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The adrenal cortex and the kidney

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The adrenal cortex regulates renal function in a number of important ways; indeed, normal renal function cannot be understood without recognition of such regulation. Well-recognized examples of such regulation are the control of body fluid tonicity through regulation of urinary solute concentration—a function controlled "primarily" by vasopressin, but secondarily and importantly by the adrenal cortex—and control of body sodium—a function controlled primarily by renal tubular sodium reabsorption but regulated by sodium-retaining steroids.

The kidney can regulate adrenal function by changing reabsorption of sodium and secretion of potassium, and also by release of renin. The primary target of such regulation is the secretion of aldosterone, which may be influenced by body fluid volume, potassium ion and angiotensin II.

Because of these interrelationships, the pathophysiology of certain disease states may be described as aberrations in feedback loops between adrenal cortex and kidney. In this paper we will consider this "system" in some detail, and attempt to explain four disorders as examples of errors in control.

In the form of "primary" aldosteronism resulting from hyperplasia of all adrenal cortical tissue, overproduction of aldosterone persists in the absence of all known stimulatory factors. In renovascular hypertension, angiotensin and aldosterone production may persist despite systemic hypertension. In the non-salt-losing form of the adrenogenital syndrome of congenital adrenal hyperplasia without treatment, failure of feedback inhibition by cortisol may result in overproduction of adrenocorticotropic hormone (ACTH) which, in turn, may lead to overproduction of progesterone. Progesterone may cause sodium loss and overproduction of renin and aldosterone while blocking their effects. In the syndrome of juxtaglomerular hyperplasia with normal blood pressure, overproduction of renin may result from unresponsiveness of blood vessels leading to a lack of feedback inhibition by pressure rise. Under certain circumstances sodium loss can potentiate both the overproduction and the unresponsiveness. Excessive renin leads to aldosteronism and potassium loss.

Adrenal cortical control of renal function

The control of renal function by the adrenal cortex can best be considered separately for steroids with predominately carbohydrate-regulating activity, e.g., cortisol, and for those with sodium-retaining activity, e.g., aldosterone.[1] In addition, progesterone may act as an aldosterone antagonist [5].

Cortisol increases the glomerular filtration rate (GFR) and, thus, the filtered load of sodium and water [6, 7]. In its absence, the GFR falls, and excretion of salt and water loads is limited. A second action of cortisol, in decreasing distal tubular reabsorption of water, must be invoked to explain the limitation of free water clearance in its absence [8, 9]. This limitation can be overcome with doses of carbohydrate-active steroids which do not increase the GFR [8].

Aldosterone has no effect on GFR except as GFR may be influenced by sodium retention and expansion

[1] The designations "glucocorticoid" and "mineralocorticoid", used as nouns for such steroids, introduce semantic and, more importantly, conceptual difficulties. Thus, rapid excretion of potassium is a function of carbohydrate-active steroids, *not* of sodium-retaining ones [1], whereas sodium-retaining steroids may cause potassium *retention* [2]. A fluorine atom in the 9-alpha position increases *both* carbohydrate activity (10-fold) and sodium-retaining activity (125-fold) [3]. The naturally occurring steroid corticosterone has both properties; indeed, cortisol produces sodium retention. ACTH stimulates not only aldosterone secretion by the zona glomerulosa but also desoxycorticosterone secretion by the zona fasciculata [4].

of extracellular fluid volume. It has no effect on distal tubular reabsorption of solute-free water, and cannot improve the water diuresis in Addison's disease. Aldosterone may increase sodium reabsorption *a*) in the proximal tubule [10–12], *b*) in the ascending limb of the loop of Henle [13], *c*) in the distal convoluted tubule [14] and *d*) in the collecting ducts [15]. In the last two sites, the increase in negative luminal potential produced by the reabsorption of sodium facilitates secretion of potassium [14] so that potassium appears to "exchange" for reabsorbed sodium. In the same two sites, secretion of hydrogen ion, facilitated by the potential difference, may also be promoted by aldosterone [16, 17].

Aldosterone also affects another renal function, to wit, release of renin. Whereas this has great clinical importance, in that renin release is suppressed in primary aldosteronism, the mechanism(s) by which this is accomplished is unknown. The suppression clearly does not result from hypertension *per se*, since the same degree of "essential" hypertension need not have the same effect; it occurs despite persistently low plasma potassium concentration, which should raise renin production. It may reflect renal vasoconstriction more "distal" than that found in "essential" hypertension, allowing the pressure rise to be sensed by the juxtaglomerular apparatus.

