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METABOLIC AND RENAL STUDIES IN CHRONIC POTASSIUM DEPLETION RESULTING FROM OVERUSE OF LAXATIVES^{1, 2}

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INTRODUCTION

It is well known that diarrhea caused by a variety of gastrointestinal disorders may lead to potassium depletion (1). This paper presents observations on two otherwise healthy women who, prior to this study, had gradually developed severe potassium depletion and hypokalemia as the result of chronic diarrhea induced by overuse of laxatives. Although in each instance there had been a loss of approximately one-third of total normal body potassium, there were no other significant disturbances of water and electrolyte balance and no overt signs of malnutrition. These two subjects thus presented an unusual opportunity to observe the clinical and physiological effects of uncomplicated potassium depletion.

The case histories described below present the clinical observations made before and after the spontaneous restoration of potassium balance which occurred when laxatives were withheld and the patients given a normal diet.

This paper reports the results of balance studies carried out in both subjects for the three-week period in which repair of their potassium deficit was accomplished. In addition, various renal functions were measured serially. In one patient renal function studies were begun immediately after the potassium deficit had been repaired, but in the second patient measurements were made both before and after treatment. The electrocar-

diographic findings in these patients will be discussed elsewhere (2).

CASE REPORTS

Case 1

R. S., a 24 year old woman, was referred for investigation of her chronic complaints of vague muscle pains, malaise, and weakness. Although her appetite was usually good and she had not lost weight, she stated that under emotional stress she often ate little or nothing for a day or two at a time. For more than a year she had observed a tendency to gain weight and to develop ankle edema whenever she ate salt. Up to the day of admission she had worked regularly as an IBM machine operator.

Physical examination revealed a somewhat thin, but otherwise healthy-appearing female. There were no abnormal findings. Muscle strength and tendon reflexes were normal.

Laboratory studies of the blood, stool and urine were not remarkable except that the maximum specific gravity of the urine after 18 hours of dehydration was 1.013. X-ray examinations of the chest, long bones, skull, kidneys, and entire gastrointestinal tract revealed no abnormalities. Sigmoidoscopic examination was negative. A routine electrocardiogram revealed flattened or diphasic T-waves in most leads and was thought to be suggestive of hypokalemia. Repeated determinations of serum potassium concentrations gave values between 2.1 and 2.3 mEq. per l. Serum bicarbonate concentration was 30 to 33.5 mEq. per l., but analyses for the following were normal: serum sodium, chloride, albumin, globulin, cholesterol, calcium, phosphorus, and blood sugar and urea nitrogen. A standard 8 lead electroencephalographic record was within normal limits.

During the next three weeks, while on balance study, she spontaneously corrected her potassium deficit and her electrocardiogram returned to normal. At this time she first admitted to the habitual ingestion of Hinkle's Cascara Compound⁴ which she had taken in quantities of 15 to 30 tablets per week in order to produce 2 to 3 watery bowel movements every day. At the completion of the period of potassium retention she was given laxatives for

⁴ Each tablet contained: .016 gm. cascara, .016 gm. aloin, .01 gm. podophyllum, .008 gm. extract of belladonna, .001 gm. strychnine sulfate, and .004 gm. oleoresin of ginger.

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³ Markle Scholar in the Medical Sciences.

a few days to observe the effect on potassium balance and the electrocardiogram. During the next six months the patient was free of diarrhea and her serum potassium concentration and electrocardiogram remained normal.

Case 2

A. B., a 42 year old widow, came to the hospital complaining of vague malaise, weakness and abdominal discomfort. She had been accustomed for a long time to taking indeterminate but large amounts of proprietary laxative compounds containing phenolphthalein, podophyllum, and aloin. These produced several watery bowel movements each day. Her appetite and intake of food were usually normal, but occasionally, at times of emotional stress, she ate little or nothing for several days at a time. For several months she had noted that her ankles swelled intermittently. Prior to admission she was able to work regularly at her job as a saleslady.

On physical examination the patient looked depressed and chronically ill. There were no other abnormal findings. Tendon reflexes were normal and her muscle strength seemed appropriate.

Routine laboratory studies of the blood, stool and urine were not remarkable except that maximal specific gravity of the urine after 18 hours of dehydration was 1.005. X-ray examinations of the long bones, chest, stomach, small intestines, and gall bladder revealed nothing of significance. A barium enema showed a moderately atonic, redundant colon, but sigmoidoscopic examination disclosed no evidence of disease.

A routine electrocardiogram showed sagging of the ST segments and prominent U-waves in most leads. Because of this suggestive evidence of hypokalemia, serum potassium analyses were done. Repeated analyses gave values between 1.6 and 2.3 mEq. per l. Serum chloride concentration was 94 mEq. per l. but analyses for the following were normal: serum sodium, carbon dioxide content, albumin, globulin, cholesterol, calcium, phosphorus, blood sugar, and urea nitrogen. A standard 8 lead electroencephalogram was within normal limits.

The patient was placed on balance study, and during the next three weeks her potassium deficit was corrected and the electrocardiogram returned gradually to normal. During this time she noted a gradual, definite improvement in vigor and appetite and in her sense of well-being. Following discharge, the concentration of serum potassium, determined at frequent intervals, was usually normal, as were electrocardiographic records made at the same time. On two occasions associated with emotional stress she suffered brief episodes of anorexia and diarrhea, which she said were not provoked by laxatives. At these times the serum potassium concentration was low and the electrocardiogram showed T-wave abnormalities.

