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Reversible Renovascular Hypertension and Renal Arterial Pressure[1] (38231)

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Previous studies have demonstrated that plasma renin activity (PRA) and blood pressure (BP) rise within minutes of reduction of renal arterial pressure in the conscious dog (1). Moreover, by blockade of the conversion of angiotensin I to II the causal relation between the rise in PRA and the elevation of BP has been established, demonstrating that the renin-angiotensin system is responsible for the initiation of renovascular hypertension in the dog (2). The present studies extend these observations to the day-by-day changes during the development of chronic renovascular hypertension. The prior implantation of a renal artery constricting cuff inflatable through an external catheter and a renal artery catheter distal to the cuff has provided the opportunity to decrease renal arterial pressure in the trained, unanesthetized dog, to maintain renal perfusion pressure at a predetermined level sufficient to produce sustained hypertension (but without nitrogen retention), and to measure distribution of renal blood flow and apparent renin secretion rates. Since the dogs were maintained on a constant diet, changes in plasma and extracellular fluid volume could be approximated from serial measurements of urinary sodium excretion, body wt and hematocrit.

Methods. The techniques and methods employed in this study are essentially those described in detail in a previous paper (1). This report is based primarily on results obtained from 2 mongrel dogs each studied over a period of several months with duplicate, chronic constrictions of the renal artery; additional confirmatory data are presented on selected aspects from 6 other dogs in which renal blood flow was not measured. The dogs were walked at least twice a day and urine was collected at these times to assure 24 hr urine collections without fecal contamination. The animals were maintained on a normal diet with the same amount of processed dog food containing approximately 20% protein provided each day. The quantity of food necessary to maintain constant body wt was determined prior to the study. The sodium and potassium intake was also held constant for each dog. Free access to water was allowed, and intake was carefully measured.

Basal PRA was measured by the radioimmunoassay of Haber *et al.* (3); basal PRA in 8 control animals on standard diet exceeded 1.0 ng/ml-hr in only one determination. In 2 dogs renal venous renin was also measured. Daily urinary sodium and potassium excretion was determined using an Instrumentation Laboratory flame photometer with lithium as the internal standard. Occasional serum samples were also analyzed for sodium and potassium. Creatinine and BUN were measured with a Technicon Autoanalyzer. Blood for hematocrit determination was obtained from the aortic catheter.

