THE EFFECT OF GLUCOCORTICOID WITHDRAWAL ON BODY WATER AND ELECTROLYTES IN HYPOPITUITARY PATIENTS WITH ADRENOCORTICAL INSUFFICIENCY AS INVESTIGATED WITH \( ^{77}\text{Br}, \quad ^{43}\text{K}, \quad ^{24}\text{Na} \) AND \( ^{3}\text{H}_2\text{O} \)

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SUMMARY

1. Simultaneous measurements of exchangeable \( \text{Na}^+ \), exchangeable \( \text{K}^+ \), extracellular fluid volume and total body water, with \( ^{24}\text{Na}, \quad ^{43}\text{K}, \quad ^{77}\text{Br} \) and \( ^{3}\text{H}_2\text{O} \), were carried out in patients with adrenocortical insufficiency due to pituitary ablation performed 1–3 months previously.

2. The first group of five patients was studied before and after withdrawal of maintenance prednisone (2.5 mg three times daily, orally). The effects of glucocorticoid withdrawal were: (a) an increase in intracellular water (all cases) and a decrease in the extracellular fluid volume (four cases) irrespective of any change in serum \( \text{Na}^+ \) concentration; (b) an increase in residual (‘intracellular’) \( \text{Na}^+ \) in all cases which was matched by a loss of extracellular \( \text{Na}^+ \), so that total body \( \text{Na}^+ \) remained unchanged, and (c) the cortisol deficiency clinical syndrome. Exchangeable \( \text{K}^+ \) remained unchanged.

3. Similar measurements were obtained with two further patients during the corticosteroid withdrawal period, throughout which they were kept on a maintenance dose of deoxycorticosterone acetate, 1.0 mg twice daily sublingually. Neither the above biochemical changes nor the cortisol deficiency syndrome developed.

4. The shift into the cells of water and \( \text{Na}^+ \) may depend on the same defect caused by glucocorticoid deficiency, and may be the cause of the cortisol deficiency syndrome.

Key words: exchangeable electrolytes, cyclotron-produced isotopes, pituitary and adrenal insufficiency.

The accepted concept (Travis & Sayers, 1965; Liddle, 1968) of the events in acute total adrenocortical insufficiency is simply that renal loss of sodium in excess of water occurs, causing hyponatraemia and a consequent passive transfer of water from the extracellular fluid into the

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cells along the induced osmotic gradient (Loeb, Atchley, Benedict & Leland, 1933; Harrop, Soffer, Ellsworth & Trescher, 1933; Harrison & Darrow, 1938). In addition, an internal transfer of sodium (from the extracellular fluid into the cells or bone) was reported as early as 1933 (Loeb et al., 1933; Harrop et al., 1933) and later by others (Swingle, Pfiffner, Vars & Parkins, 1934; Swingle, Parkins, Taylor & Hayes, 1936; Hills, Chalmers, Webster & Rosenthal, 1953), but this is still disputed (Travis & Sayers, 1965). Conflicting results have been reported on the degree to which this internal transfer is a consequence of cortisol or mineralocorticoid deficiency (Overman, Davis & Bass, 1951; Swingle, Da Vanzo, Glenister, Crossfield & Wagle, 1959).

Most of the work on this topic has been carried out in experimental adrenocortical insufficiency in rats and dogs. Very few studies of the condition in humans are available (Hills et al., 1953; Wilson & Miller, 1953; Mendelsohn & Pearson, 1955; Arons, Nusimovich, Vanderlinde & Thorn, 1958; Brown, Fraser, Lever, Robertson, James, McCusker & Wynn, 1968), and these results are difficult to compare owing to varying experimental conditions (e.g. acute and chronic insufficiency). To our knowledge, no studies in hypophysectomy adrenocortical insufficiency in man have been reported. Similar clinical symptoms occur in untreated patients with primary adrenocortical insufficiency and in patients shortly after pituitary destruction, a condition in which mineralocorticoid secretion appears to be relatively normal (Liddle, Duncan & Bartter, 1956; Davis, Bahn, Yankopoulos, Kliman & Peterson, 1959; Davis, Carpenter, Ayers & Bahn, 1960; Slater, Barbour, Henderson, Casper & Bartter, 1963). Since patients with secondary adrenocortical insufficiency can be maintained satisfactorily by prednisone replacement alone, any internal transfer of water and electrolytes which might occur after withdrawal of this drug would seem likely to be a consequence of glucocorticoid deficiency.