METHODS

The patients were allowed to be ambulatory on the ward. Diarrhea had stopped or diminished prior to the beginning of the balance study and after a few days all bowel movements were of normal frequency and con-

sistency. The patients were given constant weighed diets which contained little sodium, a low-normal amount of potassium and the approximate nitrogen and caloric content of the usual ward diet. No food was refused during the period of study. Salt was added each day in fixed amount with a weighed salt shaker in order to raise the sodium intake to a normal level. Potassium chloride, 20 to 40 mEq. per day, was added to the oral intake as indicated in Tables I and II, but at no time did the total potassium intake exceed the usual range of normal. No other medications were administered.

Organic acids in the urine were determined by the method of Van Slyke and Palmer (3) adapted for use with the Beckman pH-meter. No creatinine correction was applied. Analyses for calcium in diet, urine and stool were carried out by dry-ashing, followed by a modification of the Tisdall and Kramer titration (4). Total exchangeable potassium was determined⁵ by analysis of urine specific activity 24 hours after the administration of an oral tracer dose of $K^{42}Cl$ (5). The chemical methods used to determine electrolytes in red blood cells will be published elsewhere (6).⁶ The other analytical procedures, the methods used in the calculation of results, as well as other details of the balance technique have been described in a previous paper (7).

The measurements of inulin clearance (C_{I_n}), p-aminohippurate clearance (C_{PAH}), endogenous creatinine clearance (C_{Cr}), and the maximal tubular secretory rate for PAH (Tm_{PAH}) were made in the standard manner (8) with the patients well-hydrated and resting in the supine position for at least an hour before the beginning of each study. On one occasion the renal arteriovenous oxygen difference ($A-V O_2$) and the renal extraction of PAH (E_{PAH}) were determined in patient A. B. by the use of simultaneous samples obtained from an inlying peripheral arterial needle and a catheter placed in the right renal vein.⁷ In this case, total renal blood flow was calculated from C_{PAH} , E_{PAH} , and the peripheral venous hematocrit (Hkt). Renal oxygen consumption ($R O_2$) was estimated as the product of total renal blood flow and $A-V O_2$.

The analyses for inulin in serum and urine were done by the method of Roe (9); PAH was determined by Smith's adaptation (10) of the Bratton and Marshall diazo reaction (11), and endogenous creatinine was measured by Hare's modification (12) of Borsook's method (13), which employs Lloyd's reagent for the separation of creatinine from non-creatinine chromogens.

⁵ The authors are indebted to Dr. Belton A. Burrows, Evans Memorial, Massachusetts Memorial Hospitals, for carrying out the K^{42} measurements.

⁶ Dr. Hans Keitel, Senior Assistant Surgeon, U.S.P.H.S., Children's Medical Service, Massachusetts General Hospital, and Department of Pediatrics, Harvard Medical School, performed the red cell analyses for us, and we acknowledge this assistance gratefully.

⁷ The authors are indebted to Drs. Walter E. Judson and James D. Hatcher, Evans Memorial, Massachusetts Memorial Hospitals, for their assistance with this procedure.

TABLE I—

A. B. ♀ 42		Intake							Urine						
Day	Body weight Kgm.	H ₂ O ml.	Na mEq.	K mEq.	Cl mEq.	N gms.	P gms.	Ca mgs.	Vol. ml.	Na mEq. per day	K mEq. per day	Cl mEq. per day	P gms. per day	NH ₄ mEq. per day	N gms. per day
1	44.52	1,200	92	44	94	8.4	.56	100	981	11	9	23	.46	73	7.6
2	44.56	2,000	92	44	94	8.4	.56	100	890	11	8	22	.25	51	6.7
3	45.09	2,000	92	44	94	8.4	.56	100	1,160	17	7	23	.28	49	7.5
4	45.42	2,000	92	44	94	8.4	.56	100	1,370	18	8	20	.34	49	6.9
5	45.61	2,900	92	64	114	8.4	.56	100	1,110	22	9	26	.34	43	6.7
6	45.82	2,020	92	84	134	8.4	.56	100	1,060	27	9	34	.25	36	5.8
7	46.42	2,010	92	64	114	8.4	.56	100	1,019	27	10	32	.25	31	5.5
8	46.79	2,020	92	84	134	8.4	.56	100	1,130	37	12	44	.34	34	5.8
9	46.99	2,020	92	84	134	8.4	.56	100	1,210	45	16	56	.37	39	5.7
10	47.10	2,020	92	84	134	8.4	.56	100	1,480	73	23	89	.37	38	6.1
11	47.69	2,020	92	84	134	8.4	.56	100	1,660	80	24	90	.37	30	7.5
12	47.96	2,020	92	84	134	8.4	.56	100	1,780	128	36	143	.34	27	6.8
13	47.73	2,020	92	84	134	8.4	.56	100	1,805	152	42	165	.34	23	7.6
14	47.75	2,020	92	84	134	8.4	.56	100	3,310	313	73	328	.34	18	7.0
15	46.05	2,020	92	84	134	8.4	.56	100	2,230	168	56	191	.53	15	5.1
16	45.43	2,020	92	84	134	8.4	.56	100	2,410	194	90	224	.53	25	7.2
17	44.97	2,020	92	84	134	8.4	.56	100	2,320	152	84	181	.47	12	6.5
18	44.32	2,020	92	84	134	8.4	.56	100	1,520	77	64	107	.53	20	6.8
19	44.34	2,020	92	84	134	8.4	.56	100	1,630	66	81	108	.59	22	7.3
20	44.69														

Analyses of oxygen content of whole blood were made according to Van Slyke and Neill (14).

