# ELECTROLYTE BALANCES IN A MALE INFANT WITH ADRENOCORTICAL INSUFFICIENCY AND VIRILISM. THE EFFECT OF DESOXYCORTICOSTERONE ACETATE AND SALT THERAPY WITH SPECIAL REFERENCE TO POTASSIUM [1, 2]

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## INTRODUCTION

Elevation of serum potassium in experimental adrenal insufficiency and in patients with Addison's disease, and its reduction by desoxycorticosterone acetate have been accepted as constant findings. These changes are generally considered to depend on alterations in the renal excretion of potassium rather than on shifts of intracellular potassium (1). According to this concept, adrenal insufficiency causes: *1.* a decreased renal excretion of potassium, *2.* an increase in serum potassium and, *3.* a rise in intracellular and total body potassium. Conversely, treatment of adrenal insufficiency with desoxycorticosterone acetate leads to: *1.* increased renal excretion, *2.* decreased serum potassium, and *3.* decreased intracellular and total body potassium. If this concept is correct, prolonged treatment with desoxycorticosterone acetate could deplete the body of potassium. This view receives support from direct potassium tissue analyses in experimental animals. Increased intracellular potassium during adrenal insufficiency and decreased values following prolonged treatment with desoxycorticosterone acetate have been found consistently in both normal and adrenalectomized animals (2, 3). However, reported studies in experimental animals and in patients with Addison's disease have shown neither a consistently decreased excretion of potassium during adrenal insufficiency nor a regularly increased excretion during prolonged treatment with desoxycorticosterone acetate (4–6). In those instances when desoxycorticosterone acetate does not increase potassium excretion, the fall in serum potassium can only be explained by a large expansion of blood or extracellular fluid volume, or more reasonably, by a shift of extracellular potassium to the cells. If potassium intake is constant, total body potassium would not then be decreased.

The effect of desoxycorticosterone acetate on potassium metabolism in adrenal insufficiency has important therapeutic implications. For example, it has been shown that, in animals, heart injury due to desoxycorticosterone acetate can be prevented by diets high in potassium (7). If such treatment for adrenal insufficiency in man leads to similar damage incident to potassium loss, an adequate intake of potassium may be required to prevent the effects of overdosage (8, 9). If, on the other hand, desoxycorticosterone acetate therapy does not lead to a potassium deficit in man the requirements may be quite different.

We are presenting observations designed to define the metabolic aberrations in a male infant with adrenocortical insufficiency and virilism and the effects of substitution therapy. Our objectives in these observations were threefold: *1.* to determine the effect of varying hormone and electrolyte administration on the excretion and balance of electrolytes, particularly on shifts in intracellular potassium; *2.* to determine the role of renal mechanisms in any changes observed; and *3.* to determine the need for extra potassium in the diet in the course of treatment with desoxycorticosterone acetate and added sodium chloride (10).

## CLINICAL SUMMARY

The clinical history of the infant has been presented in detail elsewhere (11). Persistent vomiting, intermittent diarrhea and unexplained episodes of severe dehydration with collapse had led to an extreme degree of malnutrition at the age

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of one month. The serum potassium at this time reached a peak of 9.5 and serum sodium a low of 118 mM. per liter. The abnormal electrolyte levels in the serum and the clinical signs of dehydration were not corrected by giving enormous quantities of water and sodium chloride but they responded promptly to added adrenal cortical extract and later, desoxycorticosterone acetate. Subsequent withdrawal of the hormone and added sodium chloride caused a return of the symptoms and findings. Injection of adrenocorticotrophic hormone failed to lower the number of circulating eosinophiles or to raise the urinary uric acid: creatinine ratio. At one month of age the infant's penis appeared relatively large and by three months facial hair was apparent. Moreover, the urinary 17-ketosteroids totalled 4.7 mg. per 24 hours. It seemed clear, then, that this boy had the type of adrenocortical disease first recognized and described in 1939 by Butler *et al.* (12), and by Wilkins *et al.* (13) in which there is an insufficiency of the electrolyte controlling hormone or hormones and an excess production of the androgenic hormone of the adrenals. At the completion of the study in the fourth month of his life the infant was thriving and in good chemical control on a daily regimen of 3.5 Gm. of sodium chloride and 0.8 Gm. of sodium-r-lactate added to a usual diet for his age and injections of 2 mg. of desoxycorticosterone acetate in oil.

