Relation of Aldosterone Secretion to Hypertensive Vascular Disease

By John H. Laragh, M.D.

As of special interest to this group I have chosen to review briefly some of our studies of the relation of the rate of aldosterone secretion to the pathogenesis of arterial hypertension in man. Analysis of this relationship has been complicated by several considerations. First, the various known forms of high blood pressure cannot be traced to the same cause. Second, no clear-cut patterns of biochemical abnormality seem to characterize any large proportion of these patients. As a result, partly of these limitations, the study and classification of human types of hypertension have been largely descriptive.

Investigators have long associated a disorder of salt metabolism with hypertension. Moreover, they have thought that a sodium-retaining hormone of the adrenal cortex was in some way involved in this relationship. Today an enormous body of evidence suggests strongly that there is a connection between the adrenal cortex and both experimental hypertension and high blood pressure occurring as a disease state in man. Although a review of this material is impossible here, it should be pointed out that apparently mineralocorticoids such as aldosterone do not affect blood pressure directly, but influence it indirectly through their effects on sodium and potassium balance.

Aldosterone was first studied in relation to hypertension by Genest and his associates. These workers found that the mean urinary excretion of aldosterone was increased significantly in 55 per cent of patients with essential, renal, or malignant hypertension. Two other groups have made similar observations. In none of these studies were the increases of aldosterone excretion related specifically to abnormalities in electrolyte metabolism nor were they associated with any particular type of hypertensive disease.

Methods for Measuring Aldosterone Secretion as Opposed to Excretion

Before reporting our observations on patients with hypertension, I should like to discuss briefly the methods used in measuring aldosterone. Usually, studies of the role of aldosterone in man and of factors regulating its secretion have been based on measurements of the small quantities of the hormone that are excreted in the urine. This approach has certain inherent disadvantages. First, only a small part of the aldosterone actually secreted by the adrenal cortex is excreted unchanged. For this reason, changes in the amounts of the hormone found in the urine do not necessarily reflect changes in the amounts secreted by the gland and they are especially likely to confuse observations when individuals with different rates of inactivation or excretion of aldosterone are compared. Second, the quantitation of such minute amounts as are excreted is in itself difficult, and the techniques used in many reports are subject to errors resulting from losses for which no correction has been made.

We have devised a method of measurement that eliminates some of these difficulties and allows a relatively precise estimate of the amounts of aldosterone that are actually secreted by the adrenal cortex. This method employs the principle of isotope dilution, which has also been used by Pearlman, Cope, Ayres and his associates, and Peterson in determining the secretion rates of progesterone, hydrocortisone, and aldosterone.
ALDOSTERONE AND HYPERTENSIVE DISEASE

Table 1

<table>
<thead>
<tr>
<th>Secretory Rate = Cpm of Radioactive Aldosterone Injected</th>
<th>Specific Activity of Urinary Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>(pg./day)</td>
<td></td>
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</table>

Procedure:
1. Inject intravenously tracer amount of radioactive aldosterone.
2. Collect urine for appropriate time.
3. Isolate urinary metabolite and determine specific activity.

Our method is based on the isolation of tetrahydroaldosterone in pure form from the urine. This compound is the major metabolic product of aldosterone and is present in urine in much greater amounts than is the hormone itself.

One can perhaps appreciate that if the amount of this product is measured and, then, if the fraction of the hormone converted to this product could be determined, one could calculate back and measure the amount of hormone actually secreted by the adrenal.

In practice, this can be accomplished as shown in table 1 by the injection of a tracer of tritium-labeled hormone intravenously. The urine is collected for a suitable time. The labeled metabolite is then isolated from the urine and purified sufficiently to determine its specific activity, that is, the number of counts per microgram, and, from this, the amount of aldosterone secreted during the study can be calculated.