We have studied the effect of corticosteroid withdrawal on total body water, extracellular fluid volume, total exchangeable sodium and total exchangeable potassium in a group of patients who had previously undergone pituitary ablation by implantation of radioactive yttrium (Fraser & Joplin, 1961). These studies were made possible by the recent development of improved techniques for the simultaneous measurement of the isotopes involved (Skrabal, Arnot, Helus, Glass & Joplin, 1970b). The patients were undergoing the routine check for completeness of ablation a few months after operation.

**METHODS**

**Patients studied**

Nine patients were studied 1–3 months after total pituitary ablation, after being informed about the experimental nature of the studies and giving full consent.

Three were suffering from carcinoma of the breast, four from diabetic retinopathy and two from acromegaly. Eight patients had been kept on a maintenance dose of 2-5 mg of prednisone, three times daily, by mouth since the operation, and the ninth had had 12-5 mg of cortisone, three times daily, by mouth. Most of our hypopituitary patients are maintained on prednisone rather than cortisone, to minimize the fluid retention that might occur in the event of a temporary increase in dosage. None had received thyroid replacement, and none showed clinical evidence of hypothyroidism at this stage. During this readmission they were kept on a ward diet constant in Na⁺ content (80–100 mEq/day) and on a free fluid regime.
During the period of corticosteroid withdrawal steroid deficiency was shown clinically in all patients by the development of the typical syndrome of lethargy, nausea, vomiting and postural hypotension, beginning about the fourth day. Steroid deficiency was confirmed in eight patients by a low resting 09.00 hours plasma cortisol concentration of <5 μg/100 ml, nor did this value rise in four patients tested with an insulin tolerance test (Landon, Greenwood, Stamp & Wynn, 1966).

The plasma cortisol measurements were all done by C. W. Burke, with a modification of the competitive protein-binding method of Beardwell, Burke & Cope (1968). The relevant clinical data are shown in Table 1.

Design of studies

Three groups of patients were studied (Table 1).

Group (a). In these five patients, the first isotope study was undertaken while they were still on steroid replacement. Steroid therapy had to be continued for a further few days to allow decay of the isotopes to occur before the second study could be done. Then steroids were withdrawn, and the second isotope study was done a few days later, when clinical steroid deficiency had appeared.

Group (b). In two patients (6 and 7) the study could be carried out only once; this was during steroid withdrawal at a time when clinical symptoms of steroid deficiency had occurred.

Group (c). Two patients (8 and 9) received, in addition to their usual steroid treatment, a small maintenance dose of mineralocorticoid as 1.0 mg of deoxycorticosterone acetate (DOCA) twice daily sublingually for at least 1 week before the first study was done, and this dose was continued during the period that glucocorticoid was withdrawn. In these two patients the second study was done 4 days after glucocorticoid withdrawal. External balance studies could not be carried out in these patients simultaneously, because of the unpredictability of the occurrence of steroid dependency.

