CHEMICAL AND CLINICAL ENDOCRINOLOGY OF ALDOSTERONE*

RALPH E. BERNSTEIN, M.Sc., M.B., B.Ch. (RAND), D.C.P. (LOND.)

Electrolyte and Metabolic Research Unit, South African Institute for Medical Research, Johannesburg

It is less than 30 years ago that the first extracts of the adrenal cortex were used experimentally to prolong life in adrenalectomized animals[1] and purified extracts ('cortin') were employed in cases of Addison's disease. While the use of 'cortin' and subsequently desoxycorticosterone (synthesized in 1937) was accepted substitution therapy, it was well established that the 'amorphous fraction' of the adrenal extract or whole adrenal preparations had more potent action on organic and mineral metabolism in adrenal insufficiency than crystalline preparations. Further, when cortisone and cortisol became available 10 years ago, it was soon evident that doses adequate to normalize organic metabolism lacked capacity to maintain normal salt metabolism.

Discovery of the Salt-regulating Hormone of the Adrenal Cortex

Recent developments in biochemical techniques, particularly chromatography, have led to the isolation of a considerable number of discrete steroids (corticoids, androgens, progestogens and oestrogens) from the adrenal glands. The division into gluco- and mineralo-corticoids, particularly stressed by Selye, is really only relative, since each steroid has effects on organic and salt metabolism in variable degree. Examination of adrenal-vein blood and effluents from perfused glands indicated that the major active secretion in man is cortisol, with lesser amounts of cortisone and corticosterone; in other mammals, corticosterone formed a greater proportion of the secreted corticoids.[2] Consideration of desoxycorticosterone as a hormone has been controversial, since for many years after its discovery this steroid could not be detected in adrenal-vein samples. Further, despite recent identification of desoxycorticosterone in adrenal-vein blood and perfusates,[3] the amounts do not appear to be adequate for significant biological action. At best, desoxycorticosterone only resembles in part the action of a natural electrolyte-regulating adrenal hormone.[4]

Isolation of aldosterone. The impetus for the isolation and characterization of a natural salt-retaining hormone was provided by the work, starting in 1950, of Luetscher and his associates.[5,6] They found high titres of a sodium-retaining substance in the urine of patients with oedema, by assay of urinary extracts injected into adrenalectomized animals (it is a curiosity of nature that the best source of aldosterone at present is the urine of nephrotics, whose daily excretion may be 0·05-0·2 mg.). Subsequently, the Simpson and Tait group from Middlesex Hospital, using chromatographic methods for steroid separation just published by Bush[7] in England and Zaffaroni[8] in the United States, and increasing the sensitivity of the bio-assay test by using flame photometric and isotopic measurement of the urinary Na/K ratio, isolated a highly potent, pure salt-retaining hormone ('electrocortin') from the 'amorphous fraction', adrenal-vein blood and urine in 1952.[9-11] This constituted adequate evidence that 'electrocortin' is a normal secretory product of the adrenal gland; it is now generally accepted that it accounts for about 75% of the salt-regulating activity of the adrenal gland.

The *chemical constitution* of the salt-retaining hormone gave rise to much speculation, until finally the Middlesex and Basle workers in collaboration[12] determined its formula in 1954 (Fig. 1). From the figure it is seen that crystalline

* Revision of talk to the S.A.I.M.R. Scientific Club, Johannesburg, 12 May 1958.

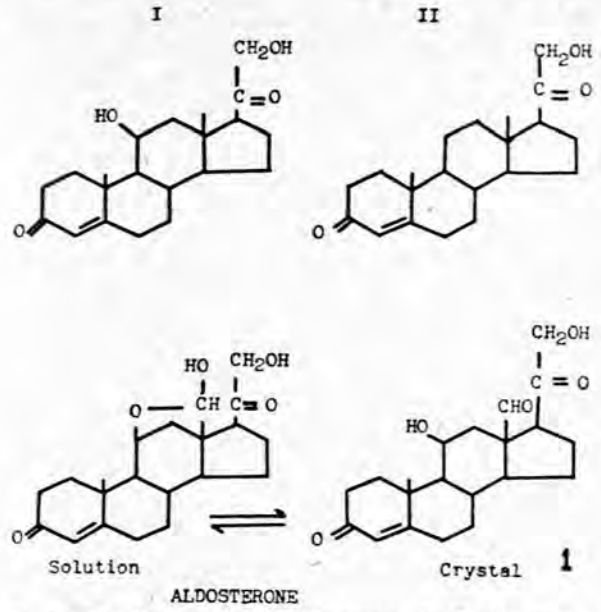

Fig. 1. Chemical structure of aldosterone. I—Corticosterone. II—Desoxycorticosterone. Aldosterone (crystalline) — note 18-aldehyde group. Aldosterone (in solution)—note 11-18 hemiacetal group.

aldosterone has the same basic structure as corticosterone and desoxycorticosterone and is, in fact, the 18-aldehyde of corticosterone (whence its name). Subsequently, independent confirmation came from various sources and Luetscher's salt-retaining substance in nephrotic urines[13] was shown to be aldosterone. The structure of aldosterone is unique among biological steroids in that it (*a*) has an 18-group, and (*b*) exists largely in solution in an hemiacetal form. This may account for its great biological activity, since recently the acetal preparations of cortisol and prednisolone have been shown to have many times the activity of the parent substances.[14]

Biosynthesis of Aldosterone

The demonstration by the Tait group[15] that incubation of beef adrenal-gland capsules gave the highest yield of aldosterone has located the site of formation in the zona glomerulosa. Decapsulated glands yielded little or no aldosterone, nor did incubation of separated fasciculata-reticularis zones. This observation has been confirmed for the rat adrenal,[16] and Conn's suggestion that the adenoma of the first described case of Conn's disease[17] arose in the zona fasciculata would appear to be in error. The present source of crystalline aldosterone is by isolation from beef or hog adrenal (0·05-0·1 mg./kg. in beef and up to 10 times as much in hog adrenal glands). Recently, the chemical synthesis of aldosterone by different processes has been announced,[18,19] and this will, it is hoped, solve the supply problem in therapy and investigation.