The validity of this technique requires certain assumptions of which five are: (a) that the urinary metabolite is derived from only one precursor, which is identical with the administered tracer substance; (b) that the radioactive precursor mixes rapidly with the endogenous precursor, and thereafter the fate of both is identical; (c) that the excretion of the radioactive metabolite into the urine is complete within the time of urine collection; (d) that the rate of secretion of the precursor equals its rate of removal; and (e) that the fraction of the precursor converted to the metabolite does not change appreciably during the study. Each of these assumptions deserves a detailed discussion; but, since space is limited, we will consider only the third, which is especially important in studying patients with renal failure. This assumption is that the radioactive metabolite is completely excreted into the urine within the period of collection. This is an important consideration because renal failure, even when it is slight, as indicated by the usual parameters, can cause delay in the excretion of isotope. If not all counts destined for excretion have been excreted at the close of the collection period, the estimates of the secretory rate will be too high and thus invalid.

Besides its ability to measure secretion rather than excretion, this technique has other advantages: It is relatively precise, quantitative recovery is not required, and it is independent of alterations in hepatic inactivation and of renal clearance because both labeled and unlabeled molecules are affected equally. These secretory rate measurements may have limitations too, and further study of the blood level of the hormone, of protein-binding, and of tissue sensitivity may possibly be helpful. However, measurement of secretion (rather than excretion) presently appears to provide additional and more meaningful information from the study of patients.

Electrolyte Metabolism and Aldosterone Secretion in Hypertensive Patients

I should now like to review briefly some of our studies of electrolyte metabolism and aldosterone secretion in patients with various forms of hypertension. It is important to recall at the beginning that the rate of aldosterone secretion, unlike that of other adrenal hormones, fluctuates widely according to salt and water balance. Therefore, electrolyte balance has to be meticulously controlled in order to prevent changes caused
Normal aldosterone response to sodium deprivation in primary (benign essential) hypertension. Metabolic balance data from two subjects with benign hypertension are presented. On normal intakes of sodium both of these subjects exhibited normal secretion rates of aldosterone. Furthermore, both exhibited a normal response to sodium deprivation characterized by prompt reduction in urinary sodium excretion. As a part of this physiological response to sodium deprivation the aldosterone secretion rate increased considerably in both patients. This response is similar to that observed in normal subjects. (From Laragh et al.13)

by physiological rather than by pathological factors. For example, we find that normal persons secrete from 100 to 350 μg. aldosterone daily, but that, if dietary salt is withheld, the secretion rate may rise as high as 1,000 μg. On the other hand, increases in dietary sodium may lead to a reduction in aldosterone secretion to levels as low as 50 μg. daily.6

In our studies of patients with arterial hypertension, changes in aldosterone secretion have been related to changes in electrolyte balance, and, when possible, to changes in the morphology of the adrenal glands. Our hypertensive patients have been simply classified into three groups. The first, labeled primary hypertension, represents patients with uncomplicated benign essential hypertension. A second group, labeled advanced hypertension, includes those patients with either nitrogen retention or retinal hemorrhages or both; and the third group, labeled malignant hypertension, is comprised of patients with severe and accelerated hypertension characterized by papilledema.

Primary Hypertension

Let us now consider the results in primary hypertension. Figure 1 shows data from controlled metabolism balance studies of two patients with primary (benign) hypertension. When ingesting normal amounts of sodium, both of these subjects secreted aldosterone at normal rates, that is of 250 and 330 μg./day. Furthermore, both of these patients exhibited a normal response to sodium deprivation characterized by a prompt reduction in the renal excretion of sodium. As part of the physiological response to sodium deprivation, the aldosterone secretion rate was shown to increase considerably to levels up to 580 and 930 μg./day. This response is similar to what we have found in normal subjects under these circumstances and therefore affords no evidence for an abnormality of aldosterone metabolism in benign hypertension.