## PROCEDURE AND METHODS

The infant entered the Metabolism Unit at 11 weeks of age and was observed for a period of six weeks during which special metabolism nurses were in constant attendance. Balances of potassium, sodium, chloride, phosphorus, calcium and nitrogen, and 24-hour endogenous creatinine clearances were measured during 20 days using the general technic previously developed and described in this laboratory [8] (14, 15). Because of the importance of minimizing loss of electrolyte from the skin in this type of study, the temperature and humidity of the metabolism room were kept at 23° C. and 50% respectively and the infant was lightly clothed. Tests of the forehead and abdomen for skin excretion of chloride as described by Vasti (17) were repeatedly negative. He was weighed daily before the 10 a.m. feeding.

Throughout the study the infant received a dilution of powdered whole milk supplying from 122 to 149 calories per kilogram of body weight per day plus added sodium chloride and sodium lactate in varying amounts. The potassium intake provided by this formula was a customary one for an infant of this age except during two days of Period VI, when potassium was added. In addition he received 50 mg. of ascorbic acid and 10 drops of an alcoholic solution of vitamins A and D daily. The technic of measuring the *intake* was a modification of that devised by Levine (14) and later described in detail by Gordon (15). The daily amount of powdered milk ingested was calculated from daily phosphorus determinations of the prepared formulas and the analyzed phosphorus content of the powdered milk. All constituents of the intake were determined directly on an aliquot of each day's formula as prepared, except for calcium and nitrogen. The latter were calculated from the known amount of powdered milk retained and the analyzed content of the powdered milk. These calculated values agreed within 5% with repeated direct analyses of the formulas.

*Blood samples* were drawn preceding the 10 a.m. feeding at intervals of one to three days. All specimens were obtained from superficial veins, transferred under oil, and separated promptly.

*Urine specimens* were collected for periods of approximately 12 or 24 hours. Individual specimens were transferred immediately after voiding and without measuring to 250 or 500 ml. volumetric flasks kept in the refrigerator. At the end of collection periods, water was added to the mark and the urine volume calculated by difference. Analyses were made on aliquots of each 12- or 24-hour specimen.

*Stools* marked by carmine were collected for two to seven day periods. The pooled samples were dried over steam in weighed dishes and the dry weight calculated by difference. Aliquots of the homogenized dry stool were taken for analysis.

Specific *renal functions* were measured before starting the balance studies by methods previously described (18).

*Chemical analyses.* Determinations on *serum* included potassium,[4] sodium (20), calcium (21), chloride (22), carbon dioxide content (23), phosphorus (24), total protein (25), creatinine (26), and urea nitrogen (27). Hemoglobin (28) and hematocrit determinations were done on oxalated venous blood. Aliquots of *urine* were analyzed for potassium, chloride, phosphorus and creatinine as for serum. Sodium,[4] calcium (29) and total nitrogen (30) were also determined. *Stool samples* were dry-ashed in a muffle furnace at 500° C. and the ash extracted with small portions of acid. Potas-

[8] The only difference was a modification of the system to signal the time of urination. Instead of utilizing the weight of the urine in a Gooch crucible to establish contact of a make and break circuit as originally described (16) the electrolyte content of the urine was utilized to complete the circuit and to ring the bell when urine dropped between two silver wires on adjustable screws approximated in a plastic mount. This type of urination announcer, suggested by Dr. F. X. Fellers, offers the advantage of simplicity and decreased dead space.

