Relation of Renin and Angiotensin II to the Control of Aldosterone Secretion

By James O. Davis, Ph.D., M.D., Charles C. J. Carpenter, M.D., and Carlos R. Ayers, M.D.

At the Laurentian Hormone Conference in 1958, evidence1 was presented to show that the immediate stimulus to aldosterone production is humoral. Cross-circulation of blood from dogs with experimental secondary hyperaldosteronism through normal isolated adrenals produced an increase in aldosterone secretion by the isolated adrenals.1,2 This finding suggests that a humoral agent in peripheral blood acts on the adrenals to augment aldosterone secretion. Concurrent independent observations in conscious sheep by Denton, Goding, and Wright3 provided similar evidence for an aldosterone-stimulating factor in peripheral blood during chronic sodium depletion. It was suggested that this humoral agent is a hormone which has been designated the aldosterone-stimulating hormone (ASH).2

In 1960, two new findings, which were reported almost simultaneously, suggested the possibility that the renin-angiotensin system is important in the control of aldosterone secretion. First, it was observed that the aldosterone-stimulating hormone is secreted by the kidney4-7 and, secondly, it was reported that synthetic angiotensin II augments aldosterone secretion when given intravenously to man.6,7 The first evidence that ASH is secreted by the kidney was obtained from studies of the effects of systematically removing different areas of the body and, subsequently, determining the response in aldosterone secretion to acute hemorrhage. A positive response to acute blood loss in the absence of the anterior pituitary was considered as presumptive evidence for secretion of ASH. The observations were made in the absence of the anterior pituitary because it is now known8,9 that ACTH is also important in the control of aldosterone secretion, and that acute hemorrhage increases ACTH release.10,11

To study the rate of aldosterone secretion, the right adrenolumbar vein was cannulated (fig. 1) and adrenal venous blood was collected by the method of Hume and Nelson.12 The open end of the polyethylene catheter extended to the lower edge of the right adrenal gland. A loose ligature at the junction of the adrenolumbar vein and the inferior vena cava was tightened to occlude the normal flow of blood; blood from the right adrenal gland was obtained by retrograde flow. The small adrenal veins were not visualized, but they empty into the dorsal and lateral surfaces of the adrenolumbar vein. The concentrations of aldosterone and corticosterone in adrenal vein plasma were determined by the double isotope derivative assay of Klinian and Peterson.13

From a series of ablation experiments, it was demonstrated that the anterior pituitary, the pineal region, and finally, the head could be removed, and that subsequently a substantial increase in aldosterone secretion occurred in response either to acute blood loss14 or to thoracic caval constriction.15 Also, removal of the liver and anterior pituitary failed to block the response in aldosterone production to acute hemorrhage.14 In contrast, removal of the kidneys in hypophysectomized dogs resulted in a fall in aldosterone secretion and prevented the usual response to acute blood loss.14,15 The results of a typical experiment are presented in figure 2. Following hypophysectomy and nephrectomy, the rates of aldosterone and corticosterone secretion were very low and failed to increase after removal of 250 cc. of blood. Infusion of a saline extract...
of the animal's two kidneys effected a striking increase in aldosterone secretion while corticosterone output was unchanged. Eleven of 13 nephrectomized-hypophysectomized dogs failed to respond to acute blood loss (fig. 3), whereas in two animals (dogs 6 and 9) the values for aldosterone secretion after acute bleeding were higher than the control values.