Evidence is accumulating that aldosterone is also formed in the placenta.[20]

Nature of adrenal precursors of aldosterone. Incubation of adrenal tissue from various animals with different steroids has resulted in somewhat different findings, probably related to slight variations in experimental conditions. However, in essence, progesterone, desoxycorticosterone and corticosterone (and only these steroids) all increase aldosterone production *in vitro*. In the conversion of cholesterol to adrenal steroids, progesterone is an essential intermediate. This keystone steroid leads to the formation of adrenal androgens, oestrogens and cortisol (with cortisone as its by-product) by one major metabolic pathway, and desoxycorticosterone, with corticosterone and aldosterone derived from it (Fig. 1) by a second major conversion.

Metabolism of Aldosterone

Knowledge of the metabolism of aldosterone has been considerably extended in the past year by the administration of ^{14}C-steroids and more recently of 16-^{3}H progesterone (with much higher specific activity) in animal and human experiments. Human secretion of aldosterone may be put at 0·2 mg./day on normal salt and 0·8 mg./day on low salt intake (by comparison, normal secretion of cortisol is 25 mg./day). Blood concentration is probably 0·05 microgram % (compare cortisol, 10 microgram %). At present the only feasible blood method is that of isotopic dilution, with addition of radioactive aldosterone *in vitro*.

A further difficulty in the study of aldosterone metabolism is that urinary excretion ranges up to 0·01 mg./day, depending on the variation in normal salt intake. Since this represents only some 5% of the daily secretion, and other aldosterone metabolites in the urine amount to less than 20%, correlation of urinary aldosterone content and adrenal secretion may be misleading. Nevertheless, urinary aldosterone estimation is at the moment the only feasible method of assessing adrenal secretion of salt-regulating hormone. Most laboratories are abandoning the bio-assay technique for chromatographic methods[21-23] (the author had the opportunity of developing a modification of a method[21] in the Department of Chemical Pathology, King's College Hospital Medical School, London). For any degree of accuracy, the methods are complicated and tedious, require great attention to technical detail, and must perforce remain in the sphere of special investigation.

Function of Aldosterone

Life maintenance. Doses of 0·001-0·002 mg./kg./day maintain life and electrolyte balance in adrenalectomized animals and Addisonian patients. Higher doses may cause some salt and water retention, but not when cortisol is given concurrently.

Electrolyte effects. Aldosterone influences the distribution of sodium and potassium (and magnesium) between the intra- and extracellular compartments by increasing the rate of exchange between cell potassium and magnesium and extracellular sodium—thus decreasing sodium and increasing potassium and magnesium in saliva, sweat, urine, etc. Quantitatively, its action on urinary composition is of particular importance, since it enhances the exchange of sodium in the tubular fluid for cellular potassium in the distal convoluted tubule (Fig. 2). Aldosterone has some 250 times the sodium-retaining potency of cortisone or cortisol for equivalent dose and 30 times that of desoxycorticosterone, and is approximately equivalent to the synthetic 9α-fluorohydrocortisone. Aldosterone has 5 times the activity of desoxycorticosterone in enhancing potassium excretion.

Effects on water excretion. The end-result is dependent on the interplay of steroid action on sodium excretion, glomerular filtration rate and tubular reabsorption of water,

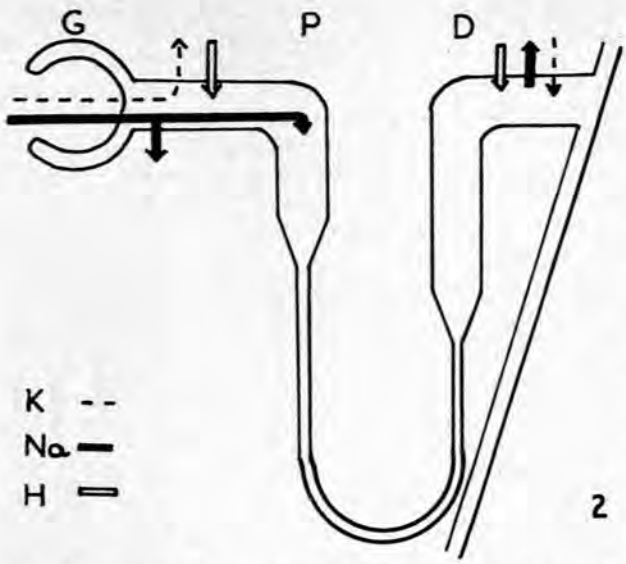

Fig. 2. Action of mineralocorticoids on the renal tubule. G—Glomerular filtrate: 600-800 mEq. K, 18,000-25,000 mEq. Na. P—Proximal tubule: all K reabsorbed, 85-90% Na reabsorbed. D—Distal tubule: Na—K and Na—H exchange modified by aldosterone.

the latter either by local action or conditioned by steroid effect on the secretion of antidiuretic hormone (ADH)—thus adrenal corticoids may be diuretic or antidiuretic according to the steroid, the dose and the particular physiological or pathological conditions operating at the time. For example, while aldosterone has been reported to have no direct effect on water excretion nor to repair the inability of the adrenalectomized dog or Addisonian patient to excrete a water load, other studies have indicated that this steroid can increase glomerular filtration and produce diuresis in adrenalectomized rats.[4]

The *glucocorticoid effects* of aldosterone are as follows:

(*a*) Carbohydrate metabolism: Aldosterone deposits liver glycogen, having 1/4th - 1/3rd the activity of cortisone and 25 times that of desoxycorticosterone.

(*b*) Stress: Aldosterone is more effective than cortisone or desoxycorticosterone in protecting against cold stress.[24] The excretion of aldosterone is increased in heat stress.[25]

(*c*) Connective tissue: Aldosterone has no anti-inflammatory or allergic action, nor does it inhibit granuloma formation.

(*d*) ACTH release: Unlike cortisone or cortisol, aldosterone does not suppress endogenous pituitary adrenocorticotropin.