TABLE I

*Balance of electrolytes and nitrogen*

| Period | Treatment | | | Date 1949 | Weight* | Potassium mM./24 hrs. | | | Sodium mM./24 hrs. | | | Chloride mM./24 hrs. | | | Additional balances Gm./24 hrs. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DOCA | Added NaCl | Na-lactate | | | Intake | Excretion† | Balance | Intake | Excretion† | Balance | Intake | Excretion† | Balance | Nitrogen | Calcium | Phosphorus |
| | mg./24 hrs. | Gm./24 hrs. | Gm./24 hrs. | | Gm. | | | | | | | | | | | | |
| | | | | Jan. | | | | | | | | | | | | | |
| I | 2 | 3.5 | 0.8 | 18 | 4088 | 31.0 | 27.7 | 3.3 | 76.7 | 71.1 | 5.6 | 84.5 | 82.5 | 2.0 | .48 | .09 | .11 |
| | | | | 19 | 4037 | 34.0 | 25.7 | 8.3 | 82.5 | 68.1 | 14.4 | 83.3 | 72.7 | 10.6 | .96 | .16 | .14 |
| | | | | 20 | 4153 | 38.6 | 29.3 | 9.3 | 90.0 | 78.0 | 12.0 | 94.5 | 83.6 | 10.9 | 1.22 | .24 | .24 |
| | | | | 23 | 4422 | 33.9 | 32.2 | 1.7 | 81.2 | 80.6 | 0.6 | 87.5 | 88.4 | − 0.9 | .50 | .10 | .13 |
| II | 0 | 3.5 | 0.8 | 24 | 4454 | 33.8 | 30.6 | 3.2 | 84.7 | 89.3 | − 4.6 | 88.8 | 94.1 | − 5.6 | .64 | .11 | .16 |
| | | | | 26 | 4456 | 29.6 | 30.1 | − 0.5 | 72.9 | 77.3 | − 4.4 | 83.2 | 79.5 | 3.7 | .40 | .08 | .14 |
| | | | | 28 | 4463 | 33.6 | 41.7 | − 8.1 | 81.2 | 92.2 | −11.0 | 88.5 | 86.3 | 2.2 | .54 | .14 | .17 |
| III | 0 | 1.4 | 0.4 | 29 | 4479 | 32.1 | 53.2 | −21.1 | 45.2 | 68.9 | −23.7 | 51.0 | 68.1 | −17.1 | .36 | .14 | .14 |
| | | | | 30 | 4368 | 32.3 | 41.2 | − 8.9 | 41.8 | 55.7 | −13.9 | 51.6 | 55.7 | − 4.1 | .28 | .13 | .11 |
| | | | | 31 | 4365 | 32.2 | 46.2 | −14.0 | 41.7 | 53.3 | −11.6 | 51.5 | 48.3 | 3.2 | .29 | .13 | .11 |
| | | | | Feb. | | | | | | | | | | | | | |
| IV | 5 / 2 | 1.4 | 0.4 | 1 | 4380 | 30.8 | 40.6 | − 9.8 | 42.8 | 30.4 | 12.4 | 50.3 | 39.7 | 10.6 | .09 | .14 | .03 |
| | | | | 2 | 4378 | 29.8 | 35.2 | − 5.4 | 45.1 | 57.4 | −12.3 | 50.1 | 51.2 | − 1.1 | −.11 | .21 | −.02 |
| | | | | 3 | 4400 | 31.1 | 33.7 | − 2.6 | 40.7 | 45.2 | − 4.5 | 47.8 | 51.1 | − 3.3 | .02 | .20 | .03 |
| | | | | 4 | 4318 | 31.6 | 29.9 | 1.7 | 41.4 | 38.4 | 3.0 | 48.6 | 43.8 | 4.8 | .27 | .21 | .05 |
| V | 2 | 3.5 | 0.8 | 5 | 4338 | 30.4 | 28.8 | 1.6 | 77.9 | 68.1 | 9.8 | 81.4 | 67.8 | 13.6 | −.21 | .09 | .00 |
| | | | | 8 | 4510 | 33.8 | 28.7 | 5.1 | 83.3 | 77.1 | 6.2 | 86.0 | 76.0 | 10.0 | .88 | .16 | .19 |
| | | | | 9 | 4597 | 33.6 | 29.1 | 4.5 | 82.7 | 67.3 | 15.4 | 85.4 | 69.5 | 15.9 | .92 | .15 | .17 |
| | | | | 10 | 4696 | 33.8 | 28.8 | 5.0 | 83.2 | 72.1 | 11.1 | 85.9 | 75.9 | 10.0 | .91 | .16 | .17 |
| VI | 1.5 Gm. KCl p.o. | | | 12 | 4793 | 47.8 | 41.8 | 6.0 | 82.9 | 77.2 | 5.7 | 99.6 | 96.7 | 2.9 | .76 | .22 | .14 |
| | | | | 13 | 4793 | 37.1 | 33.9 | 3.2 | 84.2 | 65.9 | 18.3 | 90.4 | 75.4 | 15.0 | .95 | .24 | .19 |