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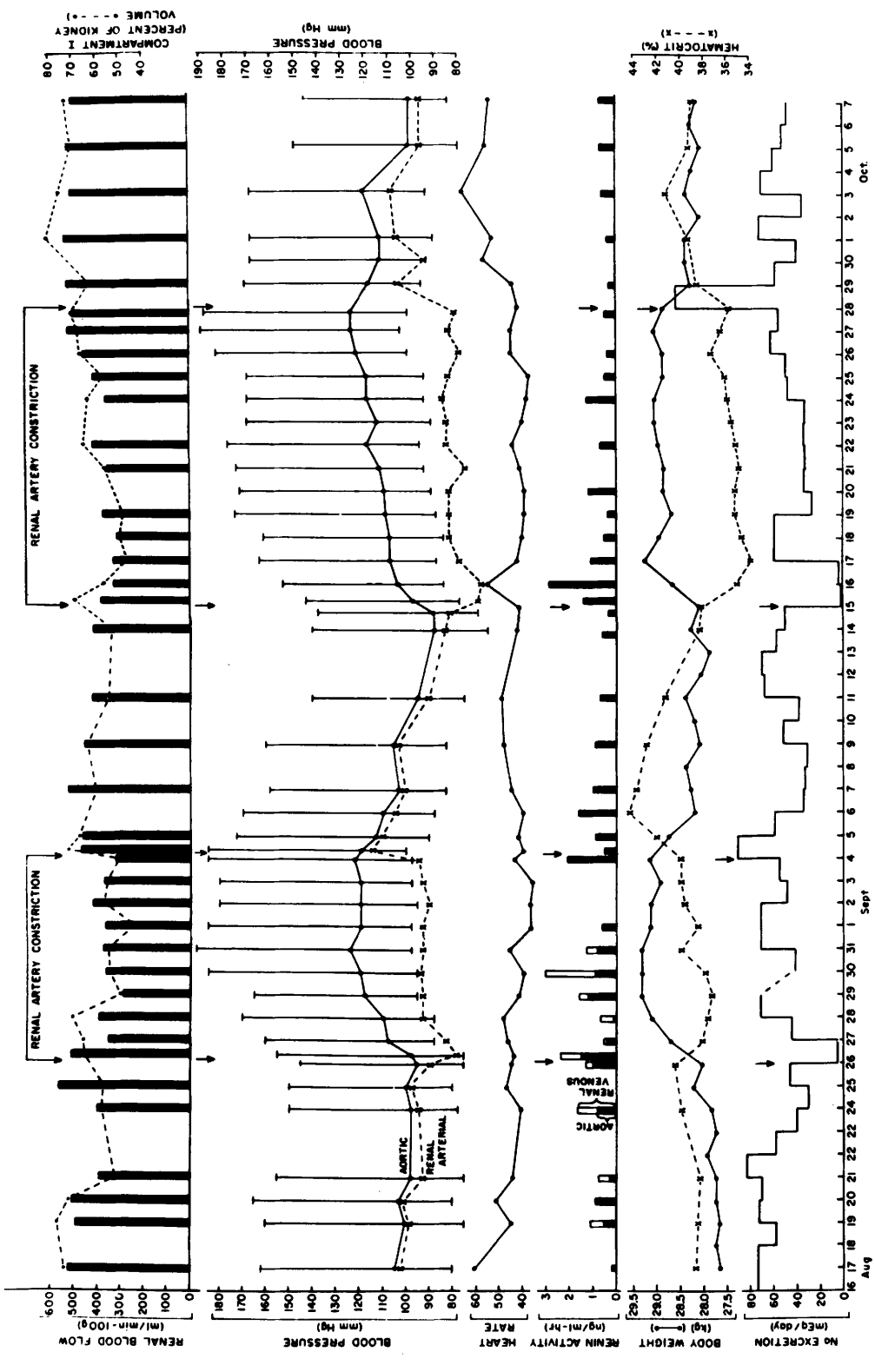

FIG. 1. Effect of constriction of renal artery on (a) total renal blood flow (ml/min-100 g) and percent volume of kidney in Compartment I (outer cortex), (b) systolic, diastolic, and mean aortic pressure, (c) mean renal arterial pressure (×---×), (d) heart rate, (e) renal venous (open bar) and systemic renin activity (solid bar), (f) body wt (solid line), (g) hematocrit of aortic blood (broken line), and (h) daily urinary sodium excretion. The renal artery cuff was inflated at the first arrow, and deflated at the second arrow in each experiment.

