WATER AND ELECTROLYTE METABOLISM IN ADRENAL AND PITUITARY INSUFFICIENCY

II. EFFECT OF GLUCO- and MINERALOCORTICOID ADRENAL STEROIDS ON SODIUM METABOLISM, WITH SPECIAL REFERENCE to EXCHANGEABLE SODIUM

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Water and Electrolyte Metabolism in Adrenal and Pituitary Insufficiency

II. Effect of Gluco- and Mineralocorticoid Adrenal Steroids on Sodium Metabolism, with Special Reference to Exchangeable Sodium

By BERNARDO LIBERMAN, BERNARDO LÉO WAJCHENBERG AND ROMULO RIBEIRO PIERONI

Six patients with adrenocortical insufficiency were studied and the data presented demonstrate discrepancies in the results obtained by the classic metabolic Na balance technic, the measurement of exchangeable sodium with Na^{22} during steroid withdrawal, and the replacement with aldosterone and/or glucocorticoids. These discrepancies arose frequently enough to suggest that during aldosterone administration some of the retained sodium may be deposited in nonexchangeable stores which may become exchangeable when glucocorticoids are given. (Metabolism 15: No. 11, November, 992–1001, 1966)

CHANGES OF BODY WATER and electrolytes have long been known to play an important role in adrenal insufficiency. Despite the many problems of interpretation besetting those who measure exchanges among variously defined anatomical and solute dilution "spaces," it has been possible to show that adrenal hormones exert an effect on those body compartments. Swingle and associates[1-3] clearly demonstrated that, despite losses of water and electrolytes, glucocorticoids enabled dogs developing advanced symptoms of adrenal insufficiency to survive without replacement of electrolytes. Desoxycorticosterone and aldosterone, even in large doses, failed to improve the animals unless sodium salts were available. They concluded that glucocorticoids maintain a normal internal distribution of fluid and certain electrolytes (Na, Cl and K) between intra-and extracellular compartments. The primary action of aldosterone would be on the kidney and through renal control of Na excretion would regulate the fluid and Na content of the extracellular compartment. Hills et al.,[4] studying fluid and electrolyte shifts in adrenalectomized human beings following withdrawal of cortisone, concluded that internal transfers of fluid and electrolytes accompany acute adrenal insufficiency. However, Men-

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delsohn and Pearson,[5] with similar studies, concluded that internal exchanges were not of great importance.

The availability of radioactive isotopes suitable for human use has introduced a new method of measuring body composition with the use of the dilution principle. Since total exchangeable sodium measured by isotope dilution technic accounts for only 85 per cent of total body sodium, because approximately 55 per cent of sodium in human bone does not exchange even after prolonged equilibration,[6,7] the bone could play a significant role in total body Na metabolism as regards the transfer of the cation from nonextracellular to the extracellular compartment, regulated by the adrenal steroids.

The concept of an endogenous, nonextracellular sodium reservoir (probably bone and cartilage) in adrenal deficiency states is supported by: (1) the failure of external sodium balance to account for restitution of extracellular stores following glucocorticoid replacement therapy,[8] and (2) the normal values for exchangeable Na reported by Arons et al.[9] in a hyponatremic patient during early Addisonian crisis.

Recently, Streeten et al.,[10] measuring exchangeable Na in patients with primary aldosteronism, suggested that aldosterone exerts an inhibitory effect on the exchangeability of bone Na. This conclusion was apparently supported by subsequent data upon in vivo uptake of aldosterone.[11]

The present studies were performed with the objective of determining the acute and chronic effects of aldosterone and/or glucocorticoids on sodium balance and exchangeable Na in patients with adrenocortical insufficiency to see whether changes of the nonexchangeable fraction of body Na do occur, in case a significant discrepancy between the balance and isotope dilution method should be found.

Material and Methods

The 6 subjects of this study were 5 patients with Addison's disease, due to South American blastomycosis in 2 (G. E. J. and F. Z.), tuberculosis in 2 (S. U. and A. P. T.), and unknown etiology in 1 (N. D. B.), and 1 patient with secondary adrenal insufficiency (Sheehan's disease) (A. O. E.). The diagnosis of adrenocortical insufficiency had been established clinically by low urinary excretion of 17-hydroxycorticosteroids and by the absence of increased excretion of these steroids during intravenous administration of ACTH for 2 consecutive days.