* Weights on days not listed but required for calculation of intracellular balances are: Jan. 21, 4192; 22, 4375; 25, 4431; 27, 4446; Feb. 6, 4380; 11, 4797; 14, 4870 Gm.

† Values given include stool excretion which was proportionately small and constant. The ranges of values for stool content were: potassium 1.0–3.0; sodium 0.7–2.1; chloride 0.4–2.3 mM./24 hrs.

sium,[4] sodium,[4] calcium (21), chloride (22) and phosphorus (24) were determined on aliquots of the ash. Nitrogen (30) in the dried stool was determined directly.

## RESULTS

Changes in therapy and 24-hour balances [5] for six metabolic periods are given in Table I. Since the significant effects were on potassium, sodium and chloride balances only these are given in detail. Concentrations in serum and blood are given in Table II.

As anticipated, sodium and chloride balances were positive while the infant was receiving both salt and hormone (Period I). They became slightly negative when first desoxycorticosterone acetate was withdrawn (Period II), and markedly so when, in addition, the sodium intake was reduced (Period III). Sodium was lost in excess of chloride during these periods. Restoration of desoxycorticosterone acetate (Period IV) reestablished positive sodium and chloride balances which reached a higher magnitude when the sodium intake was increased (Period V) and remained unchanged when the potassium intake was increased (Period VI). Levels of serum sodium and chloride changed in the expected direction but not to the extent anticipated.

[4] These analyses were done with the American Cyanamid Company flame photometer, model G (19). There was no interference among sodium, potassium, and phosphate at the dilutions used.

[5] During six consecutive days (January 28th to February 3rd) when marked changes in excretion were anticipated the 12-hour day and night urines were analyzed separately. Except for calcium concentrations which were regularly higher during the day there were no significant differences between the two periods.

TABLE II

*Blood and serum analyses*

| Period | Date 1949 | Potassium | Serum | | | | | | | Blood | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sodium | Chloride | Bicarbonate | Calcium | Phosphorus | Urea nitrogen | Protein | Glucose | Hematocrit | Hemoglobin |
| | | *mM./L* | *mM./L* | *mM./L* | *mM./L* | *mg./100 ml.* | *mg./100 ml.* | *mg./100 ml.* | *Gm./100 ml.* | *mg./100 ml.* | *%* | *Gm./100 ml.* |
| I | Jan. 18 | 5.4 | | 107 | 27.1 | 10.6 | 6.4 | 17.1 | 5.4 | 87 | 32 | 13.1 |
| | 19 | (5.5)* | | (107) | | | | | | | | |
| | 20 | 5.6 | | (108) | | | | | | | | |
| | 21 | 5.2 | | 108 | 25.2 | 10.6 | 6.3 | | 5.5 | 70 | 28 whole blood transfusion | |
| | 22 | 5.4 | | 110 | | | | | | | | |
| | 23 | 5.5 | | 112 | | | | | | | | |
| II | 24 | 5.1 | | 110 | 26.8 | 9.7 | 6.2 | 17.5 | 5.7 | 76 | 38 | |
| | 25 | 5.3 | | 108 | 24.2 | | | | | | | 16.6 |
| | 26 | 5.6 | 137.5 | 114 | | | | | | | | |
| | 27 | (5.8) | | (112) | | | | | | | | |
| | 28 | 5.9 | | 111 | | | | | | | | |
| III | 29 | 6.3 | | 111 | 22.2 | 10.7 | 7.1 | 21.7 | 5.9 | 88 | 37 | |
| | 30 | 6.8 | | 106 | | | | | | | | |
| | 31 | 7.5 | 134.6 | 107 | 22.7 | 10.1 | 7.0 | 23.9 | 6.3 | 91 | 38 | 14.6 |
| IV | Feb. 1 | 8.1 | | (106) | | | | | | | | |
| | 2 | 7.9 | 126.9 | 105 | | | | | | | | |
| | 3 | (7.3) | | (104) | | | | | | | | |
| | 4 | 6.6 | 129.5 | 103 | 21.7 | | | | | | | |
| V | 5 | 6.1 | | 104 | | | 5.9 | | | | | |
| | 6 | (5.9) | | (105) | | | | | | | | |
| | 7 | (5.7) | | | | | | | | | | 13.0 |
| | 8 | 5.6 | 126.5 | 106 | 25.0 | | | 14.4 | | 92 | 27 | |
| | 9 | (5.6) | | (108) | | | | | | | | 13.2 |
| | 10 | (5.5) | | (109) | | | | | | | | |
| VI | 11 | 5.5 | | 111 | 25.0 | 9.4 | 6.1 | 16.2 | 5.5 | 113 | 25 | 13.6 |
| | 12 | 6.2 | | (111) | | | | | | | | |
| | 13 | 7.1 | | (112) | | | | | | | | |
| | 14 | 5.4 | 132.5 | 113 | 24.9 | | 6.1 | 16.8 | 5.6 | 92 | 24 | |