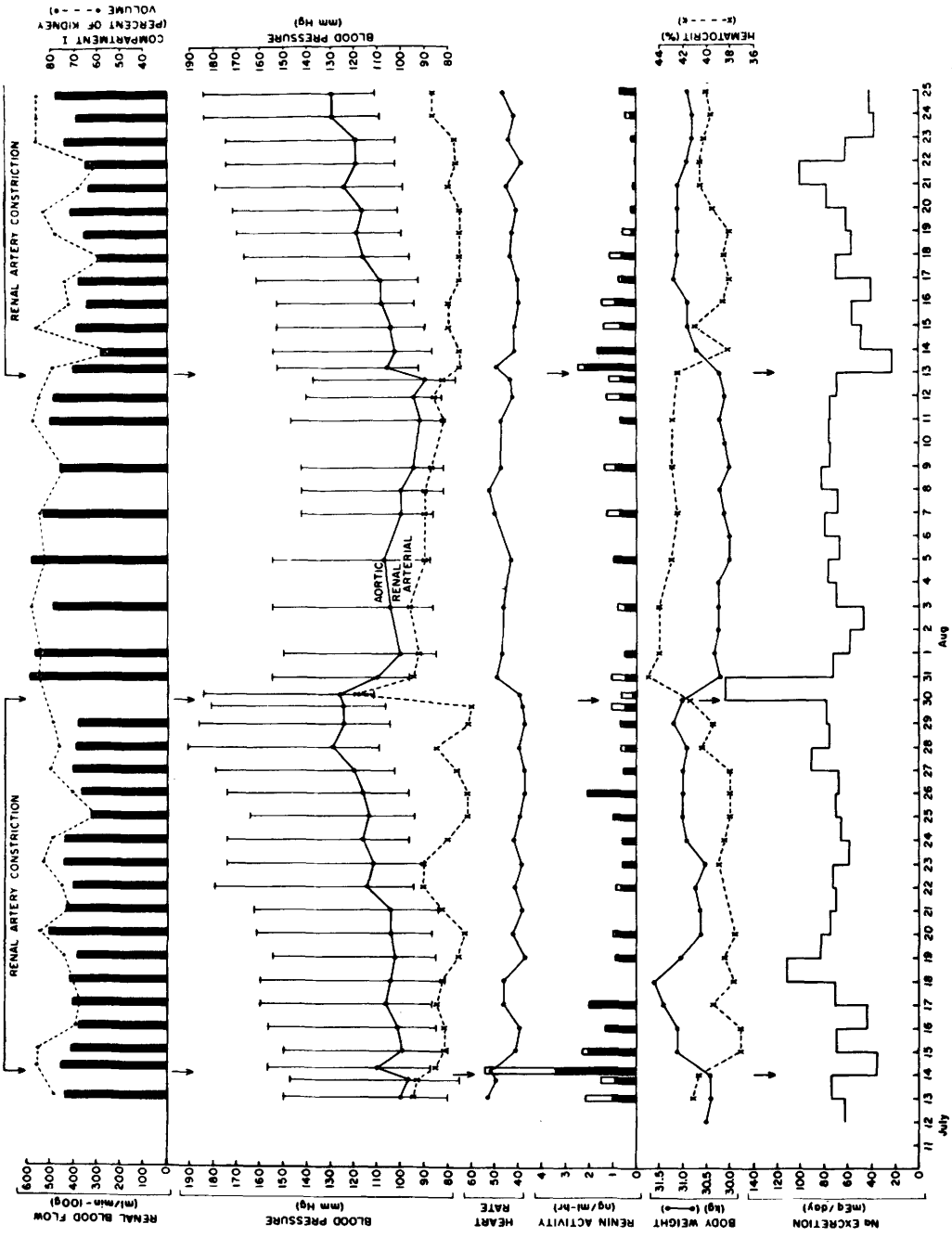

FIG. 2. Effect of constriction of renal artery in second dog. See legend of Fig. 1 for description.

The procedures employed were similar to those reported in the the previous paper (1). Each dog had a unilateral nephrectomy on the day of catheterization. A minimum recovery period of 9 days was allowed before renal artery constriction. Subsequent constriction of the renal artery was not repeated less than 5 days after release of pressure in the cuff. In order to maintain the aortic–renal arterial pressure gradient the constricting cuff was adjusted frequently, but blood samples were drawn before such adjustment. Postmortem examination of the kidneys revealed no significant pathology. The renal arterial system of 4 dogs (2 normotensive and 2 renovascular hypertensive) was injected with silicone rubber ("Microfil") at 150 mm Hg before clearing.