The subjects were given constant diets throughout the study and, in the case of the patients unable to eat the prescribed diet, the foodstuffs remaining were analysed to obtain the corrected electrolyte intake. Urine was collected in 24 hour periods starting at 8 a.m. Feces were collected in 2 patients (A. P. T. and A. O. E.) in periods ranging over several days, depending on the particular study. Blood samples were taken daily at approximately 8 a.m., although in some of the studies samples were obtained on alternate days or at longer intervals. Each patient was weighed at the same time every day.

Sodium was estimated on all samples by flame photometry using an internal standard.

All subjects received an intravenous injection of a tracer dose of radio-sodium (20 μc. of $Na^{22}Cl$ in 50 ml. isotonic saline). Two ml. aliquots of serum, obtained 24 hours later and daily thereafter, were used for measurements of radioactivity, duplicate counts of 10.000 being performed on each sample of serum in a well-type scintillation counter. Urine aliquots (2 ml.) were counted every day to determine daily losses of radioactivity in urine.

Exchangeable sodium (Na_e) was determined by dividing the amount of radioactivity

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SUMÁRIO

Seis pacientes, com insuficiência adrenocortical, foram estudados empregando-se a técnica clássica de balanço de Na e determinando-se o sódio permutável com uso do ^{22}Na. Os resultados indicam discrepâncias entre os dados do balanço e os do Na permutável durante a retirada do esteroide e a reposição com aldosterona e/ou glicocorticoides. A frequência dessas discrepâncias sugere que durante a administração da aldosterona parte do sódio retido não é permutável, tornanco-se trocável pela ação de glicocorticoides.(Metabolism 15: nº 11-Novembro, 992-1001, 1966).

SUMMAIRE

Six malades avec insuffisance adrenocorticale ont été étudiés et les données presentées demonstrent la diversité des resultats obtenus par la téchnique classique de la balance metabolique Na, par la mesure du sodium échangeable avec Na^{22} pendant la retraite des esteroides, et par la substitution avec l'aldosterone et/ou des glucocordicoides.

Ces diversités survenaient assez fréquemment pour suggèrer qu'à la course d'administration de l'aldosterone quelque sodium que fut retenu peut être placé dans les dépôts inaltérables qui, à son tour, peuvent s'alterer quand des glucocorticoides sont administrés. (Metabolism 15: nº 11 - Novembre, 992-1001, 1966).

remaining in the body after the injection of Na^{22} (i.e., injected radioactivity minus cumulative excretion of radioactivity in the urine) by the serum specific activity:

$$Na_e = \frac{Na^{22} \text{ injected} - Na^{22} \text{ excreted (urine)}}{\text{serum } Na^{22}/\text{serum } Na^{23}}$$

Measurement of Na^{22} losses in the stools was not attempted because sodium excretion in feces is negligible and accounting for only 1.8 ± 1.1 per cent of the combined urinary and fecal excretion in the studies of Martin and Walker.[12]

To facilitate comparison of the balance data (expressed as cumulative balances) with the findings of the determinations of exchangeable sodium, both were plotted on the same axes and on the same scale.

Procedure and Results

Study I. *Acute Effects of Aldosterone Administration Alone and Associated with Cortisol (Fig. 1)*

G. E. J., a 45 year old male, and F. Z., a 48 year old male, both with Addison's disease without adrenal replacement therapy for 1 week before the study, were given 0.5 mg. of d-aldosterone intravenously in 500 ml. 5 per cent glucose solution during 8 hours on the fourth or third day after Na^{22} injection, respectively. Three days afterwards, the same infusion was repeated, but with the addition of 20 mg. of cortisol hemisuccinate.

Prior to the administration of aldosterone alone, both patients were in positive sodium balance, particularly G. E. J. Exchangeable sodium was in the normal range, as obtained on the third day following the administration of the tracer dose by Martin and Walker[12] and Streeten et al.[10] After aldosterone administration, sodium excretion promptly diminished and remained so until the second infusion of aldosterone was given together with cortisol, when it increased. The expected exponential increase in Na_e with time[10] was not observed after aldosterone administration, but rather a progressive slight fall was observed. The administration of cortisol together with aldosterone increased Na_e in patient G. E. J., but had little effect in the second patient, F. Z.

