

Studies on Hyperkalemic Periodic Paralysis. Evidence of Changes in Plasma Na and Cl and Induction of Paralysis by Adrenal Glucocorticoids

DAVID H. P. STREETEN, THEODORE G. DALAKOS, and HERBERT FELLERMAN

From the Department of Medicine (Division of Endocrinology), State University of New York Upstate Medical Center, Syracuse, New York 13210

ABSTRACT In a 19 yr old male with familial hyperkalemic periodic paralysis, paralysis was consistently induced by the administration of potassium chloride, corticotropin-gel, and a variety of glucocorticoids (dexamethasone, 6-methylprednisolone, triamcinolone) but not by mineralocorticoids (D-aldosterone, deoxycorticosterone) or by adrenocorticotropin (ACTH)-gel plus metyrapone. Induced attacks were virtually identical with spontaneous attacks, being associated, after a latent period of a few hours, with a rise in plasma K^+ and HCO_3^- and a simultaneous fall in plasma Na^+ and Cl^- concentrations to an extent implying exchange of 1 K^+ with 2 Na^+ and 2 Cl^- between extracellular and intracellular fluid. ACTH-induced paralysis was preceded by rising serum inorganic P, and associated with increased plasma glucose, blood lactate, and serum creatine phosphokinase concentrations. In normal subjects ACTH, cortisol, and triamcinolone administration failed to change plasma electrolytes or strength, while ingestion of KCl produced no weakness and smaller changes in plasma K and Na than in the patient.

Since the patient and normal subjects showed the same changes in renal excretion of K after the administration of cortisol and KCl, it seems likely that paralysis in the patient resulted from abnormally slow uptake (and/or excessive loss) of K by the muscle cells, possibly caused by an abnormal "ion-exchange pump." Normal adrenocortical function and absence of a peak in plasma 11-hydroxycorticoid (11-OHCS) concentration preceding spontaneous paralysis, indicated that spontaneous paralysis did not result from changes in cortisol secretion. Similar hyperkalemic paralysis was precipitated by ACTH-gel in a brother and first cousin of the

propositus. Administration of acetazolamide and fludrocortisone reduced the rise in plasma K concentration and prevented the weakness which otherwise invariably followed KCl administration to the patient. He and two close relatives have been completely protected from severe attacks of paralysis in the past 14 months by treatment with these two medications.

INTRODUCTION

Several decades after the demonstration that attacks of periodic paralysis were associated in many patients with hypokalemia (1, 2), families with hyperkalemic periodic paralysis were first recognized by Tyler, Stephens, Gunn, and Perkoff (3) and Stevens (4) and studied intensively by Sagild, and Helweg-Larsen (5), who called this condition adynamia episodica hereditaria. In the subsequent years, the clinical and genetic features of this disorder have been carefully characterized (6-10). However, there has been little progress in understanding the pathogenesis of paralysis, perhaps because it has been possible reproducibly to induce paralysis only by the administration of large doses of potassium salts (11). In the present study, which has been reported in abstract previously (12), attention is drawn to the facility with which attacks of hyperkalemic paralysis can be induced by the administration of corticotropin and various glucocorticoids in a patient with this disorder. In these and in episodes of spontaneous paralysis it has been found that there are consistent falls in plasma Na and Cl concentrations which are closely correlated in magnitude and time with the concomitant rises in plasma K concentration. Gratifying protection from spontaneous attacks of paralysis has been accomplished by the administration of acetazolamide in combination with a steroid having a predominantly mineralocorticoid effect, fludrocortisone.

Dr. Fellerman is a U. S. Public Health Service Trainee in Endocrinology.

Received for publication 1 June 1970 and in revised form 17 August 1970.

METHODS

Case report, F.B. (SUH No. 09-39-07). This 19 yr old college student called from his home in Chicago, in May 1968, to request that he be hospitalized for study and treatment of episodic muscular weakness and paralysis which he had experienced since the age of 1½ yr. He was admitted to the Clinical Research Center of the State University Hospital from 27 May 1968 to 5 June 1968 and from 13 August 1968 to 24 December 1968. He reported that attacks varied in severity from mild weakness of a few muscles to complete quadriplegia, that the episodes were brief, lasting from a few minutes to 3 hr, and that they almost invariably occurred during the day, especially after exposure to cold, during rest after strenuous exercise, or shortly after the ingestion of a large meal. Being an ardent and successful baseball pitcher, he had learned to ward off impending attacks while waiting his turn to pitch by exercising or by eating chocolate bars. He had found that the immobilization which occurred while driving home from a game, after a hot shower, would inevitably precipitate paralysis. Knowing this, he had persuaded his father, himself a sufferer from the same malady, to drive him home whenever he had been playing baseball and to carry him, paralyzed, from the automobile into the family home where he would regain his strength after 1 or 2 hr. When he awoke at night paralyzed it was only necessary to fall asleep again in order to awaken, strong and well, in the morning. Infections and stresses of various types, especially those causing physical exhaustion, tended to be followed by attacks of paralysis. Exposure of one arm to severe cold, while taking walks with his dog in the winter, frequently led to paralysis of the exposed arm, particularly if this limb had been immobile during the walk. When weakness prevented him from leaving the classroom after a lecture, he would sit through another lecture until his strength returned, professing a sudden interest in whatever the subject of the lecture might be, in order to avoid seeking any help from or even informing his closest friends of the disorder from which he suffered. Except for these problems posed by his paralysis after lectures and after baseball games, he had managed to lead a very active, virtually normal existence between the 5 or 10 bouts of weakness or paralysis which he experienced each week. He had passed through puberty normally and had normal sexual interests and potency.

A number of the patient's close relatives were known to have suffered from the same malady since early childhood or infancy. These included his father, one of his two brothers, a sister, and several cousins and uncles.

Physical examination showed a robust and very muscular male with normal blood pressure (112/72 recumbent, 128/90 upright), pulse (72 recumbent, 92 upright), height (186.5 cm), and weight (93.0 kg). Between attacks of paralysis, there was no abnormality detectable. When he was experiencing severe weakness this was clearly evident on testing muscle strength; tendon reflexes disappeared completely during complete paralysis, but speech and respiration were virtually never impaired. The Chvostek sign could usually be elicited during paralysis. Tenderness and aching discomfort in the muscles were present during most paralytic episodes observed, together with headache, pain and mild tenderness in the epigastrium, and some tenderness in the veins which was evident upon venepuncture. An unpleasant olfactory hallucination occurred for a few minutes during severe attacks and he sometimes experienced paresthesias in the forearms and hands. Profuse perspiration was often

evident towards the end of an attack of paralysis. While he did not urinate or defecate during paralysis, the passage of a large volume of urine frequently heralded recovery and, in the patient's opinion, hastened the return of strength.