Progesterone can antagonize the effect of sodium-retaining steroids [5] on the renal tubules [18] reducing the retention of sodium produced by a given dose of aldosterone or desoxycorticosterone at a given filtered load. This effect (vide infra) may explain the secondary aldosteronism of the non-salt-losing form of the adrenogenital syndrome.

Renal control of adrenal cortical function

The kidneys can control aldosterone secretion directly, by changes in renin secretion, leading to changes in release of angiotensin I, which is converted to angiotensin II, and indirectly, by retention of sodium or by retention or loss of potassium.

Release of renin has been accomplished experimentally with diuretic administration and sodium deprivation [19–23], catecholamine [24, 25] or cyclic AMP [25, 26] administration, potassium deprivation [27–29], renal nerve stimulation [30–33], hemorrhage [34–36] and renal artery constriction [34, 35, 37, 38]. Accordingly, the precise mechanism of release in a given subject or syndrome may be difficult to assess. With many but not all of these stimuli, beta-blockade of the autonomic nervous system blocks renin release. It is clear that volume contraction, as with sodium loss, and pressure changes, as with renovascular constriction, can each serve as an independent stimulus to renin release. Experimentally, procedures which increase transport of sodium at the region of the macula densa decrease renin production.

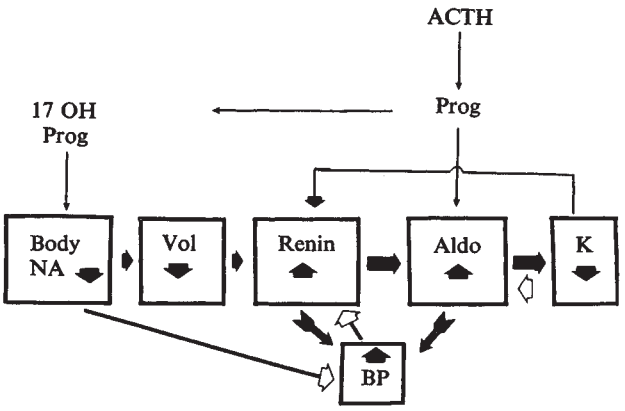


Fig. 1. *"Feedback" loops involved in blood pressure control.* The schema shows a decrease in total body sodium leading to a decrease of extracellular (ECF) volume (*solid arrow*), and lowering blood pressure (*open arrow*). 17-Hydroxyprogesterone (and also progesterone) can decrease body sodium through renal loss. ECF volume decrease produces an increase of renin which may increase blood pressure. An increase of renin produces an increase of aldosterone which may also increase blood pressure. An increase in aldosterone secretion decreases body potassium through renal loss, and a decrease in potassium may inhibit aldosterone production and stimulate renin production. Finally, a rise of blood pressure may directly inhibit renin release. (Note that ECF volume and renal arterial blood pressure control plasma renin independently.) Production of aldosterone is also under control of ACTH, and progesterone and 17-hydroxyprogesterone are by-products.

Renal retention of sodium can lower aldosterone production by suppression of renin production and also probably by mechanism(s) not involving renin [39]. Renal loss of potassium can similarly depress aldosterone production, probably as a direct cellular effect [40, 41].

Some of these relationships involved in adrenal-renal interaction are illustrated in Fig. 1.

The syndrome of primary aldosteronism resulting from primary adrenocortical hyperplasia considered as an error in feedback control

In the syndrome of primary aldosteronism resulting from adrenocortical adenoma, or Conn's syndrome, the sequence of events (adrenal adenoma → overproduction of aldosterone → hypertension → renin suppression) appears well-established even though the mechanism of renin suppression, like the mechanism for hypertension, is not clear.

The clinical criteria for diagnosis depend upon *a*) demonstration of overproduction of aldosterone and *b*) demonstration that such overproduction is "auto-

nomous", e.g., in the face of expansion of ECF and of intravascular volume. This can be attempted *1*) with sodium loads or *2*) with albumin given i.v.

When overproduction is "autonomous", sodium loads lower the serum and body potassium concentrations—a point of diagnostic value (vide infra). Potassium loss, *per se*, however, can lower aldosterone secretion. Thus, overproduction may appear to be nonautonomous, *vis-à-vis* body fluid volume when expansion with sodium loads lowers serum potassium and lowers aldosterone secretion by this mechanism. Expansion of intravascular volume can be accomplished with albumin infusion, and this does not produce potassium loss.

