THE ROLE OF THE ADRENAL CORTEX IN FLUID AND ELECTROLYTE METABOLISM*

BY

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It is apparent that in analysing the effects of the adrenal hormones on the water and electrolyte balance it is necessary to consider each separately. It is the interplay of these two factors which ultimately controls the long-term water-balance of the individual. The aspect of the problem which has received most study is the

cortone is to increase sodium and chloride reabsorption, since low serum sodium levels are rapidly elevated and excretion of these ions is decreased. Whether there is a direct effect on water reabsorption or whether this is secondary to the electrolyte change is uncertain. The work of Verney shows that under normal conditions the posterior pituitary is a rapid reactor to water losses and seems to be stimulated by hypertonicity of the plasma. In Addison's disease the plasma becomes hypotonic, and this would seem to act as a bar to the stimulation of the posterior pituitary and correction of its decreased volume.

That cortisone has a specific effect on water reabsorption, unaffected by treatment with deoxycortone, is shown by the restoration of normal diuresis to water load after the administration of 100 mg. of cortisone daily. It will be seen from the lower part of Fig. 1 that in D previous administration of 100 mg. of cortisone intramuscularly daily restored a normal diuresis in the second hour after a water load given at the arrow. The presence of an 800-mg. deoxycortone acetate (D.C.A.) implant did not modify the abnormal pattern after water-loading seen in C and E. During the

diuresis in D no increase of sodium excretion occurred, and there was therefore a fall in the urine concentration of this substance. In the upper part of Fig. 1, B shows that a dosage of 20 mg. of cortisone was insufficient to restore the diuretic effect in this instance. Fig. 2 shows the same effect of cortisone in a patient with hypopituitarism who was given 1,100 ml. of water at the time indicated at the arrows. The figure also shows the tendency to reduce the volume of urine excreted during the night.

Similar observations have been made by several other workers, and under the correct

FIG. 1.—Kepler tests applied in a woman with Addison's disease, before and after cortisone treatment. N represents urine passed between 10 p.m. and 8 a.m. At the arrow the water load was given, and 1, 2, 3, and 4 represent hourly collections of urine. The figures in quotation marks above each test represent the Kepler "factor."

renal response to these hormones, but it is now becoming clear that they may cause considerable internal transference of fluid within the body itself, and this phenomenon demands increased attention.

Water Excretion and Hydration

A patient with Addison's disease is unable to respond in a normal way to the withholding and administration of water, the basis of the "Kepler water test" for the diagnosis of this condition. Maintenance of the patient in normal hydration with deoxycortone does not rectify this abnormality. The fact that deoxycortone returns sodium and chloride losses in this disease to normal and clinically maintains hydration demonstrates that over a period of time extracellular fluid volume and composition are favourably controlled. It may be argued that an early effect of deoxy-

conditions A.C.T.H. (commercial samples of which contain appreciable amounts of "pituin") has been shown to have the same effect as cortisone in patients with hypopituitarism. It therefore seems as though the effect of cortisone in these experiments is a direct one on the reabsorption of water by the distal renal tubules. However, in spite of this there is a body of evidence

FIG. 2.—Kepler tests applied in a woman aged 30 with hypopituitarism, before and after cortisone treatment.

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to suggest that endogenous antidiuretic activity may be increased in adrenal deficiency states, both in the experimental animal and in the human, as first suggested in the hypothesis of Corey *et al.* (1939). Gaunt (1951), using rats, and Lloyd (1952), supported by Slessor (1951) with human subjects, agree that in adrenal cortical insufficiency there is excess antidiuretic "hormone" (A.D.H.) in the blood. It has been found that "pitressin" causes retention of water but not loss of sodium in man. Hence the presence of such a substance would not account for all the findings in Addison's disease, even allowing for the fact that it would inhibit normal diuresis. Water retention by A.D.H. without comparable sodium retention would be expected to lead to a hypotonic plasma and a condition of water intoxication with cellular hydration. Study of bilaterally adrenalectomized patients by Pearson *et al.* (1952) suggests that this in fact is the case. However, more remains to be known of the effects of the medullary hormones in this regard.