Malignant Hypertension

At first these observations on benign hypertension dampened our interest in the whole question of aldosterone in relation to hypertension. Then we were presented with the case of a 57-year-old man with severe hypertension in whom our data suggested, for the first time, a special relationship between aldosterone secretion and malignant hypertension. In the two years prior to study he had developed muscular weakness, episodes of nausea, mild polyuria, and papilledema. This man had renal failure with mild azotemia. Repeatedly, the plasma potassium levels ranged around 3.0 mEq./L. and the bicarbonate levels were usually over 30 mEq./L. He was found to have increased secretion of aldosterone without evidence that the adrenal cortex was overactive in any other respect. Because laparotomy did not disclose an adenoma, bilateral adrenalectomy was carried out. The adrenal glands were not enlarged but were

*Figures 1, 2, and 3 reproduced from Laragh et al.13 By permission of the authors and the Annals of Internal Medicine.
somewhat more nodular than normal. The patient died shortly after operation in terminal uremia, and autopsy confirmed the presence of necrotizing arteriolitis. We have now studied more than 20 similar patients with severe accelerated hypertension and papilledema and have found oversecretion of aldosterone in all but two.

In table 2 the clinical features of six fatal cases of malignant hypertension are summarized. All the patients had severe hypertension with the diastolic pressure ranging upwards from 130 mm. Hg. The known duration of the hypertension ranged from 3 to 20 years. At the time of our study all six manifested nitrogen retention (blood urea nitrogen [BUN] ranged from 40 to 78 mg. per cent). Despite renal failure, the plasma potassium tended to be low, with five of the six exhibiting values less than 4.0 mEq./L. The plasma bicarbonate, often depressed in other forms of renal failure, tended to be high. These patients all had normal or slightly high urine volumes, but overt polyuria was present in only two. The urinary sodium excretions are presented merely to indicate that a state of sodium retention did not exist at the time of study.

In table 3 the aldosterone secretion rates encountered in these same six patients with malignant hypertension are presented, along with a summary of subsequently obtained autopsy findings. Marked hypersecretion of aldosterone was demonstrated in all six, with the values ranging from 600 to 10,000 µg./day. All but one had overt necrotizing arteritis. However, the necrotic process was in no instance severe, in some was minimal. The adrenal glands in all six were at or slightly above the upper limits of normal in weight. All of the glands revealed moderate bilateral (often nodular) hyperplasia with increased lipid. Thus, these patients differ from patients with primary aldosteronism, not only in their clinical picture, but also because in no instance has an adrenal adenoma been found. The hypersecretion of aldosterone here appears to be the result of bilateral adrenal hyperfunction.

An effort has been made to characterize further the nature of the hypersecretion of aldosterone that is associated with malignant hypertension. In figure 2 data are presented from two metabolism balance studies of patients with severe hypertension. In both instances hypersecretion of aldosterone could not be modified significantly either by reducing or by increasing the sodium intake. This is in marked contrast to what is found in normal subjects and in patients with benign hypertensive disease. Of course, it is possible that, with more prolonged or drastic changes in sodium intake, the hypersecretion would be modified. Yet these data suggest that possibly there is a fundamental difference in the nature of aldosterone metabolism in malignant hypertension.

Aldosterone, when present in excess, characteristically leads not only to hypertension, but also to potassium depletion and to abnormal sodium retention. If aldosterone plays a part in the pathogenesis of malignant hypertension, then one might expect to find these other
Table 2

Clinical Features of Six Fatal Cases of Malignant Hypertension

<table>
<thead>
<tr>
<th>Age sex</th>
<th>Degree and duration hypertension</th>
<th>Blood HCO₃ mEq./L.</th>
<th>Urea mmol %</th>
<th>Urine Volume mℓ/day</th>
<th>Urine Na mEq./day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br 57M</td>
<td>250/150 20 yrs</td>
<td>138</td>
<td>3.2</td>
<td>34</td>
<td>92</td>
</tr>
<tr>
<td>We 48M</td>
<td>280/160 3 yrs</td>
<td>135</td>
<td>3.7</td>
<td>26</td>
<td>95</td>
</tr>
<tr>
<td>Pe 55M</td>
<td>220/130 4 yrs</td>
<td>132</td>
<td>3.6</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>Du 42F</td>
<td>250/160 5 yrs</td>
<td>140</td>
<td>4.1</td>
<td>27</td>
<td>95</td>
</tr>
<tr>
<td>Wi 44F</td>
<td>250/150 15 yrs</td>
<td>141</td>
<td>3.2</td>
<td>28</td>
<td>101</td>
</tr>
<tr>
<td>Wesi 46F</td>
<td>250/160 12 yrs</td>
<td>126</td>
<td>3.9</td>
<td>27</td>
<td>80</td>
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</tbody>
</table>