Study II. *Continued Aldosterone Administration with and without Cortisone Therapy (Fig. 2 and 3)*

A. O. E., 30 years of age, with panhypopituitarism (Sheehan's disease) received 1 mg. d-aldosterone (0.5 mg. every 12 hours) intramuscularly, daily, for 9 days (Fig. 2). The supressive action of aldosterone on the increase of Na_e was not observed in the last day of the study when Na_e was again measured, there being an "escape," and the cumulative "Na^{22} balance" became 205 mEq. greater than that of stable Na. However, during the first days after aldosterone administration, when Na_e fell 57 mEq., there was a positive stable Na balance of 174 mEq. Computing the 2 periods, there was a remarkable closeness of the results: stable sodium balance of +320 mEq. and "isotope balance" of +294 mEq.

N. D. B., a 25 year old female Addisonian (Fig. 3), was given 0.5 mg. of d-aldosterone I.M., daily, for 4 days while being maintained with 37.5 mg. of cortisone daily. Aldosterone was completely withdrawn afterwards, while cor-

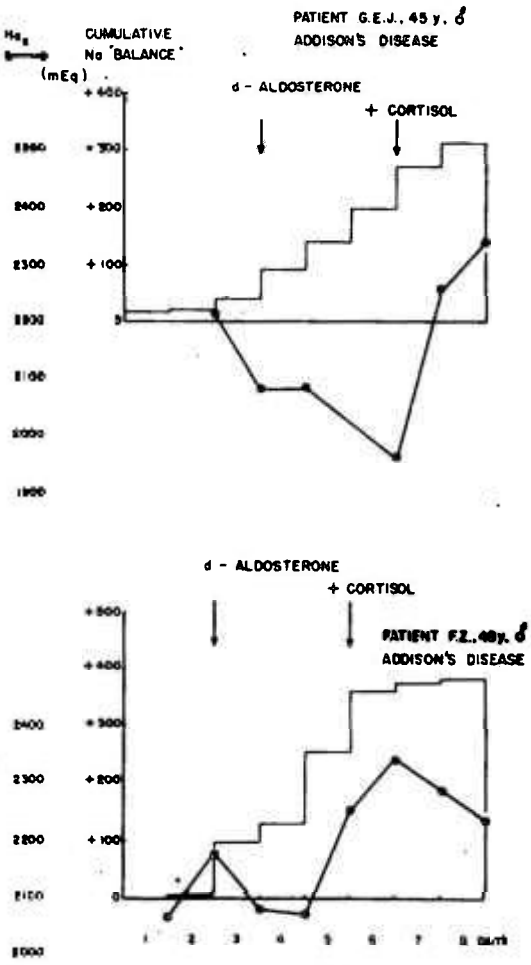

Fig. 1.—Effect of intravenous administration of d-Aldosterone, and of d-Aldosterone plus cortisol on sodium "balance" and exchangeable sodium (Na_e).

tisone was continued for 4 more days. Thereafter, cortisone was omitted for 4 days when dexamethasone 21-phosphate was administered in 2 doses of 1 mg. I.M. because of signs and symptoms of adrenal crisis. In the next day, cortisone was reinstituted. Urinary sodium fell and was lowest on the fourth day of aldosterone administration. When maintenance therapy was withdrawn, first aldosterone and later cortisone, there was a progressive increase in sodium excretion, with a significant simultaneously decrease in serum Na, from 140 mEq./L. to 127 mEq./L. Administration of dexamethasone and later cortisone resulted in a prompt retention of sodium.

In this patient, the withdrawal of d-aldosterone maintenance therapy did not induce a significant change in the Na_e at the lower limits of normal range,[13] despite the tendency to decrease. It fell, in parallel with the negative stable sodium balance (−207 mEq.) from 1307 to 1063 mEq. (244 mEq.)