Measurements and calculations

Total exchangeable sodium (Na\textsubscript{d}), total exchangeable potassium (K\textsubscript{d}), extracellular fluid volume (ECFV) and total body water (TBW) were measured simultaneously by a method described in detail by Skrabal et al. (1970b). The $^{24}$Na (20 μCi) and $^{43}$K (50 μCi) were injected intravenously at 08.00 hours (0 h) on the first day and a 24 h urine collection was begun. The $^{77}$Br (30 μCi) and $^{3}$H\textsubscript{2}O (250 μCi) were injected 12 h later. The patients fasted and took no fluids between 19.00 hours on the first day and 10.00 hours on the second day. At 24 h and 25 h, heparinized blood samples were withdrawn, and two further urine collections (24–25 h and 25–26 h) were made. Samples of all plasma and urine collections were counted for radioactivity together with standards on an automatic gamma counter, and were analysed subsequently for stable Na and K content on a flame photometer. The different gamma energies of the isotopes allowed analysis of the samples without previous separation procedures, by counting in three different channels favouring peaks of $^{24}$Na, $^{43}$K and $^{77}$Br at 1.37 MeV, 0.37 MeV and 0.24 MeV respectively. A computer program was used to perform the calculations. The $^{3}$H was measured on the same samples after decay of the other three isotopes, by using a liquid-scintillation counter with quench correction being carried out by using the external standard in two channels. Before the urine samples were counted, they were decolorized by adding charcoal and leaving for 24 h.
TABLE 1. Clinical data of patients and water and electrolyte values. Compounds were administered in the following doses, prednisone, 2.5 mg, three times daily, orally; DOCA, 1 mg, twice daily sublingually; cortisol, 12.5 mg, three times daily, orally. Abbreviations: ECFV, extracellular fluid volume; NaE, exchangeable Na⁺; Kₑ, exchangeable K⁺; TBW total body water; ICW, intracellular water; I.T.T., insulin tolerance test; n.s., not significant.

<table>
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<th>Patient No.</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (m)</th>
<th>Steroid replacement</th>
<th>Weight (kg)</th>
<th>ECFV (ml/kg)</th>
<th>Na⁺ space (ml/kg)</th>
<th>Na⁺ space/ECFV</th>
<th>Na⁺ (mEq/l)</th>
<th>3 Serum Na⁺ (mEq/kg)</th>
<th>N₂ (mEq/kg)</th>
<th>7 Serum Kₑ (mEq/kg)</th>
<th>8 TBW (ml/kg)</th>
<th>9 ICW (ml/kg)</th>
<th>10 Residual Na⁺ (mEq/100 ml)</th>
<th>Plasma cortisol (ug)</th>
<th>I.T.T. done</th>
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<td>DOCA and cortisone</td>
<td>62.6</td>
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<td>1.52</td>
<td>DOCA and prednisone</td>
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At the beginning of the second study during steroid withdrawal, blood samples were taken and urine samples collected just before each of the two isotope injections. These samples were used as background samples to correct for the radioactivity remaining from the previous study.

Standard calculations (Veal & Vetter, 1958) were used to calculate spaces and exchangeable electrolytes, intracellular water (ICW) and residual sodium. Residual sodium is the fraction of the exchangeable sodium which is outside the extracellular fluid as measured by bromide, i.e. in cells and bone. Since residual sodium is dependent on body size and since absolute values expressed as mEq might be misleading (simultaneous shifts of sodium and bromide may occur), we have chosen the Na space/ECFV ratio as a useful parameter for residual Na. We have established the range of this ratio in twenty normal subjects (Skrabal, Arnot, Clark, Helus, Glass & Joplin, 1970a). The plasma samples were used in the calculation of NaE, ECFV and TBW and the urine samples taken at 24–25 and 25–26 h were used in the calculation of KF. The 95% confidence limits for the duplicated measurements of ECFV, NaE and KF are ±3-0%, ±3-6% and ±5-6% respectively (Skrabal et al., 1970b). A factor of 0-9 was applied for correcting the measurement of the bromide space for serum water and Donnan equilibration. In the present paper the corrected bromide space will be referred to as the ECFV, although we realize the difficulties with homogeneity and the definition of this compartment (Walser, 1967).

For calculation of body water in the second study of each patient, we took the measurement of the first study and allowed for the change in weight of the patient, assuming that a 1 kg decrease or increase in weight was due to loss or retention of 1 litre of water. It was found that the direct measurement of TBW after steroid withdrawal was not sufficiently accurate to give reliable results, since in some cases the 3H radioactivity left from the first study 1 week previously amounted to one-third of the total count rate given by the samples taken in the second study.