* Parenthesis indicates interpolated values used in calculation of intracellular balances.

Serum concentrations and external balances of potassium are shown in Figure 1. In contrast to sodium and chloride, the changes in serum potassium are quite marked. On withdrawal of desoxycorticosterone (Period II) there seemed to be a beginning rise. Extension of this period might have shown how much of the subsequent rapid rise in serum potassium would have occurred without reducing sodium intake. That the hormone rather than the sodium intake was chiefly responsible is suggested by the fall in serum potassium which occurred in Period IV with replacement of desoxycorticosterone acetate and no change in sodium intake. These shifts in serum potassium followed the expected pattern. However, changes in potassium excretion and the resulting potassium balances during these periods were contrary to expectation. As serum potassium rose following withdrawal of hormone and reduction of sodium intake (Periods II and III), the urinary excretion of potassium increased strikingly, producing a marked negative balance. As serum potassium fell with replacement of desoxycorticosterone and constant sodium intake, potassium excretion decreased progressively until a positive balance was reached on the fourth day of Period IV. This positive balance was maintained throughout the seven-day period when, in addition to desoxycorticosterone acetate, an increased amount of sodium was given (Period V). Subsequent augmentation of potassium intake (Period VI) raised serum potassium but caused no increase in potassium retention.

Changes in intracellular potassium during these

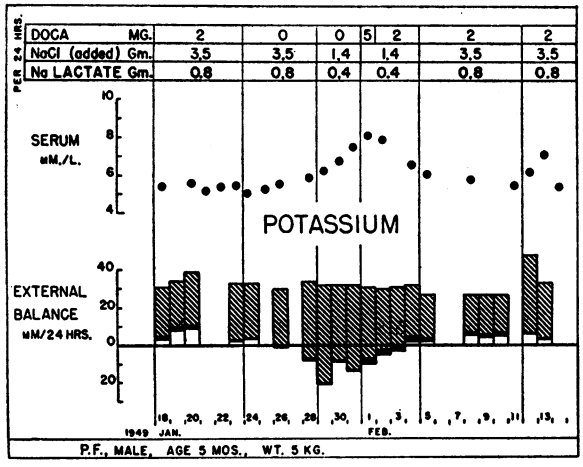


FIG. 1. CONCENTRATIONS IN SERUM AND EXTERNAL BALANCES OF POTASSIUM

Intake is shown in mM. as height of the column above the base line. Urinary output (cross-hatched area) is plotted down from the top of the column and stool output (solid) added. A clear area above the base line designates positive balances; extension of the column below the base line represents negative balances.

periods were calculated according to Darrow (31). A potassium (mM.) to nitrogen (Gm.) ratio of 3 : 1 was used to correct for loss or gain of cell protein. The data required for these calculations are incorporated in Tables I and II. Graphic analyses are shown in Figure 2. As must follow from the external balances a large loss of intracellular potassium is seen to occur as the serum potassium increased during the periods of hormone and salt withdrawal. Replacement of desoxycorticosterone led to a progressive decrease in this loss and finally to a positive intracellular balance as serum potassium fell. Again, it is apparent that increasing potassium intake (Period VI) resulted in no greater transfer of potassium to the cells.

