Hormones and the Pathogenesis of Congestive Heart Failure: Vasopressin, Aldosterone, and Angiotensin II

Further Evidence for Renal-Adrenal Interaction from Studies in Hypertension and in Cirrhosis

By John H. Laragh, M.D.

It has long been recognized that an abnormally avid retention of ingested salt and water by the kidney is necessary for the development of any state of progressive fluid accumulation. In congestive heart failure, earlier studies stressed the importance of hemodynamic factors in bringing about renal retention of fluid, with failure of the heart as a pump leading to a reduced glomerular filtration rate, and thus to a reduced capacity to excrete salt and water. More recently, it has been appreciated that, while changes in glomerular filtration rate play an important role, the fluid retention of heart failure cannot always be explained by a purely filtration rate hypothesis and can result, in large part, from an increased reabsorption of salt and water by the renal tubules.1, 2

We now know that the tubular reabsorption of salt and water is achieved by a number of active transport processes involving the expenditure of energy on the part of tubule cells.3 Present evidence indicates that, in all instances, active reabsorption of sodium is the primary event with the attendant anion then diffusing along the established electrochemical gradient. Water reabsorption is viewed as an entirely passive process secondary to osmotic gradients established by solute distribution. Water is reabsorbed isosmotically in the proximal tubule, but in the distal tubule this process is facilitated by the presence and inhibited in the absence of the antidiuretic hormone, vasopressin, which appears to increase the permeability of these tubular cells to water. Renal tubular reabsorption of sodium chloride normally serves to regulate critically the amount and tonicity of body fluids. Secondly, the sodium reabsorption, which can occur by ion exchange for secreted hydrogen or potassium, serves to regulate acid-base and potassium balance.

Aldosterone appears to act in a distal portion of the tubule to promote the reabsorption of sodium chloride, exclusive of water.4 In a recent study we found that during water diuresis aldosterone produced a decrease in salt excretion that approached or was equal to the induced increase in free water clearance, leading to the suggestion that aldosterone, through its action to abstract sodium chloride selectively, plays a role in urinary dilution. In addition, aldosterone increases potassium and hydrogen excretion, presumably by accelerating the ion exchange of Na+ for K+ or H+, probably also in a distal portion of the tubule.

The purposes of this presentation are (1) to consider the influence of hormonal control of tubular reabsorption of sodium and water in the pathogenesis of congestive heart failure and (2) to discuss the basic, as yet unsolved, problem of the physiologic mechanisms that control the rate of secretion of the sodium-retaining hormone, aldosterone.

In considering the hormonal and renal dysfunction of congestive heart failure, it is often helpful to compare the abnormalities with those encountered in the other well-known states of fluid retention of cirrhosis and nephrosis. It seems likely that, at least to some extent, similar pathophysiologic mechanisms participate in the fluid retention, re-
Evidences of Increased Aldosterone Activity in Heart Failure, Cirrhosis, and Nephrosis

1. Increased renal tubular reabsorption of sodium chloride is present.
2. Reduced Na+ and increased K+ of saliva, sweat, and feces occur.
3. Diuresis may follow adrenalectomy in hypertensive heart failure, in cirrhosis with ascites, in the nephrotic syndrome, and in experimental edema.
4. Diuresis may be induced by spiroloactone aldosterone antagonist or by inhibitors of adrenal biosynthesis.
5. Oversecretion of aldosterone is present in cirrhosis, nephrosis and, to a lesser degree, in heart failure. Also occurs early in experimental edema.
6. In experimental ascites edema formation is directly related to the dosage of sodium-retaining steroid.

Role of Aldosterone

What is the evidence that the sodium-retaining hormone, aldosterone, plays an important role in heart failure? In addition to the presence of an increased tubular reabsorption of sodium, a number of other occurrences provide indirect evidence that this hormone is involved in congestive heart failure as well as in other states of edema (table 1). There is, for example, a reduced content of sodium and an increased potassium in the saliva, sweat, and feces of patients in congestive heart failure, suggesting the presence in the circulation of increased amounts of a sodium-retaining hormone. Thirdly, diuresis has been observed after bilateral adrenalectomy in hypertensive disease with heart failure, cirrhosis with ascites, and in the nephrotic syndrome. Fourth, diuresis of edema fluid may be induced by spiroloactone aldosterone antagonists or by agents that inhibit adrenal cortical biosynthesis. Finally, in experimental ascites the edema formation can be directly related to the dosage of a sodium-retaining steroid.