The significance of the isotope results in the group (a) patients was evaluated by the paired t-test. The Na space/ECFV ratio of the group (a) and group (b) patients was also compared with the range of this value established in twenty normal subjects (Skrabal et al., 1970a).

RESULTS

Table 1 shows the clinical particulars of all nine patients studied and columns indicating the serum Na+ and K+ concentrations on the day of the tracer study, measured values of the ECFV, Na+ space, NaE, KF and TBW, and the calculated values for the Na+ space/ECFV ratio, ICW and residual Na+.

Changes after glucocorticoid withdrawal

Fig. 1 shows the findings in patient 1. Her weight was the same on the dates the two isotope studies were done (28.3.70 and 5.4.70); fluctuations in body weight occurred in this patient, but not in the others. A small decrease in the serum Na+ concentration from 138 to 133 mEq/l can be seen. The ECFV decreased by 10% from 14-84 to 13-52 litres; since body weight and therefore TBW remained unchanged, water would appear to have moved into the cells. Simultaneously the residual Na+ increased from 339 to 497 mEq.

Table 1 shows the effect of glucocorticoid withdrawal on body compartments in the first five patients (group a). There was a decrease in ECFV in all but one patient and a simultaneous
increase in the volume of distribution of tracer Na$^+$ in three patients; in the other two patients there was also an increase relative to ECFV, as shown in column 3 ($P<0.05$). Only in two patients (1 and 4) was there a clear decrease in serum Na$^+$. The total exchangeable sodium showed no distinct pattern of change; it increased in three patients, but decreased in the two patients whose serum Na$^+$ concentration fell. The residual sodium increased in all patients, the mean value for the group rising from 271 to 486 mEq ($P<0.05$); simultaneously the mean sodium content of the extracellular compartment decreased by about 150 mEq. In all patients we found an increased ICW ($P<0.01$) whether or not there was a decrease in serum Na$^+$. 

![Diagram](https://example.com/diagram.png)

**Fig. 1.** Typical changes in body water and sodium observed during glucocorticoid withdrawal. Patient 1: woman aged 50 years, 1 month after pituitary ablation for breast cancer. ——, Body weight; — — —, serum Na$^+$. 

Patient 5 was the only one who showed a clear weight gain between the two studies; as seen in columns 1 and 9, his weight increase was due to water retention occurring both in the extracellular and in the intracellular compartments. The changes in K$_E$ were inconsistent in these patients. The potassium content of the diet was not controlled.

The results of those two patients in group (b) who were studied only during corticosteroid withdrawal are shown in Table 1 (patients 6 and 7); their data are added to the group (a) patients to produce the mean values representing corticosteroid withdrawal in Fig. 3.

**Effect of DOCA administration on the changes observed during corticoid withdrawal**

Fig. 2 shows the changes observed in patient 8 during the steroid withdrawal, throughout which a small maintenance dose of 1 mg of DOCA twice daily was given sublingually. On commencing administration of the DOCA, an initial small rise occurred in serum sodium...
Water and electrolyte shifts in steroid lack

concentration after which a fairly constant serum Na⁺ concentration and body weight were achieved. As soon as the cortisone treatment was stopped, water retention occurred, as indicated by weight gain, and was shown to be due entirely to an expansion of the ECF. In contrast with the group (a) patients who were not treated with DOCA, the residual Na⁺ decreased. On the day of the second study the plasma cortisol concentration was 1 μg/100 ml but no symptoms of steroid deficiency had appeared. Subsequently, DOCA was withdrawn and after 4 days severe symptoms of steroid deficiency developed. The same clinical and biochemical changes also occurred in the other patient treated with DOCA (patient 9), whose previous maintenance therapy had been prednisone (2·5 mg three times daily).

![Diagram](image)

**Fig. 2.** Effect of corticosteroid withdrawal on the distribution of body water and sodium, in the presence of continuous DOCA administration. Patient 8: woman aged 63 years, 3 months after total pituitary ablation for breast cancer. ---, Body weight; ---, serum Na⁺.