A third criterion for diagnosis is *c*) the suppression of plasma renin activity. As suppression is normally induced by sodium loads, the possibility of suppression in primary aldosteronism is sought after volume contraction—generally with low sodium-diet and administration of diuretics.

A fourth criterion for steroid "autonomy" in primary aldosteronism lies in *d*) the ability of sodium loads to lower body and plasma potassium concentration [42]. This effect depends both upon the autonomy of aldosterone secretion in relation to the sodium load and upon the effect of aldosterone in potentiating distal tubular potassium secretion: with sodium loads, increases in absolute distal reabsorption of sodium, the (lumen negative) electrical potential for such secretion is presumably increased [14].

Fig. 2 illustrates these criteria in a patient with Conn's syndrome of primary aldosteronism resulting from adenoma. This patient presented with severe hypertension and hypokalemia. Sodium deprivation (July 7 to 20) *1*) lowered blood pressure, *2*) restored serum potassium concentration to normal and *3*) failed to stimulate plasma renin activity, which on the last day was 1.8 ng/ml/min with the patient supine and essentially unchanged with the patient upright.

Sodium loading (July 20 through 27) *1*) raised blood pressure, *2*) lowered serum potassium concentration to 2.0 mEq/liter and *3*) lowered the aldosterone secretion rate only slightly: it was 734 μg/24 hr on the 8th day of the sodium load as compared to 1000 μg/24 hr on the 12th day of sodium deprivation. The effective reversal of hypertension and hypokalemia with aldosterone antagonists and the reversal of all findings with removal of the adrenocortical adenoma argue strongly for the sequence of events we have described.

The appearance of a syndrome of primary *hyperplasia* of the adrenal cortex leading to the full syndrome of primary aldosteronism [42–44] has posed important questions: a practical one of differential diagnosis, and a theoretical one of explaining control of aldosterone

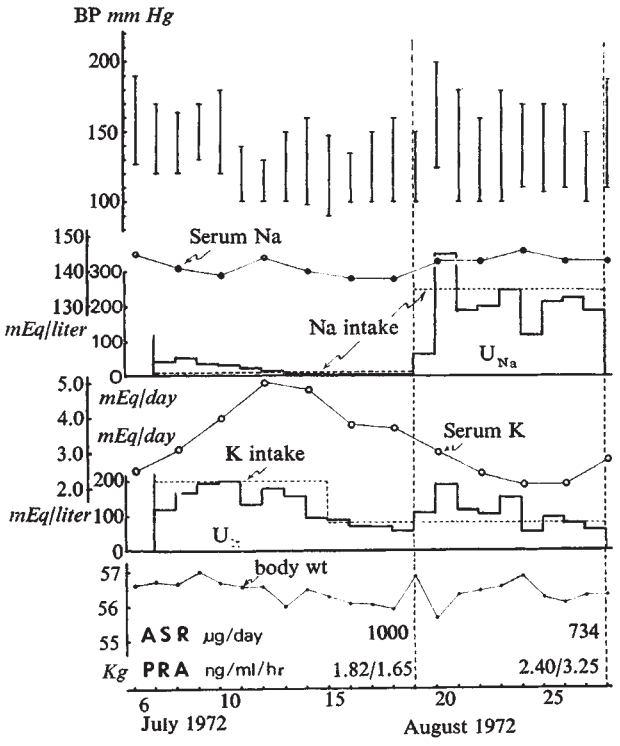


Fig. 2. *Effect of low and high sodium intakes on blood pressure, serum and urinary sodium (Na), serum and urinary potassium (K), body wt, aldosterone secretion rate (ASR) and plasma renin activity (PRA) in a 54-yr-old white female patient with primary aldosteronism resulting from an adenoma.*

secretion independently of ACTH, angiotensin and potassium ion.

Fig. 3 illustrates the results in a patient with the syndrome of primary aldosteronism resulting from "primary" hyperplasia of all adrenal cortical tissue. This patient presented with severe hypertension and a normal plasma potassium concentration (4.6 mEq/liter). With sodium intake of 109 mEq/day, serum potassium concentration decreased to 4.0 mEq/liter, aldosterone secretion rate was 1,151 μg/day (normal for this sodium intake, less than 200 μg/day) and plasma renin activity was 0. On a sodium intake of 249 mEq/day, serum potassium concentration decreased to 3.4 mEq/liter. With mercurial diuretic administration (February 16), there was a 2.2 kilo weight loss, but plasma renin activity (with the patient supine or upright) remained at zero.

