A REVIEW

Aldosterone In Clinical Medicine

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AS EARLY as 1934 it was noted that a potent substance that caused retention of salt remained in adrenal cortical extracts even after various crystalline fractions had been removed.[36] This substance was isolated, crystallized and identified as aldosterone in 1953 and 1954,[29,30] and subsequently was isolated from the urine.[26] The quantitation of aldosterone and the studies of its action that have been carried out since then have provided valuable information in understanding many clinical problems. The influence of aldosterone extends beyond electrolyte regulation and into areas of circulating volume control and blood pressure regulation.

Aldosterone is the most important mineralocorticoid secreted by the adrenal cortex. The secretory rate of aldosterone in normal subjects on salt intakes of 7 gm is 150 micrograms in 24 hours.[6,15,28,33] This is low compared with the 20 mg of cortisol, and 2.5 mg of corticosterone secreted in 24 hours.[6,15,28]

Apparently aldosterone originates in the outer zona glomerulosa of the adrenal cortex.[17] In contrast to cortisol, the factors regulating its secretion are many and varied. For example: contraction of the extracellular fluid compartment,[3] sodium deprivation,[27] potassium loading,[4,23] and administration of adrenocorticotropin (ACTH)[25] and angiotensin II,[22] cause increases in aldosterone secretion. Expansion of the extracellular fluid compartment and the circulating blood volume,[3] and potassium depletion[4] result in decreases in aldosterone secretion. In subjects with hypopituitarism, the secretion of aldosterone remains in the normal range, demonstrating the relatively slight effect endogenous adrenocorticotropin may exert on its secretion.

The major site of action of aldosterone is the nephron, where it facilitates the exchange of sodium for potassium and hydrogen ions. This action also takes place to a lesser degree in other secretory areas, such as the sweat glands, salivary glands and the gastrointestinal tract.

Aldosterone Excess

Primary aldosteronism (Conn's Syndrome)[11]

The continued administration of aldosterone or desoxycorticosterone acetate results in a condition strikingly similar to the syndrome of primary aldosteronism resulting from an aldosterone-secreting adrenocortical adenoma. The daily administration of 20 mg of desoxycorticosterone acetate (Chart 1) produces sodium retention, but after eight days a new equilibrium is reached; no further sodium retention occurs, but potassium loss continues. This new state is characterized by an increase in the extracellular fluid and in plasma volume, and by hypokalemia, hypernatremia, and hypertension.[1] These findings are also the cardinal manifestations of primary aldosteronism.

The increase in plasma volume that almost always occurs in primary aldosteronism is recorded in Table 1. After removal of the adrenocortical adenoma, plasma volume measurements eventually return to normal. The potassium depletion resulting from increased aldosterone secretion accounts for the many symptoms of this condition. Often the potassium depletion may reach extreme proportions giving rise to abnormalities in renal function, carbohydrate metabolism and in the autonomic nervous system.

Urinary concentrating defects occur, producing a condition similar to nephrogenic diabetes insipidus. Urinary output is large (2500 to 5000 ml in 24

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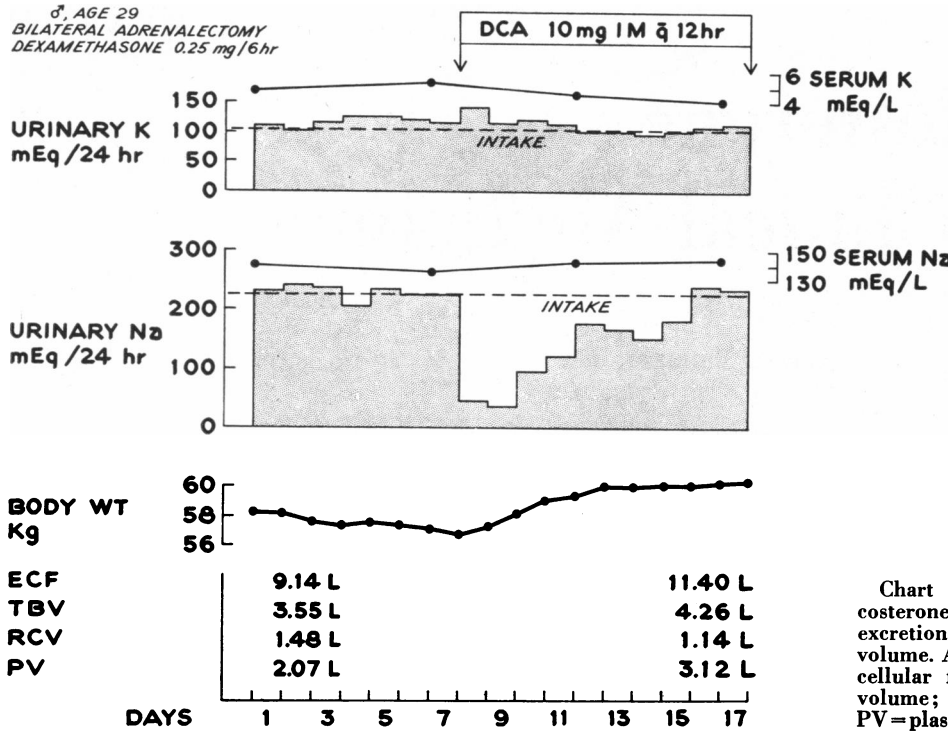