Laboratory tests, which were entirely normal between attacks of paralysis, included chest X-ray, electrocardiogram, urinalysis, hematocrit (43%), hemoglobin (13.6 g/100 ml), white cell count (7700/cubic millimeter), differential count, fasting plasma glucose concentration (86 mg/100 ml), serum cholesterol (231 mg/100 ml), blood urea nitrogen (20 mg/100 ml), serum creatinine (1.4 mg/100 ml), serum total proteins (6.8 g/100 ml), and electrophoresis; serum free thyroxine (1.9 ng/100 ml), serum Ca (5.1 mEq/liter), serum phosphorus (3.9 mg/100 ml), serum Mg (1.76 mEq/liter), and plasma Na (142 mEq/liter), Cl (104 mEq/liter), and CO₂ (24 mEq/liter). Endogenous creatinine clearance was normal (144 ml/min), urine culture was negative, and cardiolipin slide flocculation test was negative. Plasma K concentration varied from 3.2 to 4.2 mEq/liter between attacks of paralysis.

During episodes of weakness or paralysis, heparinized blood samples were obtained frequently through an indwelling venous cannula (Intracath), kept patent by filling the cannula with dilute heparin solution. Electrocardiograms (lead V2) were obtained frequently during several spontaneous and induced bouts of paralysis. Plasma Cl, HCO₃, Na, and K were measured simultaneously on an AutoAnalyzer (Technicon Corp.), the latter two by flame photometry. During the first few studies, it was found that erratic variations in plasma Na and Cl concentrations were present if the plasma was frozen prior to determinations on the AutoAnalyzer. Consistent, reproducible changes were present in all subsequent studies when the determinations were performed on the day of or the day after the blood collections had been made, and without freezing the plasma. Serial measurements of the strength of hand grip were made, using a dynamometer (C. H. Stoelting Co., Chicago, Ill.). Urinary 17-hydroxycorticoids were measured by the technique of Silber and Porter (13) as modified by Peterson, Karrer, and Guerra (14), and plasma 11-hydroxycorticoids by the fluorometric technique of Mattingly (15). In some studies measurements were made of plasma glucose (ferricyanide method) blood lactate (16) and serum inorganic phosphorus (17) concentrations on an AutoAnalyzer, and of serum concentrations of creatine phosphokinase (18).

During almost all of the studies reported here, the patient was given a constant, weighed diet containing either 205 mEq Na and 151 mEq K (August 16 to November 7), or 10 mEq Na and 91 mEq K (November 19 to December 21) daily.

Statistical computations were made by standard methods (19) using an SEL 810A computer.

RESULTS

Spontaneous bouts of paralysis. Measurements of hand grip made at 2-hr intervals during the day and at 3-hr intervals from 2 a.m. to 8 a.m. for 4 months disclosed a large number of episodes of spontaneous weakness (Fig. 1). These were transient and most commonly evident at 2 a.m. A change in dietary Na from 205 to 10 mEq daily did not reduce and may have increased the number of attacks.

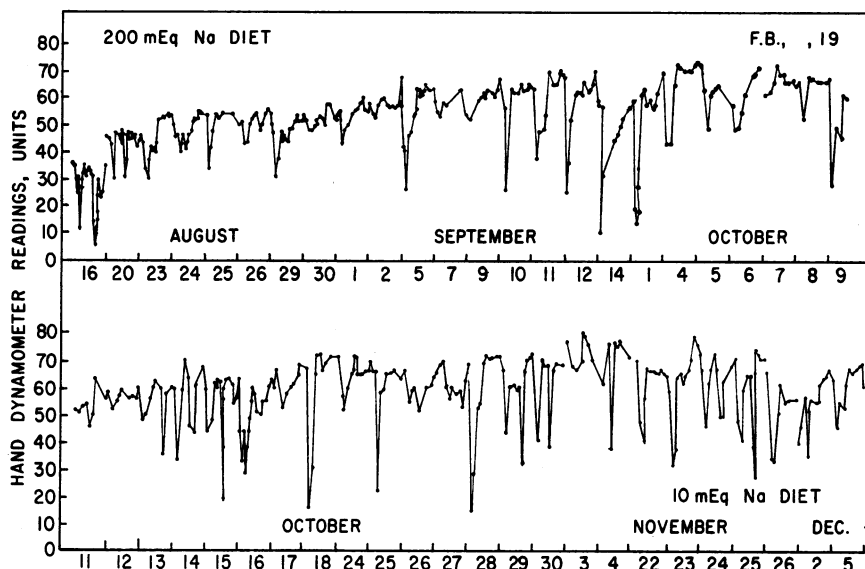


FIGURE 1 Spontaneous changes in strength of grip measured on dynamometer in patient F. B. Results are shown for all of the days during the patient's hospitalization when no attempt was made to induce paralysis. The vertical lines represent 12 midnight. It is evident that considerable reduction in strength was frequently evident at about 2 a.m.

At the height of three spontaneous bouts of severe muscular weakness, the plasma K concentration was found to have increased from its normally somewhat low levels (3.1–3.9 mEq/liter) to 6.3, 5.4, and 5.9 mEq/liter. Hourly measurements of strength and plasma K concentrations during one 24-hr period (Fig. 2) showed a spontaneous rise in plasma K concentration from 3.9 mEq/liter at 1:00 a.m. to 6.3 mEq/liter at 3:00 a.m., while strength fell rapidly from 66 to 25 U on the hand dynamometer over the same period of time. These findings clearly demonstrated that the spontaneous bouts of

weakness were associated with simultaneous increases in plasma K concentration, as is characteristic of hyperkalemic periodic paralysis.

Cold-induced paralysis. After sitting and walking about in a cold room (temperature 3°C) for almost 2 hr from 10 a.m., the patient became very weak, unable to rise from his chair, and with a fall in hand grip to 6 U by 1:30 p.m. when plasma K concentration was found to be 5.9 mEq/liter.

KCl-induced paralysis. Potassium chloride, 156 mEq given as 10% aqueous solution by mouth, caused a rapid

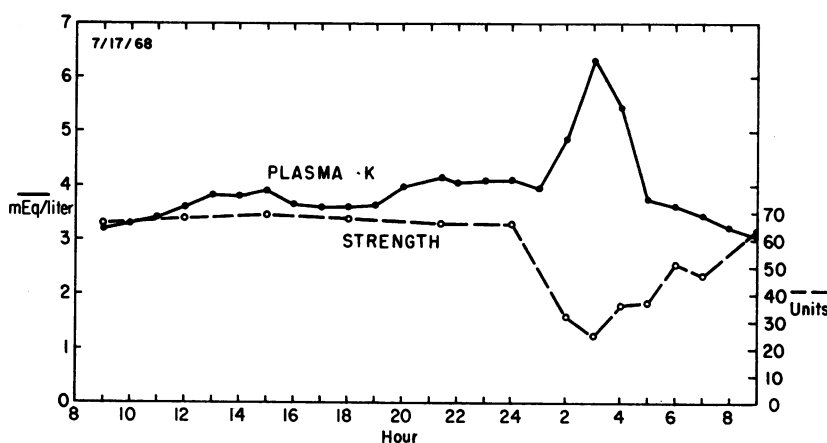


FIGURE 2 Changes in strength (measured in the right hand with a dynamometer) and in plasma K concentration during a 24 hr period which included a spontaneous nocturnal attack of weakness with hyperkalemia.

TABLE I

Effects of KCl Administration on Strength (Dynamometer U) and Plasma Concentration of K, Na, and Cl in Patient F. B.