Results. Basal observations on 2 chronic dogs over a period of 2 mo are presented in Figs. 1 and 2, showing from top to bottom: (a) total renal blood flow and percent volume Compartment I (outer cortical) (4), (b) systolic, diastolic, and mean aortic pressures, (c) mean renal arterial pressure, (d) heart rate, (e) renal venous and systemic renin activity, (f) body wt, (g) hematocrit, and (h) daily soduim excretion. Twelve periods of chronic renal artery constriction were also induced in 6 additional dogs, but renal blood flow was not measured. As illustrated for the first animal (Fig. 1) resting mean systemic pressure was approximately 100 mm Hg, with little or no pressure gradient from the aorta to the renal artery. At the first arrow, renal arterial pressure was lowered to 75 mm Hg by inflating the cuff around the vessel; a gradient of approximately 25 mm Hg was produced. Over the next 5 days mean aortic pressure rose to 120 mm Hg, and renal arterial pressure gradually increased to 90 mm Hg. A constant gradient of 25–30 mm Hg was maintained by adjustment of the cuff. Aortic systolic pressure rose from 150 mm Hg to 190 mm Hg, and diastolic pressure from 75 to 95 mm Hg. Following the deflation of the cuff at the second arrow, systemic blood pressure returned to preconstriction levels in 4 days. In the second constriction period (Fig. 1) renal arterial pressure was initially lowered to 70 mm Hg, then allowed to rise to 85 mm Hg as systemic pressure rose, and maintained at this higher level by adjusting cuff pressure. The changes in systemic blood pressure were essentially the same as those observed during the first cuff constriction. Following the release of cuff pressure in the second experiment, systemic pressure fell more slowly and was not at control level until the 7th day. Similar results, obtained in the second dog are illustrated in Fig. 2. Essentially the same changes in blood pressure following renal artery constriction were noted in 6 additional dogs in which renal blood flow was not measured.

As we have shown in the previous paper (1), when renal arterial pressure is reduced, renin secretion rises rapidly. The highest basal levels of apparent renin secretion, and PRA, were usually measured within the first 24 hr of cuff inflation. In the experiments illustrated renal arterial renin levels were essentially normal (1 ng/ml-hr or less) by the 2nd to the 5th day of constriction, although occasional values were elevated. In the 6 additional dogs with renal artery pressure maintained at 50–80 mm Hg PRA reached a peak level of 3 to 5 ng/ml-hr but was 1.0 ng/ml-hr or lower within 48 hr despite a relatively unchanged renal arterial pressure.

Total renal blood flow and intrarenal distribution (4) were measured on 77 days in 2 animals (Figs. 1 and 2) in the control state and during renal artery constriction which was maintained up to 16 days. In a previous paper (1) we noted renal blood flow was unchanged and that distribution of flow was only slightly altered in the first hours after constriction of the renal artery with renal arterial pressures of 75–80 mm Hg. However, the chronic response of renal blood flow and distribution was quite variable even within a given period of renal artery constriction and the changes are detailed in Figs. 1 and 2. For example, in Fig. 1 (first trial) total renal blood flow and percent of flow in the outer cortex were normal immediately following cuff inflation, but were significantly reduced in the following days of constriction. During the second period of renal constriction, total

renal blood flow and outer cortical flow also fell during the first days after constriction, but then gradually rose to normal levels despite a constant renal arterial pressure maintained by cuff regulation. In Fig. 2 renal blood flow changed very little during the period of the first constriction. During the second inflation of the cuff, renal blood flow and percent volume of Compartment I decreased 24 hr after renal arterial pressure was lowered to 80 mm Hg. Both total flow and percent volume of Compartment I slowly returned toward normal levels over the next 10 days. At the 12th day after constriction total flow was 510 ml/min-100 g, with Compartment I being 78%. During the period of renal artery constriction in each of the dogs BUN and creatinine levels were in the normal range. Following deflation of the cuff, renal blood flow and outer cortical blood flow increased in the presence of the elevated systemic blood pressure, and then gradually returned to normal levels. The increased diameter of the pre- and postglomerular blood vessels of the kidney removed from a hypertensive dog is illustrated in Fig. 3B and compared to the vessels of the normotensive dog (3A).

As indicated under methods, the animals were maintained on a fixed diet throughout the study, but were allowed free access to water. With each constriction of the renal