Rechromatography of the samples from dogs 3 and 9 demonstrated radiochemical purity and repeat analyses of duplicate samples yielded the same high values for aldosterone secretion after bleeding in dogs 3 and 9. Because of these two animals, another experiment was performed in which the influence of bleeding in simple hypophysectomized dogs (fig. 4, left) was studied concurrently with a group of nephrectomized-hypophysectomized animals (fig. 4, right). The numbers for the dogs show the consecutive order in which the experiments were conducted. In the simple hypophysectomized animals, aldosterone secretion increased from 0.010 to 0.017 μg./min. (P < .02). In contrast, aldosterone production increased in only one of nine of the animals without kidneys (P > 0.2). Another finding which indicates that ASH is secreted by the kidney is the low level of aldosterone secretion before bleeding in the nephrectomized dogs (figs. 3 and 4) in comparison with the values in hypophysectomized dogs with the kidneys present. The mean value for aldosterone secretion before bleeding in 16 hypophysectomized dogs was 0.009 μg./min., whereas a level of 0.0045 μg./min. was ob-
Failure of 11 of 13 dogs to show an increase in aldosterone secretion in response to acute hemorrhage (center section). The control values for aldosterone secretion before bleeding are very low, reflecting the absence of the kidney. As comparative data, mean values and standard deviations are given for the anesthetized stressed normal dogs, right and left sections. (Data from Davis, et al.).

These results raise the question of the origin of ASH in secondary hyperaldosteronism. The effects of acute nephrectomy were studied in dogs with secondary hyperaldosteronism produced by experimental congestive heart failure, chronic thoracic caval constriction, and chronic sodium depletion. Again, the anterior pituitary was removed (two to three days before the acute experiment) to exclude the influence of ACTH which might obscure changes in aldosterone production secondary to loss of ASH. The response in steroid secretion to acute bilateral nephrectomy in a dog with experimental heart failure is presented in figure 5. The animal was hypersecreting aldosterone before nephrectomy, although the absolute level of aldosterone secretion indicated that a marked drop had occurred following hypophysectomy. The average value for aldosterone secretion in a group of dogs with experimental heart failure and an intact endocrine system was 0.10 μg./min. In the animal with cardiac failure (fig. 5), bilateral nephrectomy reduced aldosterone secretion to a very low level and corticosterone output fell similarly. Infusion of a saline extract of this animal’s two kidneys produced a marked increase in aldosterone secretion and a slight rise in corticosterone output. The effects of acute bilateral nephre-
Effects of acute hemorrhage on steroid secretion in a group of hypophysectomized dogs studied concurrently with a group of nephrectomized-hypophysectomized animals. Numbers show the consecutive order of the experiments. (Data from Davis, et al."

Since alterations in sodium intake constitute one of the most important factors in the daily physiological regulation of aldosterone secretion, studies of the effects of acute nephrectomy on aldosterone production were extended to include dogs with chronic sodium depletion. All animals were hypophysectomized two to three days before the acute experiment. In spite of hypophysectomy and the resulting marked fall in aldosterone secretion, in six of the eight dogs aldosterone production was higher (fig. 7) than the average value for normal dogs stressed by laparotomy (fig. 7, right). Aldosterone secretion fell following nephrectomy of the eight sodium-depleted hypophysectomized animals (fig. 7). Corticosterone production was low from hypophysectomy in all but dog 3, in which hypophysectomy was apparently incomplete. Following nephrectomy, corticosterone secretion fell in all but dog 3; the rise in corticosterone output in this animal is probably a reflection of increased release of ACTH. It is of interest that the fall in aldosterone secretion after nephrectomy was less in dog 3 than in the other seven animals, presumably because nephrectomy was followed by release of ACTH from the remaining pituitary. The evidence that an aldosterone-stimulating factor is secreted by the kidney in three different experimental situations may indicate the existence of an ASH common to all three conditions.

What, then, is the chemical nature of the
aldosterone-stimulating factor secreted by the kidney? To answer this question, crude kidney extracts were fractionated for aldosterone-stimulating and pressor activity (fig. 8).20 Crude kidney extracts were heated to 55 C. for 10 minutes; the supernatant showed marked aldosterone-stimulating activity, and a striking increase in blood pressure occurred. To examine the possibility that the active agent is a protein, the supernatant was dialyzed overnight against a 0.03 M sodium pyrophosphate buffer solution. Neither the dialysate nor butanol extracts of the dialysate had any effect on aldosterone secretion or blood pressure. The nondialyzable protein fraction was, however, highly active. Further fractionation of the protein revealed that most of the aldosterone-stimulating activity was in the 1.7 and 2.5 M ammonium sulfate fractions. These concentrations of ammonium sulfate are known to precipitate renin selectively. Heating the crude kidney extracts to 80 C. for 10 minutes, which destroys renin,21 abolished all steroidogenic and pressor activity, a finding which also suggests that ASH is renin. Finally, assay of the dialysate from unheated kidney extracts showed no aldosterone-stimulating activity. These data from fractionation studies provide strong suggestive evidence that ASH is renin.