156 mEq KCl (9/11/68)					80 mEq KCl (12/16/68)					156 mEq KCl (12/17/68)				
Time	Strength	Plasma			Time	Strength	Plasma			Time	Strength	Plasma		
		K	Na	Cl			K	Na	Cl			K	Na	Cl
hr	U	mEq/liter			hr	U	mEq/liter			hr	U	mEq/liter		
0	60	3.7	148	106	0	55	3.6	146	108	0	55	3.6	150	108
1	60	4.0	146	107	0.5	52	—	—	—	1	51	4.6	149	108
1.5	58	5.5	145	109	1	56	4.7	145	108	1.5	37	5.2	148	110
1.75	27	6.7	143	110	1.75	19	5.6	144	108	2	26	5.5	147	110
2	11	7.5	144	108	1.9	19	5.4	145	109	2.2	39	6.0	148	111
2.2	1	7.7	141	106	2.2	28	5.6	145	108	2.5	35	6.1	145	110
2.5	4	7.6	145	110	2.3	27	6.4	144	108	2.75	34	7.1	141	108
2.75	26	7.2	144	111	2.5	37	6.0	143	108	3	39	6.2	142	109
3	32	7.2	144	113	3	41	5.4	145	108	3.25	38	6.6	142	110
3.5	41	6.5	143	111	4	47	5.0	145	107	3.5	4	7.4	141	109
4	51	5.0	147	115						3.75	10	6.6	143	110
5	58	4.4	151	115						3.9	17	6.4	142	110
										4	18	6.3	142	111
										4.2	30	6.1	142	111
										4.3	35	6.0	143	111
										4.5	45	5.4	143	111
										5	54	4.2	144	111
										5.5	52	4.0	145	111
										6	55	3.9	145	111

rise in plasma K concentration with a simultaneous fall in strength, starting 90–105 min after the administration of the KCl (Table I). Plasma K rose to a highest value of 7.7 and 7.4 mEq/liter at 2.2 and 3.5 hr in two studies, after which it began to decline over the next 2 hr to normal levels. The changes in plasma K were associated with changes in plasma Na and Cl in the opposite direction, the plasma Na falling from 148 and 150 to 141 mEq/liter as paralysis developed while plasma Cl rose slightly, as the strength declined to its lowest levels. A lower dose of potassium chloride, 80 mEq, produced less of a rise in plasma K concentration (to 6.4 mEq/liter) with a smaller fall in plasma Na concentration (to 143 mEq/liter), and a moderate, transient reduction in the strength of the grip (from a control level of 55 down to 19 U on the dynamometer).

Corticotropin administration. The administration of corticotropin (ACTH)-gel (80 IU intramuscularly) on four separate occasions was always followed by a rise in plasma K concentration to between 6.5 and 7.4 mEq/liter and a simultaneous decline in strength usually to zero on the hand dynamometer. The changes in plasma K and in muscle strength were usually greatest 4½–5½ hr after the ACTH administration. Plasma Na and Cl concentrations declined in parallel with the fall in strength and the rise in plasma K concentration, on the two occasions on which Na and Cl changes were mea-

sured after ACTH (Fig. 3). Other blood chemical changes observed after ACTH administration included a rise in serum inorganic phosphorus which preceded paralysis, a rise in plasma glucose and serum creatine phosphokinase (CPK) concentrations during paralysis, and a rise in blood lactate level which started about 30 min after the onset of detectable weakness (Fig. 3). The effects of ACTH-gel on plasma electrolytes and muscle strength were completely prevented by metyrapone, 750 mg by mouth every 2 hr, starting at the time of the first ACTH injection. Muscle strength and plasma concentrations of Na, K, and Cl measured every hour for 24 hr after the ACTH administration, showed no change.

Administration of glucocorticoids. When hydrocortisone was administered in a dose of 100 mg by mouth, or by intravenous injection or by intravenous infusion, it was invariably followed by a fall in muscle strength to values of zero on the hand dynamometer, associated with simultaneous increases in plasma K concentrations and decreases in plasma Na and Cl concentrations (Fig. 4, Table II). Plasma bicarbonate concentrations increased simultaneously with these changes, which were greatest 4½–5½ hr after the oral or intravenous injection of cortisol and after the beginning of a cortisol infusion. The recovery process was not influenced detectably by the continued intravenous infusion of cortisol at a slow rate (55 µg/min). Paralysis, associated with the same

changes in plasma Na, K, and Cl, lasted from 3 or 4 to 7 or 8 hr after the intravenous injection of 6-methylprednisolone (Medrol), 16 mg, and dexamethasone (Decadron), 3.75 mg, and after the oral administration of triamcinolone (Aristocort), 20 mg (Table II). The triamcinolone was administered while the patient was on a low Na diet (10 mEq/day) and the paralysis which resulted was more prolonged and more profound than any of the other attacks witnessed in this patient. He experienced difficulty in coughing, mild difficulty in breathing, and considerable apprehension. At the height of the paralysis, venous blood flow seemed to be reduced since it became somewhat difficult to aspirate blood through the venous cannula. An intravenous infusion of 5% sodium chloride solution was administered at this point (240 ml over 2 hr), which rapidly raised plasma Na and Cl concentrations without definite effect on plasma K concentration. The patient's difficulties in coughing

and breathing and the apprehension seemed to improve—whether in consequence of the NaCl infusion or not is unclear—but muscle grip continued to be zero on the dynamometer for more than an hour after the commencement of the NaCl infusion.

Administration of mineralocorticoids. No effects were observed on muscle strength, plasma K, or plasma Na all measured hourly for 24 hr during the intravenous infusion of D-aldosterone, 1.0 mg in 52 ml 5% dextrose solution by an infusion pump, over 24 hr, or after the intramuscular injection of deoxycorticosterone acetate (DOCA), 20 mg.

Measurements of adrenocortical function (Table III). Plasma 11-hydroxycorticoids (11-OHCS) were consistently normal, as were urinary 17-hydroxycorticoids (17-OHCS) when corrected for the patient's strikingly evident abundance of muscle mass, by expressing them per gram of creatinine (20). Urinary 17-OHCS re-