Blood pressure. Aldosterone produces none of the pathological changes seen with desoxycorticosterone of equal sodium-retaining potency. However, high dosage combined with high salt loading has produced hypertension in rats, with renal and vascular changes of mild degree.[4]

Control of Aldosterone Secretion

The stimulus to aldosterone secretion arises as a hypothalamic neuro-hormone, postulated to result from alterations in effective blood volume, which acts on hypothetical volume receptors[26] (? sited in lungs, heart atria,[27] arterial tree, brain). The response (1) shows a time delay of several hours and (2) appears to react more to rapid blood volume changes than slow; and (3) effects on renal electrolyte excretion follow several hours after alterations in aldosterone secretion.

The neuro-humoral transmitter must be regarded as separate from ACTH action, since aldosterone continues to be secreted at about 50% of normal rate after hypophysectomy and continues virtually unaltered after ACTH administration. The administration of ACTH in therapy or to normal individuals produces a small increase of aldosterone secretion. Similarly, suppression of endogenous corticotropin with large doses of cortisone alters aldosterone secretion to a slight degree.

However, by the use of purified ACTH fractions, Farrell *et al.*[28] has shown that A-corticotropin, comprising about 10% of his ACTH preparations, had 20 times the aldosterone-stimulating activity compared with B-corticotropin, so that variation in the amounts of the different components in therapeutic preparations or actually secreted by the pituitary gland will account for variation reported by different investigators. In any event, it is apparent that the secretion of aldosterone is not under complete and direct control by ACTH. The complexity of the problem is indicated by the fact that injection of growth hormone in animals and man appreciably increases the secretion of aldosterone.

If the effective blood volume is the stimulus to the diencephalon, then the following sequence of reactions may

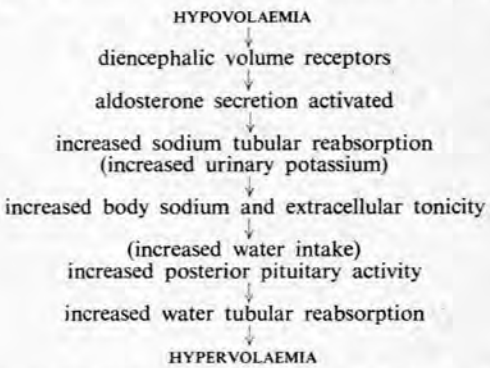

Fig. 3. Homeostatic regulation of extracellular fluid. Aldosterone controls body sodium (slow action). ADH controls body water (rapid action).

be postulated to occur as a dual 'feed-back' mechanism (Fig. 3). Allied to this homeostatic regulation of body fluid, consideration must be given to the possibility that changes in blood volume or flow may alter the flow through the liver and so alter the degree of hepatic inactivation of aldosterone and ADH.

The stimulus continues to act if the compensating mechanisms cannot function. For example, large amounts of aldosterone are present in the urine of cirrhotics with ascites, since the retained fluid fails to inactivate the retention mechanism because the fluid becomes progressively segregated in a non-circulating compartment.

Increased secretion of aldosterone (indicated by elevated urinary aldosterone) occurs (1) during deprivation or depletion of sodium and (2) during addition of potassium. Apparently the potassium loading must cause sodium loss to produce the increase in secretion. Since haemorrhage, sweating, diamox diuresis etc. all increase aldosterone

secretion, the common factor is sodium and water loss, i.e. loss of body fluid.[29] Conversely, sodium addition and, to a lesser extent, potassium depletion depresses aldosterone secretion.

While the secretion of aldosterone is subservient mainly to the requirements of body-fluid volume control, other factors, e.g. sodium excretion,[6] renal haemodynamics, concentration of tissue electrolytes etc. are probably also involved.

CLINICAL ALDOSTERONISM

In retrospect, it is apparent that aldosterone dysfunction was responsible for many of the signs and symptoms in adrenal insufficiency; yet, on the other hand, Cushing's syndrome shows no clear signs of aldosterone hyperfunction. This is due to the fact that other adrenocortical hormones have effects on mineral metabolism; for example, the daily secretion of cortisol is about 100 times that of aldosterone, so that although the electrolyte action of cortisol on an equivalent weight basis is small compared with aldosterone, its total effect is quite considerable, apart from qualitative differences in its electrolyte effects. *The relative proportions of secretion and inactivation of corticosterone, cortisol and aldosterone control the net effect of the adrenal cortex on electrolyte metabolism.*

Syndromes of Primary Hyperaldosteronism

1. *Aldosteroma* (Conn's Disease)

Excessive wastage of potassium by the kidneys, with severe and persistent hypokalaemia leading to periodic paralysis, had for some years been attributed to a primary renal lesion, viz. potassium-losing nephritis.[30-33] However, Conn, finding low Na/K ratios in excretory body fluids in a similar case, together with a sodium-retaining factor and no increase in 17-hydroxycorticoids in the urine, concluded (October 1954) that the excess excretion of electrolytes might be due to overaction of the then newly discovered hormone, aldosterone.[17] Exploration revealed an adrenal adenoma, removal of which cured the disorder.[34,35] Once the cause had been found, several cases of 'potassium-losing nephritis' were identified as Conn's disease in retrospect, adrenocortical adenomata being found at operation or *post mortem* and indicating clearly that the patients had been suffering from primary aldosteronism.

To date, some 35 cases are recorded in the literature and others are known to the author. They occur mainly in adults. An interesting feature of the first 15 cases described is that symptoms had been present for long periods ($\frac{1}{2}$ - 15 years) and that the patients had been admitted on several occasions before the correct diagnosis was made. The clarification of the aetiology and symptomatology is a considerable advance for this essentially remediable condition.

Clinical features. The characteristic signs in the fully developed case may be classified as follows:

(*a*) Severe electrolyte disturbances—hypokalaemic, hypochloraemic alkalosis, with gross body-potassium depletion; high normal or raised plasma sodium.

(*b*) Attacks of muscular weakness or paralysis, with occasional paraesthesiae or tetany. Despite considerable potassium depletion, most patients are surprisingly well between attacks.

(*c*) Hypertension, moderate to severe. Every case of hypertension with neutral or alkaline urinary pH in a young person should probably have plasma-potassium and bicarbonate estimations and a potassium-repletion test done (followed by steroid studies if required).