Renal concentrating ability was tested by determining the maximum urinary specific gravity (measured by a calibrated urinometer or by direct weighing of urine on an analytical balance) after 18 to 24 hours of dehydration.

RESULTS

I. Metabolic Studies

A. Potassium balance and serum potassium

In the lower halves of Figures 1 and 2 are shown the daily outputs of potassium in urine and stools

superimposed on the total daily intake of potassium. The upper part of each figure depicts the cumulative balance of potassium (corrected for nitrogen with an assumed K/N ratio of 2.7) and the serum potassium concentration. Tables I and II present the complete balance data from which these and subsequent figures are derived.

The two figures are alike in demonstrating a rapid steady rise in serum potassium concentration and cumulative potassium balance. During the first week large positive balances resulted from the

TABLE II—

R. S. ♀ 24		Intake							Urine						
Day	Body weight Kgm.	H ₂ O ml.	Na mEq.	K mEq.	Cl mEq.	N gms.	P gms.	Ca mgs.	Vol. ml.	Na mEq. per day	K mEq. per day	Cl mEq. per day	P gms. per day	NH ₄ mEq. per day	N gms. per day
1	43.56	2,000	85	44	88	8.3	.57	90	1,930	55	3	45	.71	66	7.7
2	43.44	2,000	127	44	130	8.3	.57	90	1,450	62	3	42	.59	45	7.3
3	43.82	2,200	127	44	130	8.3	.57	90	1,450	72	4	54	.46	40	8.4
4	44.36	2,200	127	44	130	8.3	.57	90	1,420	63	4	48	.40	38	6.5
5	44.74	2,200	128	44	131	8.3	.57	90	1,440	68	4	56	.53	36	5.9
6	45.10	2,210	127	64	150	8.3	.57	90	1,550	92	6	78	.43	37	5.9
7	45.47	2,150	127	64	150	8.3	.57	90	1,494	97	6	85	.34	34	6.3
8	45.85	2,210	127	64	150	8.3	.57	90	1,675	92	6	85	.34	39	7.7
9	46.10	2,210	127	64	150	8.3	.57	90	1,870	124	8	116	.34	35	5.4
10	46.09	2,210	127	64	150	8.3	.57	90	2,080	171	10	152	.37	51	5.6
11	45.72	2,210	127	64	150	8.3	.57	90	2,550	249	14	213	.31	42	6.9
12	44.95	2,183	127	73	159	8.3	.57	90	2,743	268	24	240	.24	30	6.0
13	44.10	2,200	127	44	130	8.3	.57	90	3,235	319	34	294	.28	24	6.6
14	42.79	2,200	127	44	130	8.3	.57	90	2,410	207	43	180	.43	13	6.3
15	42.12	2,200	127	44	130	8.3	.57	90	2,210	192	55	160	.71	11	7.1
16	41.64	2,200	127	44	130	8.3	.57	90	1,700	139	60	122	.71	14	7.1
17	41.41	2,200	127	44	130	8.3	.57	90	1,360	80	51	85	.56	19	6.9
18	41.79	2,200	127	44	130	8.3	.57	90	1,710	67	49	77	.53	23	6.5
19	41.78	2,200	127	44	130	8.3	.57	90	1,350	62	36	71	.40	24	6.8
20	41.95	2,200	127	44	130	8.3	.57	90	1,680	84	34	92	.40	25	7.2

Analytical data

T.A. mEq. per day	Org. acids mEq. per day	Ca mgs. per day	pH	Stool						Serum					
				Na mEq. per day	K mEq. per day	Cl mEq. per day	N gms. per day	P gms. per day	Ca mgs. per day	pH	CO ₂ mM per l.	Na mEq. per l.	K mEq. per l.	Cl mEq. per l.	P mM per l.
17	53	6	6.4	21	13	10	1.4	.16	221	7.4	28.0		2.1	94	
9	38	3	6.6	21	13	10	1.4	.16	221			141	2.2		
9	38	4	6.8	21	13	10	1.4	.16	221	7.5	30.5	139	2.2	92	
8	35	6	6.6	25	10	1	1.6	.25	226			139	2.3		
8	35	6	6.8	25	10	1	1.6	.25	226	7.4	28.0	141	2.4	94	0.90
6	34	9	6.8	25	10	1	1.6	.25	226				2.7		
7	34	14	6.9	13	8	7	1.2	.16	151	7.4	28.0	140	3.1	99	1.13
8	35	18	6.7	13	8	7	1.2	.16	151			148	2.9		
6	31	29	6.9	13	8	7	1.2	.16	151	7.4	27.5	145	3.2	101	1.37
8	30	56	6.7	13	8	7	1.2	.16	151			146	3.7		
9	29	66	6.7	13	8	7	1.2	.16	151				4.0		
7	33	66	6.9	13	8	7	1.2	.16	151	7.4	27.0		4.0	104	1.26
8	31	69	6.8	4	10	3	0.9	.12	159				4.2	102	
4	27	91	6.9	4	10	3	0.9	.12	159	7.4	25.5	141	4.6	102	1.52
8	38	73	6.8	4	10	3	0.9	.12	159			142	4.8		
12	38	49	6.9	4	10	3	0.9	.12	159	7.4	27.5		5.1	103	1.34
13	38	58	6.9	4	10	3	0.9	.12	159				5.0	104	
15	37	61	6.0	4	10	3	0.9	.12	159						
15	38	36	6.5	4	10	3	0.9	.12	159	7.4	26.0	140	4.4	105	1.45
												141	4.9		

low renal excretion of potassium. The average urine potassium in this period was only 4 mEq. per day in R. S. and 9 mEq. per day in A. B., despite the fact that both subjects excreted approximately 1 to 2 l. of urine per day containing 6 to 8 gms. of total nitrogen.