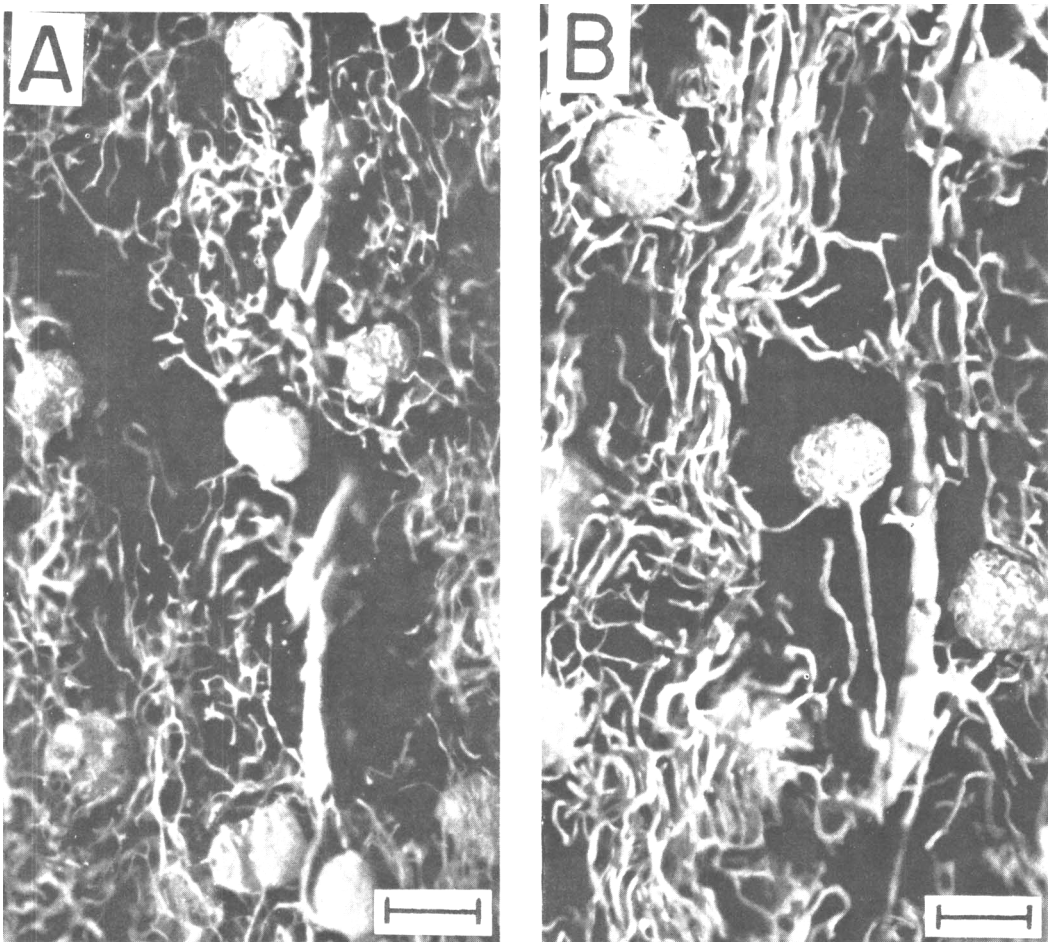

FIG. 3. Microvasculature of kidney filled with silicone rubber in (A) normotensive and (B) renovascular hypertensive dogs. The diameter of the small blood vessels are increased in the animal sacrificed while hypertensive. Bar = 150 μ.

artery in all of the dogs, urinary sodium retention occurred; water intake also increased on the day of constriction in each of the 8 dogs with an average increase in 24 hr water intake of 434 ml (range 220–1100). Body wt gradually rose for the first 3–4 days, and hematocrit decreased (Figs. 1 and 2, bottom). Urine volume was relatively unchanged following constriction except in one dog in which renal arterial pressure inadvertently fell below 50 mm Hg. During the renal artery constriction, the dogs gained 1–1.5 kg. The weight gain was considerably larger than the increase in plasma volume estimated from the changes in hematocrit, suggesting an increase in extravascular body water as well as plasma volume. No significant change in serum sodium or potassium concentration was observed. Urinary potassium excretion was unchanged except in the dog with renal arterial pressure below 50 mm Hg. Statistical analysis of the data in figures 1 and 2 revealed a highly significant correlation between systemic blood pressure and body wt ($P < 0.001$). With deflation of the cuff, a natriuresis and diuresis was observed in each experiment, with body wt falling rapidly, and hematocrit returning to preinflation levels. Although body weight and hematocrit were essentially normal within 24 hr, systemic blood pressure returned to control levels more slowly.