Renal mechanisms during the six metabolic periods are given in Table III. Simultaneous inulin and endogenous creatinine clearances determined previously in this infant had shown a ratio of one, so that 24-hour endogenous creatinine clearances were taken as a measure of glomerular

TABLE III

*Rates of filtration, reabsorption, and excretion of potassium*

| Period | Date 1949 | Creatinine | | Urine volume | Filtration rate | Potassium | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Serum* | Urine | | | Serum* | Filtered | Excreted | Reabsorbed | Reabsorbed / Filtered × 100 |
| | | *mg./100 ml.* | *mg./100 ml.* | *ml./min.* | *L/24 hrs.* | *mM./L* | *mM./24 hrs.* | *mM./24 hrs.* | *mM./24 hrs.* | |
| I | Jan. 18 | .283 | .125 | .363 | 23.08 | 5.5 | 126.9 | 26.1 | 100.8 | 79 |
| | 19 | .285 | .126 | .347 | 22.09 | 5.6 | 123.7 | 24.1 | 99.6 | 81 |
| | 20 | .265 | .127 | .358 | 24.70 | 5.4 | 133.4 | 27.7 | 105.7 | 79 |
| | 23 | .215 | .120 | .381 | 30.61 | 5.3 | 162.2 | 31.0 | 131.2 | 81 |
| II | 24 | .225 | .110 | .416 | 29.28 | 5.2 | 152.3 | 29.4 | 122.9 | 81 |
| | 26 | .235 | .126 | .365 | 28.18 | 5.7 | 160.6 | 28.9 | 131.7 | 82 |
| | 28 | .265 | .136 | .352 | 26.01 | 6.1 | 158.7 | 40.5 | 118.2 | 74 |
| III | 29 | .262 | .123 | .383 | 25.89 | 6.6 | 170.9 | 52.2 | 118.7 | 69 |
| | 30 | .275 | .142 | .353 | 26.24 | 7.2 | 188.9 | 40.2 | 148.7 | 79 |
| | 31 | .290 | .142 | .350 | 24.67 | 7.8 | 192.4 | 45.2 | 147.2 | 77 |
| IV | Feb. 1 | .269 | .145 | .347 | 26.93 | 8.0 | 215.4 | 37.6 | 177.8 | 83 |
| | 2 | .262 | .136 | .366 | 27.35 | 7.6 | 207.9 | 32.2 | 175.7 | 85 |
| | 3 | .267 | .145 | .341 | 26.65 | 7.0 | 186.6 | 30.7 | 155.9 | 84 |
| | 4 | .242 | .134 | .352 | 28.07 | 6.4 | 179.6 | 26.9 | 152.7 | 85 |
| V | 5 | .228 | .138 | .352 | 30.67 | 6.0 | 184.0 | 26.9 | 157.1 | 85 |
| | 8 | .250 | .137 | .367 | 28.96 | 5.6 | 162.2 | 26.8 | 135.4 | 83 |
| | 9 | .250 | .149 | .350 | 30.04 | 5.6 | 168.2 | 27.2 | 141.0 | 84 |
| | 10 | .250 | .151 | .349 | 30.34 | 5.5 | 166.9 | 26.9 | 140.0 | 84 |
| VI | 12 | .261 | .113 | .446 | 27.79 | 6.7 | 186.2 | 40.6 | 145.6 | 78 |
| | 13 | .270 | .128 | .366 | 24.98 | 6.3 | 157.4 | 32.7 | 124.7 | 79 |

* Values interpolated to mid-point of period.