In A. B. (Figure 1), urinary excretion rose rapidly after the eleventh day, resulting in an abrupt termination of the potassium-retention phase. Potassium uptake was complete after 13 days when A. B. had retained a total of 536 mEq.

in excess of nitrogen (12 mEq. per kgm. of final weight). At the same time serum potassium concentration reached normal levels. Thereafter, urine output of potassium kept pace with intake and there was no further significant change in serum potassium or external potassium balance.

The course of events in R. S. was quite similar to that in A. B. except that retention of potassium continued until serum potassium had reached abnormally high levels. Serum drawn a few hours after the evening meal on the twelfth day had a

Analytical data

T.A. mEq. per day	Org. acids mEq. per day	Ca mgs. per day	pH	Stool						Serum					
				Na mEq. per day	K mEq. per day	Cl mEq. per day	N gms. per day	P gms. per day	Ca mgs. per day	pH	CO ₂ mM per l.	Na mEq. per l.	K mEq. per l.	Cl mEq. per l.	P mM per l.
17	32	56	6.5	4	6	2	1.2	.37	170	7.43	30.0	147	2.7	100.5	1.42
12	34	30	6.6	4	6	2	1.2	.37	170				2.2		
9	31	35	6.8	4	6	2	1.2	.37	170	7.47	33.5		2.8	101.0	0.97
9	32	34	6.7	4	6	2	1.2	.37	170				3.3		
11	33	33	6.7	4	6	2	1.2	.37	170	7.46	32.5	146	3.2	102.0	1.26
10	36	46	6.8	4	6	2	1.2	.37	170	7.47	32.0	144	3.3	102.0	
8	34	57	6.6	4	6	2	1.2	.37	170			147	3.5		1.29
2	37	35	7.2	4	6	2	1.2	.37	170	7.43	28.0	145	3.2	107.0	1.35
4	30	54	6.9	13	6	7	0.8	.12	83			147	4.0	108.0	1.31
none	37	71	7.7	13	6	7	0.8	.12	83	7.45	29.0	147	4.0	107.0	1.32
none	39	78	7.7	1	2	1	0.2	.06	35						
none	35	70	7.6	1	2	1	0.2	.06	35	7.45		146	5.0	105.0	1.32
4	36	76	7.3	1	2	1	0.2	.06	35	7.45	28.0	145	5.6	108.0	1.41
11	34	33	6.7	1	2	1	0.2	.06	35			145	5.6	105.0	1.36
13	33	51	6.6	1	2	1	0.2	.06	35	7.45	27.5	146	6.1	105.0	1.34
16	32	51	6.5	1	2	1	0.2	.06	35			144	5.6	107.0	
20	35	46	5.7	1	2	1	0.2	.06	35	7.44	25.0		5.2	107.0	1.52
21	34	72	5.7	1	2	1	0.2	.06	35						
17	35	41	5.7	1	2	1	0.2	.06	35	7.42	26.0	143	4.3	108.0	1.52
19	34	60	5.3	1	2	1	0.2	.06	35		26.0			107.0	

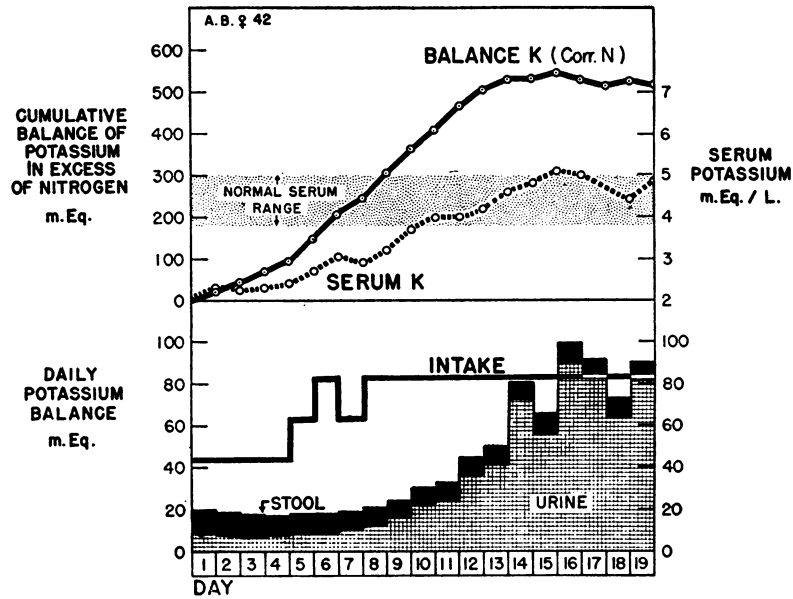


FIG. 1. SERUM POTASSIUM, CUMULATIVE POTASSIUM BALANCE, AND DAILY EXTERNAL BALANCE OF POTASSIUM, PATIENT A. B.

potassium concentration of 7.5 mEq. per l. At this time, electrocardiographic tracings showed evidences of hyperkalemia and it was deemed advisable to reduce the patient's oral intake of potassium from 73 to 44 mEq. per day in order to avoid further intoxication. On the fifteenth to eighteenth days of the study urinary excretion exceeded intake and the cumulative retention of

potassium in excess of nitrogen gradually declined to a final level of roughly 445 mEq. (10.8 mEq. per kgm. of final weight), while the serum concentrations returned to normal.

