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Short stature, hyperkalemia and acidosis: A defect in renal transport of potassium

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Short stature, hyperkalemia, and acidosis: A defect in renal transport of potassium. An eleven-year-old boy presented with short stature, hyperkalemia, and metabolic acidosis. No endocrine cause for a short stature could be demonstrated. Renal function, as assessed by inulin and PAH clearances, concentrating and diluting capacity, and ability to acidify the urine and to excrete net acid, was normal. No defect was detected in adrenal secretion of, or renal responsiveness to, aldosterone. A low renal threshold for bicarbonate was documented which apparently explained the acidosis. However, correction of the acidosis by administration of sodium bicarbonate did not influence the hyperkalemia, making it unlikely that an abnormality in bicarbonate reabsorption was the primary defect. Chlorothiazide induced a fall in serum potassium and a rise in serum bicarbonate to normal levels. During bicarbonate loading the rates of excretion of potassium in urine were consistently below those observed in control subjects. It appeared, therefore, that the patient had a primary abnormality in potassium excretion. The resulting hyperkalemia caused urinary loss of bicarbonate and systemic acidosis. Correction of both the acidosis and hyperkalemia by chronic administration of chlorothiazide and sodium bicarbonate has resulted in resumption of normal growth.

Retard de croissance, hyperkaliéme et acidose: Un déficit du transport rénal du potassium. Un enfant de 11 ans avait un retard de croissance, une hyperkaliémie et une acidose métabolique. Aucune cause endocrine du retard de croissance n'a été trouvée. La fonction rénale, estimée par les clearances de l'inuline et du PAH, la capacité de concentration et de dilution et la capacité d'acidifier l'urine, était normales. Aucun déficit de la secrétion d'aldostérone ou de la réponse rénale à l'aldostérone n'a été mis en évidence. Un seuil rénal bas des bicarbonates a été découvert, qui explique apparemment l'acidose. Cependant la correction de l'acidose par l'administration de bicarbonate de sodium n'a pas influencé l'hyperkaliémie, ce qui rend peu probable que le déficit de la réabsorption de bicarbonate soit la cause de l'ensemble. Le Chlorothiazide a déterminé une baisse de la kaliéme et une augmentation du bicarbonate plasmatique jusqu'à des valeurs normales. Pendant une charge en bicarbonate les débits d'excretion du potassium dans les urines ont été nettement inférieurs à ceux obtenus chez des sujets témoins. Il apparaît donc que le malade a une anomalie primitive de l'excrétion de potassium. L'hyperkaliémie qui en est la conséquence a déterminé une perte de bicarbonate dans les urines et une acidose systémique. La correction de l'acidose et de l'hyperkaliémie par l'administration permanente de Chlorothiazide et de bicarbonate de sodium a eu pour résultat une reprise de la croissance normale.

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A relationship between renal tubular transport of potassium and bicarbonate has been documented in both animal and human experiments. Acute and chronic administration of potassium chloride has been shown to cause alkalinization of the urine, with urinary loss of bicarbonate, and a consequent fall in the concentration of bicarbonate in plasma. Despite this metabolic acidosis, the urine remains alkaline. These findings are considered to account in part for the acidosis of chronic renal insufficiency. There is only one previous report [1], however, of a patient in whom hyperkalemia, causative of acidosis, was not the result of decreased glomerular filtration rate, but rather of a primary renal defect in the transport of potassium. The present report describes an 11-year-old boy who presented with short stature and was found to have hyperkalemia and proximal renal tubular acidosis. A defect in renal transport of potassium at the level of the distal tubule was demonstrated and was considered to be causative of the acidosis. Therapy with chlorothiazide and sodium bicarbonate corrected the hyperkalemia and acidosis and resulted in "catch-up" growth.

Clinical description

M. C., an 11-year-old white boy, was admitted to the Hospital of the Albert Einstein College of Medicine on

November 11, 1968, for evaluation of short stature. The patient was the product of a 31 week uncomplicated gestation. At birth his length was 47 cm and his weight 2.5 kg. His failure to grow was first noticed by his parents at the age of 5 years. The past history included herniorrhaphies in 1958, scarlet fever in 1965, and two fractures of the clavicle. A heart murmer was noted at 22 months of age. There was no history of episodes of muscular weakness.

The father is 178 cm tall and the mother 161 cm. There are four siblings in good health and of normal height. All have normal levels of potassium and bicarbonate in serum.