evidences of its biological action. In figure 3, the averages and the ranges of plasma potassium and bicarbonate values are presented as found in our patients with benign, advanced, and malignant hypertensive disease. In benign hypertension electrolytes were normal with the plasma K+ averaging 4.3 mEq./L. and HCO₃ averaging 26 mEq./L. In 16 cases of malignant hypertension, however, the values appear to differ appreciably from those found in benign hypertension. In malignant hypertension the average plasma potassium value was 3.6 mEq./L. and the average plasma bicarbonate level, 29 mEq./L. These abnormalities may have additional significance because they were obtained in a group of patients with an average BUN of 43 mg. per cent. Ordinarily, with such renal failure, retention of fixed anions tends to lower plasma bicarbonate and raise plasma potassium (so-called renal acidosis). Notwithstanding this, abnormalities in plasma potassium and bicarbonate seem to remain a reasonably good guide to the presence of aldosterone. It is of interest that similar abnormalities of plasma electrolytes in hypertensive disease have been commented on by others.14

Figure 4 summarizes our experience in the study of patients with various types of hypertensive vascular disease. The adrenal secretion rates for aldosterone are shown on the top line in micrograms per 24 hours, and just below the urinary sodium content for the corresponding 24-hour urine is presented. In benign hypertension the secretion rate of aldosterone fell in a range of from 190 to 330 μg./day, values similar to those found in normal subjects. In addition, two patients with hypertension resulting from unilateral renal disease were found to have normal aldosterone secretion. This is an old chart, and we have now studied many more patients. The general pattern has remained the same, with the exception that certain patients with unilateral renal disease do have high aldosterone-secretion rates, which I will discuss shortly.

Marked hypersecretion of aldosterone was demonstrated in five cases of primary aldosteronism resulting from an adrenal adenoma, with the values ranging from 510 to 1690 μg./day. However, 14 of 15 patients with malignant hypertension manifested the most severe degree of hypersecretion, with the values ranging upward from 510 to as high as 10,000 μg./day. In only two instances in more than 20 studies was the aldosterone secretion rate found to be normal in this disease, and in one of these two the subsequent course suggests that the malignant state had been arrested at the time of study.

From the data on this chart, aldosterone hypersecretion does not appear to participate...
Aldosterone Secretion and Morphological Findings in Six Fatal Cases of Malignant Hypertension

<table>
<thead>
<tr>
<th>Pt</th>
<th>Aldosterone secretory rate (mg./day) (normal range 150 to 375)</th>
<th>Renal pathology (+ to 4+)</th>
<th>Adrenal wt. Gm.* (Normal range 12.1 ± 2.7, septic range 16.6 ± 4.0)</th>
<th>Adrenal pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>600</td>
<td>++ necrotizing arteritis</td>
<td>16.5</td>
<td>moderate hyperplasia, slight nodularity, increased lipid but in no definite zonation</td>
</tr>
<tr>
<td>Web</td>
<td>860</td>
<td>+++ intimal sclerosis, but no necrosis</td>
<td>27.0</td>
<td>&quot;</td>
</tr>
<tr>
<td>Pe</td>
<td>1220</td>
<td>+ necrotizing arteritis</td>
<td>17.0</td>
<td>&quot;</td>
</tr>
<tr>
<td>Du</td>
<td>2180</td>
<td>+ necrotizing arteritis</td>
<td>15.0</td>
<td>&quot;</td>
</tr>
<tr>
<td>Wi</td>
<td>2730</td>
<td>+ necrotizing arteritis</td>
<td>17.5</td>
<td>&quot;</td>
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<tr>
<td>Wea</td>
<td>10000</td>
<td>+ necrotizing arteritis</td>
<td>12.5</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

(17.8) av.

