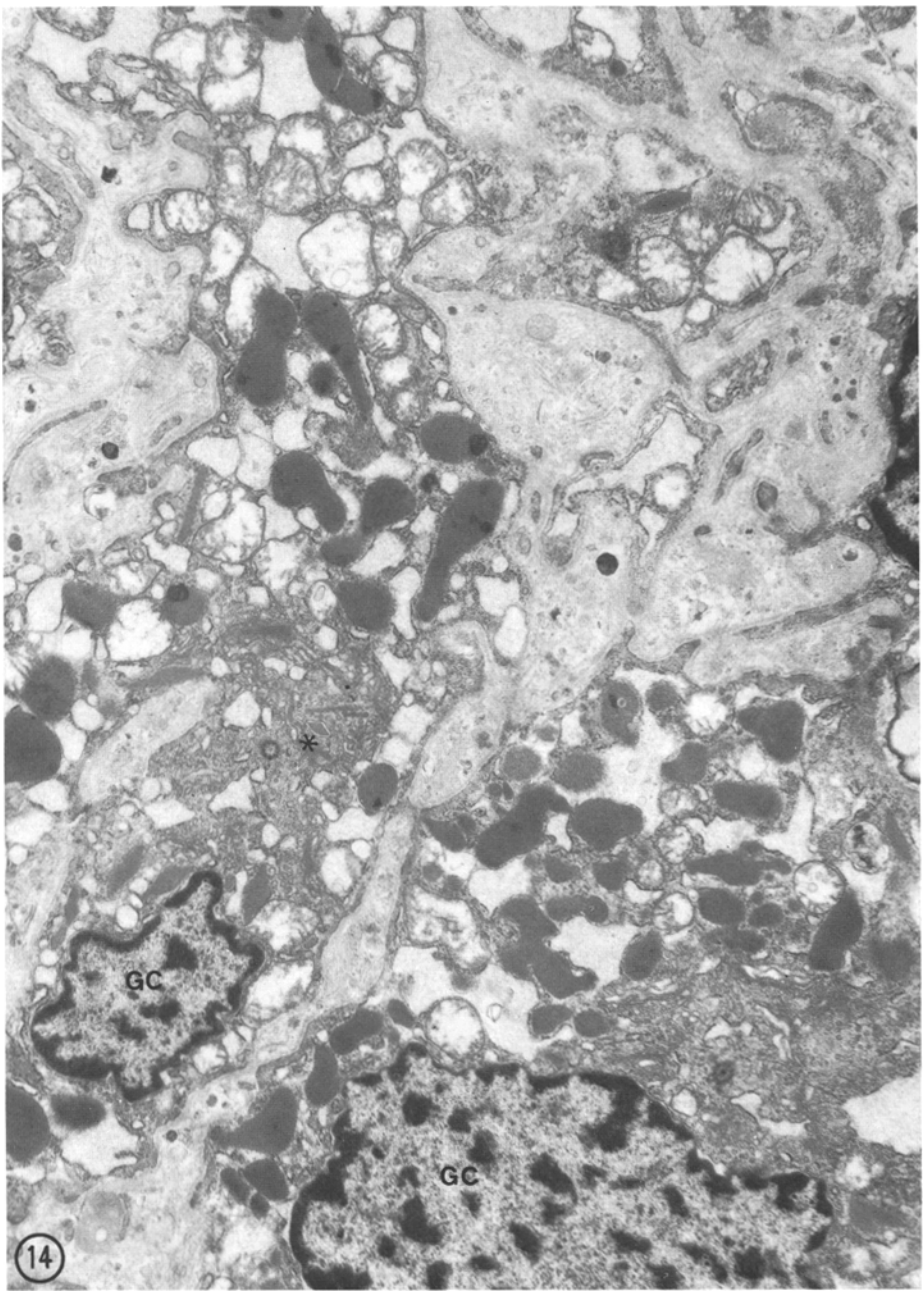


Fig. 14. The granular juxtaglomerular cells (*GC*) contain crystal-shaped protogranules (*) in close association with the Golgi apparatus. Among the granular cells there is basement membrane, granular, and fibrillar material. In some fibrils periodicity of collagen is present. Electron micrograph. × 10,500

(Fig. 8). The latter stained positively with the Bowie stain, but their granules were larger and showed metachromasia with the toluidine blue stain. This made them clearly distinguishable from the juxtaglomerular granular cells. Finally, there were also rare foci of lymphocytes and plasma cells.

The Bowie stain showed the juxtaglomerular granules in the same areas demonstrated with the toluidine blue preparations (Figs. 9, 10). In some areas the cortex appeared normal except for marked intimal proliferation of the arteries. The juxtaglomerular apparatuses found in these areas showed no granules with the Bowie stain (Fig. 11).