The patient was first investigated[1] for his failure to thrive at the age of ten. X-rays of the skull and an intravenous urogram were normal. Serum potassium was found to be 7.3 mEq/liter. The child was able to acidify (pH 5) and to concentrate (sp. gr. 1.025) the urine. The electrocardiogram revealed peaked T-waves, mainly in leads I and II. Urinary excretion of 17-ketosteroids was 2.2 mg/24 hr. Serum growth hormone was 2 µg/ml after an overnight fast.

Physical examination performed on admission to this hospital revealed an alert boy. Height (122.8 cm) and weight (23.7 kg) were both below the third percentile for age, and would be average at age $7^1/_2$ years. The only other abnormal finding was a grade 3/6 systolic murmur heard maximally at the upper left sternal border, which was interpreted as functional. Blood pressure was 110/70 mm Hg.

X-rays of the chest, skull and abdomen were normal and epiphyseal maturation was that of a 7-year-old boy.

Initial laboratory data included blood hematocrit 36%, hemoglobin 12 g/100 ml, WBC 8,800 per c. mm with a normal differential count, reticulocyte count 2.8%, erythocyte sedimentation rate 18 mm at one hr.

Serum chemistries were Na 142, K 7.7 and Cl 114 mEq/liter, tCO_2 16 mmoles/liter; Ca 9.5, P 5.2, BUN 12, creatinine 0.6, glucose 86 mg/100 ml; total protein 7, albumin 4 g/100 ml; serum cholesterol 190, total bilirubin 0.4 mg/100 ml; SGOT 68 and SGPT 16 SFU, alkaline phosphatase 16 KAU, LDH 220 U and CPK 6 BMU. Subsequent SGOT determinations were normal.

Urinalysis revealed a pH of 5, a specific gravity of 1.025, and no protein, glucose, or ketone bodies. The sediment was normal. Absence of generalized renal disease was further documented by normal inulin and PAH clearances, urinary concentration and dilution, and urinary acidification and excretion of titratable acid and ammonium. A titration study revealed a renal threshold for bicarbonate of 18 mmoles/liter, which was consistent with spontaneous serum levels usually encountered in the patient. The amount of bicarbonate infused was calculated to raise the plasma level at a rate of 2 mmoles/liter/hr. A solution of 0.5 M $NaHCO_3$ was infused at a rate of 1 ml/min, and the total amount received by the patient at the time threshold was reached was 160 ml, or less than 1 per cent of body weight. This minimizes the possibility that the threshold for bicarbonate was artificially depressed by extracellular volume expansion.

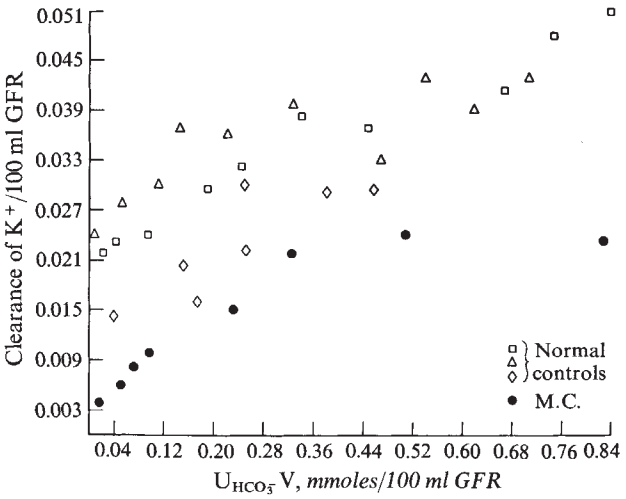

Fig. 1. *Relationship between urinary excretion of bicarbonate and the clearance of potassium during intravenous infusion of sodium bicarbonate.*

The excretion of potassium during the bicarbonate infusion test increased from 0.028 mEq/100 ml glomerular filtrate, at a bicarbonate excretion rate of 0.02 mmoles/100 ml glomerular filtrate, to 0.1 mEq, at a bicarbonate excretion rate of 0.24. In normal adult subjects studied under similar conditions of volume expansion, the excretion of potassium at comparable rates of bicarbonate excretion was consistently greater, especially at low rates of bicarbonate excretion when the difference was at least threefold. The relationship between the clearance of potassium and the excretion of bicarbonate is shown in Fig. 1.