The question arises, "Will renin or angiotensin II stimulate aldosterone secretion?" As you know, both Genest and associates6 and Laragh and co-workers7 have reported that synthetic angiotensin II augments aldosterone production in man. This finding has been confirmed in experimental animals.22 The results from injection of renin, which was prepared by the technique of Haas and Goldblatt,23 are presented in figure 9. The rates of secretion of aldosterone, corticosterone and Porter-Silber chromogens were increased. The increase in aldosterone production was to a level of physiologic significance, whereas the slight elevations in corticosterone and Porter-Silber chromogen output, although definite, were to levels of approximately 10 per cent and 3 per cent, respectively, of the values observed following stress of normal dogs and, consequently, were of little or no importance physiologically. Similar qualitative results were obtained with large doses of synthetic angiotensin II.25 However, small amounts of angiotensin II, which had no effect on blood pressure, increased aldosterone and corticosterone secretion.22 The elevations in corticosterone and Porter-Silber chromogen
production during injections of synthetic angiotensin II, renin, and crude kidney extracts, and the declines in secretion of corticosterone and Porter-Silber chromogens following nephrectomy, indicate that angiotensin II acts at an early stage in the biosynthesis of adrenal steroids rather than solely to convert corticosterone to aldosterone.

If ASH is renin, the renin content of kidneys of dogs with secondary hyperaldosteronism should be elevated. Extraction and assay of renin from kidneys of normal dogs, dogs with thoracic caval constriction, and dogs with cardiac failure was carried out by a slight modification of the methods of Haas and Goldblatt. A six-fold elevation in the renin content of kidneys from dogs with caval constriction was observed and the renin content of kidneys from two dogs with heart failure was higher than in the normal animals (fig. 10). These findings are consistent with the report of Merrill et al. that secretion of renin by the kidney is increased in patients with cardiac failure.

The suggestion that dogs with secondary hyperaldosteronism have a high blood level of angiotensin II raises the question of the absence of hypertension in these animals. It was reasoned that the blood pressure response to angiotensin II might be less in secondary hyperaldosteronism. To test this hypothesis, the blood pressure response to intravenous injection of synthetic angiotensin II was measured in conscious dogs. Four dose levels (0.5, 1.0, 2.0, and 4.0 μg.) of synthetic angiotensin II were studied twice in five normal dogs, five dogs with thoracic caval constriction, and five sodium-depleted dogs (fig. 11). A log-dose response occurred in all three groups of animals, but the increase in mean arterial pressure was markedly reduced at all four dose levels in the dogs with caval constriction and in the sodium-depleted animals.

Evidence for the intrarenal locus of secretion of ASH or renin has been obtained from studies of the juxtaglomerular cells. Pitcock, Hartroft, and Newmark found a direct correlation between the amount of renin in the kidney and the degree of granulation of the juxtaglomerular cells in sodium-deficient and control rats. A similar relationship was reported by Tobian, Janecek and Tomboulian in hypertensive rats and in rats fed an excess of dietary salt. More recently, Hartroft observed a marked increase in the granularity of the juxtaglomerular cells in sodium-depleted dogs.
Effects of renin on steroid secretion and on arterial pressure. (Data from Carpenter, et al.)