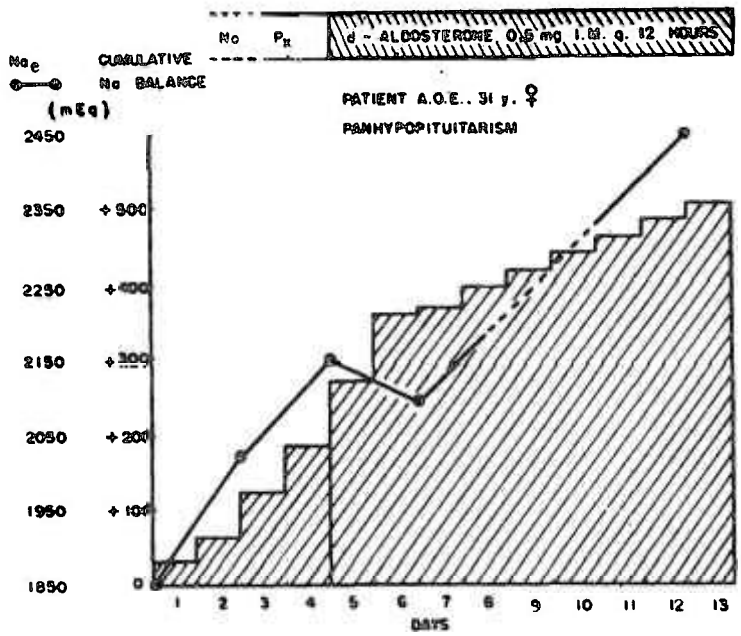

Fig. 2.—Effect of chronic d-Aldosterone administration on sodium balance and exchangeable sodium (Na_e).

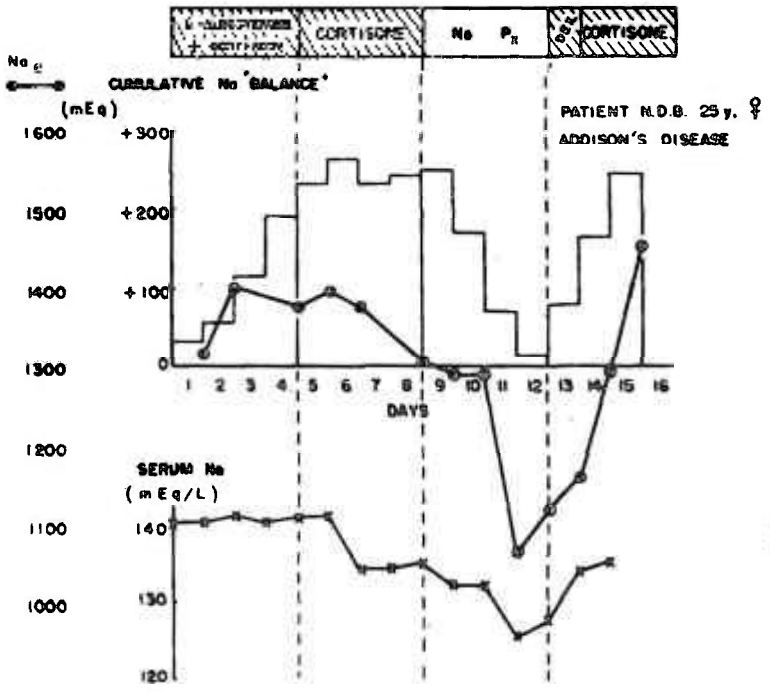

Fig. 3.—Effect of d-Aldosterone and of cortisone withdrawal on sodium "balance," exchangeable sodium and serum Na concentration.

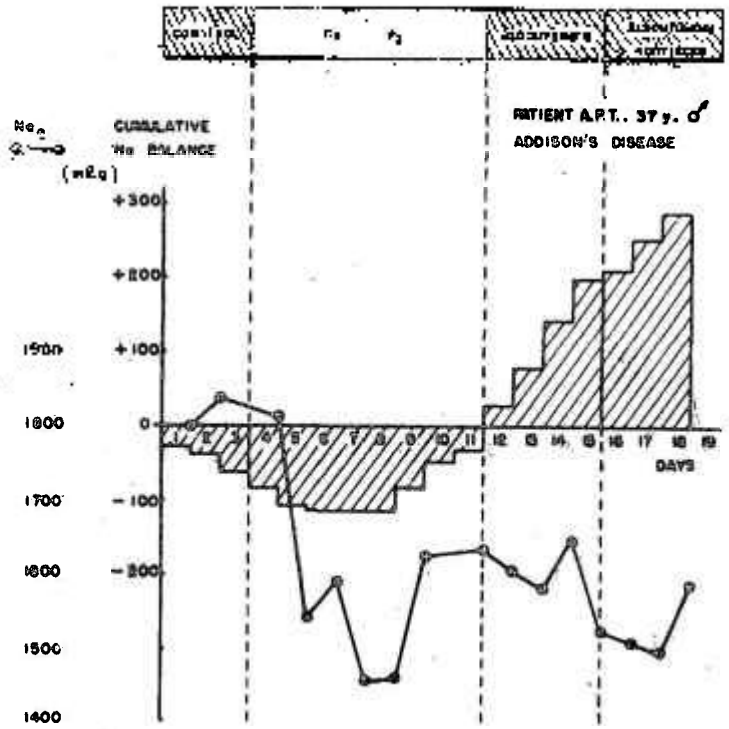

Fig. 4.—Effect of cortisol withdrawal followed by *Aldosterone* alone and associated to cortisone on sodium balance and exchangeable sodium (Na_e) in a patient with chronic hypoadrenocorticism and intermittent paralysis.