By *electron microscopy*, the smooth muscle cells and juxtaglomerular granular cells were seen in a similar relationship to the vascular channels (Figs. 12, 13). Both types of cells were in loosely arranged nests separated by granular and fibrillar material often displaying collagen periodicity. The juxtaglomerular cells showed evidence of hyperactivity with large amounts of crystalline protogranules in the Golgi region (Figs. 13, 14). They were often seen in the interior of the cisternae of the Golgi apparatus. Aggregates of protogranules and large mature granules were also found in the cytoplasm.

Discussion

The more common renal causes of severe hypertension in childhood are diffuse renal parenchymal disease, renal artery stenosis and segmental hypoplasia or the "Ask-Upmark kidney" (Fay and Kaufman, 1974; Barratt, 1976).

It has been proposed that the use of the term hypoplasia be confined to those kidneys in which the small size is exclusively due to decreased numbers of nephrons and a corresponding decrease of numbers of reniculi and calyces (Boissonnat, 1962; Kissane, 1974). A second accepted use of the term hypoplasia is when organs display "atrophy due to destruction of some of the elements" (Stedmans, 1966). The extensive tubular atrophy and glomerular hyalinization present in the affected portions of the small kidney justify the use, of the term hypoplasia in our case. The designation of segmental renal hypoplasia has been given to the Ask-Upmark kidney. In that entity, apparently there is a solitary focus of atrophic tubules containing casts together with marked fibrosis in the affected cortex (Kissane, 1974). In the Ask-Upmark kidney the lesion involves only one or a few adjacent renal lobules and the rest of the cortex is histologically unremarkable. In our case large sections of the renal cortex were involved and only a small amount of renal parenchyma was left unaffected. This remaining unaltered renal tissue must have contributed to the residual renal function, as shown by visualization of the small kidney in the contrast studies. Both our case and the Ask-Upmark kidney are associated with high renin hypertension.

The angiographic findings of absence of the inferior vena cava, the affected right kidney draining into a venous plexus, and the hypertrophic left one apparently draining independently into a vein, indicate the presence of a congenital vascular anomaly. A causal relationship between the vascular anomaly and the renal disease, perhaps occurring prior to the formation of the vena cava,

could be proposed. Early in fetal life the kidneys drain separately into the cardinal system. Thrombosis of this venous system, at the level of the right subcardinal vein, one of the future components of the inferior vena cava (Bryce, 1908; Patten, 1953), might prevent the development of the latter and induce massive ischemic changes in the right kidney. The left kidney might then drain into the hemizygous vein. These changes could have occurred as early as four weeks post-fertilization and coincided with the maternal viral infection.

Demonstration of increased numbers of juxtaglomerular granular cells in unilateral renal ischemia has been well-documented in man (Turgeon and Sommers, 1961; Barajas et al., 1967) and in the experimental animal (Goormaghtigh and Grimson, 1939; Hartroft, 1957; Tobian et al., 1959). In man, however, the literature refers more often to increased juxtaglomerular cell counts (Crocker et al., 1962; Godard et al., 1973) with little or no reference to the population of granular juxtaglomerular cells, the ones that synthesize and secrete renin. The significance of cell counts without demonstration of increased numbers of granular JG cells in the etiology of hypertension is questionable.

Increase in renin secretion by the segmentally hypoplastic or ischemic kidney is also well-documented (Favre, 1967; Mozzinconacci et al., 1968; Fikri et al., 1973; Rosenfeld et al., 1973; Fay and Kaufman, 1974). In our case this increase in plasma renin concentration was observed in the peripheral plasma renin activity. The massive increase in granular cells in the affected renal tissue accompanied by their absence in the unaffected regions, points to the affected renal cortex as a source of renin.

This is supported by the ultrastructural finding of large numbers of crystal-shaped protogranules associated with a prominent Golgi apparatus in the cytoplasm of the juxtaglomerular granular cells. These changes have been reported in the juxtaglomerular cells of patients (Barajas et al., 1965; Barajas, 1966; Biava and West, 1966) and experimental animals with renovascular hypertension secondary to unilateral renal ischemia (Barajas, 1966). This interpretation of the microscopic finding also correlates with the clinical findings in that blood pressure and plasma renin activity became normal after the unilateral nephrectomy.

In this patient, it appears that injury in utero may have led to complete disruption of the cortical anatomy with loss of the glomeruli and tubular function of a large portion of the cortex. However, the juxtaglomerular cells survived and thrived, increasing renin secretion and resulting in hypertension. The anatomical distribution of the granular cells in the scarred kidney (scattered in the interstitium or adjacent to and sometimes apparently in the interior of hyalinized glomeruli in a massively distorted cortex) points to an increased activity of the juxtaglomerular cell uncontrolled by arteriolar or tubular mechanisms leading to hypertension. This mechanism of renin release may also be analogous to that seen in renin secreting tumors.

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