B. Total exchangeable potassium

In A. B. total exchangeable potassium was determined at the beginning and end of the balance

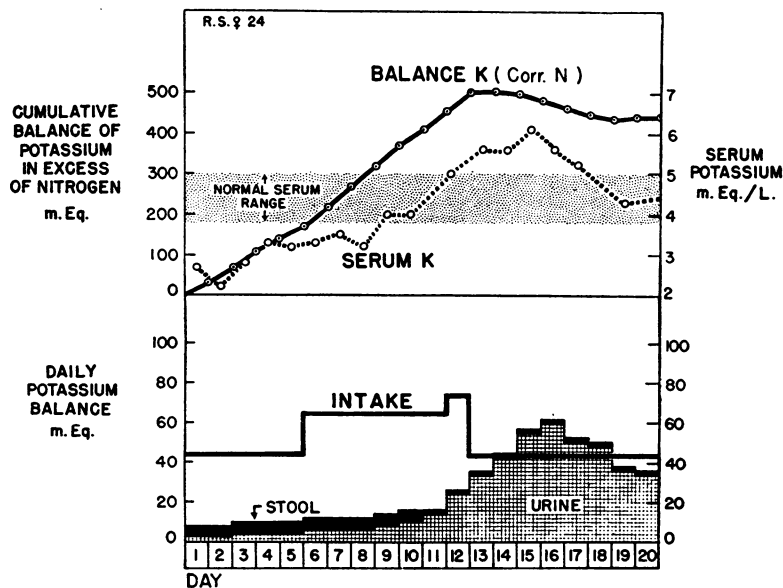


FIG. 2. SERUM POTASSIUM, CUMULATIVE POTASSIUM BALANCE, AND DAILY EXTERNAL BALANCE OF POTASSIUM, PATIENT R. S.

TABLE III
Correlation of potassium balance and exchangeable potassium, patient A. B.

Time	Exchangeable K mEq.	Change in exchangeable K mEq.	Change in K balance mEq.
Day 0	1,120	—	—
Day 19	1,659	+539	+548

period. These values are compared in Table III with the observed change in potassium balance. It will be seen that, at the beginning of the study, this patient's total exchangeable potassium was only 1120 mEq., or 25.2 mEq. per kgm. (Mean normal for women by this technique is 41 mEq. per kgm. [15].) At the end of the balance this figure was 1659 mEq., or 37.3 mEq. per kgm. This increase of 539 mEq. is almost identical with the

observed total cumulative retention of 548 mEq. over the same period.

In R. S. the first determination of exchangeable potassium was made on the sixth day of study. Correcting the observed figure of 1425 mEq. for the over-all retention of potassium prior to, and subsequent to, this determination, one derives an estimate for initial exchangeable potassium of 27.0 mEq. per kgm. and a final figure of 40.4 mEq. per kgm. Several weeks after this study was completed, total exchangeable potassium, determined on two occasions, averaged 39.4 mEq. per kgm.

In each instance, therefore, initial body potassium content was far below normal limits, but was restored to normal at the end of the balance. The potassium deficit was approximately one-third of the normal total exchangeable potassium content.