(*d*) Widespread impairment of kidney function—polyuria; inability to concentrate urine; iow maximum urinary specific gravity resistant to pitressin; alkaline or neutral pH with little response to ammonium-chloride administration; intermittent proteinuria; and reduced clearances. The changes are partly or completely reversed when the potassium deficiency is corrected by removing the adrenal adenoma. Since experimental potassium depletion or deficiency from extrarenal causes leads to similar renal effects, the urinary alterations may be attributed in major degree to potassium deficiency. Once the condition has been present for several years, clear-cell nephrosis and nephrosclerotic changes may supervene, with hypertension and pyelonephritis (potassium-depleted kidneys secreting an alkaline urine are prone to infection). In these cases, recovery of renal function may be incomplete once the tumour has been removed.

(*e*) Endocrine aspect. The reported values for urinary aldosterone in Conn's disease are not impressively increased;[36] they may be at upper normal or slightly raised levels, and are noticeably less than in secondary hyperaldosteronism. The problem arises, how can such levels account for the severe electrolyte and hypertensive disturbances? Undoubtedly a time factor is involved. No urinary aldosterone values are yet available for the early stages in the development of the aldosteroma; once the condition is fully developed, the body-potassium depletion will considerably reduce the secretion of aldosterone from normal adrenal tissue.

Diagnosis of Aldosteroma

In the fully developed case, the combination of history, signs and the assembly of biochemical and radiological (air insufflation to demonstrate adrenal tumour) data are sufficiently clear-cut to make a probable diagnosis fairly certain in the light of current knowledge; however, in the early stages of the condition, the mildness of the symptoms make the diagnosis more uncertain. Early operation is of some importance, since renal changes produced by persistent potassium deficiency eventually become irreversible; however, considerable correction of electrolyte and renal abnormalities can be produced with potassium supplements and a low-sodium diet.

The progressive changes produced by the hormonal disorder and the considerable range of presenting symptoms is well illustrated in 2 case reports by Milne and Muehrcke.[37] The one case was a most severe example with a 12-year history of prolonged hypokalaemic paralytic episodes (up to 21 days in duration) and irreversible renal failure. This patient had been previously diagnosed as 'potassium-losing nephritis';[31] considerable improvement followed the removal of an adenoma.[38,38a] The other subject was asymptomatic except for slight hypertension and an electrocardiogram suggestive of potassium depletion. Renal biopsy was normal, and perirenal air insufflation showed no tumour, but some potassium deficiency with excess urinary loss was found. At operation the smallest adrenal adenoma (1·5 cm.) yet recorded was found. The difficulties in diagnosis presented by this case are also reflected in a report by Crane *et al.*[39] The patient had hypertension with occasional attacks of polydipsia. A left Smithwick sympathectomy was done, and

the left adrenal was seen to be normal at the operation. With no improvement in blood pressure and the finding of transient muscular weakness and hypokalaemia, an adenoma of the right adrenal gland and the right sympathetic chain were removed at a second operation, with disappearance of symptoms. In retrospect, it is evident that removal of the adenoma alone would have cured the disorder.

To date, practically all the reported cases of Conn's disease had had more than one admission before Conn's paper[17] indicated the correct diagnosis. In the first described case from South Africa, Eales and Linder[40] concluded, at the time of her discharge (June 1953) after the first admission, that the patient had renal disease and that activity of a 'DOCA-like' substance was responsible for the hypernatraemic, hypokalaemic alkalosis; after several episodes of muscular weakness, a second admission disclosed no change in electrolyte abnormalities, but the patient remained well provided she took supplemental potassium (September 1954). In October 1955 readmission for air insufflation studies revealed a left adrenal tumour, and the adenoma was successfully removed, with disappearance of symptoms.

Brooks *et al.*[36] and Milne and his collaborators,[37,38,38a] discuss the considerable difficulties encountered in distinguishing between potassium deficiency due to renal tubular or adrenal cortical origin. While renal tubular acidosis is rare in adults and can be identified by hyperchloraemic acidosis with a neutral or acid urine, potassium-losing pyelonephritis etc. are not readily differentiated from aldosteroma with secondary renal changes.

For the *differential diagnosis*, the measurement of urinary aldosterone is complicated, tedious and more difficult to interpret than a study of potassium balance and renal function. Asymptomatic hypokalaemia may be the earliest presenting sign. A repletion test with potassium will indicate the degree of body-potassium depletion, and a continuance of low plasma potassium with excessive urinary potassium loss indicates the resistance of the mineralocorticoid excess to correction of the potassium deficit. In mild cases, potassium loss on a low potassium intake will expose the inadequate renal conservation of potassium; but in a case with definite symptoms such a test would precipitate a severe reaction. Alkalosis and hypochloraemia without obvious cause is suggestive; so is benign hypertension in association with an alkaline urine not due to an active urinary infection. The reduced salivary sodium and increased K/Na ratio are considered valuable evidence by some investigators. However, the author has found that only estimations on pure salivary juice under controlled conditions provide a range of normal values to permit assessment of deviations; this finds confirmation in that examination of reported values from aldosteroma cases shows no clear-cut characteristic values.

Excess urinary potassium, with polyuria somewhat resistant to ADH, and a neutral or slightly alkaline (fresh and negative for bacteria) urine with a slight or moderate response to NH_4Cl administration, is evidence of renal changes secondary to the steroid-induced potassium deficiency.

The ultimate diagnosis rests on surgical procedures—renal biopsy, perirenal air insufflation to outline the adrenal gland for radiological examination, and operation by the abdominal route so that both adrenal glands can be examined. In the majority of aldosteromas reported to date, only operation or post-mortem provided certain diagnosis.

2. *Variants of Conn's Disease*

Oedema is not a feature in Conn's disease. However, cases have been reported with oedema and the classical signs described by Conn, and in which, on removal of an adrenal adenoma, the oedema, electrolyte abnormalities and hypertension[41] disappeared. The possibility that other sodium-retaining hormones with qualitatively different effects are secreted by the adrenal cortex requires investigation in such instances.