*Control adrenal weights (both glands) as determined in autopsy population at Presbyterian Hospital, New York City:
34 normal specimens 12.1 ± 2.7 Gm.
21 subjects with septic illness 16.6 ± 4.5 Gm.
25 subjects with benign hypertension 13.0 ± 2.6 Gm.
5 subjects with renal hypertension 11.8 ± 2.1 Gm.

These pathological data have been kindly provided by Dr. Fred Lucas and Mr. John Sheagren.

Table 3

Aldosterone Hypersecretion as a Possible Cause of Malignant Hypertension

Let us now consider the role of aldosterone hypersecretion in malignant hypertension. Possibly the hypersecretion is the cause of this form of human hypertension as it can be in animals. However, several lines of evidence suggest that it is more likely to be either a secondary or an associated phenomenon. First, the clinical and pathological features of malignant hypertension differ from those seen in the condition of primary aldosteronism caused by adrenal adenoma. Second, since adrenal adenomas are not usually present in malignant hypertension, it seems likely that some extra-adrenal stimulus is responsible for the adrenal overstimulation. Third, adrenalectomy does not ordinarily correct malignant hypertension. Fourth, aldosterone hypersecretion is present only in the malignant form of hypertension, which appears to be a complication superimposed on underlying hypertensive disease.

However, even if increased aldosterone secretion does not participate in causing the hypertensive state, it could still play a part in the development of the malignant syndrome. Since renal damage is always present in malignant hypertension, we theorized that a renal factor may be involved in the increase
The average values and the ranges of the plasma potassium and bicarbonate are presented for three groups of hypertensive patients. In eight patients with benign hypertension the average values were: $K^+$ 4.3, $HCO_3^-$ 26, urea 17. In nine subjects with advanced hypertension: $K^+$ 4.0, $HCO_3^-$ 28, urea 31. In 16 cases of malignant hypertension: $K^+$ 3.6, $HCO_3^-$ 29, and urea 43. The results obtained in malignant hypertension indicate a tendency to hypokalemic alkalosis. The values may have added significance, since in the presence of renal failure anion retention usually tends to lower the plasma bicarbonate. (From Laragh et al.)

Figure 3

Mechanisms Involved in Aldosterone Hypersecretion in Malignant Hypertension

Finally, I should like to consider some of the factors that may be concerned in the oversecretion of aldosterone associated with malignant hypertension. Unfortunately, little is known about the physiological mechanisms involved in controlling aldosterone secretion either in normal persons or in those with various types of edema and secondary increase of aldosterone. However, it is definitely known that the potassium balance and changes in intravascular volume have some influence on the rate of aldosterone secretion. Some investigators have noted that changes in right atrial or venous pressure or in the pulse pressure of the carotid arteries seem to affect the output of the hormone. The association of changes in aldosterone secretion with alteration of intravascular pressure or volume suggested to us a possible relationship with release of pressor substances by the autonomic nervous system. For this reason, we began to study the effects of epinephrine and norepinephrine on aldosterone secretion even before we appreciated the relationship between aldosterone and malignant hypertension.

Our studies of the mechanisms of aldosterone secretion in relation to hypertension have thus followed three directions. First, we have examined the effect of changing the blood pressure itself on aldosterone secretion in normal persons and in patients with hypertension. Second, we have studied the effects of the pressor hormones, epinephrine and norepinephrine, on aldosterone secretion. Finally, we have compared the effects of these pressor hormones with the effects of a pressor substance released by the kidney, the octapeptide, angiotensin. This substance, as you have heard, is freed from a plasma alpha-2-globulin by renin, which in turn is a protein released by the damaged kidney. As we have mentioned already, angiotensin was selected because renal damage is so frequently associated with
The adrenal secretion rates of aldosterone in micrograms per 24 hours are presented for 8 normal subjects, 3 patients with primary hypertension, 8 patients with primary hypertension with complications ("advanced" hypertension), and 15 patients with malignant hypertension. For comparative purposes two patients with unilateral renal disease and five patients with primary aldosteronism are presented. The urine sodium content of the corresponding 24 hour urine collection is also shown. There is no evident hypersecretion of aldosterone in primary hypertension. In malignant hypertension marked hypersecretion of aldosterone was found and the values were often higher than those encountered in patients with primary aldosteronism. The patients with malignant hypertension resembled those with primary aldosteronism in that the hypersecretion was not associated with grossly reduced sodium excretion. (From Laragh et al.12)