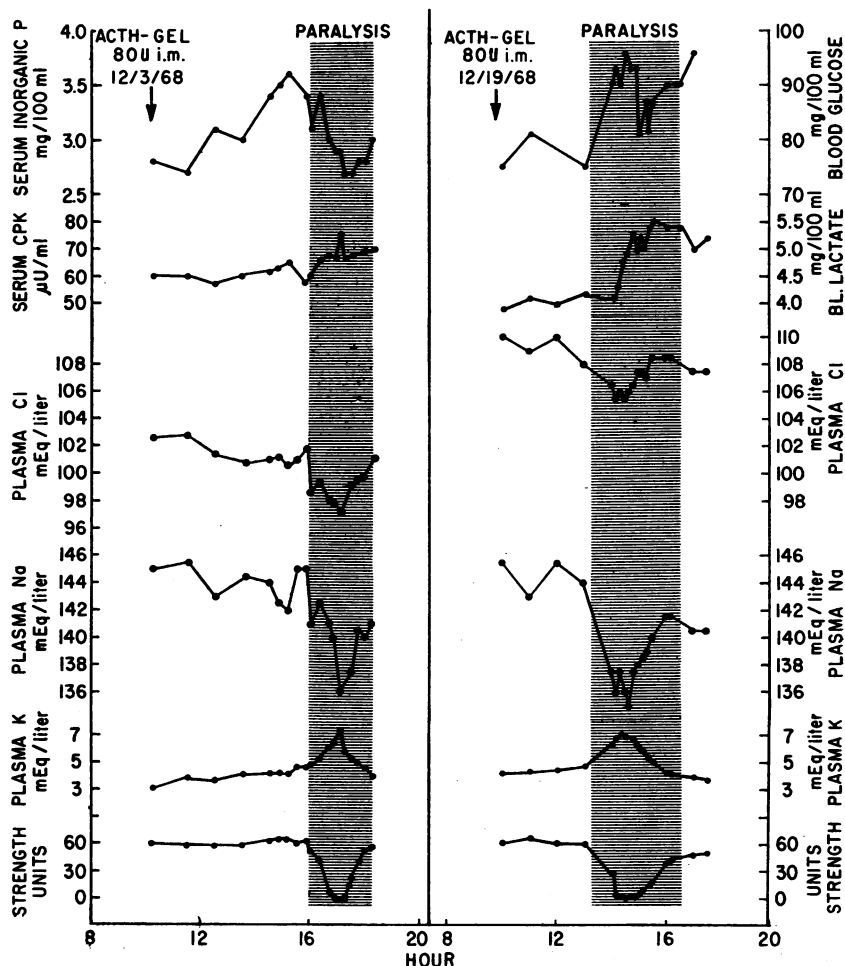


FIGURE 3 Effects of ACTH-gel, 80 U, i.m., on plasma K, Na, Cl, glucose, and blood lactate concentrations, on serum P, and creatine phosphokinase concentrations, and on the strength of grip in F. B.

sponded normally to the administration of ACTH, metyrapone, and cortisol. Urinary 17-OHCS excretion showed no rise on a day of KCl-induced paralysis (10.7 mg/day or 3.7 mg/g creatinine per day) or on a day of cold-induced paralysis (13.3 mg/day or 3.8 mg/g creatinine/day). Aldosterone excretion was normal on the 205 mEq Na diet, 6.8–14.0 μ g/day, and rose normally to 39.2 μ g/day on a day of ACTH-gel administration and the same dietary Na intake. Plasma renin activity on a 10 mEq Na diet was normal, 730 ng/100 ml in recumbency. Serial measurements of plasma 11-OHCS were made on a day when two episodes of mild weakness were recorded by the dynamometer readings, each associated with a small increment in plasma K concentration (Fig. 5). Plasma 11-OHCS showed the normal pattern of diurnal changes and there was no evidence of any abnormal peak in plasma 11-OHCS concentration 4–6 hr before either of the episodes of weakness and hyperkalemia or at any other time of the day.

Electrocardiographic changes. The T wave in the electrocardiogram (lead V2) increased during the development of spontaneous and induced attacks of paralysis, having the following relationships with plasma electrolyte concentrations:

$$T = 2.85 + 1.22 [\text{plasma K}],$$

$$r = +0.69, n = 125, P < 0.001;$$

$$T = 71.4 - 0.44 [\text{plasma Na}],$$

$$r = -0.60, n = 124, P < 0.001;$$

$$T = 24.1 - 0.14 [\text{plasma Cl}],$$

$$r = -0.25, n = 124, P < 0.005;$$

$$T = 1.56 + 1.35 (\Delta[\text{plasma K}]),$$

$$r = +0.87, n = 102, P < 0.001.$$

KCl administration: comparison of the effects in the patient and in normal subjects. The same dose of 10% KCl solution, 156 mEq, was given by mouth to three robust, healthy males whose ages, heights, and weights were similar to those of the patient (Fig. 6). Plasma Na showed a fall after the plasma K had reached its highest level following KCl administration in two of the normal subjects but always fell as K rose in the patient. Plasma Cl rose by 3.5–5.5 mEq/liter in the normal subjects and by 9.5 mEq/liter in the patient. The normal subjects showed rises in plasma K concentration to peak concentrations 1½–2 hr after the KCl ingestion. The plasma K concentration in these men seldom reached 6.0 mEq/liter and never exceeded 6.15 mEq/liter, compared with peaks usually above 7.5 mEq/liter in the patient. These plasma electrolyte changes were associated with no significant alterations in muscle strength in the normal subjects but with

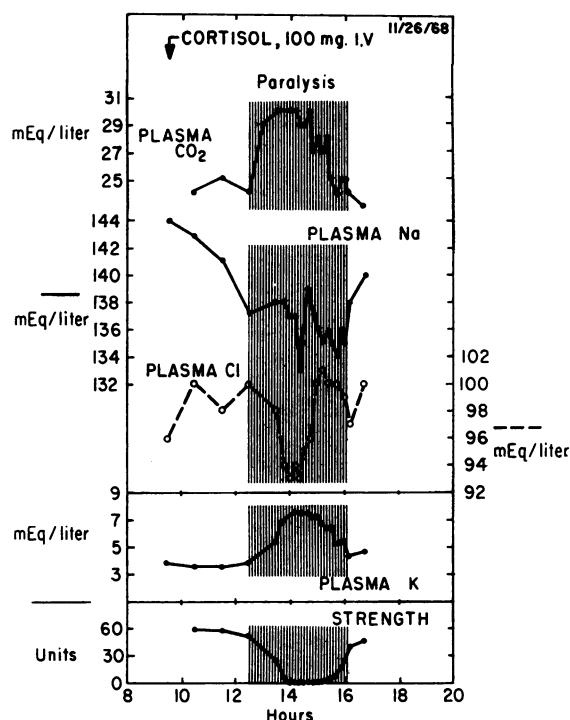


FIGURE 4 Effects of cortisol, 100 mg given by intravenous injection, on plasma bicarbonate, Na, Cl, K, and muscle strength in F. B.

profound reduction in hand grip in the patient with hyperkalemic periodic paralysis.

ACTH and glucocorticoid administration: effects in normal subjects. The administration of ACTH-gel (80 U intramuscularly), cortisol (100 mg intravenously), and triamcinolone (20 mg by mouth) produced variable and probably insignificant changes in plasma Na, plasma Cl, plasma K, and muscle strength, in three normal males.

Changes in K excretion in the patient and in normal subjects. Measurements of urinary Na, K, and creatinine during a day on which an attack of muscular weakness was recorded between 2 and 6 a.m. showed (Fig. 7) a nocturnal fall in Na excretion (probably normal), a striking rise in K excretion at the time of hyperkalemia and weakness, and a slight nocturnal fall in creatinine excretion. There was no change in 24 hr excretion of Na, K, or water or in body weight on the day before, the day of, or the day after either of two bouts of spontaneous paralysis. Paralytic episodes precipitated by cortisol (100 mg intramuscularly) and by KCl (156 mEq by mouth) were associated with increases in cumulative excretion of K in the patient which were similar to those recorded in normal subjects given the same amounts of cortisol and KCl respectively (Table IV).

TABLE II

5% NaCl infusion, 240 ml

TABLE III
Adrenal Function in F. B.