Indices of thyroid function were normal: serum thyroxine by column chromatography 3.9 µg/100 ml, T_3 uptake 23 percent, and 24-hour radio-iodine uptake 32 percent. Twenty-four hour excretion of 17-ketogenic steroids was 5 mg under control conditions, increased to 17.7 mg following administration of metyrapone (0.5 g every 6 hr for 2 days) and to 12 mg following administration of a single intramuscular dose of 40 U of ACTH gel. Fasting plasma cortisol level was 8 µg/100 ml. This value rose to 25 µg within 4 hr after intravenous administration of 5 U of ACTH. Twenty-four hour excretion of aldosterone was 22 µg on a regular diet, 50 µg following five days of chlorothiazide (0.5 g twice daily) while on a diet providing 10 mEq of sodium and 40 mEq of potassium daily, and 8 µg following four days on an intake of 50 mEq of sodium and 40 mEq of potassium per 24 hr. Fasting serum growth hormone was less than 2 µg per ml. Following a 30 minute intravenous infusion of arginine HCl (0.5 g/kg body wt), serum levels of growth hormone reached 7 µg at 30 min,

[1] By Theodore Kushnick, M. D., Professor of Pediatrics, New Jersey College of Medicine and Dentistry, who subsequently referred him to Dr. Henneman.

decreased to 4 μg at 60 min, and returned to less than 2 μg by 90 min. These levels were considered to reflect an intact but slightly blunted capacity to secrete growth hormone following arginine infusion.

An ECG revealed high peaked T-waves in all precordial leads. Repeated determinations confirmed the elevation in serum potassium, which varied spontaneously between 7.3 and 7.7 mEq/liter, and the low tCO_2 which ranged from 14 to 16 mmoles/liter. Simultaneous determinations of blood pH ranged from 7.28 to 7.33, demonstrating a partially compensated metabolic acidosis. On 11/19/68 the patient was started on fludrocortisone acetate, 0.5 mg/day for four days and 1.0 mg/day for another four days. A slight reduction in serum potassium to 6.1 mEq/liter and an increase in tCO_2 to 20 mmoles/liter were noted during the first half of this period. During the last few days, however, the concentration of potassium rose again to 6.9. Administration of $NaHCO_3$, 100 mmoles/day for 24 days, corrected the acidosis (tCO_2 rose to 24 mmoles/liter) but failed to influence serum potassium (average value 7 mEq/liter).

Balance studies

In February 1969, the patient was admitted to the General Clinical Research Center; he was placed on a constant diet and all stools and urines were collected quantitatively. Serum and urine electrolytes were determined on a Technicon AutoAnalyzer, employing standard techniques. The electrolytes in the stool were determined following ashing and resuspension in a known volume of fluid.

The details of the initial study are depicted in Fig. 2. At the onset, the patient manifested his usual hyperkalemia (6.7 mEq/liter) and acidemia (bicarbonate 21.4 mEq/liter). Metyrapone produced a sodium diuresis and slight retention of potassium. Serum K did not change significantly. Following metyrapone, sodium excretion decreased to almost zero while potassium excretion increased slightly. Chlorothiazide, 1 g/day, produced marked diuresis of both sodium and potassium and a loss in weight of 850 g (4 percent of body wt). Serum potassium decreased from 6.1 to 3.4 mEq/liter and serum sodium from 134 to 130 mEq/liter. This coincided with a cumulative negative balance for sodium of about 200 mEq and for potassium of about 125 mEq. The serum concentration of bicarbonate rose from 21.4 to 34.4 mEq/liter. Concomitantly net acid excretion increased by approximately 50 mEq/24 hr. Administration of $NaHCO_3$ further lowered serum potassium and raised serum bicarbonate. This period was followed by administration of supplemental potassium chloride, which was retained almost quantitatively. The final 14 days of ob-