Chart 1.—Effect of desoxycorticosterone on sodium and potassium excretion, body weight, and blood volume. Abbreviations: ECF = extra cellular fluid; TBV = total blood volume; RCV = red cell volume; PV = plasma volume.

hours). In the absence of uremia, failure to concentrate the urine after dehydration and administration of vasopressin may be presumptive evidence of potassium depletion.

The carbohydrate abnormalities that occur in primary aldosteronism resemble those that occur in the "peripheral type" of diabetes mellitus.[19] The blood sugar level is frequently elevated, and the glucose tolerance test curve resembles that found in diabetes mellitus. Insulin levels are increased. With correction of the potassium depletion, carbohydrate metabolism returns to normal. The glucocorticoid effects of aldosterone are negligible at the level of secretion found in primary aldosteronism.

Abnormal circulatory reflexes are frequently present in severe and chronic potassium depletion.[7] These abnormalities are reversible and appear to be uniquely characteristic of primary aldosteronism. Normally, the response to a change in posture from squatting to standing, consists of tachycardia with little or no change in arterial pressure. If decreases in both systolic and diastolic pressure occur after changes of position, without changes in pulse rate, the presence of baroreceptor deficiencies in primary aldosteronism is suggested. Valsalva's maneuver also tests baroreceptor activity. The normal hypertensive "overshoot" and reflex bradycardia following the release of increased intrathoracic pressure fails to occur in these patients. The observation of decreases in blood pressure on postural change, without acceleration in pulse rate, in an untreated hypertensive patient may well be presumptive evidence of primary aldosteronism. The higher blood pressure in the supine position combined with the failure to concentrate urine may well account for the pronounced nocturia and the reversal of the normal diurnal excretion of sodium and water found in these patients (Chart 2). Potassium replacement will correct the abnormal circulatory reflexes.

TABLE 1.—*Plasma Volume Determinations in Primary Aldosteronism*

Patient	Predicted Plasma Volume (Liters)	Observed Plasma Volume (Liters)	Deviation Pre-Operative (Liters)	Per Cent Post-Operative (Liters)
1	1.97	3.48	+76	+37
2	2.95	4.37	+48	0
3	1.61	1.97	+22	− 4
4	2.48	3.39	+37	− 3
5	2.25	2.76	+23	+ 4
6	1.91	1.83	+ 5	− 1

Hypertension occurs in primary aldosteronism, and although the cause is obscure a hypothesis can be presented. Blood volume and nervous regulation of arterioles are two factors in determining arterial pressure. The combination of hypervolemia and defects in baroreceptor activity is unique to primary aldosteronism. With diminished reflex control of blood pressure, the mechanical effects of increase in blood volume may be the critical factor in the production of hypertension. There is a decided similarity to patients with autonomic insufficiency.[34] Both have baroreceptor abnormalities and with both

there is a rise in blood pressure when blood volume is increased. After removal of the adrenal tumor, the blood pressure gradually returns to normal, paralleling the restoration of baroreceptor activity and normal blood volume.

The use of anti-aldosterone agents, such as spironolactone, has proven diagnostically useful.[9] Spironolactones block the effect of aldosterone in the nephron. The administration of sufficient amounts of spironolactone should aid in correcting the sodium retention and potassium loss of aldosterone excess. In patients with primary aldosteronism, administration of 1 gm of spironolactone (or 400 mg of spironolactone-A) daily in divided doses for three days results in a sodium diuresis with potassium retention and a return of the serum potassium concentration to normal. Withdrawal of the drug is followed in seven days by a recurrence of potassium loss and hypokalemia. Thus, a low serum potassium concentration which is corrected by spironolactone but which returns to previous low levels when the drug is discontinued, is presumptive evidence of aldosterone excess.

Measurement of the serum potassium concentration is the single most useful initial diagnostic test for primary aldosteronism. However, it must be measured under the proper conditions for correct interpretation. Dietary intake of salt must be normal (greater than 3 gm of sodium chloride) for four days before the determination is made. The importance of sufficient sodium ion is demonstrated in Chart 3. Sodium ions must reach the exchange site in the nephron before the influence of aldosterone can be observed. If only limited amounts of sodium ions reach this site, as when a patient is on a restricted sodium intake, actual potassium retention will occur, even though abundant amounts of aldosterone are present.[9] Serum potassium concentrations will become normal and the abnormalities of potassium depletion will be corrected.