of the juxtaglomerular cells from kidneys of dogs with hyperaldosteronism secondary to thoracic caval constriction; also, hyperplasia of the juxtaglomerular cells was frequently present. By use of the fluorescent-antibody technique, Edelman and Hartroft have provided convincing evidence that the juxtaglomerular cells secrete renin. These findings, and the recent observation of Hartroft of hypergranulation and hyperplasia of the juxtaglomerular cells in dogs with hyperaldosteronism secondary to thoracic caval constriction, support the view that hypersecretion of renin by the juxtaglomerular cells occurs in experimental secondary hyperaldosteronism. A logical site or location, then, for the "receptor," the so-called "volume receptor," would be the renal afferent arterioles since the juxtaglomerular cells are located in the media of the afferent arterioles of the kidney.

The stimulus to the juxtaglomerular cells to release renin was studied by reducing renal arterial pressure and renal blood flow by acute constriction of the aorta immediately above the renal arteries. This experiment was suggested by the earlier observation that acute hemorrhage, which reduces the blood pressure and blood flow through the kidney, augments aldosterone secretion. The results of a typical experiment are presented in figure 12. Hypophysectomy was performed before control observations were made. Following aortic constriction, aortic pressure below the ligature fell and renal blood flow (not included in figure 12) decreased. The rates of secretion of aldosterone and corticosterone increased. Although the increase in corticosterone production was definite, the absolute level of steroid secretion reached was very low and was probably of no physiologic significance. In contrast, aldosterone secretion increased to a level greater than the rate of aldosterone output observed in normal dogs subjected to the stress of laparotomy; therefore, the level of aldosterone production achieved was of physiologic importance. The average data on steroid secretion for 15 hypophysectomized dogs subjected to aortic constriction are presented in table 1. The response was almost identical to that observed following acute hemorrhage of hypophysectomized animals (table 1). A decrease in arterial pressure and blood flow through the kidney, with a resultant decrease in stretch of the walls of the renal afferent arterioles, as suggested by Tobian, constitutes a plausible explanation for the stimulus to increased aldosterone secretion via the renin-angiotensin system.
In connection with studies of the stimulus for release of renin, aldosterone secretion was measured in experimental renal hypertension. Bilateral renal artery constriction was produced by use of Goldblatt clamps. Chronic benign experimental hypertension occurred in eight dogs (table 2) whereas seven animals developed malignant renal hypertension (table 3). In every dog with benign hypertension, a striking increase in blood pressure occurred. In this group, aldosterone and corticosterone secretion were measured at the time of laparotomy for placement of a chronic indwelling catheter in the right adrenolumbar vein; consequently, the animals were "stressed." Aldosterone secretion was within the range observed in similarly studied normal "stressed" dogs with one exception (dog 6). This animal was included in the group of benign hypertensive dogs because he survived an acute phase of severe malignant hypertension and developed chronic benign hypertension. The measurements of aldosterone secretion were made during this phase of malignant hypertensive disease and aldosterone secretion was elevated. In addition to the measurements at laparotomy, aldosterone production was normal during daily measurements which were made while these benign hypertensive animals were conscious. It should be emphasized that these studies were made early in the course of the experimental hypertensive disease.

In sharp contrast, all dogs with malignant experimental renal hypertension showed striking hyperaldosteronism. A 175 per cent increase in aldosterone secretion was observed during measurements made from adrenal venous blood collected during laparotomy for placement of the chronic adrenal catheter. Observations made in the same dogs in the conscious state showed a 6- to 14-fold increase in aldosterone secretion. The elevation in arterial pressure was essentially the same as in the dogs with benign experimental renal hypertension.

A possible explanation for the difference in
the rates of aldosterone secretion in the benign and malignant experimental hypertensive animals is provided by the data on the renin content of kidneys from the two groups of dogs (fig. 13). The renin content of kidneys from dogs with benign hypertension was about two-fold greater than the renin content of normal dog kidneys, whereas a 10-fold elevation in renin content of kidneys from dogs with malignant hypertension and hyperaldosteronism occurred. The results are consistent with the view that increased aldosterone secretion in malignant experimental renal hypertension is secondary to release of large amounts of renin.