hypersecretion of aldosterone in malignant hypertension. We were also influenced by the large body of evidence suggesting an interaction of the kidneys and adrenal glands in experimental hypertension. Gross22 and Tobian23 have recently reviewed this interaction, relating sodium balance, renin release from juxtaglomerular cells of the kidney, and aldosterone secretion.

First then, let us consider the effect on aldosterone secretion of changing the arterial pressure or pulse pressure. In the past three years we have studied patients with low, normal, and high blood pressure. We have observed the effects of raising the blood pressure of those who had low, using various pressor substances, and of lowering the pressure of those who had high, using various hypotensive agents. All observations were carried out under conditions of controlled metabolism. These studies show that changes in arterial or pulse pressure or in both do not alter the rate of aldosterone secretion either after a 24-hour study or after longer periods of up to two weeks. Our experiment is quite different from that reported by Bartter and Gann.21 However, our observations do not seem to support their suggestion that aldosterone secretion is affected by changes in the pulse pressure in the carotid arteries.
Now let us consider the effects of epinephrine and norepinephrine. Figure 5 summarizes the results of 28 paired experiments investigating the effects of epinephrine and norepinephrine on the rate of aldosterone secretion. Some of the patients in this study had hypertension or edema, but most were normal volunteers. These catecholamines were given in glucose solutions by slow intravenous drip for periods up to 24 hours. Each person given epinephrine or norepinephrine served as his own control and at least once each subject was given isotonic glucose infusion without the pressor hormone. The chart shows on the ordinate the percentage of secretory rate change after administration of the pressor substances as compared with the control values. On the abscissa are placed values according to the increasing levels of aldosterone secretion observed in the control state.

The study shows that the medullary hormones affect the aldosterone secretion variably. An initially low secretion rate is often increased, but an initially high secretion rate, such as occurs in sodium depletion, was quite consistently profoundly decreased. In other studies we have shown that depression of the aldosterone secretion by these hormones is clinically significant. For example, oral administration of sympathomimetic drugs to a patient with massive anasarca and aldosterone hypersecretion led to sustained correction of the excessive aldosterone secretion and diuresis of the edema fluid. Moreover, these drugs have maintained the improvement better than conventional diuretic agents.

Finally, let us now consider the effect of a pressor substance released by the kidney on the secretory rate of aldosterone. Figure 6 summarizes the results of eight angiotensin-infusion studies. The substance was given in amounts that would produce pressure changes similar to those occurring after the use of norepinephrine. However, the effects of angiotensin on aldosterone secretion differed very sharply from the effects of norepinephrine. In all eight instances, angiotensin increased the rate of aldosterone secretion to a level of 35 to 250 per cent above the control levels. Also in contrast to epinephrine and norepinephrine, the effect of angiotensin was independent of sodium balance. As is shown at the bottom of the figure, angiotensin regularly caused a reduction in sodium excretion, which may have been a sign of increased aldosterone. Dr. Genest and his associates have now found that angiotensin also increases the urinary excretion of aldosterone, and their results seem to be in harmony with our observations based on measurements of the secretory rate.

Taken altogether, these observations suggest that there may be an interaction of renal and adrenal systems which might be involved in the causation of malignant hypertension. Thus, as has been shown by Page and Braun-Menendez, renin released by the damaged kidney gives rise to angiotensin, a
pressor peptide. Our studies, in turn, demonstrate that angiotensin stimulates aldosterone secretion by the adrenal cortex. Animal studies by others have suggested that salt depletion or adrenalectomy increase the renin content of the kidney, while additional salt or aldosterone reduces it. There may therefore be a mechanism that normally sustains the renal perfusion pressure by promoting sodium conservation through stimulating the adrenal cortex. This mechanism may become inappropriately overactive in malignant hypertension.