Plasma 11-OHCS (untreated): 8 a.m.: 20.2, 26.0, and 24.5 $\mu\text{g}/100\text{ ml}$.	
Urinary 17-OHCS: untreated: 10.7–13.4 mg, mean 12.8 mg/day (or 3.5–4.0 mg/g creatinine per day, mean 3.73) (12 determinations)	
during cortisol infusion, 166 mg:	31.6 mg/day
during cortisol injection, 80 mg:	21.9 mg/day
during cortisol injection, 100 mg:	21.1 mg/day
during cortisol injection, 120 mg:	24.6 mg/day
during exposure to cold:	13.3 mg/day (3.8 mg/g creatinine per day)
during spontaneous coryza:	12.0 mg/day (3.4 mg/g creatinine per day)
after metyrapone administration (750 mg q2h):	31.9 mg/day (8.3 mg/g creatinine per day)
during KCl administration (156 mEq):	10.7 mg/day (3.7 mg/g creatinine per day)
during ACTH administration (80 U gel b. i. d.):	42.0 mg/day (11.3 mg/g creatinine per day)
Aldosterone excretion (205 mEq Na intake): 13.7, 14.0, 6.8 $\mu\text{g}/\text{day}$	
(205 mEq Na diet and ACTH-gel): 39.2 $\mu\text{g}/\text{day}$	
Plasma renin activity (10 mEq Na diet, lying: 730 ng/100 ml)	

Protective effects of therapy with fludrocortisone and acetazolamide. The administration of fludrocortisone (0.5 mg twice daily by mouth) induced mild paralysis, presumably because of the glucocorticoid effect of this steroid. However (Fig. 8) when small doses of fludrocortisone (9 αFF , 0.1 mg twice daily by mouth) and acetazolamide (250 mg twice daily by mouth) were combined, the hyperkalemia resulting from 156 mEq of KCl was greatly reduced and the patient was protected from muscle weakness. Because of these findings, the patient was discharged from the hospital on treatment with fludrocortisone (0.1 mg daily) and acetazolamide (250 mg twice daily). During the subsequent

14 months he experienced no attacks of severe paralysis, such as he had experienced several times each week before the treatment, and only occasional attacks of mild weakness, never severe enough to interfere in any way with his daily occupation.

Correlations between the parameters measured. The following correlations were found to be present between the various simultaneous sets of measurements made.

(a) During the development of paralysis, from the time of administration of ACTH, cortisol, triamcinolone, dexamethasone, and 6-methylprednisolone until the height of paralysis (i.e. first zero readings on the dynamometer)

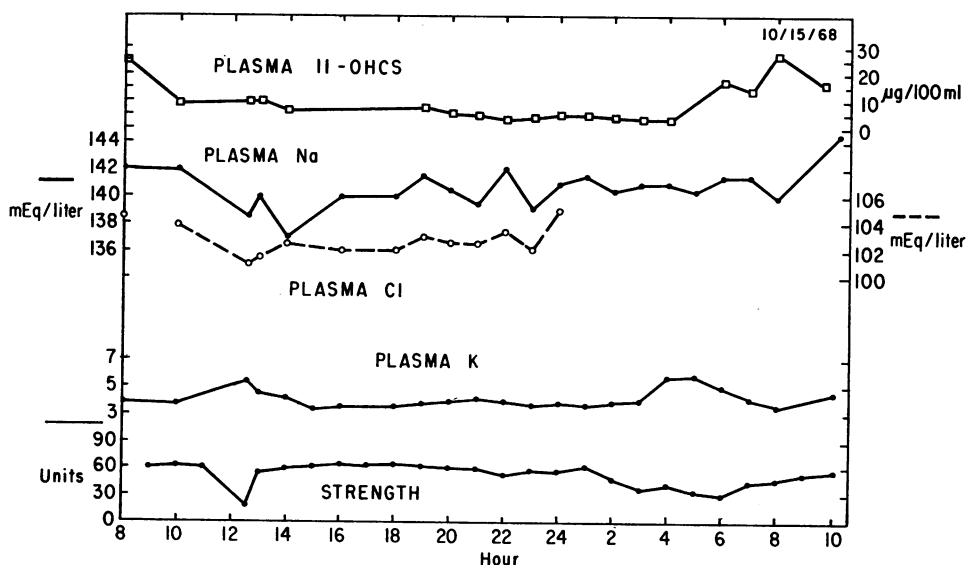


FIGURE 5 Showing normal diurnal variation in plasma 11-OHCS associated with spontaneous bouts of hyperkalemic weakness in F. B.

$$\Delta[\text{plasma K}] = 1.68 - 0.40 (\Delta[\text{plasma Cl}]),$$

$$r = -0.58, n = 73, P < 0.001;$$

$$\Delta[\text{plasma K}] = 0.20 - 0.43 (\Delta[\text{plasma Na}]),$$

$$r = -0.80, n = 78, P < 0.001 \text{ (Fig. 9);}$$

$$\Delta[\text{plasma Na}] = 0.58 - 0.69 (\Delta[\text{plasma K}] - \Delta[\text{plasma Cl}]),$$

$$r = -0.61, n = 73, P < 0.001.$$

(b) In all attacks of weakness or paralysis, spontaneous or induced by ACTH, glucocorticoids, cold, and KCl

$$\text{strength of grip} = 113 - 14.8 [\text{plasma K}];$$

$$r = 0.84, n = 429, P < 0.001$$

$$\text{strength of grip} = 587 + 4.45 [\text{plasma Na}];$$

$$r = -0.60, n = 377, P < 0.001$$

$$\text{strength of grip} = -58 + 0.94 [\text{plasma Cl}];$$

$$r = +0.17, n = 316, P < 0.001$$

$$\text{strength of grip} = 89 - 5.6 (\text{T-wave height});$$

$$r = -0.61, n = 122, P < 0.001.$$

(c) In all attacks of weakness or paralysis, spontaneous or induced by ACTH, glucocorticoids, cold, *but not by KCl*,

$$\text{strength of grip} = 118 - 16.1 [\text{plasma K}],$$

$$r = -0.88, n = 306, P < 0.001 \text{ (Fig. 10).}$$

It is evident from Fig. 10 that the points representing changes produced by KCl administration, which were not used to determine the regression depicted, have been superimposed and tend to fall above the 95% confidence limits of the correlation between strength and plasma K concentration. These findings indicate that strength is less severely reduced at a given level of plasma K in response to KCl administration than in response to the other stimuli studied, implying that some factor other than the rise in plasma K concentration per se contributed to the spontaneous weakness and to the weakness induced by glucocorticoids.