Several clinicians have reported the occurrence of mild diabetes mellitus associated with proven aldosteromas.[42,43] The glucocorticoid activity of aldosterone is relatively slight, and whether one is dealing with a random association or with diabetes mellitus caused by adrenal steroid (or steroid glucosuria) must await further investigation and reports in other cases.

3. *Mineralocorticoid Excess and Mixed Syndromes*

Apart from localized adenomas of the adrenal (aldosteromas), hyperplasia of the adrenal cortex[32,44-46] and primary[36,47] and secondary[48] carcinoma produce symptoms almost identical with those described by Conn.[17,34,35] *Cases with proved aldosteromas should be called Conn's disease, and other primary adrenal cases with no obvious alteration in glucocorticoid function would be classified as Conn's syndrome.*

The reported cases of hyperplasia of the adrenal cortex leading to Conn's syndrome have occurred almost entirely in children, with a decrease or disappearance of symptoms on partial or total adrenalectomy. Cerebral disturbances[44,46] (hyperpyrexia, convulsions), presumably resulting from excessive hypothalamic stimuli to the adrenal cortex, are considered causative in 2 cases. The rates of secretion of aldosterone and of cortisol can be differentially affected by experimental brain-stem lesions in animals.[49] The relationship between these two cases and the condition of cerebral hypernatraemia and the secondary hyperaldosteronism of idiopathic oedema (discussed below) is obscure at the moment.

While it is noteworthy that none of the described cases of Conn's disease and syndrome have the usual signs of Cushing's syndrome, it is probable that pure aldosteromas or conditions of specific hypersecretion of aldosterone are rare. Tumours or hyperplasia of the adrenal cortex may involve the secretion of aldosterone, corticosterone, cortisol and other adrenocortical hormones in varying degree. This would alter the amount and proportion of sodium retained and potassium excreted and thus the total mineralocorticoid effect. Further, mixed syndromes of mineralo- and glucocorticoid hyperfunction are being recognized. For example, cases of Cushing's syndrome frequently show decreased plasma and body potassium and, where such cases have been examined, the urinary adrenocortical hormones indicate normal or subnormal aldosterone with increased cortisol and corticosterone.[50] Cases of salt-losing adrenogenital syndrome exhibit normal urinary aldosterone values;[51,52] although the synthesis of cortisol has been shown to be defective, with deviation of steroid metabolism to produce excessive amounts of urinary pregnanetriol, a theoretical salt-losing hormone is also considered to be a possible cause of the sodium loss.

Secondary Hyperaldosteronism

In a wide range of conditions, urinary aldosterone excretion increases as a result of abnormalities situated outside the adrenal gland, which responds in a normal manner to the stimuli. The most notable increases occur in conditions of oedema, where the secretion of other adrenocorticoids may be virtually normal. The considerable electrolyte disturbances, with little or no oedema and moderate increase in urinary aldosterone, of the fully developed primary disease contrast sharply with the preponderant fluid disturbances and greater aldosterone output in oedematous conditions. While the volume-control theory (Fig. 3) fits many of the observations in secondary hyperaldosteronism, some investigators are not prepared to accept it as valid; e.g. Conn states, 'Precise physiological or biochemical stimuli for secondary aldosteronism are unknown'.

1. *Oedema and Aldosterone*

The triad of oedema, sodium retention and elevated urinary aldosterone is only found in severe forms of congestive heart failure, in liver cirrhosis with ascites, in nephrosis, in pregnancy with and without toxaemia, and in idiopathic oedema. The *effective* blood volume is low in these cases from other factors (abnormal peripheral and renal haemodynamics, hypoproteinaemia, etc.) and the excess fluid or oedema is segregated in a non-circulating form.

This constitutes a continuing stimulus to an increased production of aldosterone, accentuated since such cases have been salt-restricted or under diuretic therapy for some time. In addition, diminished effective flow through the liver and other organs may decrease the inactivation of aldosterone. Normally, about 5% of secreted aldosterone is excreted in the urine in a biologically active form. The possibility arises that in these conditions more free aldosterone is excreted, with an enhanced effect on sodium reabsorption in the renal tubule.

In *heart disease* the excretion of aldosterone is normal and increases only occur secondarily to the development of cardiac cirrhosis with decreased inactivation of free aldosterone, and oedema as a result of altered peripheral and renal haemodynamics. Therapy aimed at sodium depletion is a further potent stimulus to aldosterone secretion.[53] The disturbance in fluid distribution and sodium metabolism (the reduced effective intravascular volume being the critical factor) fails to inactivate the retention mechanism and reduce aldosterone activity. Sodium and water will be continuously retained until the cycle is broken by rest, digitalis and diuresis. High urinary aldosterone values are associated with intractable oedema and low urinary sodium.

In *liver disease* there is evidence of increased urinary aldosterone. This is due to reduced hepatic inactivation of aldosterone,[54] as a result of which a higher proportion of biologically active hormone circulates and is excreted in the urine. The detection of metabolic products of aldosterone in urine will enable this aspect to be clarified. In hepatic cirrhosis with ascites, the urinary aldosterone rises rapidly with the reaccumulation of ascitic fluid after paracentesis. It is thus probable that the increase in salt-retaining hormone follows the collection of peritoneal fluid precipitated by portal hypertension. The progressive shift of fluid into a segregated compartment leads to further activation of the dual retention mechanism in an attempt to replace sodium and water losses and to prevent hypovolaemia. The failure of the retained sodium and water (because it is not part of the effective blood volume) to reduce aldosterone and antidiuretic hormonal activity results in continuous sodium and water retention by the kidney, unless the cycle is broken by reduction of portal hypertension, restoration of the normal osmotic pressure of the blood, and sodium restriction or diuresis.

In *nephrosis* the aldosterone excretion is greatest during the accumulation of oedema consequent on a decrease in circulating blood volume as a result of hypoproteinaemia. Injection of concentrated human serum albumin or prednisone decreases urinary aldosterone output, but only when diuresis occurs.