Such a hypothesis may provide an explanation for the disappointing results of adrenalectomy in patients with malignant hypertension because adrenalectomy would provoke a greater release of renin and angiotensin. The effect of noradrenaline should be noted in this regard because this hormone may suppress aldosterone secretion by improving the renal circulation and reducing renin release. Whatever the case, it appears once more that the approach to malignant hypertension should be directed at measures to define and improve the circulation to the kidney. In this latter regard, the feeding of salt rather than deprivation as heretofore popular may also aid the renal circulation.

The effect of angiotensin might also provide an explanation for the difference in the clinical syndromes of primary aldosteronism caused by an adrenal adenoma and that of malignant hypertension in which an adrenal tumor is not found. In the former conditions there is autonomous hypersecretion of aldosterone, and a benign disorder characterized by potassium wastage and mild hypertension is produced. Conversely, in malignant hypertension, aldosterone hypersecretion is possibly secondary to impaired renal circulation and the release of a pressor substance which stimulates aldosterone secretion. Here, the clinical picture is instead one of severe and accelerated hypertension associated with necrotizing arteriolitis.

These new results are provocative. But, on the other hand, we do not know whether either renin or angiotensin plays a part in normal homeostasis, nor has either substance been clearly demonstrated in human plasma. Since renin is definitely present in renal tissue, its function may be entirely intrarenal. If this be true, the effects of angiotensin on aldosterone secretion may be accidental or nonspecific. Furthermore, pressor substances do not seem to be associated with the marked oversecretion of aldosterone that occurs in such conditions as cirrhosis of the liver. We have observed that this oversecretion is usually much greater than that associated with malignant hypertension. More work is therefore necessary to evaluate these new findings properly. From what you have heard this morning, it appears that it may be especially important to study secretory and excretory rates in the same subjects in an effort to resolve some of the differences in the results obtained by these two techniques.

However, our studies relate the rate of aldosterone secretion to a pressor substance of
renal origin. Further, these studies appear to relate this renal pressor substance to salt metabolism and to aldosterone secretion by the adrenal cortex in a particular type of human arterial hypertension.

References

Discussion

**Dr. Helmer:** We have found indications for a pressor substance in the plasma of patients such as those discussed by Dr. Laragh. Interestingly enough, Dr. Judson and I had one patient with a high aldosterone level in whom we did not find this pressor substance. It seems to me that the determination of aldosterone secretion and plasma levels of pressor substances may help us to clarify the nature of different forms of hypertension.

**Dr. Tainter:** I should like to ask Dr. Laragh to amplify his comments on the diuretic actions of orally administered sympathomimetic amines. I should like to know which agents were used and the dosages. Also, I want to ask the various speakers to help us in the interpretation of their infusion experiments. We have heard a number of descriptions of epinephrine and norepinephrine infusions in which various physiological responses were described. In general, the authors have failed to report the circulatory effects in sufficient detail to allow interpretation of these hemodynamic changes. It should be remembered that epinephrine and norepinephrine are biphasic in their action on blood vessels. They can either dilate peripheral vessels, particularly at lower dosages, or they can constrict them. Unless the blood volume moving through the various tissues is known, the effect of the infusion on local hemodynamics cannot be determined. This is particularly important in trying to assess the meaning of the renal changes and their effects on aldosterone secretion. Because of compensatory alterations in heart rate and local vessel tone, it is possible to produce profound changes in blood distribution and flow without inducing any change in systolic and diastolic pressures.

**Dr. Masson:** I was much interested in the suggestion of Dr. Laragh that angiotensin or renin in association with aldosterone may be responsible for malignant hypertension. I should like to remind you of our observation that renin injection in rats pretreated with desoxycorticosterone elicits a syndrome characterized by acute renal and vascular lesions and renal failure. Some of the animals died days after cessation of treatment. This would agree with the observation that bilateral adrenalectomy has no effect on the evolution of malignant hypertension.