Studies in brother and first cousin of patient. The authors visited the patient's family in Chicago to verify the similarity of attacks of paralysis studied in the pa-

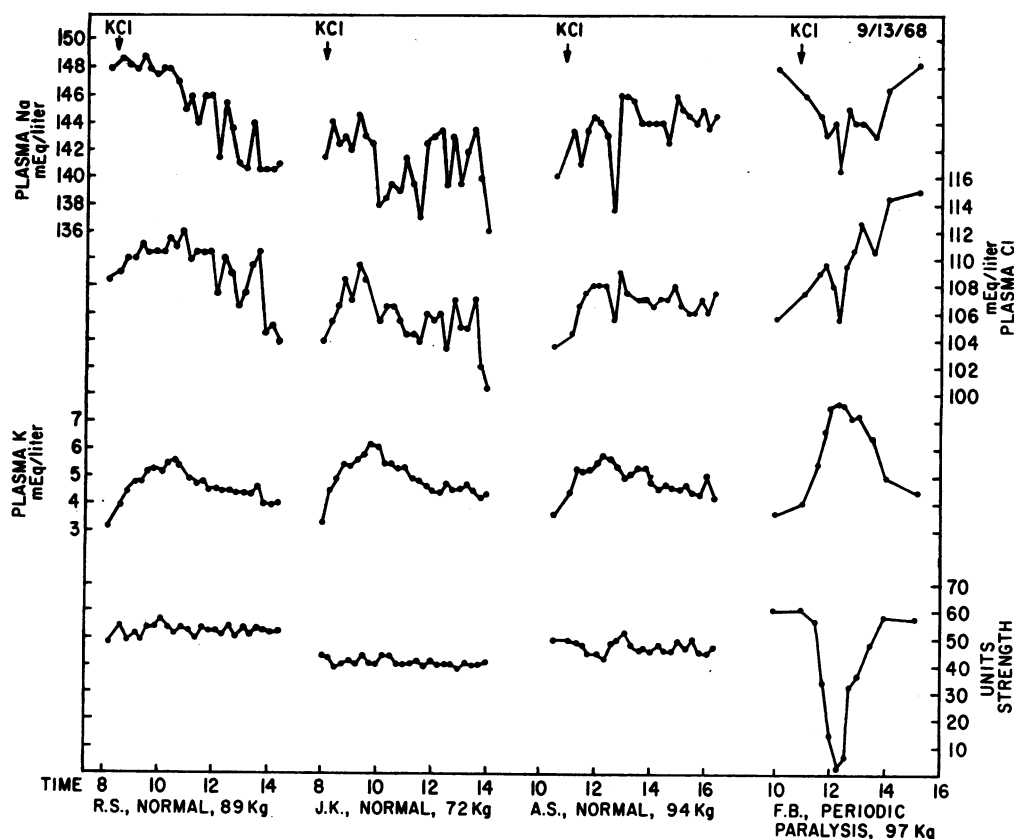


FIGURE 6 Comparison of effects of 156 mEq KCl by mouth on plasma electrolytes and muscle strength in three normal young adult males (R. S., J. K., and A. S.) and in patient F. B.

tient with those in other members of the family. ACTH-gel, 80 U intramuscularly, induced an attack of quadriplegia in a younger brother (E. B.) aged 14, which resembled the attacks induced in the propositus (F. B.) very closely (Table V). The same dose of ACTH-gel given on the same afternoon to a first cousin (A. B., male, 14 yr of age) induced weakness in the legs, thighs, and left arm, but not in the right arm, from 2 until 6 hr after the injection, and the grip in the left hand had still not returned to normal at the end of 7 hr. Plasma Na and K changes in E. B. were identical with those seen in the propositus, but A. B. showed a transient rise in plasma K at 4 and 5 hr, a fall in plasma Na at 5-7 hr, and relatively poor correlation between these changes and the changes in strength.

DISCUSSION

The patient described in this paper has typical familial periodic paralysis of the hyperkalemic type. His history of transient paralytic episodes since infancy, the evidence that spontaneous attacks were associated with hyperkalemia, and the reproducible induction of paralysis by the administration of potassium chloride in amounts which had no effect on the strength of normal subjects are all characteristic of this disorder. It was of interest to find that transient muscular weakness was clearly demonstrable at times, commonly about 2 a.m., when the patient had been quite unaware of its existence.

Attacks of paralysis were consistently induced by injections of corticotropin, after a latent period, usually of 4½-5½ hr. That this effect resulted from the cortisol secreted in response to stimulation by ACTH was indicated by the precipitation of paralysis a similar period of time after the administration of 100 mg of cortisol. The in-

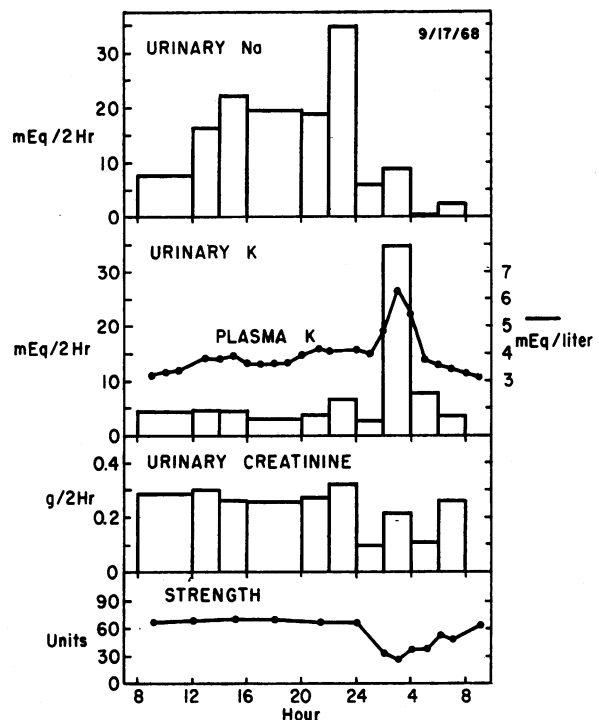


FIGURE 7 Measurement of urinary Na, K, and creatinine, plasma K concentration, and muscle strength during a spontaneous bout of weakness in F. B.

duction of paralysis was a specific effect of steroids with glucocorticoid actions since it was consistently reproduced by approximately equipotent doses of dexamethasone, 6-methylprednisolone, and triamcinolone, whereas the mineralocorticoids, aldosterone and deoxycorticosterone, had no such action. The observation that metyra-

TABLE IV
Cumulative Urinary Excretion of K after KCl or Cortisol

KCl, 156 mEq by mouth						Cortisol, 100 mg i.v.			
J. K.		R. S.		F. B.		F. B.		J. K.	
Time	Cumulative K excretion	Time	Cumulative K excretion	Time	Cumulative K excretion	Time	Cumulative K excretion	Time	Cumulative K excretion
hr	mEq	hr	mEq	hr	mEq	hr	mEq	hr	mEq
0-1	18.2	0-1	15.8	0-1	3.5	0-1	3.3	0-2	6.3
0-2	39.9	0-2	42.5	0-2.5	44.5	0-3	15.3	0-4	28.1
0-3	61.1	0-3	78.8	0-3	56.8	0-5	64.5	0-6	48.0
						0-6	98.0	0-7	77.8
						0-8	114.3	0-9	85.5
						0-10	122.0		
Normal		Normal						Normal	
72 kg		89 kg						72 kg	
				Periodic paralysis					
				97 kg					