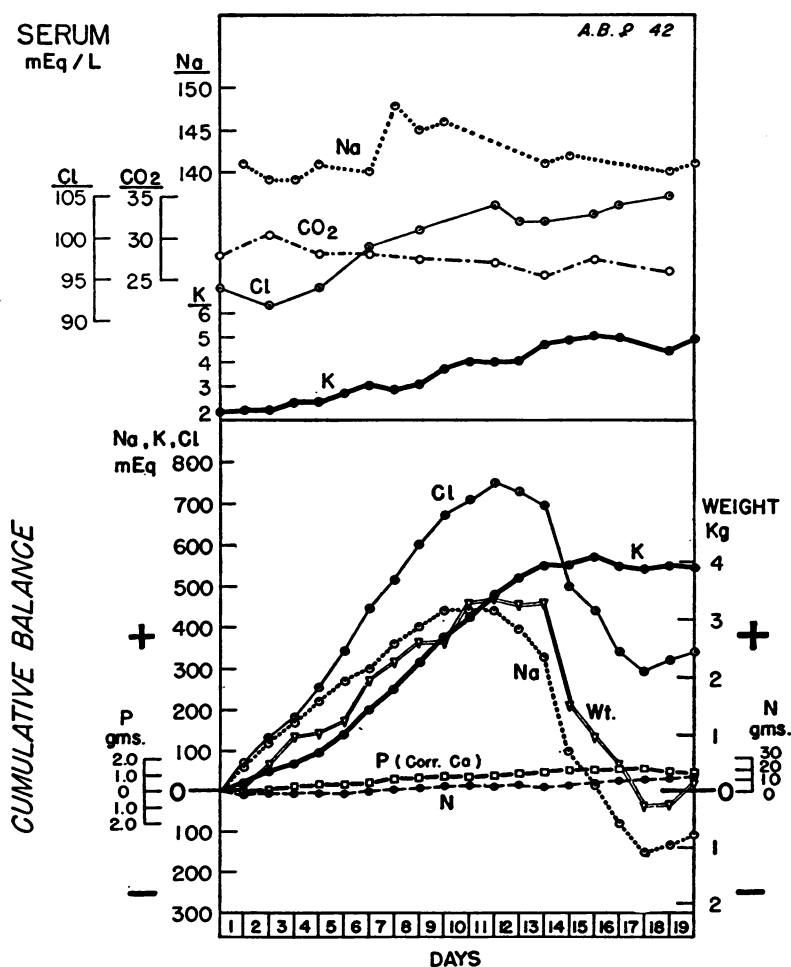


FIG. 3. CUMULATIVE ELECTROLYTE AND NITROGEN BALANCE, WEIGHT CHANGES, AND SERUM ELECTROLYTES, PATIENT A. B.

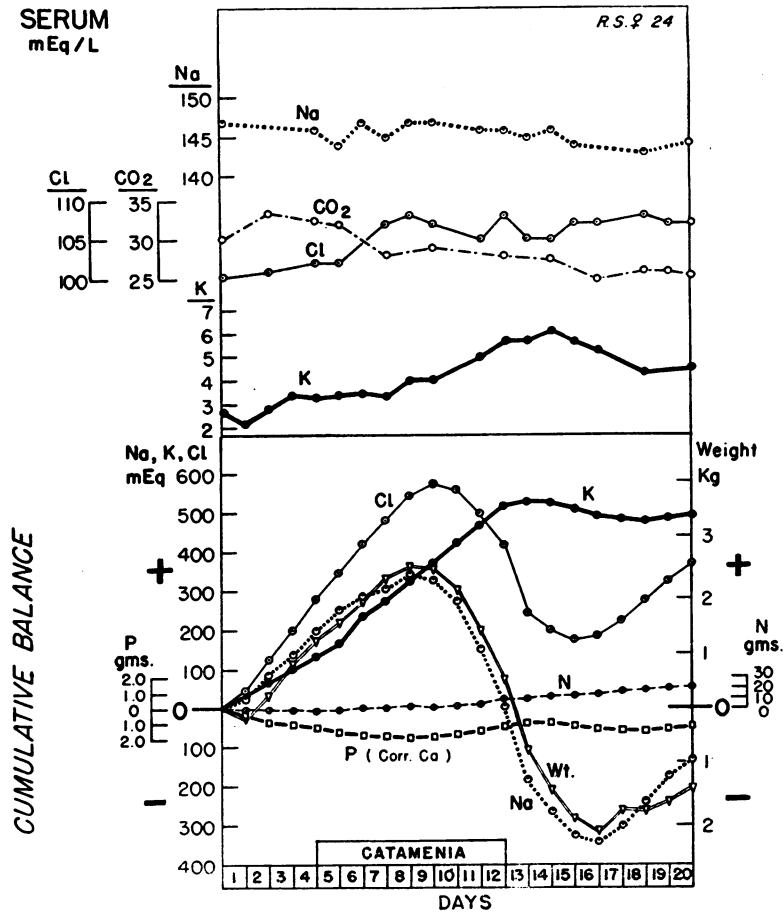


FIG. 4. CUMULATIVE ELECTROLYTE AND NITROGEN BALANCE, WEIGHT CHANGES, AND SERUM ELECTROLYTES, PATIENT R. S.

C. Serum electrolytes and pH

The upper sections of Figures 3 and 4 show the values for serum electrolyte concentrations. Both subjects initially had a marked hypokaliemia which improved gradually as described in Section A. Sodium concentrations were normal in both subjects and did not change significantly. Serum chloride concentration was a little low in A. B., but only in R. S. (Figure 4) was there a slight increase in initial serum bicarbonate. As potassium balance was restored in this patient, serum bicarbonate concentration returned to normal. In A. B. (Figure 3), although serum bicarbonate fell only 2 mEq. per l., chloride concentration rose 10 mEq. per l. This suggests the disappearance from the serum of some unmeasured anion, possibly an organic acid, which had been present during the potassium-depleted state. Serum pH (Tables I

and II) was always within normal limits and did not vary significantly as potassium was accumulated.

D. Electrolyte balances and weight changes

In the lower halves of Figures 3 and 4 are plotted cumulative changes in body weight and in external balance of electrolytes and nitrogen. The scale for the cumulative weight change is so chosen that one kilogram on the weight scale is equivalent on the electrolyte scale to 140 mEq. (This latter value was the approximate mean sodium concentration in extracellular fluid.) When changes in weight are due solely to changes in extracellular fluid volume the lines indicating sodium balance and weight should be parallel, provided that extracellular sodium concentration remains the same. Unmeasured skin losses would cause deviation of the weight and the sodium curves. Little or no sweat-

ing occurred during these experiments so that unmeasured losses of sodium through the skin were probably only 5 to 10 mEq. per day (16).