Summary

1. Evidence is presented to show that the renin-angiotensin system leads to increased aldosterone secretion following acute blood loss, during experimental heart failure, during thoracic inferior vena cava constriction, during chronic sodium depletion and in malignant experimental renal hypertension. Since alterations in sodium intake constitute

### TABLE 2

Aldosterone Secretion and Mean Arterial Pressure in Dogs with Benign Experimental Renal Hypertension.*

<table>
<thead>
<tr>
<th>Dog</th>
<th>Aldosterone secretion (µg./min.)</th>
<th>Average arterial pressure (mm. Hg)</th>
<th>Duration of bilateral renal artery constriction (days)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>At laparotomy</td>
<td>In conscious state</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>0.012</td>
<td>0.007</td>
<td>137</td>
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<td>0.008</td>
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<td>—</td>
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</tr>
<tr>
<td>Average</td>
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<td>0.007</td>
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</tr>
<tr>
<td>Normal</td>
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<td>0.006</td>
<td>129</td>
</tr>
</tbody>
</table>

*From Carpenter, Davis, and Ayers.*

### TABLE 3

Aldosterone Secretion and Mean Arterial Pressure in Dogs with Malignant Experimental Renal Hypertension.*

<table>
<thead>
<tr>
<th>Dog</th>
<th>Aldosterone secretion (µg./min.)</th>
<th>Mean arterial pressure (mm. Hg)</th>
<th>Duration of life with hypertension (days)</th>
</tr>
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<td>—</td>
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<td>—</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>0.043</td>
<td>0.076</td>
<td>132</td>
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<tr>
<td>15</td>
<td>0.168</td>
<td>0.087</td>
<td>124</td>
</tr>
<tr>
<td>Average</td>
<td>0.066</td>
<td>0.070</td>
<td>124</td>
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<tr>
<td>Normal</td>
<td>0.024</td>
<td>0.006</td>
<td>124</td>
</tr>
</tbody>
</table>

*From Carpenter, Davis, and Ayers.*
one of the most important factors in the daily regulation of aldosterone secretion, studies of sodium-depleted animals suggest that the renin-angiotensin system is important in the physiological regulation of aldosterone secretion.

2. Renin appears to be secreted by the juxtaglomerular cells of the kidney. Some hemodynamic alteration secondary to a decrease in pressure and flow through the kidney leads to release of renin by the juxtaglomerular cells. Available data indicate that angiotensin II acts on the zona glomerulosa of the adrenal cortex to promote aldosterone production.

References


Dr. Little: Since many of these dogs were hypophysectomized prior to nephrectomy, with consequent effect on the two inner zones of the adrenal cortex, I wonder if a demonstration of an increase in aldosterone secretion resulting from the renin-angiotensin system is necessarily evidence that this is a specific effect, because there was also an increased secretion of other corticoids. Even though this, as you say, was not physiological, it was observed in a gland which was probably somewhat atrophied at the time that the experiment was carried out. At least it was a gland in hypofunctional state.

I might comment on the suggestion that this phenomenon is due to a change in renal flow and/or a change in mean arterial pressure in the kidney. In some of the experiments which we reported this morning, we studied the rate of excretion of electrolyte in animals in which there was an elevation of diastolic pressure and a depression of pulse pressure. We found that these animals lose an intravenous sodium chloride load at a much more rapid rate than under control circumstances. So it is possible that a change in renal pulse pressure or renal arterial diastolic pressure may be the particular stimulus which is involved in this mechanism of which you speak.

Dr. Davis: In answer to your first question about the influence of hypophysectomy on the two inner zones of the adrenal cortex, in the experiments in which acute blood loss was the stimulus, hypophysectomy was carried out only two hours before acute nephrectomy. In the dogs with heart failure or with caval constriction, hypophysectomy was performed two to three days before the acute effects of nephrectomy were evaluated. Consequently, in neither instance would there have been adequate time for adrenal atrophy to occur. The slight effect of renin and angiotensin II on corticosterone and Porter-Silber chromogen secretion indicates that angiotensin II acts at an early stage in the biosynthesis of adrenocortical steroids. Whether or not the stimulus is a decrease in pulse pressure, we have no information other than that which I have related today.