Discussion. The present experiments were designed to examine the day-by-day changes induced by renal artery constriction on basal PRA, renal blood flow distribution, salt and water balance, and blood pressure. Although Goldblatt *et al.* (5) originally suggested that ischemia may be responsible for renin release, a number of studies in dogs with renovascular hypertension have shown that renal blood flow may be normal (6, 7). In the previous studies (1) we noted that in the first hours after constriction of the renal artery, renal blood flow (ml/min-100 gm) and intrarenal distribution were essentially normal. During the chronic phase in this study there was no significant correlation between the level of renal blood flow, or the distribution of flow to the outer cortex (the area of high renin content), and the rate of renin secretion ($P > .05$). Forty-eight to seventy-two hours after constriction, renal blood flow was generally slightly reduced. Later blood flow returned to normal as renal resistance fell further; Fig. 3B provides visual evidence for the decreased resistance. These observations on blood flow are similar to those reported by Ferrario and McCubbin (6); they differ from those reported by Harris and Ayers (8). However, in the latter study, the control values for renal blood flow were unusually low, averaging less than 200 ml/min-100 g, or less than 50% of normal flow.

In the present study of chronic renal artery constriction we have shown that systemic renin activity rose rapidly, reached a peak within the first 24 hr and then gradually decreased. These observations are in agreement of those reported by previous workers (9–13). In addition, we have noted that the PRA returned to normal even though renal arterial pressure was maintained at a constant hypotensive level. These latter observations, which have not been previously reported as far as we are aware, rule out a rise in renal perfusion pressure as the feedback control restoring PRA to normal.

Although the initiation of renovascular hypertension may be causally related to the rise in systemic renin activity (2), the gradual decline of PRA during chronic constriction suggests that other factors, such as salt and water balance, may play a role in maintenance of BP in this latter phase. Several groups (14–17), using inhibitors of the renin-angiotension system, have been unable to detect a significant role of the system in the maintenance of blood pressure in one-kidney Goldblatt animals on normal sodium diet, but Gavras *et al.* (18) have presented evidence for a role in such animals when sodium depleted.

With reduction in renal perfusion pressure and elevation of PRA sodium excretion decreased, water intake increased, body wt increased 1–1.5 kg, and hematocrit fell. The converse was observed following the release of the cuff pressure. These observations on sodium retention are in agreement with findings of Tobian *et al.* in the one-

kidney Goldblatt rat (19), and those of Conway in the dog (20). The large increase in water intake on the first day may be, in part, due to altered levels of angiotensin II as suggested by the studies of Fitzsimons and coworkers (21) and Severs *et al.* (22). Simpson and Routtenberg (23) have recently reported that application of as little as 0.1 ng of angiotensin II to the subfornical organ (which lies outside the blood-brain barrier) elicited short-latency drinking in water-sated rats. Thus, the increase in plasma and extracellular fluid volume induced by decreased urinary excretion of sodium, and by increased water intake may be an important factor in the elevated pressure of chronic renovascular hypertension, and the gradual feedback decrease in plasma renin activity. Coleman *et al.* (24) have shown that overhydration in the anephric patient leads to persistent hypertension, and Guyton, Cowley and Coleman (25) have emphasized the key role that the renal control of sodium balance plays in regulation of blood pressure. Ames and coworkers (26) have shown during prolonged infusions of angiotension II that the rate of administration needed to maintain elevated pressure gradually decreased as sodium retention occurred.

Summary. In the conscious, trained dog we have noted an increase in apparent renin secretion following renal artery constriction and reduction of renal arterial pressure, with little or no change in renal blood flow, and without significant change in distribution of cortical blood flow. Within 2–5 days, however, basal renin secretion rates declined toward normal despite maintained renal arterial hypotension; body fluid volume was increased. A highly significant correlation between systemic blood pressure and body wt was noted. With release of the cuff, a natriuresis and diuresis was observed, with a return of body weight and hematocrit to normal within the first 24–48 hr. However, despite the decrease in body fluid, and the decrease in renin secretion and PRA, blood pressure returned to control level more slowly, suggesting a resetting of the baroreceptor reflex.

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