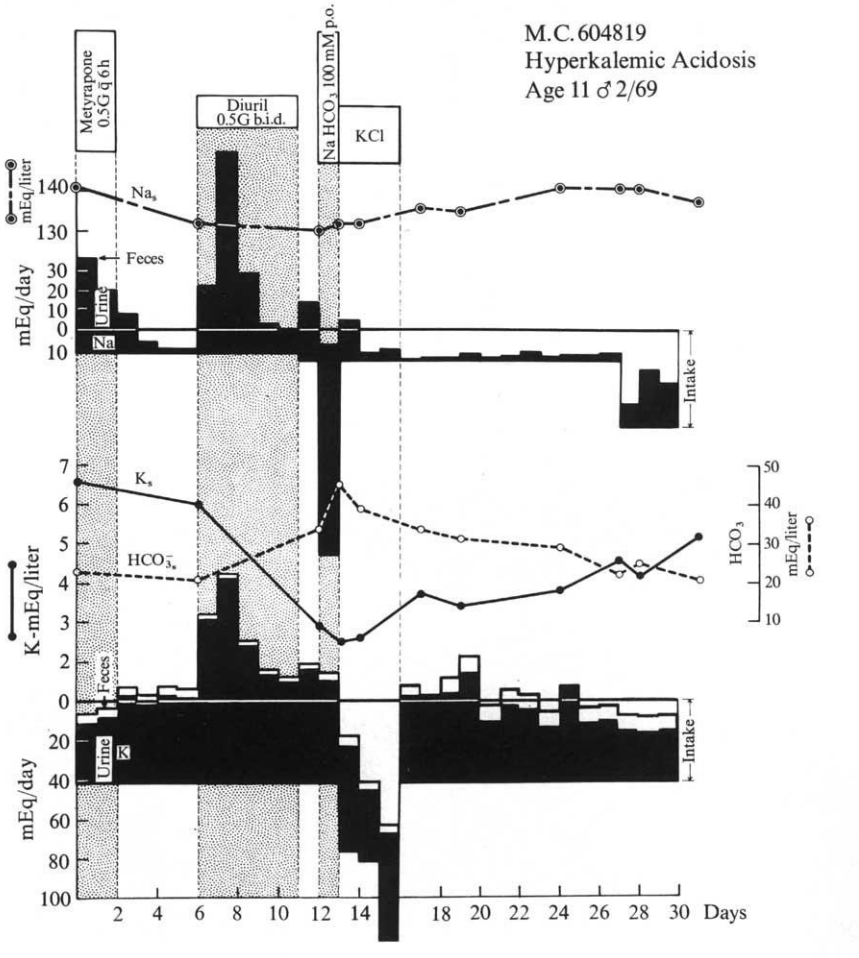

Fig. 2. *First metabolic study.* Intake is plotted down from the zero line, output is plotted up from this level. Changes in serum values are shown by the solid and interrupted lines.

servation, on no medication, were characterized by sodium retention and by decrease in serum bicarbonate levels towards initial values. A concomitant rise in serum potassium reflected both a slightly positive balance of this ion, as well as its movement from the intracellular space, due to recurrence of acidemia.

In May 1969, the patient underwent a second balance study (Fig. 3). The purpose of this was to test the response to a lower dose of chlorothiazide and to examine the effects of aldosterone and spironolactone. The diet contained 50 mEq of sodium and 45 mEq of potassium daily. Serum and urinary electrolytes were determined as in the previous balance study; stool analyses were not performed. d-Aldosterone[2], 0.5 and then 4 mg intramuscularly per day, failed to elicit any change in serum or urinary potassium and bicarbonate. Chlorothiazide, in a daily dose of 250 mg, showed a qualitatively similar but quantitatively lesser effect than observed in the first study. Body weight decreased by 500 g (2.3 percent) concomitant with a diuresis of sodium and potassium. Serum sodium did not change; potassium decreased from 6.3 to 3.2 mEq/liter. Serum bicarbonate increased from 19.3 to 29.8 mEq/liter. Net acid excretion increased by 15 mEq/day, accounting only in part for the observed change in the buffering capacity of the extracellular fluid. Total body potassium, determined by external counting, was found to be 44 mEq/kg body wt following five days of chlorothiazide administration and 50 mEq/kg body wt under basal conditions. These values are within normal limits [2]. The potassium content of the red cells varied in parallel with total body potassium, being 77 mEq/liter of packed cells after treatment with chlorothiazide and 84 mEq/liter thereafter.

During the administration of spironolactone, a markedly positive balance of potassium was observed, serum potassium rose, sodium balance became negative, and both sodium and bicarbonate in serum fell. Since a similar phenomenon was observed during the administration of metyrapone, this was interpreted as being related to aldosterone inhibition. Although urinary excretion of potassium reached its nadir during spironolactone administration, potassium retention preceded this by two days when large supplemental doses of potassium were given.

Following this hospitalization, the patient was maintained on chlorothiazide, 10 mg/kg body wt per day, and sodium bicarbonate 1.8 mmoles/kg body wt per day. With this treatment the levels of potassium in serum varied between 3.8 and 4.9 mEq/liter, and of bicarbonate between 25 and 36 mmoles/liter. He grew 15.6 cm in 2 years and height-age increased three years.

[2] Obtained through the courtesy of J. Pfitzner, M. D., Ciba Pharmaceutical Company, Summit, New Jersey.