In *toxaemia of pregnancy* the urinary aldosterone excretion is considerably elevated. However, the increase in aldosterone output only contributes in part to the sodium and fluid retention, since increases in aldosterone excretion of a greater magnitude occur in normal pregnancy.[55,56] Several operative mechanisms may be suggested: impaired hepatic inactivation of active aldosterone; alteration in the proportion of aldosterone, cortisol, and other hormones secreted by the adrenal; adrenocortical response to maintain effective circulating blood volume in the face of sodium and water loss into maternal and foetal cells; and compensatory response for the sodium-diuretic properties of the increased progesterone output.

Cases have been described in women with emotional stress and tension, of *idiopathic oedema*, in which the only prominent sign was an increased output of aldosterone.[57-59] The condition was unrelated to the menstrual cycle and the oedema subsided on a low-sodium diet. Partial adrenalectomy did not improve the condition in those operated on, nor was any abnormality of the adrenal gland found. A persistent stimulus to the zona glomerulosa of the adrenal cortex from hypothalamic or higher centres is postulated.

A case of massive oedema with sodium retention and no evidence of disease of the heart, liver or kidney illustrates the many complexities in the study of aldosterone function.[60,60a] The patient had had oedema since 1945 attributable to abnormal *capillary permeability to proteins* (high protein content of pleural and oedema fluids). When aldosterone estimations became available, high urinary values were found associated with very low urinary sodium. On exploration, the left adrenal gland containing an adenoma was removed (none of the symptoms and signs of primary hyperaldosteronism were present), with subsequent adequate excretion of sodium and normal urinary aldosterone levels. Six months later, urinary aldosterone again became elevated and only minimal amounts of sodium were being excreted, and a hypertrophied right adrenal gland was then removed. The continued attempts to reduce sodium intake and induce sodium excretion by vigorous diuretic and other therapy led to excessive secretion of aldosterone. The adenoma was functional and the adjacent adrenal tissue contained no aldosterone. With the continuance of the stimulus, the remaining adrenal gland then proceeded to produce excessive amounts of aldosterone. The original cause of oedema persists—when the patient's weight falls below a certain level, symptoms of sodium depletion occur and oedema ensues on sodium administration.

2. *Hyperaldosteronism without Oedema*

Experimentally, aldosterone is less liable to produce *hypertension* than desoxycorticosterone or cortisol with steroid overdosage. Patients with severe benign hypertension have a slight increase of urinary aldosterone,[61] but the increase is moderate and may be related to a deviation in salt intake or metabolism in hypertensives.

Cerebral damage, with the development of chronic hypernatraemia and alkalosis, may result from hypothalamic stimulation of the aldosterone-secreting cells of the adrenal cortex.[62]

In *sodium-losing nephritis* of long standing, the sodium depletion will invoke a secondary hyperaldosteronism;[63] according to the degree and duration of aldosterone hyperactivity, potassium excretion may then increase and renal changes due to potassium deficiency may be superimposed on the original defect.

3. *Temporary Hyperaldosteronism*

Certain conditions produce an episode of increased urinary aldosterone without oedema. Raised levels of urinary aldosterone (and cortisol) with associated retention of sodium and water and increased excretion of potassium occur in the immediate *post-traumatic*[64] and *post-operative*[65] periods. Although the factors involved are necessarily complex, loss of fluid and electrolytes and circulatory inadequacy may be responsible for evoking the adrenal response. Haemorrhage (phlebotomy) will increase urinary aldosterone,[29,66] and so will exposure to high environmental temperatures.[25,67] It is noteworthy that not all stress factors will increase urinary aldosterone (and cortisol); for instance, hard physical exercise has no effect.

In *periodic paralysis* intermittent aldosteronism occurs (Conn *et al.*[68]); both spontaneous and induced paralysis is preceded by large increases in urinary aldosterone and intense sodium retention, followed by excessive loss of potassium. With subsidence of the attack, considerable sodium diuresis occurs, with decrease in urinary aldosterone to normal. Conn concludes that intracellular transfer of sodium precipitates the attack of paralysis and may be prevented or decreased in severity by a low-sodium diet.

HYPO-ALDOSTERONISM

Primary Hypo-aldosteronism

A primary decrease in aldosterone secretion with otherwise unaltered adrenocortical function has been reported.[69,70] The patients had clinical signs attributable to hyperkalaemia (including heart block[69]), and also hyponatraemia and absence of demonstrable urinary aldosterone with normal excretion of other adrenocortical hormones and no evidence of renal dysfunction. As yet, it is not possible to conclude whether the primary error is in the adrenal gland or affects some extra-adrenal regulatory mechanism.

In the hypo-adrenocorticism (decreased aldosterone and cortisol) of Addison's disease or in adrenalectomized subjects, the inadequacy of electrolyte regulation is rapidly demonstrated by any measure that would normally increase the secretion of aldosterone, viz. sodium deprivation or excessive intake of potassium. Neither aldosterone nor cortisone alone is effective in the treatment of adrenal insufficiency. The adrenal crisis that may develop in hypopituitarism shows decreased secretion of cortisol, but urinary aldosterone is usually within normal limits, as would be expected since aldosterone secretion is only slightly influenced by pituitary secretion.

Secondary Hypo-aldosteronism

A transient hypo-aldosteronism occurs after removal of the aldosteroma, until the secretion of aldosterone by the normal adrenal tissue 'revives'. A more persistent decrease in aldosterone excretion occurs during renal insufficiency, oliguria or acidosis; this may be a reflection of potassium retention.