We have studied 13 patients shown to have this syndrome. All of them have shown overproduction of aldosterone and hypertension. Sodium loads could not lower aldosterone secretion significantly, but did lower serum potassium concentration in all; infusion of albumin did not lower aldosterone secretion; plasma renin was suppressed despite administration of a low-sodium diet and diuretics.

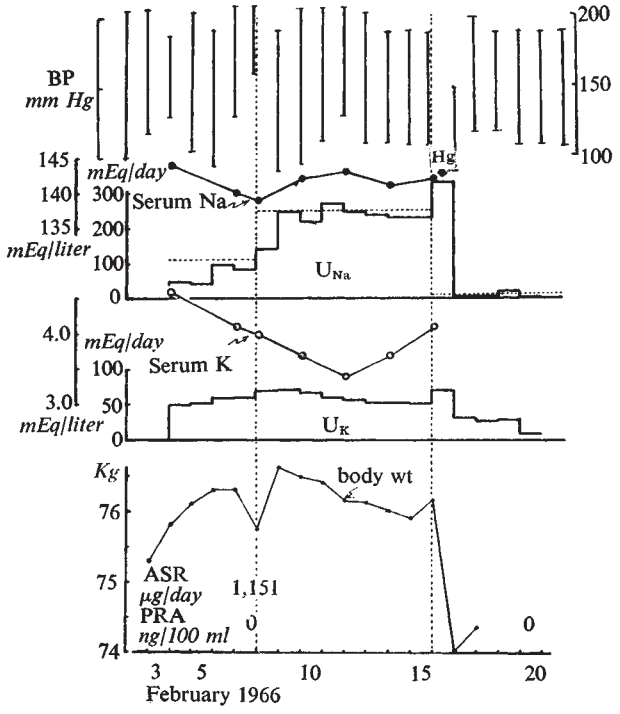


Fig. 3. *Effect of normal, high and low sodium intakes on blood pressure, serum and urinary sodium (Na), serum and urinary potassium (K), body wt, aldosterone secretion rate (ASR) and plasma renin activity (PRA) in a 57-yr-old male patient with primary aldosteronism resulting from adrenal hyperplasia.*

It is not possible to fit the syndrome of primary aldosteronism with adrenal hyperplasia into the schema of Fig. 1, since none of the stimuli to aldosterone production in that schema will account for the aldosteronism. Specifically, ACTH cannot be involved, since all these patients secreted normal amounts of cortisol and of 17-ketosteroids, and the syndrome could not be suppressed by treatment designed to suppress ACTH. Clearly, the adrenal overactivity cannot result from elevated plasma renin or potassium concentrations, since each of these is suppressed to subnormal values. Accordingly, the existence of the syndrome provides *prima facie* evidence for a stimulus, as yet unknown, to aldosterone secretion.

Renal vascular hypertension as an error of feedback control

Since the discovery by Tigerstadt and Bergman [37] that constriction of a renal artery induces ipsilateral release of renin, which in turn can raise blood pressure by release of angiotensin, hypertension of renovascular disease has been satisfactorily explained in many cases according to this sequence of events.

A number of differences, however, prevent acceptance of this explanation for all renovascular hypertension.

1. It was shown that whereas antibodies to angiotensin [45] and renin [46] could reverse the early hypertension of experimental renal artery constriction, such hypertension soon becomes refractory to such antibodies.

2. It was shown that plasma renin becomes normal in experimental renovascular hypertension when the opposite kidney is removed [47]. Furthermore, sarcosine 1, ala 8-angiotensin, which appears to block endogenous angiotensin specifically in the rat [48], will lower blood pressure in the two-kidney animal with renal vascular constriction, but will not do so when the opposite kidney has been removed [45].

In those species (dog and man) in which angiotensin increases aldosterone secretion, it is likely that in renovascular hypertension, if it results from sustained overproduction of angiotensin, there should also be sustained hypersecretion of aldosterone. This need not be true either in the dog [49] or in patients with renovascular hypertension [50].

Clinically it has been found that a number of patients with renovascular constriction and hypertension may have normal plasma renin activity and normal aldosterone secretion, and yet respond to removal of the constriction with a lowering of the blood pressure. It may be that some factor(s) other than renin is released or inactivated by the kidney with vascular constriction or that the current methods of measuring plasma renin activity do not measure the "effective" 24-hr angiotensin-producing capacity of the system.

We here describe a patient with renovascular constriction, hypertension, overproduction of aldosterone and normal renin activity, whose hypertension, nonetheless, responded only to beta blockade and to surgical release of the constriction.