The position concerning the possible increase of an A.D.H. is confused. The action of pitressin in the experiments of Chalmers and Lewis (1951) was uninfluenced by cortisone in Addison's disease, suggesting that deficiency of adrenal hormone is not responsible for the suggested decreased destruction of A.D.H. or increased renal tubular sensitivity to it. This leaves open the unlikely hypothesis that if in adrenal insufficiency posterior pituitary A.D.H. is increased there is an alteration of the response of the osmoreceptors in the face of hypotonicity. Nearly all the reported experiments on the increase of A.D.H. in adrenal insufficiency depend upon the assay technique of Birnie *et al.* (1949), using intraperitoneal injection, a method of administration criticized on the grounds of lack of specificity at a recent symposium of the Society for Endocrinology on "The Posterior Pituitary." Pending further elucidation of the problem of A.D.H. it is wisest to regard the effect of cortisone on the promotion of normal water-handling in Addison's disease as a direct one in restoring flexibility of distal tubular water reabsorption.

Effects on Sodium and Chloride Excretion

The injection of A.C.T.H. for periods of days produces now-well-recognized effects, but these are at present unpredictable in a given individual. There can, for example, be

FIG. 3.—Effect of continued A.C.T.H. injections (25 mg. six-hourly) on sodium retention in a man aged 39 with rheumatoid arthritis.

long-continued sodium and water retention with oedema formation, even requiring careful "unephral" (formerly "neptal") administration. This is largely avoidable by employment of low sodium diets. Fig. 3 is an example of this type of response. The balance data for sodium are plotted so that intake is measured downwards from the horizontal zero line and urine excretion upwards from the base. It

can be seen that between days 12 and 32 sodium retention continued to take place, as only on three days did excretion exceed intake. The rise in weight is largely accounted for by fluid retention. Plasma volume and extracellular fluid volume, as indicated by the inulin space, are seen to be increased. After reduction of dosage of the hormone,

FIG. 4.—Effect of A.C.T.H. (given intramuscularly in divided dosage six-hourly) and cortisone (given intramuscularly once daily) on sodium retention in a woman aged 64 with rheumatoid arthritis.

diuresis occurred, particularly of sodium. At the other extreme, in other individuals, sodium retention may be transitory, but even here sodium concentration in the serum has been observed to rise significantly.

Many cases seem to show an intermediate type of response. Excretion of sodium with water loss may occur, either during A.C.T.H. administration or perhaps to a greater extent after withdrawal. It has been suggested that the sodium and water loss may be due to a sudden relative adrenal cortical insufficiency after withdrawal of the hormone. The fact that sodium loss occurs during A.C.T.H. administration or during cortisone administration started at the time of stopping A.C.T.H. is against this being the only cause. Fig. 4 shows the loss of sodium and water which can occur under these conditions. Intramuscular cortisone after the end of A.C.T.H. therapy permitted continued losses. It will also be noted that on a free fluid intake this patient's intake of fluid, and urine volume, both increased towards the end of the period of observation. The presence of pituitrin in the commercial preparation of A.C.T.H. available for study renders difficult the interpretation of findings of water retention and weight gain with oedema formation so frequently observed.

Experiments using more highly purified preparations of A.C.T.H.—pepsin digest (Luft *et al.*, 1949); the oxycellulose preparation of Astwood (Renold *et al.*, 1952)—indicate that these substances have similar properties to those of the cruder protein preparations in this respect. In addition, Sprague's (Sprague *et al.*, 1951) observation with cortisone in rheumatoid arthritis has shown that this adrenal cortical steroid is capable of reproducing the same effects as A.C.T.H., and it has been shown by Fourman *et al.* (1950), too, that in experiments of three days' duration hydrocortisone (compound F) has similar sodium- and water-

retaining properties. Fig. 5 summarizes the classical sequence of events with regard to sodium and water retention with these hormones, showing three phases: (a) active retention, (b) the reversal of this process, and (c) a diuresis after

FIG. 5.—Effect of A.C.T.H. and adrenal cortical hormones on sodium and water excretion.

hormone withdrawal with loss of sodium, often so great as to cause the net sodium losses to exceed the initial gain. In a recent report of cases of dermatomyositis (Prunty, 1952) the tendency for A.C.T.H. and cortisone to cause diuresis in the presence of oedema was clinically valuable, and many diuretic responses are now on record in cases of subacute nephritis. We, and others, have found that not only do these substances cause increased reabsorption of sodium by the kidney, but they also cause reduction of the volume and sodium content of induced sweat, and reduction of the amount of sodium rejected in the faeces.