Discussion

M. C.'s presenting complaint was failure to grow, and this growth retardation was attended by a similar degree of retardation of epiphyseal maturation. The only abnormali-

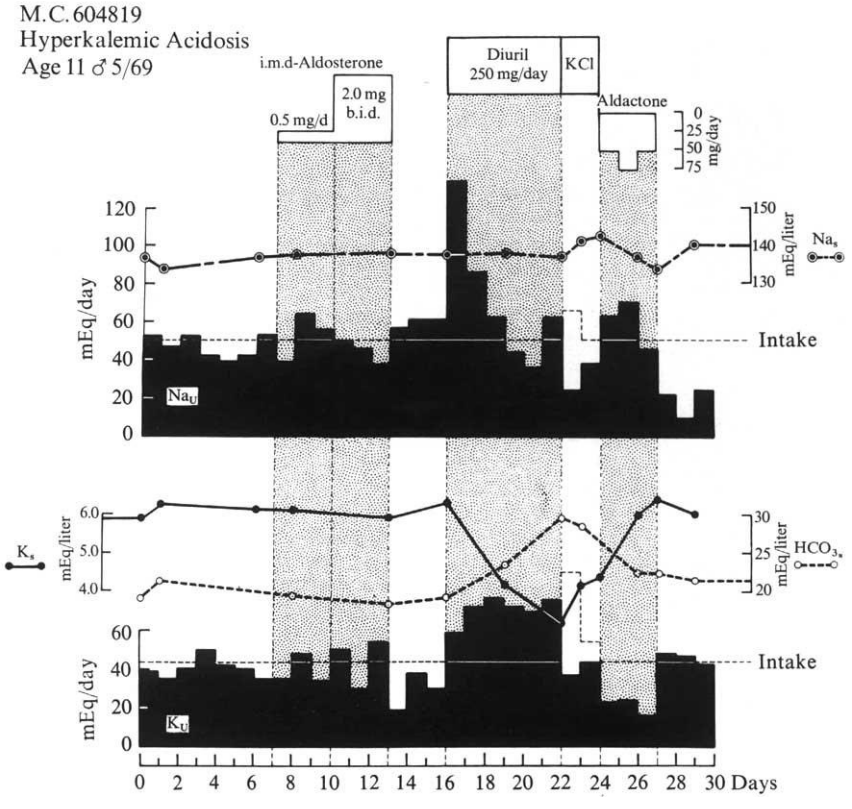

Fig. 3. *Second metabolic balance study.* Intake and urinary excretion of sodium are plotted in the upper panel, corresponding data for potassium in the lower. Serum values are shown by the solid and interrupted lines.

ties found to account for his growth failure were hyperkalemia and systemic acidosis. Growth failure is known to occur in renal insufficiency with acidosis (with or without hyperkalemia) and in renal tubular acidosis (with normo- or hypokalemia) [3]. In M. C., correction of the acidosis and hyperkalemia resulted in "catch-up" growth which supports the argument that growth failure was due to these abnormalities.

The origins and interrelations of the acidosis and the hyperkalemia are more difficult to define. Hyperkalemia was a consequence neither of renal glomerular insufficiency nor of dietary excess. It was not due to lack of cortisol or of aldosterone production [4] or to renal unresponsiveness to aldosterone.

It must be considered whether the defect in potassium could be related to an abnormality in the renal handling of sodium, since extensive clinical and experimental evidence indicates that low rates of excretion of sodium are accompanied by similarly low rates of potassium excretion [5–7]. The possible mechanisms accounting for this relationship have been thoroughly investigated during the last few years [8–12]. As shown at the end of the first balance study, M. C. was able to reduce his urinary sodium concentration nearly to zero in response to salt restriction and pretreatment with chlorothiazide. He was also able to increase urinary sodium appropriately in response to administration of sodium bicarbonate. Concentrating and diluting capacity were normal. There were no clinical features to suggest either an increase or a decrease in total body sodium, and his vital signs were normal throughout. Thus no disturbance in renal tubular transport of sodium was demonstrated.