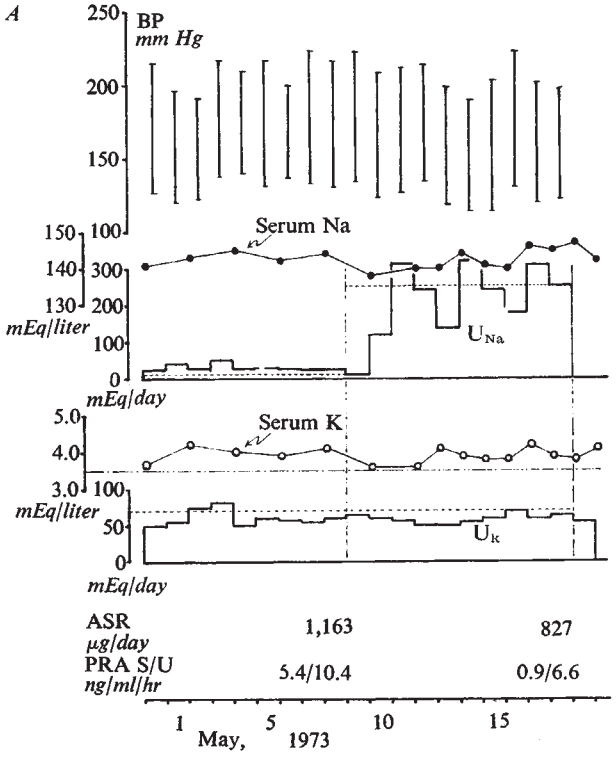
Fig. 4*A* shows the metabolic data on a 39-yr-old woman with renovascular hypertension resulting from bilateral fibromuscular hyperplasia. This patient presented with a six-year history of hypertension, hypokalemia (K = 3.2 mEq/liter) and normal plasma renin activity and high aldosterone secretion rates partly suppressible by high-sodium diet. As shown in the chart (Fig. 4*B*), hypertension persisted despite combined treatment with alpha-methyldopa, 3 g/day; hydralazine, 200 mg/day; hydrochlorothiazide, 50 mg/day; and spironolactone (Aldactone), 400 mg/day. The patient's blood pressure was completely controlled with beta blockade when propranolol was superimposed (days June 28 through July 17); when propranolol was discontinued, the blood pressure returned to daily average values of 168/127 mmHg.

Fibromuscular hyperplasia was demonstrated radio-

graphically and corrected surgically, and the hypertension was cured.

It is clear that in this patient the fibromuscular hyperplasia increased renin production, and that such overproduction was, at least in part, dependent upon beta-adrenergic regulation [32]. The overproduction of renin had a relatively greater effect on blood pressure than on aldosterone production.

The sequence of events (renovascular constriction → renin release → blood pressure rise and aldosterone secretion → hypokalemia) explains the symptom complex. The effect of salt loading in decreasing renin activity suggests that this control mechanism is not without effect, despite the overriding stimulus of vasoconstriction.



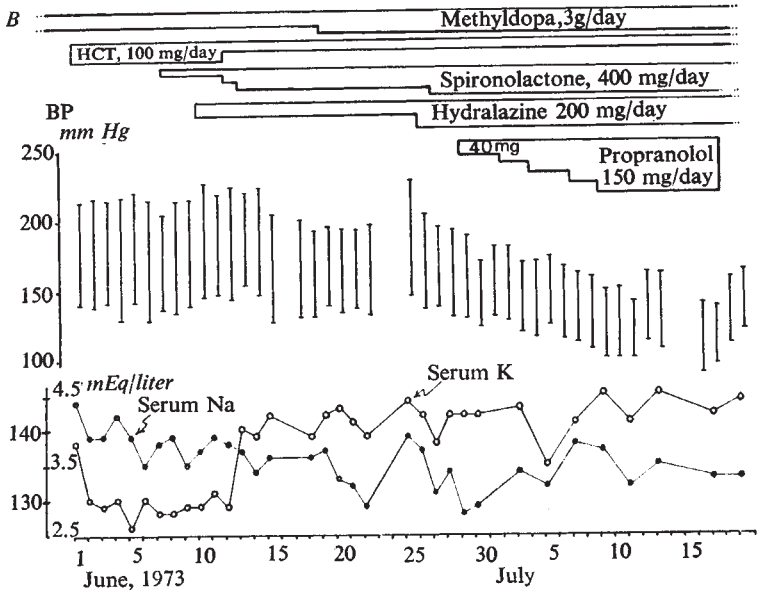


Fig. 4. *A, Effect of low and high sodium intakes on blood pressure, serum and urinary sodium (Na), serum and urinary potassium (K), aldosterone secretion rate (ASR), and plasma renin activity in a 38-yr-old white female patient with renovascular hypertension. B, Effect of antihypertensive agents on blood pressure and serum sodium (Na) and potassium (K) in the same patient.* HCT, hydrochlorothiazide. Note that the blood pressure does not return toward normal until propranolol is added. Later, propranolol alone controlled the blood pressure.