Secondary Aldosteronism

Edematous States. Increased secretion of aldosterone is seen in edematous states, such as cirrhosis with ascites, nephrosis, idiopathic edema, and congestive heart failure. Obviously, the increased secretion is a consequence of the underlying disease process. How does one reconcile the presence of increased aldosterone secretion in an edematous patient when increases in the extracellular fluid normally depress aldosterone secretion? Reduced blood flow or blood pressure in some critical area may well be the mechanism involved.[2] Correction or improvement of the basic disease is usually accompanied by reduction of aldosterone secretion.

In cirrhosis with ascites, the continuing loss of fluid into the abdominal cavity may initiate over-

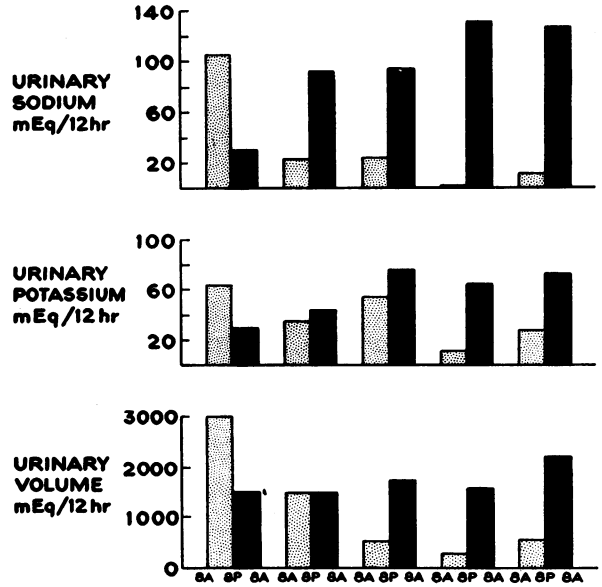

Chart 2.—Diurnal patterns of urinary sodium, potassium and volume in primary aldosteronism.

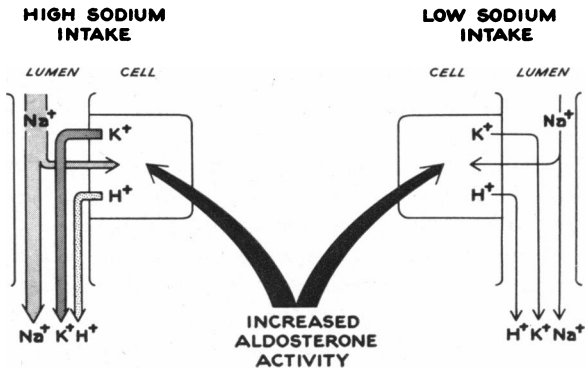

Chart 3.—Effect of salt intake on electrolyte excretion in primary aldosteronism.

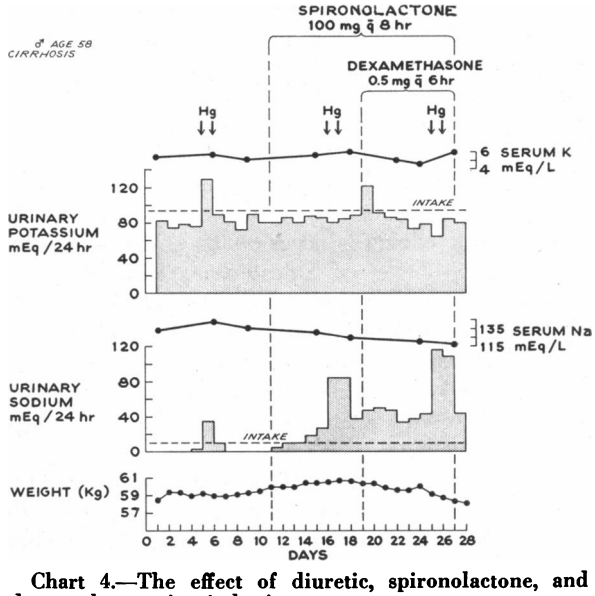

Chart 4.—The effect of diuretic, spironolactone, and dexamethasone in cirrhosis.

secretion of aldosterone resulting in compensatory fluid retention. The glomerular and capillary leaks of nephrosis may provide a similar stimulus to hypersecretion of aldosterone. In secondary aldosteronism of these edematous states, the electrolyte abnormalities of primary aldosteronism do not occur. An explanation for their absences is diagrammed in Chart 3. If aldosterone is to exert its influence in the nephron, adequate sodium ion must reach the exchange site. When sodium retention is greatly increased, little sodium ion reaches this site so that the renal loss of potassium is not observed. Certainly, if enough sodium ion were present in the exchange site, a mechanism for the loss of potassium would be readily available.