During the initial phase of potassium repletion there was a striking retention of sodium and chloride which was followed by rapid diuresis of these ions just as potassium retention was approaching completion. In R. S. retention of sodium occurred just prior to and during menstruation, but A. B., who was not menstruating, showed similar retention of sodium.

The cumulative weight curve in each subject was closely related to the change in extracellular fluid volume predicted from sodium balance, and the close adherence of the two curves would suggest that expansion and contraction of extracellular fluid volume was responsible for the changes in weight. The curve of chloride balance paralleled that of sodium, but chloride retention always greatly exceeded sodium retention. On the thirteenth day in R. S. (Figure 4) and on the fifteenth day in A. B. (Figure 3), when the cumulative changes in weight and sodium balance were approximately zero, it should be noted that there were positive balances of potassium and chloride of approximately 500 mEq. each. This retention occurred without significant change in body fluid tonicity as measured by the sum of the concentrations of extracellular sodium and potassium.

E. Calcium, phosphorus and nitrogen balance

The scales for nitrogen and phosphorus balances in Figures 3 and 4 are related to each other and to the scale for electrolytes so that 1 gm. of phosphorus equals 14.7 gms. of nitrogen or 39.7 (14.7 × 2.7) mEq. of potassium. These are the approximate relations of these substances in protoplasm (17) and parallel curves for nitrogen, phosphorus, and potassium are therefore presumed to indicate that changes in the balance of these substances are due to gain or loss of tissue.

It is immediately obvious from a consideration of the figures that nitrogen retention was small and the retention of potassium was far in excess of the retention of nitrogen.

Using a Ca/P ratio for bone of 2.23 (17), the phosphorus balances plotted in Figures 3 and 4 have been corrected for calcium balances (Tables I and II). The small negative balances of calcium probably were the result of the relatively low cal-

TABLE IV
Internal balances

Subject	Intracellular sodium mEq.	Intracellular potassium mEq.
A. B. Days 1-15	-483	+505
R. S. Days 1-14	-454	+462

cium intake (18). The cumulated corrected phosphorus retention for A. B. (Figure 3) exceeds the retention predicted from nitrogen balance by +.54 gm. This is within the limits of error in analysis and balance technique (17). In R. S. (Figure 4) the corrected phosphorus balance was 2.6 gms. less than that predicted from the nitrogen balance. This may indicate a small loss of phosphorus from cells. In any event, it is quite clear from these figures that potassium retention occurred with little or no change in the cell balance of phosphorus.

F. Cell balances of sodium and potassium

Shifts of sodium and potassium to and from intracellular fluid at the end of the two-week period

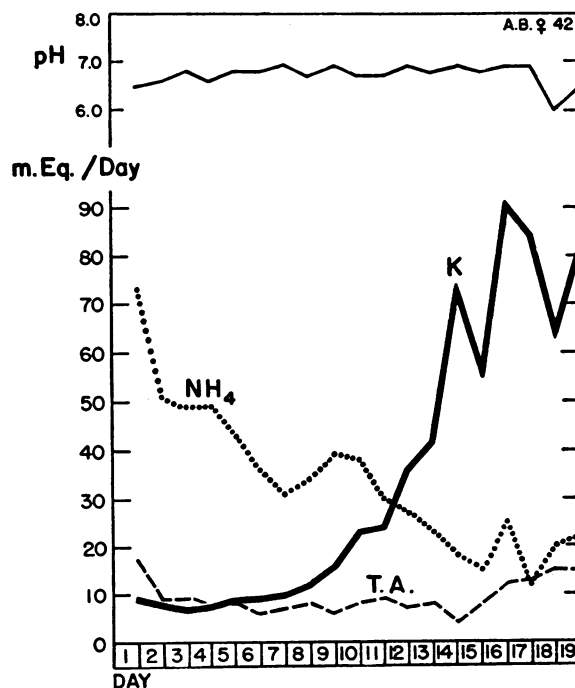


FIG. 5. RENAL EXCRETION OF AMMONIUM, TITRATABLE ACID AND POTASSIUM, AND URINE pH, PATIENT A. B.

of potassium repletion are shown in Table IV. The similarity of the magnitude of the shifts at the time of complete repair in both subjects and the almost equal exchange of sodium for potassium are striking. In R. S. it is estimated that 462 mEq. of potassium entered cells in exchange for 454 mEq. of sodium. In A. B. 483 mEq. of sodium left cells while 505 mEq. of potassium were taken up.

G. Red blood cell composition

Initial concentrations of sodium, potassium and phosphorus, expressed either as "per kgm. of red

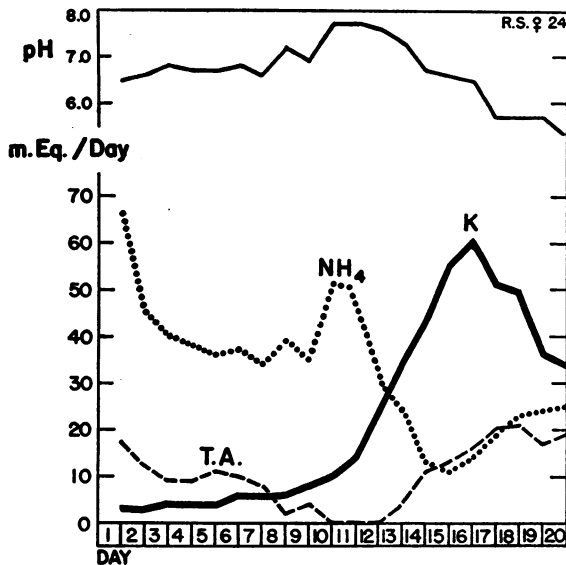


FIG. 6. RENAL EXCRETION OF AMMONIUM, TITRATABLE ACID AND POTASSIUM, AND URINE pH, PATIENT R. S.