The secondary aldosteronism of adrenal hyperplasia, non-salt-losing, as an error in feedback control

In the adrenogenital syndrome resulting from congenital adrenal hyperplasia, patients with the non-salt-losing form regularly show hypersecretion of aldosterone [51, 52]. In Fig. 5, this is shown for an average and low-salt diet for nine patients with the syndrome contrasted with results for normal subjects and results of the same procedure for five subjects with the salt-losing variety, in whom aldosterone production is very low. Despite the hyperaldosteronism, it is noteworthy that the patients with the non-salt-losing form of the disorder have not been reported to show hypertension, and do not suffer from hypokalemic alkalosis, a complication expected in subjects with autonomous hypersecretion of aldosterone.

Both of these forms of the adrenogenital syndrome of congenital adrenal hyperplasia have been shown to result from a deficiency in the adrenal 21-hydroxylase, required for conversion of 17-hydroxyprogesterone to 11-deoxycortisol. There results a limitation in production of cortisol, with failure of plasma cortisol to inhibit ACTH production normally, and a consequent overproduction of ACTH, leading to overproduction of progesterone and of 17-hydroxyprogesterone. The progesterone and 17-hydroxyprogesterone can act as

antagonists of sodium-retaining hormones [5, 53] and induce renal sodium loss. Such renal sodium loss leads to overproduction of renin and overproduction of aldosterone [51, 52]. Because such overproduction of aldosterone is compensatory, resulting from sodium loss of renal tubular origin, it does not produce the hypertension or the hypokalemic alkalosis that result from autonomous overproduction.

The suppression of ACTH in this syndrome promptly lowers not only the excessive excretion of 17-ketosteroids, by-products of the overproduction of 17-hydroxyprogesterone, but also aldosterone production to the value normal for the sodium intake [51].

This syndrome thus appears as an error in feedback control of aldosterone production, presenting with the following sequence of events: cortisol deficiency → ACTH excess → overproduction of progesterone and 17-hydroxyprogesterone → renal tubular sodium loss → overproduction of renin → overproduction of aldosterone.

Aldosterone cannot induce potassium loss because its action on the renal tubule is blocked by progesterone and 17-hydroxyprogesterone. Its failure to induce hypertension presumably relates also to the primary salt loss: hypertension is not characteristic of the secondary aldosteronism of salt depletion.

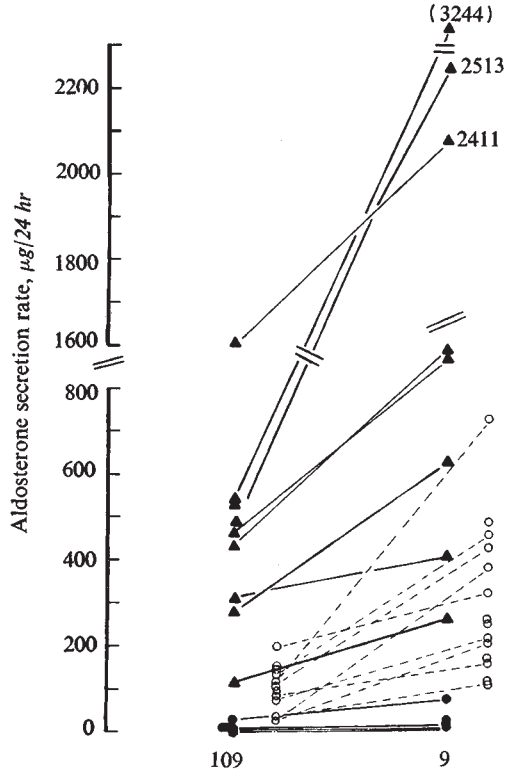


Fig. 5. *Effect of high and low sodium intakes on aldosterone secretion rates in normal subjects* (○), *in patients with adrenogenital syndrome of the salt-losing type* (●) *and of the non-salt-losing type* (▲).