Various drugs decrease the secretion of aldosterone. Amphenone reduces biosynthesis and the release of aldosterone, and of other adrenocortical hormones to a lesser degree.[71] Similarly, the insecticide DDD and pinacolone compounds decrease adrenocortical secretion.[72] Prednisone reduces aldosterone activity, either by hypothalamic action or by competition in the electrolyte reabsorptive process of the renal tubule. Synthetic 'spirolactone' steroids, apparently antagonistic to the action of aldosterone or desoxycorticosterone on renal tubular cells, have recently been developed with potent sodium-diuretic effects in the presence of these two mineralocorticoids.[73,74]

SODIUM-RETAINING AND SODIUM-DIURETIC HORMONES

Comparison of normal secretion rates and the sodium-retaining capacities of adrenocortical hormones brings out the fact that cortisol, secreted at 25 mg./day, has only slightly less total influence on sodium retention than aldosterone (secretion, 0·2 mg./day), while normal circulating desoxycorticosterone contributes little to total electrolyte control. With few exceptions, however, the degree of alteration in aldosterone secretion in disease processes is many times that of other corticoids that have sodium-retaining properties, and aldosterone is thus the mineralocorticoid *par excellence*. However, in some cases of Cushing's syndrome and salt-losing adrenogenital syndrome (described above), the electrolyte disturbance is due to other adrenocorticoids than aldosterone. While synergism or antagonism between the actions of the currently known steroid hormones may provide the correct explanation, it would appear that further investigation of the 'amorphous' fraction of adrenal extracts may prove profitable, since aldosterone may not be the only sodium-retaining hormone of high potency.

Paradoxically, the discovery of aldosterone has set off an intensive search for sodium-diuretic hormones. Under certain conditions (as yet not well defined), both cortisone and cortisol will produce sodium diuresis, possibly due to their action in increasing the glomerular filtration rate. The synthetic 'spirolactone' steroids[73,74] only exert their sodium-diuretic effect in the presence of desoxycorticosterone or aldosterone, and suggest the tantalizing prospect that the adrenal gland may secrete a sodium-diuretic hormone.

While the discovery of aldosterone has solved one fragment of the adrenocortical 'complex' and certain aspects of body-fluid and electrolyte metabolism, it has posed further enigmas for elucidation in the field of adrenal endocrinology.

I am indebted to Prof. C. H. Gray, Department of Chemical Pathology, King's College Hospital Medical School, London, for laboratory facilities to develop methods of aldosterone estimation, while holding a Cecil John Adams Fellowship in 1956. I am also grateful to various workers (Drs. S. A. S. and J. F. Tait, Middlesex Hospital; Drs. I. H. Mills and R. V. Brooks, St.

Thomas's Hospital: Dr. R. Neher, Ciba, Basle; Drs. R. Gaunt and J. J. Chart, Ciba, New Jersey; Dr. F. C. Bartter, National Institutes of Health, Bethesda; and Drs. R. Dorfman and O. Hechter, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.); whose laboratories I had the opportunity and pleasure of visiting.