**Dr. Doyle:** As Dr. Laragh has said, the one thing that distinguishes malignant from benign hypertension is the presence of renal failure, either incipient or established. Not uncommonly, however, one sees patients who have renal failure and normal blood pressure. I think it would be extremely interesting to know the aldosterone excretion in such patients. This might help to decide whether increased aldosterone production is, in fact, due to angiotensin.

**Dr. Gitloiv:** A question about the procedure: In our studies with radioactive nor-epinephrine we found that the route of administration and dosage of a substance may exert an effect upon its quantitative metabolic degradation. Thus, findings derived from such studies can be misleading insofar as indicating actual endogenous production. I wonder whether a similar situation pertains to aldosterone.

**Dr. Laragh:** Dr. Tainter asked about the type and dosage of oral sympathomimetic drugs and then about the hemodynamic effects of norepinephrine and epinephrine. The induction of sodium diuresis and suppression of aldosterone by oral sympathomimetic drugs seems to occur in special situations. I don't want to imply that diuresis can be produced by ephedrine or amphetamine in cases of cardiac failure and cirrhosis of the liver with ascites. The point is that a small group of patients with idiopathic edema have responded to chronic oral administration of these drugs by suppression of aldosterone and marked diuresis. We don't understand this effect but tentatively attribute it to an elevation of blood pressure and an improvement in renal circulation. In one patient improved glomerular filtration was associated with decreased aldosterone excretion.
It has been suggested that the kidney elaborates a factor which stimulates the adrenal when better renal perfusion is needed. This concept of the kidney has been supported by workers other than Dr. Genest and myself. Dr. Davis has removed the kidneys of dogs with ascites and found that aldosterone oversecretion returned to normal; Dr. Mulrow has found the same thing in animals that were bled.

There has been so much work related to the hemodynamic effects of norepinephrine and epinephrine that we didn't set out to study these at all. I can only tell you the dosages we gave and how they were decided upon. If the patient was hypotensive, we attempted to produce a mild pressor effect and sustain it at a constant level by continuous infusion. You are quite right that epinephrine has a very different effect from norepinephrine. In fact, blood pressure often goes down after small intravenous doses and pulse pressure is increased. After 56 such experiments we decided that no hemodynamic parameter was associated with any particular change in aldosterone. There was no correlation between aldosterone output and either high or low blood pressure induced by different agents.

We were able to correlate blood pressure with changes in sodium metabolism and the state of sodium balance. Hypertensive subjects may differ in their renal response to pressor agents. This question was raised before, but we have some data on it. When different pressor substances were given to hypertensive patients eating a balanced sodium intake, they were found to excrete more sodium than normotensive controls. This may be analogous to the salt rejection that follows rapid infusion of saline or other solute loads to hypertensive subjects. There is no explanation for this phenomenon as yet. The dosage of epinephrine or norepinephrine in any given patient was 2 to 12 mg. per day; the infusions were for 8, 10, 12, and 15 hours.

I should like to express my belief that Dr. Masson's experiment was a very important one. It represents, perhaps, the animal counterpart of a patient with malignant hypertension who makes both renin and aldosterone at the same time.

Dr. Doyle's very pertinent question about aldosterone secretion in patients with renal disease who do not have malignant hypertension is one that I wish I could answer. You may have noted on one of my slides an intermediate group, designated "advanced hypertension," that frequently manifested cardiac failure and other complications. It is difficult to appraise such patients because of the uncertainty about whether they start with pyelonephritis or essential hypertension. Extensive studies will be necessary to unravel the relationships in these patients with renal disease or cardiac complications because some have high and some normal aldosterone production.

Dr. Gitlow asked about possible similarities between problems consequent upon infusion of labeled epinephrine or norepinephrine and aldosterone. The evidence is that with aldosterone there is rapid and uniform mixing in one or two metabolic pools of the body. Without fulfilling that requirement, of course, we could not determine secretory rates. Norepinephrine is so rapidly metabolized that there is probably little chance of equilibration being established, whereas the slower turnover rate of aldosterone—the half-life of radioactive aldosterone in the blood is about 40 minutes—allows ample time for good mixing.
Relation of Aldosterone Secretion to Hypertensive Vascular Disease
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