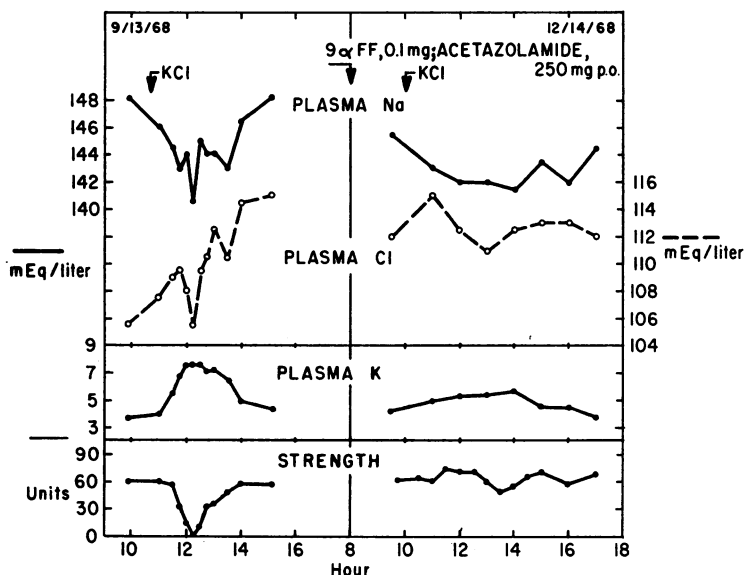


FIGURE 8 Protective effect of acetazolamide (250 mg) and fludrocortisone (0.1 mg) by mouth on KCl-induced paralysis in F. B.

pone prevented the otherwise invariable effects of ACTH on plasma electrolytes and muscle strength indicated that the presence of an hydroxyl radical in the C-11 position was essential for the paralytic action of steroids in this patient.

The negative results with mineralocorticoids and with metyrapone and ACTH in experiments of which the outcome could not be predicted in advance by the patient or his doctors, may be considered to have served as placebo studies which eliminated the possibility that the steroid-induced paralytic seizures were psychogenic in origin. The glucocorticoid-induced bouts of paralysis were virtually identical with the spontaneous episodes and with the paralyzes precipitated by the administration of po-

tassium chloride. In fact, the correlation between plasma K concentration and muscular strength during spontaneous attacks of paralysis was more closely simulated by glucocorticoid- than by KCl-induced paralysis. It seemed reasonable, therefore, to use the attacks precipitated by glucocorticoids as models for the study of the electrolyte changes which occurred before and during the episodes of paralysis in this patient. However, since the patient's adrenal function was entirely normal and since there was no evidence of a change in plasma 11-OHCS concentration before spontaneous or KCl-induced attacks of paralysis, it is clear that increased adrenocortical release of cortisol was *not* involved in the mechanism of the spontaneous or the KCl-induced episodes of paralysis. Rather, it seems likely that glucocorticoid administration, exposure to cold, and ingestion of potassium chloride all had the same effects at the muscle membrane as occurred during spontaneous bouts of paralysis.

The observations recorded in this patient have disclosed for the first time the occurrence of a consistent fall in plasma Na and Cl concentrations and a rise in plasma CO_2 , simultaneously with the dramatic rise in plasma K and in serum inorganic P (7) concentration which ushered in the paralytic seizures. During the development of paralysis, i.e. between the application of the stimulus and the development of complete muscular paralysis, the correlation between these electrolyte changes indicated that for every mmole of K entering the extracellular fluid, approximately 2 mmoles of Na and 2 mmoles of Cl left the same compartment. One might assume that these changes reflected the entry of 2 Na^+ and 2 Cl^- ions into the muscle in exchange for 1 K^+ ion. Such a shift

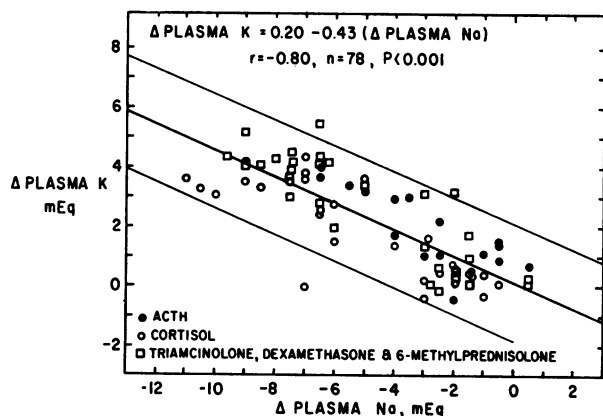


FIGURE 9 Correlation between changes in plasma Na and K from control values, during the development of ACTH- and steroid-induced paralysis in F. B.

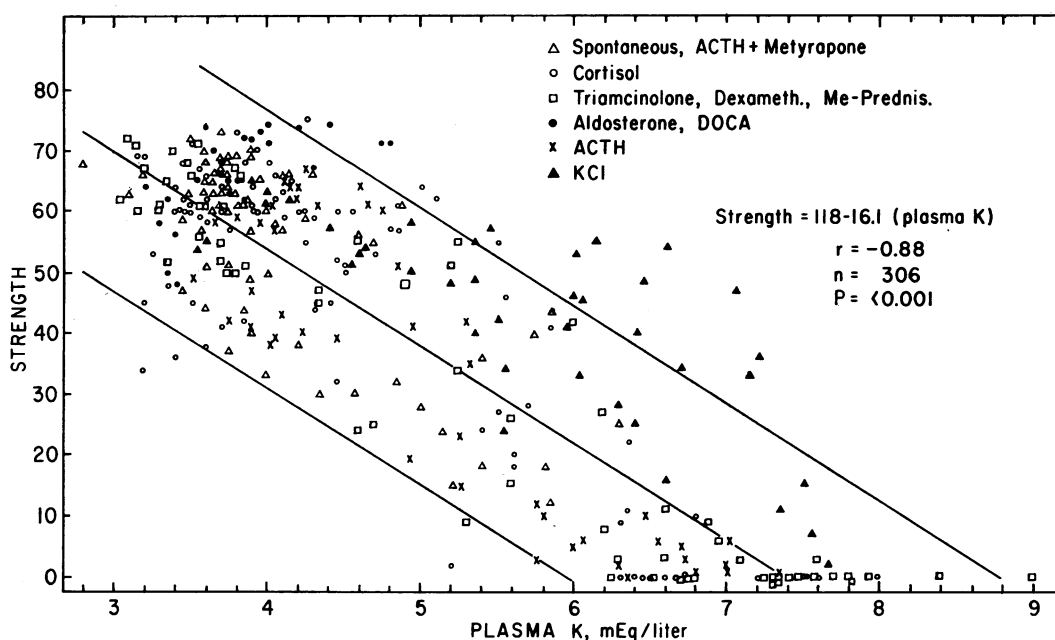


FIGURE 10 Correlation between plasma K concentration and muscle strength during spontaneous, steroid-induced and KCl-induced attacks of paralysis in F. B. The relatively lesser degrees of paralysis at any given levels of plasma K concentration induced by KCl administration are evident. The lines enclose the 95% confidence limits of the regression relating plasma K and muscle strength in all experiments except those involving administration of KCl.

would undoubtedly have reduced the resting membrane potential, during paralysis, as Creutzfeldt, Abbott, Fowler, and Pearson (21) and Brooks (22) have shown by

direct measurement, and these changes might well be the cause of the paralysis. It was surprising to find, however, that when plasma potassium concentration was