In 1950, Deming and Luetscher provided the first evidence that a sodium-retaining hormone might be present in increased amounts in urine of patients forming edema. This work led the way to the subsequent isolation and characterization of aldosterone. In our laboratory we have employed a technic of isotope dilution that measures with precision the amount of aldosterone that is actually secreted by the adrenal cortex in a 24-hour period. With this technic, we were able to

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demonstrate that marked oversecretion of aldosterone occurs in cirrhosis and nephrosis. In congestive heart failure, however, the values are, in general, only slightly elevated above the normal, perhaps pointing to the relatively greater importance of hemodynamic rather than hormonal factors in the edema of heart failure, as compared with that of nephrosis or cirrhosis.

By our present method normal subjects on an unselected diet secrete of the order of from 75 to 175 \( \mu \text{g} \text{m}^{-1} \text{d}^{-1} \) of aldosterone. In normal subjects, however, the rate of secretion of aldosterone fluctuates widely, depending on the dietary sodium content (from 5 \( \mu \text{g} \text{m}^{-1} \text{d}^{-1} \) on a high-sodium diet to 1,000 \( \mu \text{g} \text{m}^{-1} \text{d}^{-1} \) on a low-sodium diet). Usually, it is necessary to evaluate the aldosterone secretion serially in relation to the concurrent state of sodium balance before deciding whether a deviation is of pathologic or of physiologic origin. This is not always necessary because in patients with cirrhosis and nephrosis or with malignant hypertension, the values are frequently much increased above the physiologic range to as high as 2,000 \( \mu \text{g} \text{m}^{-1} \text{d}^{-1} \) or even higher.

These points are illustrated in figure 1, where representative aldosterone values are presented as they may be encountered in various diseases. Each patient shown was studied on a constant, low-sodium regimen, and then again after sodium chloride had been added to the diet. Note the marked oversecretion that is found in cirrhosis and nephrosis as well as in malignant hypertension and in primary aldosteronism. Note also that the oversecretion of these disorders is not readily suppressed by adding salt to the diet.

Our experience in the study of advanced congestive heart failure is relatively limited. We have made nine secretory rate measurements in six different patients. The values in these six patients have ranged from 160 to 515 \( \mu \text{g} \text{m}^{-1} \text{d}^{-1} \)—levels that appear either normal or only somewhat elevated and that are considerably lower than those encountered in cirrhosis and nephrosis. All of the patients in heart failure were studied while receiving a low-sodium diet and maintenance digitalis. Two of them were then given added dietary salt, and there occurred a gain in weight, and, paradoxically, a rise in aldosterone secretion (table 2). Further study of this phenomenon is obviously necessary.

From these data the exact role of increased aldosterone in the pathogenesis of congestive heart failure is not clear. The oversecretion of heart failure, however, appears to differ

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Table 2

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<th>Stimuli for Aldosterone Secretion</th>
<th>Indirect (†)</th>
<th>Direct</th>
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<tr>
<td>(a) Electrolyte</td>
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<td>Na⁺ deprivation</td>
<td>Plasma K⁺</td>
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<td>K⁺ administration</td>
<td>Angiotensin</td>
<td>(ASH)</td>
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<td>(b) Hemodynamic</td>
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<tr>
<td>Caval occlusion</td>
<td>ACTH (transiently)</td>
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<tr>
<td>Bleeding (reduced ‘volume’)</td>
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from that of cirrhosis and nephrosis, not only in its lesser magnitude, but also because in heart failure sodium administration may produce a paradoxical increase in hormone secretion. These observations perhaps point to a fundamental difference in the nature of the stimulus to aldosterone secretion in heart failure, as compared with cirrhosis and nephrosis. Possibly, measures that lead to more circulatory failure, such as sodium administration, accentuate a defect that elicits more aldosterone secretion. Then the increased hormone could well play an important, if secondary, role in promoting renal sodium retention and leading to further embarrassment of the already deficient heart. Similarly, the paradoxically lower aldosterone secretion following sodium depletion could be a consequence of an improvement in cardiac function. In this regard, we have also observed that diuretics that cause sodium depletion also may reduce aldosterone output in heart failure, whereas they increase it in normal subjects.