Table 1 shows that both patients (group c) showed an expansion of the extracellular fluid (and of the volume of distribution of sodium), while a decrease in intracellular water occurred. The mean Na_re did not increase, so the observed weight increase of about 1·6 kg in both patients could not have been due to sodium retention. Residual sodium decreased in both patients.

**Changes in ratio of Na⁺ space/ECFV**

The values for this index of residual sodium are shown in Table 1. Fig. 3 shows the results in the present series of hypopituitary subjects compared with the values obtained in twenty normal subjects (Skrabal et al., 1970a). This ratio increased in all five patients of group (a) during steroid withdrawal. Four out of the total of seven patients studied during steroid
withdrawal (groups a and b) reached values outside the upper limit of normal. In contrast, the Na⁺ space/ECFV ratio decreased in both patients who were kept on DOCA during corticosterone withdrawal.

\[
\text{Na}^+ \text{ space/ECFV}
\]

\[
\begin{array}{|c|c|c|}
\hline
\text{Normal subjects} & \text{Hypopituitary subjects} \\
\hline
\text{On glucocorticoids} & \text{Off glucocorticoids} & \text{On DOCA} & \text{Off glucocorticoids On DOCA} \\
\hline
\text{1.3} & \text{1.2} & \text{1.1} & \text{1.08} \\
\hline
\end{array}
\]

**FIG. 3.** Effect of corticosteroid withdrawal on the Na⁺ space/ECFV ratio is compared with the ratio in the presence of continued DOCA administration (1 mg twice daily sublingually). Mean values are shown by horizontal bars.

**DISCUSSION**

The definitive interpretation of isotope-dilution studies of the type reported here must await the discovery of an ideal tracer for the critical measurement of ECFV. The limitations of tracer bromide for this purpose have been extensively discussed by Walser (1967). The actual measurement of bromide space can be made with reasonable accuracy, the 95% confidence limits of the results based on duplicate samples as used here being ±3\% (Skrabal et al., 1970b), but the problem we face is doubt not only about the exact anatomical boundaries of the ECF itself, but also the anatomical distribution of tracer bromide, especially in the pathological condition of corticosteroid insufficiency. As the ECFV enters the calculation of both residual sodium and ICW, these three measurements are interdependent: for example, if tracer bromide were to underestimate the ECFV during glucocorticoid insufficiency the effect would be to overestimate both the residual sodium and ICW. The following interpretation, based on currently available isotopes and knowledge of their distribution, is proposed.

The consistent effects of glucocorticoid withdrawal in the five group (a) patients were a shift of both water and sodium from the extracellular fluid compartment to cells or bone; simultaneously, all these hypopituitary patients clinically showed the cortisol deficiency syndrome.
These shifts are shown by a fall in ECFV in four patients, and a concomitant rise in ICW in all five patients; Na\textsubscript{E} remained substantially unchanged, yet in all cases there was a sharp rise in residual sodium and in the Na\textsuperscript{+} space/ECFV ratio. This shift of water may well be the basis of the withdrawal syndrome of postural hypotension, weakness, nausea and vomiting. Results of such measurements have not been reported before in secondary adrenocortical insufficiency, but our findings are consistent with those of workers who found a shrinkage of ECFV in adrenalectomized dogs (Gaudino & Levitt, 1949; Flanagan, Davis & Overman, 1950) and in subtotally adrenalectomized humans with severe hypertension (Hills et al., 1953). Pituitary destruction may have a number of effects on water and electrolyte metabolism but it would seem reasonable to attribute the observed changes to glucocorticoid insufficiency because steroid withdrawal was the only change made in the regime of our patients. The mechanism may be complex and involve other hormones (Ahmed, George, Gonzales-Aubert & Dingman, 1967). The low absolute values of K\textsubscript{E} in some of the patients are consistent with the severity of their underlying disease (Aikawa, Felts & Harrell, 1953). Whether pituitary ablation and/or steroid replacement therapy has an influence on body potassium will require further investigation.