The ability of cortisone and hydrocortisone to cause retention of water and sodium and potassium loss in a similar way to A.C.T.H. and deoxycortone has led to the formulation of the view that a single adrenal cortical hormone (hydrocortisone) would account for all the phenomena of increased adrenal cortical activity. We have carried out balance studies in an Addisonian (Fig. 6) with D.C.A. and cortisone acetate. When entirely depleted of D.C.A. this patient's response to the intramuscular injection of 2.5 mg. of D.C.A. was compared with that of 100 mg. of oral cortisone daily. Each substance was given alone and two periods of D.C.A. administration were employed. It will be seen that during the first six days and during the 17th to 22nd day, when the patient received D.C.A. alone, she was in positive sodium balance. During the 7th to the 16th days, whilst receiving cortisone only, the sodium balance became very definitely negative. Both urine volume and fluid in-

FIG. 6.—Effect of deoxycortone or cortisone on sodium balance in a woman aged 50 with Addison's disease.

take increased and serum sodium rose during this period. She lost 2 kg. in weight. These results are in agreement with those of Sprague *et al.* (1951) under similar conditions, but using intramuscular injection of the hormone.

If it can be assumed that comparable biological doses of these substances were used there is a striking difference in their effects in these circumstances. In the absence of endogenous adrenal cortical activity (Addison's disease) D.C.A. overdosage with salt has so far been found to cause sustained sodium retention and oedema, and death from cardiac failure. In patients with intact adrenals its behaviour is more like that of cortisone, sustained dosage being accompanied by spontaneous diuresis of retained water and sodium (Luft and Sjögren, 1952). On the other hand, totally adrenalectomized patients have been kept in good condition by the use of cortisone alone by Pearson *et al.* (1952) and others. These facts are conflicting when one is considering the problem of whether there exists a natural adrenal cortical hormone of special potency in electrolyte metabolism. Ingle has again emphasized (Ingle *et al.*, 1952) that cortisone and hydrocortisone will not quantitatively account for the biological potency of natural products in his "work test," and he once more reminds us of the active material present in Kendall's amorphous fraction. Simpson *et al.* (1952) have also presented convincing evidence of the multiplicity of secretion by the separation of natural material from the adrenal blood of the monkey and dog with quantitatively far greater electrolyte effects than those of cortisone. These experiments give new impetus to the problem of the number of biologically active adrenal cortical secretions in man.

Internal Transference of Fluid and Electrolyte

It has been shown that the rapid increase of weight of patients treated with A.C.T.H., together with measurements of fluid balance, indicates that water is retained along with sodium and chloride and oedema may become a problem. However, clinically, oedema has been noticed both by us and by Soffer *et al.* (1951) to occur in the absence of obvious fluid retention, suggesting internal transference of fluid in the body from cells to extracellular fluid. It will be recalled that increases of extracellular fluid are indicated by measurement of inulin space, and plasma volume may rise to a lesser extent. Study of daily weight changes compared with calculated changes of extracellular fluid volume from chloride balances has suggested confirmation of the view that fluid shifts occur outwards from the tissues.

Fig. 7 shows the data obtained from a patient with rheumatoid arthritis. The data on the top line show the effect of A.C.T.H. on the extracellular fluid volume calculated from chloride balances. The hatched blocks represent changes in extracellular fluid volume occurring during each period, blocks above the line representing an increase, those below the line a decrease. In the same way the second line shows the weight changes from period to period, which can be taken as a fair measure of fluid retention or loss over a relatively short time period. The bottom line shows the volume changes superimposed on the weight changes. In periods 2 and 3, the volume increase far exceeds the weight increase, whilst in period 6, during diuresis, the reverse occurs. This would seem to indicate expansion of extracellular fluid, as we have previously found by this technique (Prunty *et al.*, 1948). However, recent work indicating the presence of large quantities of chloride in the tissues would seem to question the validity of this line of approach, which necessitates the assumption that significant amounts of chloride are not transferred to the tissues.