TABLE V
Changes in Strength (Dynamometer U) and Plasma K and Na Concentrations in a Brother (E. B.) and a First Cousin (A. B.) of the Propositus, after ACTH-Gel, 80 U Injected i.m. at Zero Time

E. B.					A. B.				
Time	Strength		Plasma		Time	Strength		Plasma	
	Right	Left	K	Na		Right	Left	K	Na
hr	U		mEq/liter		hr	U		mEq/liter	
0	47	35	3.6	149	0	28	21	3.2	147
1	47	32	3.9	146	1	25	20	3.2	147
2	33	18	—	—	2	29	10	3.4	147
2.25	46	34	5.0	150	2.5	28	10	3.7	149
2.5	43	33	4.4	147	3	25	6	3.9	147
3	47	37	4.0	148	3.5	28	10	3.9	145
4	47	40	4.0	145	4	28	10	5.5	146
5	34	24	4.6	146	5	21	7	4.3	143
5.25	36	23	—	—	5.5	24	7	—	—
5.5	29	19	6.0	140	6	28	9	4.1	145
5.75	8	3	6.3	141	6.5	25	6	—	—
6	22	19	5.3	144	7	25	13	4.0	142
6.3	45	34	4.4	143					
6.75	46	33	—	—					
7	48	35	3.9	144					

raised by absorption of administered KCl from the gastrointestinal tract, plasma Na fell, as it did in the glucocorticoid-induced attacks. In these experiments, plasma Cl concentration rose slightly or fell less than in the other attacks of paralysis studied, presumably because of absorption of Cl ion administered. Thus, the paralysis induced by KCl was probably associated with no loss—perhaps even a gain—of intracellular K, though like the paralysis induced in other ways, KCl-induced attacks were probably associated with a gain in intramuscular Na and Cl. The demonstration of changes in plasma Na concentration during the development of paralysis is consistent with the prediction of Creutzfeldt et al. (21) that a change in the permeability of the muscle membrane to Na^+ occurs in hyperkalemic periodic paralysis. This prediction was based on calculations showing that the observed fall in membrane potential was far greater than could be explained by a simple shift of K from intracellular to extracellular fluid.

The findings in the patient with periodic paralysis were compared with those in normal young adult males of similar size. The normal subjects showed no consistent or significant changes in plasma electrolytes or muscular strength in response to doses of corticotropin, cortisol, and triamcinolone which were identical with those which were followed by hyperkalemia, hyponatremia, hypochloremia, and muscular paralysis in the patient. Potassium chloride, 156 mEq by mouth, consistently raised the plasma K concentration to a higher level in the patient than in any of three normal subjects. These differences were not related to abnormalities in the renal excretion of potassium by the patient. They might have resulted from excessively rapid absorption of the administered KCl from the gastrointestinal tract in the patient but the similar time course of the potassium changes in the normal and abnormal individuals is evidence against this possibility. The best interpretation would seem to be that the cell membranes of the patient were excessively sensitive to the K-extruding effects of glucocorticoids and unduly slow in their uptake of potassium from the extracellular fluid. Such an abnormality in K transport across the cell membranes would be expected to make the patient susceptible to excessive increases in plasma K in response to the administration both of glucocorticoids and of potassium chloride, allowing plasma K concentrations to rise to levels which might induce membrane depolarization. Although the changes in plasma Na after KCl administration were not convincingly different in the normal and the abnormal subjects, the obvious fall in plasma Na after glucocorticoid administration to the patient suggests that this change might well have contributed to the excessive depolarization which presumably led to paralysis in the patient. Many of the observations made in these ex-

periments might be interpreted as the consequences of a disorder of the $\text{Na}^+\text{-K}^+$ pump in the cells of the patient, as Brooks (22) has suggested. Thus, the “pump” might respond inadequately to the stimulus of the rising plasma K after KCl administration, so that normal intracellular influx of the administered K would be retarded. An abnormal “pump” might be excessively sensitive to the inhibitory effects of cold, and perhaps excessively inhibited by glucocorticoids, with consequent rises in extracellular K and intracellular Na. However, it is difficult to explain the changes in plasma Cl, HCO_3 , and P by a defect in the $\text{Na}^+\text{-K}^+$ “pump” alone.

No systematic study was made of the relative efficacy of acetazolamide and fludrocortisone in protecting the patient from paralysis. However, it was found that a combination of these agents greatly reduced the changes in plasma Na and K and protected the patient from the paralytic effects of KCl, 156 mEq by mouth. This therapeutic combination has been used by the patient and by his brother and cousin for the past 14 months. In this period of time none of these patients has had an attack of paralysis severe enough to interfere in any way with normal activities, except for the brother of the *propositus* who forgot to take his tablets on one occasion and suffered an attack of severe paralysis the same evening. The therapeutic efficacy of acetazolamide was first described by McArdle (7) and has been confirmed by other authors (10). The use of fludrocortisone was suggested to us by the finding of McArdle (7) that treatment with deoxycorticosterone acetate resulted in diminution of the hyperkalemia and of the severity of paralysis following KCl administration in a patient with hyperkalemic periodic paralysis. Mertens, Schimrigk, Volkwein, and Voigt (23) showed that aldosterone (1.5 mg/day) conferred protection from KCl-induced paralysis.

There was a striking similarity in the pattern of changes in plasma electrolytes and muscular strength in the *propositus* and his brother. However, a first cousin showed less obvious electrolyte changes and a different time course of the changes in muscle strength in response to corticotropin. These differences even within members of the same kindred suggest that the syndrome of hyperkalemic periodic paralysis might constitute a group of disorders in which some of the minutiae of the pathogenesis might vary considerably from patient to patient but in which all subjects are alike in experiencing excessive hyperkalemia and weakness in response to KCl and to those stimuli which precipitate spontaneous paralysis.

It is interesting to find that several of the biochemical features of the paralytic attacks in the patient described here are apparently diametrically opposite to those observed in the common type of hypokalemic periodic paralysis. Hyperkalemic paralysis was induced by glu-

cocorticoids but not by mineralocorticoids, was associated with a rising plasma K and a falling plasma Na, and was reduced by mineralocorticoids but not by spironolactone. On the other hand, in at least some patients with the hypokalemic disorder, paralysis is readily induced by several mineralocorticoids but not by glucocorticoids (24), is associated with a fall in serum K and a rise in serum Na (25), and is prevented by spironolactone (24). Whether or not the intracellular mechanisms of paralysis are disparate in the two types of periodic paralysis can only be decided by further studies.

ACKNOWLEDGMENTS

We are glad to express our thanks to Mr. Sterling Wilson and Miss Bonita Bell for technical assistance, to the nurses of the Clinical Research Center for their diligent and skilled nursing, to the normal volunteers, and to the patient for his intelligent cooperation throughout these studies.

This work was supported by a Graduate Training Grant in Endocrinology (AM 05252) from the National Institute of Arthritis and Metabolic Diseases, and Clinical Research Center Grant RR 00229 from the Division of Research Facilities and Resources, U. S. Public Health Service. The statistical computations were performed in the Department of Bioelectronics and Computer Sciences, supported by Special Research Resources Grant FR00353 from the U. S. Public Health Service.

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