An illustration of such a mechanism is given in Chart 4. The data were obtained from a patient who was cirrhotic, had refractory ascites, excessive aldosterone secretion, and no urinary sodium excretion. After equilibration on a controlled diet he was given 2 ml of Mercurhydrin on two successive days. Natruresis was minimal but kaluresis occurred. Mercurial diuretic drugs act on the proximal tubule to interfere with sodium reabsorption. As a result more sodium ions are delivered to the exchange site, and since excessive aldosterone is present a potassium diuresis occurs. The greater incidence of digitalis intoxication in patients with congestive heart failure treated with oral diuretic agents may be related to this potassium-wasting phenomenon.

Administration of spironolactone to the patient, starting on day 11, resulted in only slightly increased sodium excretion. When the same dose of the mercurial diuretic agent was repeated five days later, pronounced sodium diuresis occurred without potassium diuresis. The excessive aldosterone present was effectively blocked, and the additional sodium ions that reached the site of aldosterone activity did not participate to any great extent in the exchange of potassium. The addition of dexamethasone on day 19 further increased the natruretic response to the same dose of mercurial diuretic drug but the continuing blockade of the renal effect of aldosterone prevented potassium loss.

Idiopathic edema is occasionally accompanied by increased secretion of aldosterone. That this syndrome may also occur without increased aldosterone secretion supports the supposition that aldosterone may not be an essential factor. The associated finding of hypokalemic alkalosis in such patients may indicate excessive secretion of other mineralocorticoids.[5]

Non-edematous States. Hypertension is a common finding in nonedematous states with secondary aldosteronism. Increased secretion of aldosterone has been observed in severe essential hypertension and accelerated or malignant hypertension.[16,24] In unilateral renal obstruction, a state similar to primary aldosteronism is occasionally seen.[24,37] These observations have produced two questions: Why is aldosterone secretion increased in hypertension? and How can one distinguish these patients from those with an aldosterone-producing tumor?

An explanation for the increased secretion of aldosterone in these conditions has been suggested.[21,32] Extrarenal occlusion of a renal artery decreases the mean blood pressure to the kidney where the juxtaglomular cells of the afferent arterioles may function as a pressure receptor. Granularity increases within these cells and renin content rises. Renin is a proteolytic enzyme which changes an alpha-2 globulin fragment into angiotensin I, which is further converted into angiotensin II. Angiotensin II is not only a potent vasopressor agent but also a potent stimulator of aldosterone secretion.[22] The excessive secretion of aldosterone may produce effects on the nephron similar to those seen in primary aldosteronism. Aldosterone may be viewed as an undesirable and contributory physiological consequence of the basic disease process.

In accelerated or malignant hypertension diffuse narrowing of the intrarenal arterioles may initiate the same series of events, but it is not known if this is the sole mechanism responsible for the increased secretion of aldosterone.

Certain features distinguish these hypertensive states from primary aldosteronism.[31] Malignant hypertension is an extremely rare occurrence in adult patients with primary aldosteronism—only one such case has been reported.[20] The urinary levels of aldosterone are approximately the same in this group of hypertensive patients and in patients with primary aldosteronism. While serum potassium concentrations tend to be reduced in accelerated hypertension, they infrequently reach the concentrations observed in primary aldosteronism.[12] The serum sodium concentration often provides a useful clue for differentiating between the diseases. In accelerated hypertension, it is usually normal or low, whereas in primary aldosteronism it is increased.[3,12,31] The blood volume is usually depressed in hypertension,[35] in contrast to the hypovolemia of primary aldosteronism. The hypervolemia possibly can be attributed to the generalized vasoconstriction as well as to the natruretic effect of angiotensin in the hypertensive state.[14] The circulatory reflex abnormalities of primary aldosteronism are not found in accelerated hypertension. In our experience, patients with renal vascular hypertension, secondary aldosteronism and hypokalemia respond well to renal artery reconstruction or nephrectomy.

Measurements of exchangeable sodium and potassium may also aid in distinguishing between the two groups. These measurements are usually normal

in severe hypertension.[10] Increased exchangeable sodium and decreased exchangeable potassium are observed in primary aldosteronism.[13]

Aldosterone Lack

Aldosterone lack is characteristic of Addison's disease. It is well known that decreases in blood pressure associated with changes in posture in patients with untreated Addison's disease are corrected by administration of mineralocorticoids. The same is true of patients with autonomic insufficiency and postural hypotension. The symptoms of the latter are frequently improved, although not cured, by treatment with mineralocorticoids.[18] These patients are also similar to patients with Addison's disease in that secretion of aldosterone is low and the usual responses that increase aldosterone secretion, (for example, corticotropin and angiotensin) are blunted or absent.[8] This relatively low and fixed secretion of aldosterone could account for the benefit resulting from treatment with mineralocorticoids.

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