when cortisone was stopped. When glucocorticoid therapy was reinstated, Na_e increased 382 mEq., whereas, the stable sodium "balance" was only +229 mEq. No significant changes in body weight were observed during the study.

Study III. *Glucocorticoid Withdrawal Followed By Aldosterone and Cortisone Therapy (Fig. 4)*

A. P. T., a 37 year old man with Addison's disease and intermittent paralysis, similar to the case of Faw and Ewer,[14] while receiving 35 mg. of cortisol hemissuccinate daily, I.M., was in negative sodium balance and remained negative during cortisol withdrawal. The exchangeable sodium, initially low, still decreased after 2 days of cortisol withdrawal, from 1811 to 1542 mEq. (−260 mEq.) when an external loss of 29.4 mEq. was recorded on metabolic balance. The Na_e still decreased further at a time when there was no further sodium loss. On the 6th day after withdrawal of cortisol, the Na_e increased from 1459 to 1625 mEq. (+166 mEq.) and remained the same on the third day of aldosterone administration. The increase in Na_e was noticed with the positivity, although slight, in Na balance. During this period, serum sodium fell. After aldosterone administration (0.5 mg., I.M., b.i.d.), sodium balance became more positive, without significant change in Na_e. Serum sodium re-

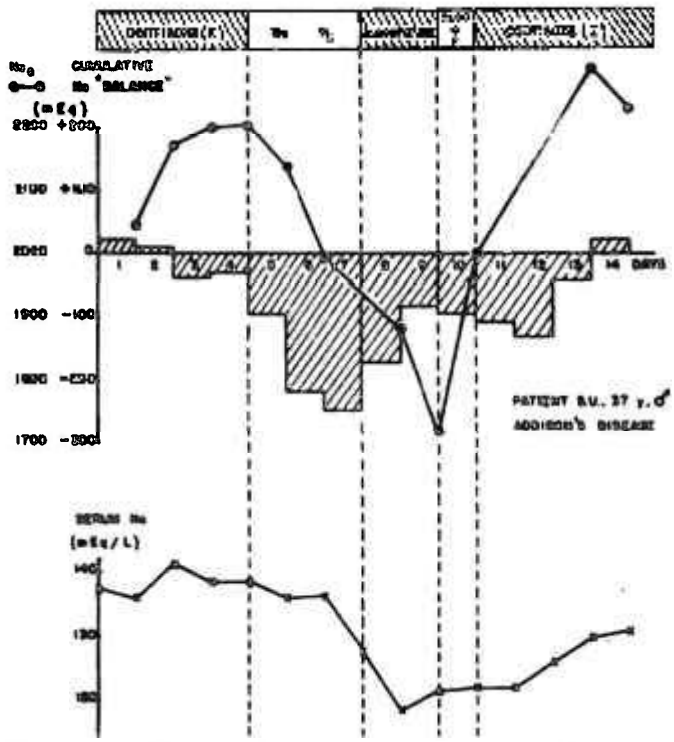

Fig. 5.—Effect of cortisone withdrawal followed by Aldosterone* and cortisone therapy on sodium "balance," exchangeable sodium (Na_e) and serum Na concentration.

*Alone and associated with cortisol.

turned to normal levels. During aldosterone therapy, cortisone 25 mg. oral daily was introduced with Na balance continuing positive, particularly on the first day. Na_e did not change significantly after glucocorticoid administration. The body weight was constant during this study.