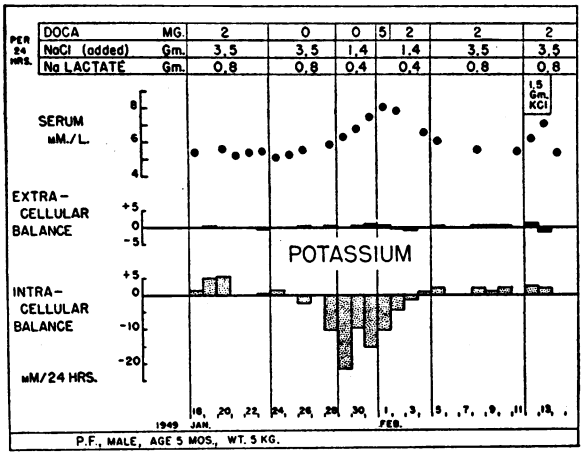


FIG. 2. CONCENTRATIONS IN SERUM AND EXTRA- AND INTRACELLULAR BALANCES OF POTASSIUM

filtration rate.[6] There was no significant change in glomerular filtration rate which was within the normal range for an infant of this age. The quantity of potassium filtered, therefore, varied directly with changes in serum potassium. Subtracting the quantity of potassium excreted from that filtered gives an overall estimate of the quantity reabsorbed; this reabsorbate tended to increase as serum potassium and the amount filtered increased. At this time, the proportion of filtered potassium reabsorbed was somewhat decreased.

## DISCUSSION

It is clear from the data presented that, under the conditions of these observations in a male infant with adrenocortical insufficiency and virilism, *withdrawing desoxycorticosterone acetate and reducing sodium intake* produced a shift of *potassium from cells to extracellular fluid and serum. Potassium excretion increased* in response to this shift but not enough to prevent a *rise in serum potassium. Readministration of desoxycorticosterone acetate* resulted in a progressive daily decrease in the rate of transfer of potassium from cells to extracellular fluids until *potassium actually entered rather than left the cells* on the fourth day of treatment. The rate of *potassium excretion decreased* during this period but since the rate of excretion decreased less than the rate of transfer of potassium from cells to extracellular fluid and serum, *serum potassium fell.* Changes in volume of extracellular fluid and/or blood could produce changes in serum potassium independent of its movement between intra- and extracellular fluids. However, in the calculation of intracellular potassium balances, corrections are made for changes in the volume of extracellular fluid as estimated from concentrations and balances of chloride. The constancy of the hematocrit and hemoglobin values and the fact that serum sodium and chloride changed in the opposite direction during periods of maximum change in serum potassium offer strong evidence against the occurrence of marked changes in blood volume.

The data do not indicate a primary effect of electrolyte and water hormones on renal control of potassium excretion under the conditions of the observations in this infant. In addition, no changes were observed in the rate of glomerular filtration. A decreased filtration rate during adrenal insufficiency has been found consistently by others (32–35). It is possible that a similar decrease might have been observed if the period of insufficiency had been extended beyond that considered justifiable. A slight elevation of blood urea nitrogen is noted in Table II during the period when desoxycorticosterone acetate was withdrawn and sodium intake reduced (Period III). This may indicate a slight reduction in glomerular filtration rate which is not within the limits of measurement. The only suggestive effect on renal mechanisms points toward a relative decrease in tubular reabsorption of filtered potassium as serum potassium increased with withdrawal of desoxycorticosterone acetate and reduction of sodium intake. This is contrary to Harrison and Darrow's interpretation of their findings in adrenalectomized dogs (32) but, as has been pointed out (36), if our method for calculating the ratio of reabsorbed to filtered potassium is used, the results are not so dissimilar. From the data it cannot be stated categorically that no impairment in renal excretion of potassium occurred during the periods of insufficiency when serum potassium was elevated since the maximum rate of potassium excretion for normal infants of this age is not known. However, elevation of serum potassium to a comparable level by increasing potassium intake dur-

[6] Values for additional renal functions measured on January 15, 1949, were as follows: *inulin clearance,* 16.5 ml. per minute; *para-aminohippurate clearance,* 47.0 ml. per minute; *para-aminohippurate tubular maxima,* 4.4 mg. per minute; *urea clearance,* 7.8 ml. per minute. Calculated surface area: 0.25 $M^2$.

ing a period of desoxycorticosterone therapy (Period VI) did not raise the rate of excretion beyond that found during insufficiency. It can be stated, therefore, that if there was impairment of renal excretion of potassium it was not corrected by desoxycorticosterone acetate.