The syndrome of juxtaglomerular hyperplasia, aldosteronism and normal blood pressure as an error in feedback control

In the syndrome of juxtaglomerular hyperplasia, hyperaldosteronism, hypokalemic alkalosis and normal blood pressure [54], the response of blood pressure to angiotensin II is severely limited, representing from one-tenth to one one-hundredth of the normal response. This limitation is not removed with expansion of intravascular volume to normal or supernormal values, nor by restoration of body potassium to normal. Accordingly, even very large increases in endogenous renin and angiotensin production fail to raise blood pressure above normal. Such increases, which persist even in the face of induced hypervolemia, can stimulate aldosterone production, which becomes excessive, and this in turn can induce hypokalemia by renal loss; the hypokalemia in turn may limit further aldosterone production. It probably also potentiates further overproduction of renin.

In some patients with a syndrome similar to this, a persistent obligatory renal loss of sodium appears to be present [55]. In this group of patients an error of feedback control of renal and adrenal function may occur, according to the following sequence of events: obligatory renal tubular sodium loss → hypovolemia → overproduction of renin → overproduction of aldosterone → hypokalemia because of aldosterone-stimulated renal loss. According to this sequence, the resistance of blood pressure to exogenous angiotensin is interpreted as a change secondary to the hypovolemia [56].

This sequence of events will not explain the syndrome in patients [57] who conserve sodium normally. It will probably not explain the extreme resistance to angiotensin found in most patients with this syndrome, which is one or more orders of magnitude greater than the resistance found with simple sodium deprivation. In the patients who conserve sodium normally, another sequence of events must be invoked to explain the pathophysiology. For this we have suggested the most satisfactory sequence according to current concepts as resistance to angiotensin → tendency to hypotension → overproduction of renin → overproduction of aldosterone → hypokalemia. The hypokalemia may limit further production of aldosterone while inducing even greater production of renin. This may explain the finding in some of these patients of very high plasma renin values together with only moderate elevation of aldosterone production (F. C. Bartter, unpublished observations).

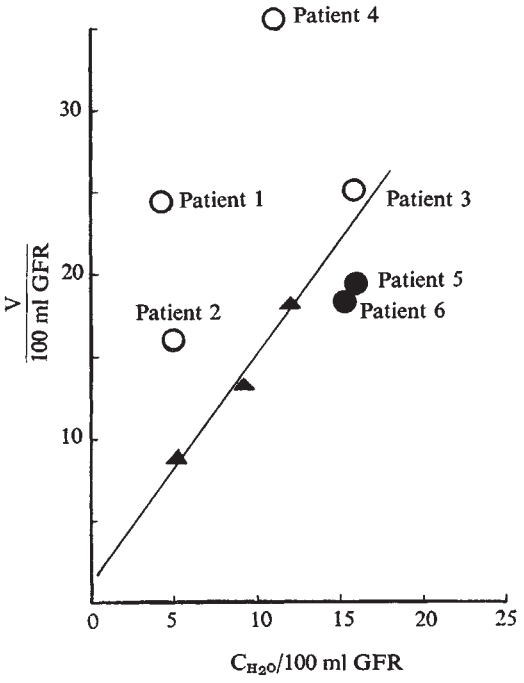


Fig. 6. *Averaged figures of urine flow/glomerular filtration rate (V/GFR) under conditions of maximal free water clearance for four patients with the syndrome of juxtaglomerular hyperplasia contrasted with the results in 12 normal young women.*

A further defect in renal function is regularly found in patients with this syndrome. Under conditions of maximal free water clearance, they manifest *1*) excessive delivery of proximal tubular fluid to distal sites, and *2*) a limitation in the percentage of such fluid which is converted to "free" water by reabsorption of sodium. This second limitation is especially prominent in view of the excessive production of aldosterone shown by most subjects. Fig. 6 shows averaged figures for urine flow/GFR (V/GFR) under conditions of maximum free water clearance for four patients with this syndrome contrasted to the results in 12 normal young women. Whereas delivery of proximal fluid to distal sites may be very high in the subjects, their ability to convert such fluid to free water is limited.

Rubini found a limitation in maximum urine flow and in minimal urinary osmolality resulting from experimental potassium depletion in man [58].