S. U., a 36 year old Addisonian (Fig. 5), after a 4 day control period, when he was receiving 75 mg. cortisone acetate daily given orally, had glucocorticoid therapy withdrawn for as long as the patient's condition allowed (5 days). Sodium "balance," which was slightly negative in the control period, became definitively negative during the 3 days of cortisone withdrawal and became less negative when aldosterone (0.5 mg., I.M., b.i.d.) was introduced. The serum sodium level, which was normal during the control period, fell to 127.8 mEq./L. before aldosterone was started, but continued to fall to 118.4 mEq./L. and increased only on resumption of cortisone. During the period of cortisone withdrawal, the body weight decreased 1.5 Kg. After aldosterone was introduced, the patient still lost 1 Kg., but maintained the weight when cortisone was reintroduced. The Na_e, in the normal range when cortisone was withdrawn, fell from 2200 to 1993 mEq. (−207 mEq.) after 3 days. During this time, the metabolic sodium "balance" showed a loss of 180 mEq., in

excellent agreement with the "isotope balance." The Na_e, measured on the third day of aldosterone therapy (0.5 mg., I.M., b.i.d.), was 1723 mEq., i.e., it decreased 269 mEq. when the chemical "balance" recorded a gain of 164 mEq. On the third day of aldosterone, because the patient appeared critically ill, cortisol hemisuccinate was given intravenously (100 mg.) with a dramatic clinical improvement in 4 hours. By the next morning, the measured Na_e had increased 277 mEq., but a loss of 15 mEq. was recorded in the chemical "balance" at the time the Na ingestion decreased from 118.3 mEq. to mEq./day, on the day of adrenal crisis. Following cortisone resumption (75 mg./day, orally), the Na measured after 4 days increased from 2000 to 2291 mEq. (+291 mEq.). During this period, the metabolic "balance" showed a gain of only 50 mEq.

Discussion

The finding, which appears to be reasonably consistent from our data, is that withdrawal of steroid therapy (Fig. 3, 4 and 5) almost always causes a fairly parallel fall in exchangeable sodium and in the positivity of the external sodium balance, while aldosterone administration usually produces positive sodium balance (that is, reduced sodium excretion), associated with little or no change in exchangeable sodium (except in patient A. O. E. (Fig. 2) where the discrepancy is dependent on a single determination of exchangeable sodium). In contrast to these effects of aldosterone, the administration of cortisone or cortisol appears almost always to produce a sharp increase in the exchangeable sodium, frequently with little or no effect on sodium balance, in accordance with the concept that glucocorticoids are primarily concerned with the electrolyte equilibrium between the extracellular and nonextracellular compartments. The progression in the degree of hyponatremia in one of our patients (S. U., Fig. 5), together with the positive sodium balance during aldosterone administration, corrected only when cortisone was introduced, is in favor of our suggestion.

The findings on the short-term administration of aldosterone and the modification of the renal handling of sodium when cortisol was added (Fig. 1) confirm previous similar observations by Ross et al. [15]

The observed lack of rise in Na_e despite Na retention after aldosterone administration implies that the Na retained under the influence of aldosterone is not freely exchangeable with Na.[22] These findings are consistent with the observations of Streeten et al.[10,11]

The unexpected finding was the persistent action of the intravenously administered d-aldosterone, which is at variance with the data of Ross et al.[15]

Both patients referred to in Figure 1 showed little or no effect on external balance of sodium, although there was a sharp rise in exchangeable sodium following the administration of aldosterone plus cortisol. On the other hand, the withdrawal of aldosterone (Fig. 3) was not followed by an increase in Na_e, which, however, decreased in parallel with the urinary sodium losses with the withdrawal of cortisone.

The findings in the remaining patients appear to be somewhat inconsistent,

since, in some patients, such as A. O. E., the changes in balance and in exchangeable sodium appear to follow one another fairly closely, while in other individuals, such as A. P. T., there is a wide dichotomy between these results. However, we were unable to judge the relative significance of the residual gluco- and/or mineralocorticoid activity of the remaining adrenal tissue.

It is not known why the patient with Addison's disease and intermittent paralysis was unable to correct his Na_e despite the use of glucocorticoid and aldosterone (Fig. 4). One possible explanation is that the patient was in a state of severe Na depletion at the start of our studies. To our knowledge, Na_e has never been measured in this type of patient and from observation made after the present studies we have learned that he could be well controlled only with doses of mineralocorticoid above what is usual for Addisionians maintained on more than 30 mg. of cortisone daily (unpublished data).

In conclusion, our data might suggest: (1) a nonextracellular sodium reservoir (probably bone and/or cartilage) which is regulated by glucocorticoids, and (2) the failure of aldosterone in the maintenance of a normal sodium balance.

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