The results in this infant are contrary to the generally accepted concept of the action of electrolyte and water hormones of the adrenal on potassium metabolism. Treatment of our patient with desoxycorticosterone acetate and added sodium led to retention rather than loss of total body potassium. Furthermore, increased potassium intake raised serum potassium and potassium excretion but did not increase potassium retention. These findings are difficult to reconcile with the consistent finding of low muscle potassium in treated experimental animals. The levels of sodium and potassium intake or the dosage and duration of treatment with desoxycorticosterone acetate may account for the difference. A more likely explanation, however, is the postulated interrelationship between the different adrenal hormones. For example, it has been shown that an excess production of androgens and perhaps other steroids can affect the action of electrolyte and water hormones on potassium metabolism. In a similar infant, Darrow found desoxycorticosterone acetate to be relatively ineffective in restoring normal concentrations of sodium and potassium and suggested that this failure might be due to overproduction of androgens (10). Even more striking are the observations of Talbot *et al.* in a girl with Addison's disease who had been treated with both testosterone and desoxycorticosterone acetate (37). After testosterone had been discontinued, withdrawal of desoxycorticosterone acetate resulted in an elevation of serum potassium and an *increase* in potassium excretion. This similarity in response again suggests the possibility that excess androgen production in our infant might have influenced the action of desoxycorticosterone acetate on potassium metabolism.

Further evidence that one adrenocortical steroid may influence the action of another is provided by recent reports. Forsham *et al.* (38) demonstrated that patients with Addison's disease who show marked sodium retention during treatment with desoxycorticosterone acetate exhibit a paradoxical increase in sodium excretion when supplemental Compound E is given. Lewis and Wilkins (39) observed that administration of adrenocorticotrophic hormone to two girls with congenital adrenal hyperplasia and female pseudohermaphroditism resulted in a moderate to marked increase rather than a decrease in sodium excretion. These observations suggest an explanation for the discrepancy between our finding of retention of potassium during treatment with desoxycorticosterone and added sodium, and the demonstration of low muscle potassium in similarly treated experimental animals. Although our findings *may* be peculiar to this particular type of adrenocortical disease, critical examination of reported studies in adult patients with uncomplicated Addison's disease (5, 6) and in experimental animals (4) indicates that the effect of adrenocortical insufficiency and desoxycorticosterone acetate administration on potassium metabolism may vary even when insufficiency of the water and electrolyte hormones is not accompanied by manifestations of abnormal production of other hormones.

## SUMMARY AND CONCLUSIONS

1. In a three month old male infant with adrenocortical insufficiency and virilism, observations were made on the effect of administration and withdrawal of desoxycorticosterone acetate and changes in sodium and potassium intake on electrolyte balances, serum electrolyte concentrations, and glomerular filtration rate. The most striking effects were noted on potassium metabolism. Withdrawal of the hormone and reduction of sodium intake produced a rapid elevation of serum potassium which was associated with *increased excretion of potassium* and with *markedly negative external and intracellular potassium balances.* Treatment with desoxycorticosterone acetate reversed these changes. Increased potassium intake raised serum potassium but neither increased potassium balances nor decreased sodium balances.

2. Changes in treatment produced no significant changes in glomerular filtration rate. There were also no striking effects on tubular reabsorption of potassium although there may have been reabsorption of a smaller proportion of filtered potassium following withdrawal of desoxycorticosterone acetate and reduction of sodium intake.

3. It is concluded that under the conditions of the observations in this infant the effects of changes in treatment on potassium metabolism were mediated through shifts of potassium between intra- and extracellular fluids rather than by renal control of excretion. Furthermore, since treatment with desoxycorticosterone and added sodium caused retention rather than loss of potassium, additional dietary potassium was not required. Possible explanations for the discrepancy between these findings and others are discussed.

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