I would like to emphasize here that while these data point to an important role for aldosterone in the pathogenesis of fluid retention, a number of observations should be cited that indicate that aldosterone may not always be an entirely essential factor. Thus, (1) edema can occur or persist in patients treated with aldosterone inhibitors or even in adrenalectomized subjects; (2) edema occurs in potassium depletion with a lowered aldosterone output; (3) certain normal subjects appear to conserve sodium without increasing their aldosterone output or when aldosterone is blocked by spirolactone; (4) massive edema may occur in the nephrotic syndrome with repeatedly normal aldosterone secretion rates. All these observations, combined with the fact that aldosterone per se in normal subjects does not produce edema, perhaps suggest that other factors may be involved that influence tubular reabsorption or that increase the sensitivity of the tubule to aldosterone.

The Problem of the Normal Control of Aldosterone Secretion

Probably the exact role of aldosterone in heart failure will not be exposed until more is known about the nature of the mechanisms involved in the normal regulation of the rate of secretion of the hormone. In pursuing the latter problem, helpful information may be derived from study of other disorders in which oversecretion of aldosterone occurs.7–9

Overscretion of Aldosterone in Other Disorders

Overscretion of aldosterone is not necessarily associated with progressive sodium retention and edema formation. Thus, in addition to the edematous states of heart failure, cirrhosis, and nephrosis, aldosterone oversecretion occurs and may participate in the pathogenesis of diseases that are characterized instead chiefly by either potassium wasting (primary aldosteronism) or by severe accelerated (malignant) hypertension.

Primary aldosteronism is the spontaneous expression of increased aldosterone secretion by an autonomous adenoma. Arterial hypertension is present, but most of the signs and symptoms are referable to potassium deficiency. Edema is characteristically absent, providing strong evidence that a continued increase in aldosterone output, in an otherwise normal subject, does not lead to progressive renal retention of sodium and fluid accumulation.

Except for primary aldosteronism, the disorders characterized by increased secretion of aldosterone appear to result from bilateral adrenal cortical hyperfunction. In this sense all these other disorders are examples of secondary aldosteronism because presumably the increased aldosterone secretion arises from
stimulation of the adrenal glands by sources extraneous to them. Secondary aldosteronism is thus typified by the increased secretion of the hormone seen in the edematous states of heart failure, cirrhosis, and nephrosis. Oversecretion of aldosterone is also a most consistent finding in the syndrome of malignant hypertension. This may be tentatively classified as another form of secondary aldosteronism because, while increased secretion of aldosterone by itself might cause malignant hypertension, for reasons that have been given we have considered that it is an associated or participating event.

Evidence for an Aldosterone-Angiotensin Interaction from Studies in Malignant Hypertension

Our studies in malignant hypertension, where there is always renal damage, led us to suspect that a renal factor might be involved in the regulation of aldosterone release. We therefore studied the influence of angiotensin, a pressor substance of renal origin, on aldosterone secretion. In normal human subjects infusion of angiotensin consistently stimulated a marked increase in aldosterone secretion of from 35 to 250 per cent above the control values. Other types of pressor agents, such as norepinephrine and epinephrine, did not increase the secretory rate. These results led to the suggestion that a renal-adrenal interaction may be involved in the causation of malignant hypertension. Thus, renin, a protein released by the damaged kidney, liberates angiotensin from a specific circulating plasma globulin. Angiotensin, in turn, stimulates aldosterone release by the adrenal cortex. Animal studies have shown that salt depletion or adrenalectomy increases renal renin content whereas additional salt or aldosterone reduces it. There may, therefore, be a mechanism that normally maintains and protects renal perfusion pressure by promoting sodium conservation via stimulation of the adrenal cortex. Derangement of this mechanism could conceivably result in malignant hypertension and could explain the difference in the clinical and pathologic features of malignant hypertension as compared with primary aldosteronism. A coexistence of a high concentration of aldosterone and of renin might produce the necrotizing vasculitis of malignant hypertension. In the same way, animals, when given renin together with a mineralocorticoid, have been shown to develop severe vascular damage.

"Afferent and Efferent" Stimuli that Elicit Aldosterone Secretion

The studies described support the possibility that a renal-adrenal mechanism exists for the normal control of sodium and potassium balance. Let us now view this mechanism in relation to other well-known stimuli for aldosterone secretion.

Stimuli that elicit aldosterone secretion (table 2) can be arbitrarily divided into direct (or efferent) and indirect (or afferent) factors. Such terminology is not meant to assume the presence of a reflex arc type of arrangement for which there is, as yet, no evidence.

Angiotensin and ACTH are direct (or efferent) stimuli to aldosterone secretion because each has been shown to act directly on the adrenal cortex. While ACTH can be a potent stimulus to aldosterone release in acute experiments, over longer periods of time it probably plays only an indirect or supportive role in aldosterone secretion. Thus, in the various diseases with oversecretion of aldosterone, hydrocortisone is not increased, providing strong evidence that an increased ACTH secretion is not the usual cause of aldosteronism. Also, angiotensin has relatively less effect on adrenal hydrocortisone output, and therefore appears to be a more selective and specific stimulus for aldosterone than ACTH is.