The increase in residual sodium during glucocorticoid deficiency implies that the sodium outside the extracellular fluid either became more readily exchangeable or that the amount in this compartment (cells and bone) increased. Although the specific radioactivity of tracer sodium after 24 h and of tracer bromide after 12 h is constant and equal to that of plasma in all soft tissues, this is not so in bone (Edelman, James, Baden & Moore, 1954), so it is possible that the observed increase in residual sodium reflected an increased exchangeability within the bone crystals. The exchange of ions between the bone and extracellular fluid is largely dependent on the area of 'active' surface of bone, and has been shown in studies with calcium isotopes (Miravet, Matrajt, Bordier, Tun, Gruson & Hioco, 1969); but there is no obvious reason why the active surface of bone should have changed in our patients during the week in which both studies were carried out. An absolute gain of sodium in bone is also very unlikely in the presence of a fall in serum Na\textsuperscript{+} concentration (Bergstrom & Wallace, 1955); further, in experimental adrenocortical insufficiency in animals the total sodium content and the exchangeable fraction of sodium in bone is reported not to increase (Stern, Cole, Bass & Overman, 1951; Lobeck & Steinraus, 1960; Rovner, Streeten, Louis, Stevenson & Conn, 1963). Therefore it would seem that the most likely location of the rise in residual sodium is an actual increase of sodium within the cells. Consistent with this proposal is our finding of a transfer of water from the extracellular fluid into the cells which matched the simultaneous increase in the sum of the intracellular cations. Hills et al. (1953) carried out balance studies and measured the inulin space during steroid withdrawal in patients who had previously undergone subtotal adrenalectomy for severe hypertension, and found evidence for a transfer of sodium and water out of the inulin space. Since the inulin space does not include the connective tissue water they suggested that steroid withdrawal might lead to increased hydration and sodium content of connective tissue. However, the volume of distribution of bromide used in our study does also include the connective tissue water (Nichols, Nichols, Weil & Wallace, 1952), and since we found a transfer of sodium and water out of the ECFV, our results do not confirm their suggestion.

Swingle et al. (1936), using adrenalectomized dogs, were the first to find that the external loss of sodium did not account for the degree of extracellular depletion. This group and
Flanagan et al. (1950) suggested that cells or bone may act as a labile store for sodium in this condition. However, other workers (Harrison & Darrow, 1938; Muntwyler, Mellors, Mautz & Mangun, 1940; Buell & Turner, 1941) found no increase in tissue sodium content in adrenalectomized dogs, and Rolf, Armstrong, Steiger, Audia & White (1959) reported that in adrenalectomized rats the external loss of sodium accounted for the degree of extracellular depletion.

Our results indicate a gain of about 200 mEq of Na⁺ in the residual compartment in hypopituitary subjects after withdrawal of maintenance steroid. This would account for a transfer of about 1·4 litres out of the ECF into the cells, and in the presence of an unchanged body potassium it approximates to the observed increase of about a litre in cellular hydration.

In both group (c) patients maintained on DOCA we observed a massive water retention in the extracellular compartment as soon as glucocorticoids were stopped. This confirms that DOCA cannot maintain water excretion by the kidney, and in that respect cannot replace glucocorticoids. In contrast with the group (a) patients, the residual Na⁺ and the Na⁺ space/ECFV ratio decreased in both patients; however it is difficult to draw firm conclusions about the significance of this finding from such limited observations. In this connection it is interesting that Rovner et al. (1963) found a decreased bone uptake of ²²Na in rats after administration of mineralocorticoids.

Although a technique for the simultaneous measurement of TBW, ECFV, exchangeable sodium and exchangeable potassium was introduced for human studies more than 10 years ago (Veal & Vetter, 1958), the present study is to our knowledge the first time that repeat measurements of these four spaces have revealed internal transfers of water and electrolyte in this condition. Previous investigations were based on repeated measurements of ECFV and simultaneous balance studies. We ascribe the consistency of our results to the use of a recently developed technique (Skrabal et al., 1970b) that allows the accurate measurement of all four isotopes in previously untreated plasma and urine samples. We suggest that serial measurements with this method could replace balance studies where these are not feasible, giving in addition the interesting information about the distribution of water and electrolytes within the body.

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