Having dismissed as unlikely an abnormality in the adrenal or in the renal response to aldosterone and a defect in sodium reabsorption, we must next consider a primary defect in the tubular transport of potassium or bicarbonate or both. A possible relationship between the renal handling of potassium and bicarbonate was first assumed in 1932 by Loeb et al [13], and confirmed repeatedly since that time [14–17]. The nearly complete reabsorption of potassium in the proximal tubule [18, 19] is not affected by even extreme changes in systemic acid-base balance [18, 20]. Both metabolic and respiratory alkalosis enhance potassium secretion in the distal tubule [15, 21, 22] and, of more relevance to the present study, metabolic and respiratory acidosis markedly inhibit the distal secretion of potassium despite elevated concentrations of potassium in plasma [23–26]. Part of this effect can be related to changes in intratubular pH, with potassium secretion falling as tubular fluid pH falls [27]. Of greater importance, however, is intracellular pH, a fall in which markedly impairs potassium secretion [17, 18, 28]. According to recent evidence obtained by tracer flux studies, this effect is the result of a decrease in the potassium transport pool which is, in turn, the consequence of a diminished potassium uptake at the peritubular level [29].

These considerations suggest the possibility that a primary disturbance in reabsorption of bicarbonate, with consequent metabolic acidosis, could have caused a decreased capacity in this patient for secretion of potassium, with resulting hyperkalemia. That this is unlikely, however, is evidenced by our experience with patients with primary proximal renal tubular acidosis who have marked impairment in bicarbonate reabsorption, chronic metabolic acidosis, but no impairment in potassium excretion and absence of hyperkalemia [30]. Furthermore, prolonged administration of sodium bicarbonate to M. C., a procedure which enhances potassium secretion in normal subjects, corrected the acidosis but not the hyperkalemia.

If a primary abnormality in reabsorption of bicarbonate as the sole defect can be excluded, could a primary defect in potassium excretion explain the impaired capacity to reabsorb bicarbonate? As cited above, there is considerable evidence that potassium loading does result in urinary loss of bicarbonate. It has been further established that the site of action is primarily the proximal tubule. Clapp and Bernstein [31] observed a rise in proximal bicarbonate concentration during acute administration of KCl, and microperfusion of peritubular capillaries at the level of the proximal tubule with solutions containing high concentrations of K resulted in inhibition of bicarbonate reabsorption [32]. An opposite result was described by Rector, Buttram and Seldin [20] when rats were made hypokalemic. The possible role that ECF volume might have played in these changes was ruled out by Kunau et al [33]. The effects of chronic hyperkalemia on bicarbonate excretion have not been studied experimentally. The well-known process of adaptation to prolonged administration of a high potassium diet precludes development of hyperkalemia and consequent disturbance in acid-base balance [34–36]. Nevertheless, the peritubular micropuncture experiments of Brandis, Keyes and Windhager [32] provide convincing evidence of the direct effect of potassium on bicarbonate reabsorption independent of any systemic change or variation in the amount of filtered potassium.

It is conceivable, therefore, that the hyperkalemia in this patient may have resulted in impaired proximal reabsorption of bicarbonate, with its loss in the urine, and resulting acidosis. The acidosis, in turn, would then interfere further with secretion of potassium, exaggerating the magnitude of the abnormality. Suggestive evidence that a renal defect in the secretion of potassium was present in this patient was obtained from his bicarbonate titration test (Fig. 1).

Without treatment the patient was acidotic and, as a consequence, little or no bicarbonate was delivered into the distal part of the nephron, a condition strongly favoring potassium retention. At higher levels of bicarbonate excretion, although the rate of potassium excretion remained below that of the controls, the difference was minimized. This was insufficient, however, to correct hyperkalemia, at least over a course of three weeks' therapy with sodium bicarbonate.

During the balance studies, both the hyperkalemia and the acidosis were corrected by administration of the diuretic

chlorothiazide. As potassium was lost into the urine and normokalemic levels were achieved in response to chlorothiazide, bicarbonate reabsorption returned to normal, with resulting correction of the acidosis. It is unlikely that this effect was due to extracellular volume contraction, since the change in body weight at this point was negligible. With more vigorous diuretic therapy and marked sodium loss, the patient actually became alkalotic, reflecting now both hypokalemia and volume contraction. Under these circumstances his intrinsic capacity for unimpaired reabsorption of bicarbonate was clearly demonstrated.

The lack of knowledge regarding the primary factor responsible for the anomalies observed complicates the characterization of the disease. It is, for instance, impossible to establish if the patient described here has the same disease as the one previously studied by Arnold and Healy [1]. They both seem to have a defect in potassium excretion. Arnold and Healy's patient was not short but had hypertension which apparently varied directly with the degree of hyperkalemia. M. C. consistently had normal blood pressure. Other symptoms that were missing in M. C. but present in the other patient were muscular weakness and a defect in hydrogen ion excretion. However, both of them improved markedly following the administration of chlorothiazide. The fact that the younger patient showed less symptomatology might suggest a time-related course of the disease.

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