Included in the category of indirect (afferent) factors are the stimuli produced by changes in electrolyte balance and by certain
hemodynamic alterations. These stimuli may not appear to act directly on the adrenal cortex, but the pathways of their mediation are unknown. Sodium deprivation, discussed above, is the most well-known stimulus to aldosterone secretion. Changes in potassium balance also affect aldosterone. The aldosterone response to sodium deprivation is prevented by potassium depletion and augmented by potassium administration when hyperkalemia is produced. These findings led to the suggestion that a rise in plasma potassium is a stimulus to aldosterone release. Other studies have shown that aldosterone release is inversely related to an induced change in vascular volume so that bleeding increases it, and albumin infusion may reduce it. In dogs, occlusion of the vena cava above the liver produces a prompt rise in aldosterone output that leads to progressive ascites formation. Recently it has been shown that the aldosterone rise after caval occlusion is prevented by nephrectomy, again pointing to an important role of a renal factor in mediating stimuli to the adrenal cortex. It seems possible then that at least some of these various afferent stimuli for aldosterone release might be mediated to the adrenal by causing release of a renal aldosterone-trophic hormone (renal renin).

Is Angiotensin the Trophic Hormone for Aldosterone? Studies in Secondary Aldosteronism

We may now ask the question: To what extent can instances of physiologic or pathologic oversecretion of aldosterone be explained by the operation of a renal-adrenal mechanism involving the release of angiotensin? The concept of a renal-adrenal interaction fits well with the finding of oversecretion of aldosterone in malignant hypertension. But, in malignant hypertension severe renal damage might cause an inappropriate release of renin peculiar to this disease. You will recall that neither renin nor angiotensin has been incontrovertibly demonstrated in normal human plasma.

Patients with cirrhosis and ascites are a particularly useful model for pursuit of this problem because they so consistently exhibit marked oversecretion of aldosterone and avid renal retention of sodium. Furthermore, increased aldosterone output is known to play an important role in the pathogenesis of their edema. Accordingly, in an effort to determine whether increased amounts of circulating angiotensin are responsible for the oversecretion in this typical example of secondary aldosteronism, we have studied the effect of angiotensin infusion on (1) blood pressure, (2) aldosterone secretion, and (3) renal hemodynamics and the excretion of sodium. The results were compared with those obtained from similar studies of normal subjects and were also controlled by always comparing the effect of angiotensin with equipressor amounts of norepinephrine.

Effect of Angiotensin on Blood Pressure

In view of the fact that angiotensin is a most potent pressor agent, one might expect these patients with cirrhosis to manifest arterial hypertension unless some sort of resistance or tachyphylaxis to angiotensin had developed. Actually, such patients rarely exhibit significant arterial hypertension.

We found that patients with cirrhosis and ascites are relatively resistant to the pressor effects of synthetic angiotensin, so that sometimes infusion rates up to 10 times higher than that required for normal subjects must be given in order to produce a given equipressor response. The reduced pressor responsiveness in these patients, moreover, is rather unique for angiotensin because they may not be less sensitive to norepinephrine than normal subjects. Angiotensin also seems to differ from norepinephrine because, with prolonged infusion of angiotensin for periods longer than 24 hours, marked tachyphylaxis can develop so that veritably enormous dosages of angiotensin (up to 13 mg./24 hours) may be required to sustain a pressor response. This tachyphylaxis to angiotensin raises interesting points about this peptide and possibly suggests that its pressor action is a pharmacologic phenomenon. The data also
Effect of continuous infusions of angiotensin or of norepinephrine in a patient with secondary aldosteronism (cirrhosis with ascites). There is a reduced pressor responsiveness to both pressor agents. Note that increasing dosages of angiotensin were necessary to produce a pressor response, particularly when the infusion was given the second time. Natriuresis produced by angiotensin was of strikingly greater magnitude than that of norepinephrine. The pressor agents had variable effects on aldosterone secretion, but the normal stimulating effect of aldosterone is not seen in this condition (not shown).