Dr. Hollander: I assume you ligated the inferior vena cava above the liver.

Dr. Davis: Yes. In all of the experiments described today, the inferior vena cava was constricted above the liver.

Dr. Hollander: Did you ligate the inferior vena cava below the liver and if you did, did you get an increase in aldosterone excretion? I ask this because I have been told that if one ligates above the liver, fluid retention and ascites occur, but if one ligates below the liver, salt and water retention do not result.

Dr. Davis: Yes, we have constricted the inferior vena cava below the liver both acutely and chronically. In animals with chronic subdiaphragmatic caval constriction, sodium retention does not occur and ascites fails to develop. In acute studies, however, aldosterone secretion increased in about 50 per cent of the experiments. Hypersecretion of aldosterone was present in the instances in which the venous pressure elevation was highest and the fall in arterial pressure and presumably in cardiac output was greatest. These experiments, together with the results reported today, suggest that with constriction above the liver, there was sufficient pooling of blood below the constriction to activate consistently the mechanism leading to release of renin.

Dr. Merrill: Le Grain in Paris has shown that three out of four patients with hyperaldosteronism are found to have unilateral renal ischemia and that we can't depend on aldosterone secretion studies to determine primary aldosteronism. I wonder if others have had this experience.

Dr. Laragh: We reported some six or eight patients with unilateral renal disease; some had aldosterone secretion but others had hyperaldosteronism and hypokalemic alkalosis with the clinical picture of malignant hypertension (J.A.M.A. Sept. 17, 1960). In some of this latter group, nephrectomy, or repair of the renal circulation, led to correction of both the hypertension and the hypokalemic
alkalosis and hyperaldosteronism. Also there are reports of several cases from Dollery in England and a larger series by Laidlaw in Canada.

Of special interest to the group here is the problem of the relation of aldosterone secretion to hypertension. I would like to say that our concept of the situation seems to be completely supported by what Dr. Davis has now found in dogs. In man we found, as you may know, normal aldosterone secretion rates in the benign forms of hypertension (either "essential" or renal) and very high aldosterone secretory rates in malignant hypertension. I think this experimental counterpart, which I followed with interest in conversations with Dr. Davis during the course of his work, bears out in a very controlled way what we had found in man. Apropos of what was discussed this morning, namely, the relationship of the arterial pulse pressure in the carotid sinuses, in particular, to aldosterone secretion, both Dr. Davis and I have different kinds of information which indicate that this does not influence aldosterone secretion. I will summarize ours briefly and then I think it would be appropriate if he would say something about his results. In man, we have lowered blood pressure with various hypotensive drugs and raised it with various pressor agents and found no correlation between the level of blood pressure or in the character of pressure—that is, the pulse pressure, and the secretion rate of aldosterone. We think these data indicate that the systemic arterial pressure does not in itself influence the secretion rate of aldosterone. Dr. Davis can tell you more about this problem.

**Dr. Davis:** We began to investigate the problem of the neural control of aldosterone secretion about two to three years ago. The possibility was considered that nervous afferents might arise from the upper part of the central arterial tree and connect with the central nervous system. We approached this problem by denervating the upper part of the central arterial tree from about the middle of the thoracic aorta to the uppermost accessible parts of the external and internal carotid arteries. We cut both vagi and the carotid sinus nerves and then we stripped the vessels of nerve attachments; subsequently, 5 per cent phenol and absolute ethyl alcohol were applied to the vessels to destroy remaining nerve endings. Application of the stimulus of thoracic inferior vena caval constriction produced a normal response with hyperaldosteronism, almost complete sodium retention, and ascites. The opposite type of experiment was performed in which a dog with hyperaldosteronism was subjected to these extensive denervation procedures, with no effect on the hypersecretion of aldosterone or on sodium retention or ascites formation. Therefore, we found no evidence that nervous afferents from the upper arterial tree were concerned with the primary control of aldosterone secretion. I would like to emphasize this point because we believe that the renin-angiotensin system constitutes the primary control mechanism. We know, of course, that there are afferents that lead to release of ACTH but ACTH is not the primary mechanism regulating aldosterone secretion.