REFERENCES

1. Swingle, W. W. and Pfiffner, J. J. (1930): Science, **71**, 321.
2. Singer, B. and Stack-Dunne, M. P. (1955): J. Endocr., **12**, 130.
3. Farrell, G. B., Rauschkolb, E. W., Royce, P. C. and Hirschmann, H. (1954): Proc. Soc. Exp. Biol. (N.Y.), **87**, 587.
4. Gross, F. and Lichtlen, P. in Muller *et al.* (1958): *Op. cit.*[20]
5. Luetscher, J. A. Jr. (1954): J. Clin. Invest., **33**, 276.
6. Luetscher, J. A. Jr., Deming, Q. B. and Johnson, B. B. (1952): Ciba Colloq. Endocr., **4**, 530.
7. Bush, I. E. (1952): Biochem. J., **50**, 372.
8. Zaffaroni, A. and Burton, R. B. (1951): J. Biol. Chem., **193**, 749.
9. Grundy, H. M. and Simpson, S. A. (1952): Nature, **169**, 795.
10. Simpson, S. A. and Tait, J. F. (1952): Endocrinology, **50**, 150.
11. Simpson, S. A., Tait, J. F. and Bush, I. E. (1952): Lancet, **2**, 226.
12. Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., Von Euw, J., Schindler, O. and Reichstein, T. (1954): Helv. chim. Acta, **37**, 1163 and 1200.
13. Luetscher, J. A. Jr., Neher, R. and Wettstein, A. (1954): Experientia, **10**, 456.
14. Fried, J., Borman, A., Kessler, W. B., Grabowich, P. and Sabo, E. F. (1958): J. Amer. Chem. Soc., **80**, 2338.
15. Ayres, P. J., Gould, R. P., Simpson, S. A. and Tait, J. F. (1956): Biochem. J., **63**, 19P.
16. Giroud, C. J. P., Stachenko, J. and Venning, E. H. (1956): Proc. Soc. Exp. Biol. (N.Y.), **92**, 154.
17. Conn, J. W. (1955): J. Lab. Clin. Med., **45**, 3.
18. Schmidlin, J., Anner, G., Billeter, J-R., Heusler, K., Ueberwasser, H., Wieland, P. and Wettstein, A. (1957): Helv. chim. Acta, **40**, 1034 and 1438.
19. Johnson, W. S., Collins, J. C., Pappo, R. and Rubin, M. B. (1958): J. Amer. Chem. Soc., **80**, 2585.
20. Muller, A. F. and O'Connor, C. M., ed. (1958): *An International Symposium on Aldosterone*, p. 141. London: Churchill.
21. Neher, R. and Wettstein, A. (1956): J. Clin. Invest., **35**, 800.
22. Nowaczynski, W., Koiw, E. and Genest, J. (1957): Canad. J. Biochem., **35**, 425.
23. Ayres, P. J., Garrod, O., Simpson, S. A. and Tait, J. F. (1957): Biochem. J., **65**, 639.
24. Gaunt, R., Gordon, A. S., Renzi, A. A., Padawer, J., Fruhman, G. J. and Gilman, M. (1954): Endocrinology, **55**, 236.
25. Hellman, K., Collins, K. J., Gray, C. H., Jones, R. M., Lunnon, J. B. and Weiner, J. S. (1956): J. Endocr., **14**, 209.
26. Smith, H. W. (1957): Amer. J. Med., **33**, 623.
27. McCally, M., Anderson, C. H. and Farrell, G. B. (1958): 40th meeting, Endocrine Society, San Francisco, USA, 19 June; abstr. no. 184.
28. Farrell, G., Rauschkolb, E. W., Fleming, R. B. and Yatsu, F. M. (1957): 39th meeting, Endocrine Society, New York, USA, 1 June; abstract no. 38, in discussion.
29. Bartter, F. C. (1958): Proc. Roy. Soc. Med., **51**, 201.
30. Earle, D. P., Sherry, S., Eichna, L. W. and Conan, N. J. (1951): Amer. J Med., **11**, 283.
31. Evans, B. M. and Milne, M. D. (1954): Brit. Med. J., **2**, 1067.
32. Wyngaarden, J. B., Keitel, H. K. and Isselbacher, K. (1954): New Engl. J. Med., **250**, 597.
33. Mader, I. J. and Iseri, L. T. (1955): Amer. J. Med., **19**, 976.
34. Conn, J. W. (1955): J. Lab. Clin. Med., **45**, 661.
35. Conn, J. W. and Louis, L. H. (1956): Ann. Intern. Med., **44**, 1.
36. Brooks, R. V., McSwiney, R. R., Prunty, F. T. G. and Wood, F. J. Y. (1957): Amer. J. Med., **23**, 391.
37. Milne, M. D. and Muehrcke, R. C. (1956): Proc. Roy. Soc. Med., **49**, 883.
38. Aird, I., Milne, M. D. and Muehrcke, R. C. (1956): Brit. Med. J., **I**, 1042.
38a. Milne, M. D., Muehrcke, R. C. and Aird, I. (1957): Quart. J. Med., **26** 317.
39. Crane, M. G., Vogel, P. J. and Richland, K. J. (1956): J. Lab. Clin. Med., **48**, 1.
40. Eales, L. and Linder, G. C. (1956): Quart. J. Med., **25**, 539.
41. Goldsmith, R. S., Bartter, F. C., Rosch, P. J., Meroney, W. H. and Herndon, E. G. Jr. (1958): J. Clin. Endocr., **18**, 323.
42. Hewlett, J. S., McCullagh, E. P., Farrell, G. L., Dunstan, H. P., Poutasse, E. and Proudfit, W. L. (1957): J. Amer. Med. Assoc., **164**, 179.
43. Sorce, R. C. and Whitstone, W. E. (1958): Arch. Intern. Med., **102**, 131.
44. Holten, C. and Petersen, V. P. (1956): Lancet, **2**, 918.
45. van Buchem, F. S. P., Doorenbos, H. and Elings, H. S. (1956): Lancet, **2**, 335 and 574.
46. Bartter, F. C. and Biglieri, E. G. (1958): Ann. Intern. Med., **48**, 647.
47. Foye, L. V. Jr. and Feichtmeir, T. V. (1955): Amer. J. Med., **19**, 966.
48. Spaulding, W. B., Ollie, W. A. and Gornall, A. G. (1955): Ann. Intern. Med., **42**, 444.
49. Newman, A. E., Redgate, E. S., Yatsu, F. M. and Farrell, G. L. (1958): Fed. Proc., **17**, 117.
50. Muller, *et al.* (1958): *Op. cit.*,[20] pp. 221-2.
51. Prader, A. (1955): Schweiz. med. Wschr., **85**, 1085.
52. Bongiovanni, A. M. (1958): Pediatrics, **21**, 1031.
53. Wolff, H. P., Koczorek, K. R. and Buchborn, E. (1957): Lancet, **2**, 63.
54. Chart, J. J., Gordon, E. S., Helmer, P. and LeSher, M. (1956): J. Clin. Invest., **35**, 254.
55. Venning, E. H. and Dyrenfurth, I. (1956): J. Clin. Endocr., **16**, 426.
56. Rinsler, M. G. and Rigby, B. (1957): Brit. Med. J., **2**, 966.
57. Venning, E. H., Dyrenfurth, I. and Beck, J. C. (1957): J. Clin. Endocr., **17**, 1005.
58. Mach, R. S. in Muller *et al.* (1958): *Op. cit.*[20]
59. Luetscher, J. A. Jr. and Lieberman, A. H. (1957): Trans. Assoc. Amer. Phycns., **70**, 158.
60. Thorn, G. W., Ross, E. J., Crabbé, J. and Van't Hoff, W. (1957): Brit. Med J., **2**, 955.
60a. Ross, E. J., Crabbé, J., Renold, A. E., Emerson, K. Jr. and Thorn, G. W. (1958): Amer. J. Med., **25**, 278.
61. Genest, J., Koiw, E., Nowaczynski, W. and Leboeuf, G. (1958): Clin. Res. Proc., **6**, 28; Proc. Soc. Exp. Biol. (N.Y.), **97**, 676.
62. Natelson, S. (1958): Clin. Chem., **4**, 32.
63. Stanbury, S. W. and Mahler, R. F. (1958): Quart. J. Med., **27**, in press.
64. Venning, E. H., McCorriston, J. R., Dyrenfurth, I. and Beck, J. C. (1958): Metabolism, **7**, 293.
65. Llaurado, J. G. and Woodruff, M. F. A. (1957): Surgery, **42**, 313.
66. Fine, D., Meiselas, L. E. and Auerbach, T. (1958): J. Clin. Invest., **37**, 323.
67. Streeten, D. H. P., Conn, J. W., Louis, L. H., Fajans, S. S., Seltzer, H. S., Johnson, R. D., Gitter, R. D. and Dube, A. H. (1955): J. Lab. Clin. Med., **46**, 957.
68. Conn, J. W., Louis, L. H., Fajans, S. S., Streeten, D. H. P. and Johnson, R. D. (1957): Lancet, **1**, 802.
69. Hudson, J. B., Chobanian, A. V. and Relman, A. S. (1957): New Engl. J. Med., **257**, 529.
70. Skanse, B. and Hökfelt, B. (1958): Acta endocr., **28**, 29.
71. Renold, A. E., Crabbé, J., Hernando-Avendano, L., Nelson, D. H., Ross, E. J., Emerson, K. Jr. and Thorn, G. W. (1957): New Engl. J. Med., **256**, 16.
72. Gaunt, R., Chart, J. J., Howie, N., Sullivan, B. and Sheppard, H. (1958): 40th meeting, Endocrine Society, San Francisco, USA, 19 June; abstract no. 25.
73. Liddle, G. W. (1957): Nature, **126**, 1016.
74. McCrory, W. W. and Eberlein, W. R. (1958): J. Clin. Invest., **37**, 917.