In spite of this, measurement of the extracellular space with inulin in patients on low sodium intakes receiving cortisone or A.C.T.H. has revealed in the hands of Levitt and Bader (1951) considerable increase in its volume. In this instance chloride apparently was supplied from the tissues. Potassium depletion occurring at the initiation of these changes is also indicative of tissue losses of this sub-

stance, probably associated in part with loss of tissue water, and reminds us of the need in some patients for the increased administration of this substance. Only recently have extensive studies begun to reveal the effects on renal

tissues to the extracellular fluid, the sodium concentration of which is often found to rise. The tissue water loss seems to account for some of the urinary losses of potassium, and, in addition, the serum level of this substance falls. With extracellular fluid thus expanded, water intake and excretion show a tendency to rise. After the action of the hormone ceases there is a large diuresis of water and sodium from the expanded extracellular fluid. This diagram admittedly glosses over many gaps in our knowledge, which we hope will be better explained after future research.

Summary

The problem of how the adrenal cortex affects abnormalities of renal handling of water and electrolytes has been examined. Primary and secondary adrenal cortical insufficiency leads to impairment of normal diuresis, and this may be corrected with cortisone and, in the case of the latter, with A.C.T.H. It is uncertain how far antidiuretic activity in the serum of these patients may be a factor in this abnormality.

Sodium and chloride retention is induced by cortisone and A.C.T.H., but may not persist as long as the hormone is administered. Under certain conditions diuresis may occur with increased excretion of these ions.

Further data on the effect of cortisone on sodium retention in Addison's disease again raise the question of the secretion of a "salt hormone" by the adrenal cortex.

It is pointed out how internal shifts of fluid from the cells occur with administration of these substances, and the difficulty of integrating all the effects observed is discussed.

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FIG. 7.—Effect of A.C.T.H. on fluid shifts within the body of a woman aged 56 with rheumatoid arthritis (see text).

excretion of water and electrolytes in response to expansion of extracellular fluid volume—a basic requirement in evaluating the response to cortical hormones. These observations have also stressed the importance of posture and of diurnal variation in the responses obtained. Increase in extracellular fluid volume seems to limit the water- and electrolyte-retaining properties of the adrenal hormones in the normal individual, the concentration of sodium in the fluid being a matter of secondary importance.

FIG. 8.—Working concept of effects of adrenal cortical hormones on water and electrolyte metabolism (see text).

Fig. 8 indicates a working hypothesis for the effects of these hormones, indicating how extracellular fluid volume expansion occurs, with resulting tendency to increase in water exchange and even diuresis. On the left, adrenal cortical hormone is seen to cause initial sodium and water retention. At the same time water is transferred from the

Reports of initial victories made in the fight against yaws were made at a recent conference at Bangkok organized by the World Health Organization in collaboration with the Government of Thailand. Yaws is prevalent in humid tropical climates, and particularly common among undernourished people living in overpopulated areas. Doctors trying to combat its spread must break down a barrier of popular local superstition. Results so far obtained indicate that one, or at most two or three, intramuscular injections of a repository penicillin are sufficient to ensure a definite cure. Up to the end of 1952 nearly eight million people had been examined in Haiti, Indonesia, Thailand, and the Philippines, of whom some three million (mostly in Haiti) were found to be affected and have been treated. The individual figures are: Haiti, 2,270,051 examined and 2,270,051 treated; Indonesia, 3,529,831 examined and 553,587 treated; Thailand, 1,679,342 examined and 216,047 treated; and Philippines 415,000 examined and 24,000 treated. It is calculated that the cost of treatment given, including expenditure on staff and equipment, amounts to less than three dollars per head.