**Dr. Hawthorne:** There is one thing that concerns me about Dr. Davis' very interesting paper, and that is, how does this thought that renin is the primary agent for aldosterone release fit the finding that no significant elevation in aldosterone secretion occurs in the benign experimental renal hypertension? Wakerlin found that anti-renin reduced the blood pressure of animals with chronic benign experimental hypertension to normal, an observation which leads us to believe that chronic experimental renal hypertension produced by renal artery constriction is due to renin, and that one would see an elevation in aldosterone secretion.

**Dr. Davis:** Our data show that the renin content of the kidney is elevated only two-fold in benign renal hypertension and that aldosterone secretion is normal. The finding implies that the amount of renin released by the kidney in benign renal hypertension is not adequate to stimulate aldosterone secretion. These results are in striking contrast to the 10-fold elevation in renin content of the kid-
ney and the consistent occurrence of hyperaldosteronism in the malignant hypertensive animals. In answer to your last question, I would say that both the relatively low renal renin content and the normal rate of aldosterone secretion in benign hypertension do constitute evidence against the pathogenic role of the renin-angiotensin system in benign renal hypertension.

Dr. Helmer: I should like to comment on Dr. Merrill’s question. In patients with elevated aldosterone levels it may be possible to differentiate between primary aldosteronism and renal vascular occlusive disease by the determination of renin in the blood plasma. Overdosage with DOCA or aldosterone in rats leads to a low renin content of the kidneys. In one questionable case of primary aldosteronism, we did not find an elevated renin content in the blood. On the other hand, in renal vascular occlusive disease, we have regularly found an elevated renin content in the blood.

In regard to the antirenin studies that Dr. Hawthorne mentioned, we have found renin present in the plasma of dogs in the chronic stage of experimental hypertension of the Goldblatt type.

Dr. Davis: I am well aware of these studies and of those of Dr. Wakerlin, but I do not know how to explain these apparent discrepancies.

Dr. Masson: I want to congratulate Dr. Davis on these studies showing the physiological effects of renin on the secretion of the adrenal cortex, especially since they complement our early morphologic observation that renin stimulated the zona glomerulosa. I would like to add that evidence exists for an inhibitory effect of adrenal steroids on renin secretion. Desoxycorticosterone and aldosterone decrease the juxtaglomerular index, renin content and secretion of kidneys. All these observations provide strong support for the existence of a functional interplay between kidney and adrenals.

Dr. Davis: In an attempt to establish a steroid feedback mechanism for the control of aldosterone secretion, we have infused fairly large amounts of aldosterone into peripheral blood. The peripheral plasma level was presumably markedly elevated, but there was no immediate measurable influence on aldosterone secretion. It appears, therefore, that renin release is not mediated by a direct action of aldosterone on the juxtaglomerular cells.

Dr. Tobian: I think Dr. Davis’ work is beautifully elegant. I want to add a recent experimental observation which also fits into the pattern. We gave amino nucleoside to a number of rats, some of which developed sodium retention and some didn’t, even though they all had the same dose of amino nucleoside. Those that had considerable ascites showed a distinct increase in the granulation of the juxtaglomerular apparatus indicating hypersecretion, whereas those that did not have ascites had a distinctly lower degree of granulation. In other words, the activity of the juxtaglomerular cells seemed to be correlated with the amount of sodium retention.
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_Circ Res._ 1962;11:171-184
doi: 10.1161/01.RES.11.1.171

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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