Fig. 7 shows these results plotted as the relationship between the fraction of fluid delivered distally which is converted to free water, $C_{H_2O}/C_{H_2O}+C_{Na}$, to the fraction so delivered, $C_{H_2O}+C_{Na}/GFR$. Results in normal subjects show that from 7 to 17% of the filtered fluid is delivered distally under these conditions of maximal free water clearance. Of the fluid so delivered, 80% is converted to free water. In the patients, on the other hand, some 10 to 35% of the filtrate is delivered to distal sites, but the percentage converted to free

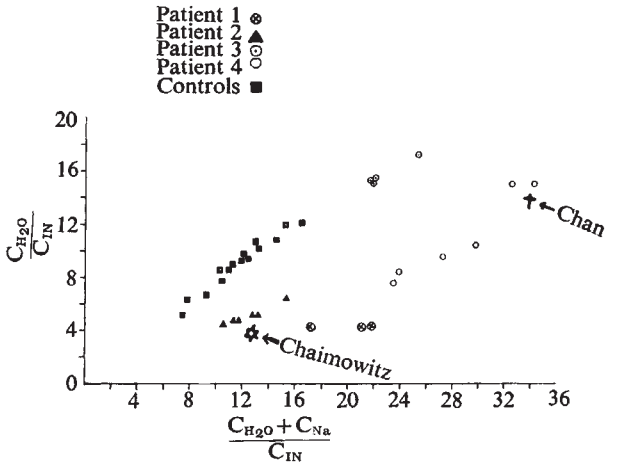


Fig. 7. *Relationship of the fraction of fluid delivered distally which is converted to free water to the fraction so delivered.*

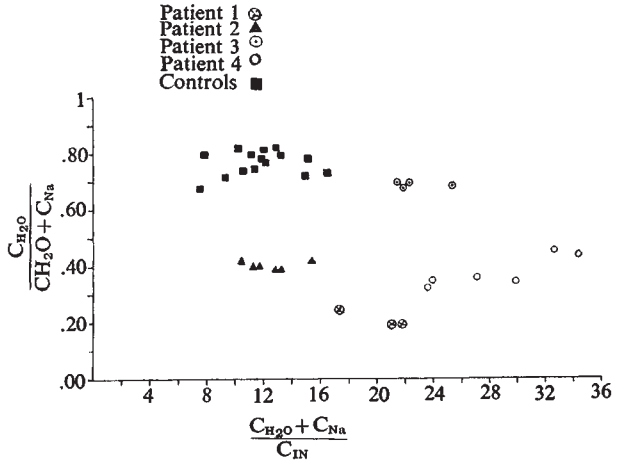


Fig. 8. *Relationship of free water clearance to fluid delivered distally.*

water varies from 19% in patient 1 to 70% in patient 3. Fig. 8 shows these results in another way, representing the relationship of free water clearance to fluid delivered distally. It is again apparent that patients 1 and 2, delivering relatively normal percentages of filtrate distally, showed severe limitation in free water clearance, whereas patients 3 and 4 could produce normal amounts of free water (expressed as percentages of GFR) only by delivery of very large amounts of filtrate to the distal tubules.

This last figure shows also the results of the three published papers giving studies of this type in patients with this syndrome [59–61]. It is apparent that the patient described by Chaimowitz et al closely resembled our patient 2, whereas the patient described by Chan, Malekzadeh and Anand closely resembled our patient 4 in the indexes here reported.

This abnormality of renal function in this syndrome suggests that another sequence of events may play a

part, to wit, under conditions of maximum free water clearance: water loading → expansion of extracellular fluid volume → abnormal decrease in proximal tubular reabsorption → limitation of sodium reabsorption → excessive sodium loss. Despite the increased delivery of proximal fluid to distal sites, the limitation of free water production should result in retention of free water, and further hypotonic expansion of extracellular fluid volume. Such expansion might in turn augment the defect in proximal tubular reabsorption.

In four patients with this syndrome functional glomerulo-distal-tubular shunts have been described [62]. This lesion, which has been interpreted to represent early glomerulitis, allows the filtrate to escape from the glomerulus into the interstitial area and occasionally into the distal tubule. Since the epithelium remains intact despite destruction of basement membrane, formed elements are prevented from following this route. Such a lesion might, by delivery of proximal fluid into the distal convoluted tubule, stimulate production of renin by the action of sodium on the macula densa [63]. It might also explain the apparent delivery of excessive amounts of proximal fluid distally, with limitation in the production of free water from such fluid, which would never be exposed to the ascending limb of the loop of Henle.

Whereas the resistance of blood vessels to angiotensin appears to be the most "proximal" event in the sequence manifested by this syndrome, the ultimate cause of such resistance remains the subject of future investigation.

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