Effect of Angiotensin on Aldosterone Secretion in Cirrhosis with Ascites

Secondly, let us consider the effect of angiotensin on the rate of aldosterone secretion in cirrhosis. Here again, the response was different from that of normal subjects. Angiotensin failed to augment significantly the secretion rate of aldosterone in eight of nine paired infusion studies of five patients.\(^\text{17}\)

Effect of Angiotensin on Sodium Excretion in Cirrhosis

In this third respect too the response of angiotensin was opposite from that of normal subjects. As shown in figure 2, marked and sustained natriuresis can be produced by the infusion of angiotensin with the values rising from a control of 0.5 mEq./day to as high as 68 mEq./day in this patient and in other patients to as high as 520 mEq./day. The natriuresis of angiotensin is of far greater magnitude than that of equipressor dosages of norepinephrine. The natriuretic response has been produced in seven of nine studies. It seems to be related to the amount of angiotensin given, but not to the pressor response.

These three unusual responses to angiotensin infusion in cirrhosis are open to a number of interpretations. As stated above, reduced pressor responsiveness might mean that increased amounts of angiotensin could be circulating in cirrhosis or in various other states
of secondary aldosteronism without manifest arterial hypertension. Failure of infused angiotensin to augment aldosterone secretion might mean that these patients are already maximally stimulated by an endogenous trophic substance, possibly angiotensin. These results thus can be used as circumstantial evidence for a role of angiotensin as the trophic hormone for regulating aldosterone secretion in a model type of secondary aldosteronism.

The angiotensin natriuresis in secondary aldosteronism is more difficult to explain. A number of renal clearance studies indicate that it occurs without a change in glomerular filtration rate or with a lesser change as compared with norepinephrine, thus indicating that angiotensin can have a profound effect on the tubular transport of sodium. The natriuresis is also accompanied by a depression in renal blood flow. Further studies of this new phenomenon are under way.

**Summary**

The role of hormones that can influence renal tubular reabsorption of salt and water in congestive heart failure and other states of abnormal fluid retention has been discussed.

Available evidence indicates that the antidiuretic hormone of the neurohypophysis plays a nonessential role in the pathogenesis of edema.

Oversecretion of aldosterone can be an important, or even an essential, mechanism in the pathogenesis of certain states of edema, such as those of nephrosis and cirrhosis. Advanced congestive heart failure, however, can occur with a normal or only a moderately elevated rate of aldosterone secretion. The observations perhaps suggest that more immediate hemodynamic consequences of heart failure, such as a reduced glomerular filtration rate, also play an important role in causing renal retention of sodium. Increased aldosterone secretion is provoked by an unidentified hemodynamic consequence of cardiac decompensation. When oversecretion occurs, it undoubtedly adds to circulatory embarrassment by promoting more sodium retention.

An understanding of the exact role of aldosterone in heart failure awaits clarification of the fundamental problem of the mechanisms involved in the normal control of the secretion of the hormone. Studies of other diseases have yielded helpful clues in this latter regard. The finding of oversecretion of aldosterone in malignant nephrosclerosis led to the demonstration that angiotensin is a potent stimulus to aldosterone secretion and to the suggestion that sodium balance may be regulated by a renal-adrenal (angiotensin-aldosterone) mechanism, which is deranged in malignant hypertension.

Recent studies in our laboratory have been designed to determine whether increased amounts of circulating angiotensin could be responsible for the oversecretion of aldosterone of typical secondary aldosteronism. In a model state of secondary aldosteronism (cirrhosis with ascites), it has been found that the pressor responsiveness to infused angiotensin is reduced, a finding that could explain the absence of manifest arterial hypertension even if angiotensin were present in increased amounts in secondary aldosteronism. Angiotensin also failed to increase the rate of aldosterone secretion in cirrhosis with ascites. This might mean that the adrenal cortex is maximally engaged by increased amounts of endogenous trophic hormone (? angiotensin). In further contrast to its effects in normal subjects, in cirrhosis with ascites angiotensin caused a marked natriuresis by modifying the renal tubular reabsorption of sodium. The very potent effects of angiotensin on sodium transport also raised the possibility that an intrarenal action for this substance may be physiologically more important than its effect on aldosterone release.

Thus far, crucial experiments are lacking, and other interpretations are possible. It remains to be shown that increased amounts of renin or of angiotensin appear in the circulation of either sodium-depleted normal subjects or patients forming edema. The observations to date suggest, however, that a renal humoral factor (? angiotensin) may be
involved in the normal regulation of sodium balance and in the pathogenesis of various states of fluid retention. Furthermore, this renal factor may mediate various stimuli that are known to increase aldosterone secretion to the adrenal cortex. Some critical change in the renal circulation may determine the release of this factor.

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References
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