(The ammonium excretion for the eleventh day has been plotted incorrectly. It should be 42 mEq.)

blood cell solids" or "per kgm. of red blood cell water," were both within normal limits (19). During potassium repletion there was a rise in each patient of approximately 13 per cent in red cell potassium content, but the final values were still normal. Red cell phosphorus did not change significantly.

H. Urine pH, excretion of ammonium, titratable acid, and organic acids

The changes in urine pH, ammonium, and titratable acid, and the relation of these values to urinary potassium are shown in Figures 5 and 6.

TABLE V*
Renal function data, patient R. S.

Patient R. S. ♀ 24	Before K therapy 10/2/51	After K therapy		
		11/6/51	11/29/51	2/7/52
C_{Ia} ml./min.	—	103	99	116
C_{Cr} ml./min.	—	88	111	133
PCr † mgm. %	—	.82	.76	.71
C_{PAH} ml./min.	—	379	462	507
FF %	—	27.3	21.4	22.9
Hkt %	—	37.4	39.0	42.5
ERBF ‡ ml./min.	—	606	758	882
TMP_{PAH} mgm./min.	—	74	90	93
Sp. Gr.	1.013	1.013	—	1.026

* All clearance and TMP_{PAH} values corrected to 1.73 sq. m.

† Serum creatinine concentration.

‡ Effective renal blood flow, calculated from C_{PAH} and Hkt.

An outstanding feature of each figure is the progressive decline in excretion of ammonium. In A. B. (Figure 5), ammonium decreased without significant alteration in urine pH or titratable acid. In R. S. (Figure 6), the sharp decline in urinary ammonium which began on the twelfth day was associated with a fall in urine pH and a rise in titratable acidity.

Except for the period of the initial fall in ammonium excretion when the balance regime was started, there was a roughly inverse relationship between excretion of ammonium and potassium.

Excretion of total organic acids did not change significantly at any time in either patient.

TABLE VI*
Renal function data, patient A. B.

Patient A. B. ♀ 42	Before K therapy 1/16/52	After K therapy		Following diarrhea 7/15/52
		2/5/52	3/21/52	
C_{Ia} ml./min.	43	72	103	73
C_{Cr} ml./min.	56	88	125	87
PCr mgm. % §	.87	.94	.70	.79
C_{PAH} ml./min.	315	376	584	346
FF %	14.0	19.2	17.7	21.0
Hkt %	38	29	35	35
ERBF † ml./min.	508	530	897	531
TMP_{PAH} mgm./min.	45	53	71	69
EP_{PAH}	—	.71	—	—
RBF ‡ ml./min.	—	746	—	—
A-V O_2 vols. %	—	1.33	—	—
R O_2 ml./min.	—	9.9	—	—
Sp. Gr.	1.005	1.015	1.025	—

* All clearances, TMP_{PAH} and R O_2 corrected to 1.73 sq. m.

† Effective renal blood flow, calculated from C_{PAH} and Hkt.

‡ True renal blood flow, calculated from ERBF and EP_{PAH} .

§ Serum creatinine concentration.

II. Renal Function Studies

The renal function data are presented in Tables V and VI. All clearances and T_m values are corrected to a standard surface area of 1.73 sq. m.

1. Patient R. S. (Table V):

The first observations were made approximately a week after this patient's potassium deficit had been corrected. C_{In} and T_{mPAH} were at the lower limits of normal, but C_{Cr} and C_{PAH} were slightly below normal. Prior to restoration of potassium balance as well as immediately thereafter, dehydration for 18 hours had resulted in a maximum urine specific gravity of only 1.013.

During the subsequent months, the patient remained well and her serum potassium concentration and electrocardiographic records did not show any evidence of recurrence of potassium depletion. Three weeks after the first observations C_{Cr} and C_{PAH} were at the lower limits of normal and T_{mPAH} had increased from low normal to high normal values. Final observations made 10 weeks later (14 weeks after the restoration of potassium balance) revealed that all renal functions were unequivocally normal. As indicated in Table V, C_{Cr} , C_{In} , and C_{PAH} increased slightly, but T_{mPAH} remained at its previous high normal level. The patient was now able to concentrate her urine to 1.026.

2. Patient A. B. (Table VI):

A. B.'s renal function was first measured immediately before restoration of her potassium deficit was begun. C_{In} was 43 ml. per min. and C_{Cr} was 56 ml. per min. T_{mPAH} was also greatly reduced and C_{PAH} was little more than half of normal. Maximum urine specific gravity was only 1.005.

The second observation was made immediately after body potassium had been completely restored. At this time all functions measured were considerably improved, but nevertheless they were still far below normal. Renal A-V O_2 difference was normal, but renal oxygen consumption was 9.9 ml. per min. (normal about 16 ± 2.9 ml. per min. [20]), and E_{PAH} was only .71. True renal blood flow (RBF) was therefore considerably higher than the effective blood flow (ERBF) and was near the lower limit of normal. Maximum specific gravity was 1.015.

During the next six weeks the patient remained well, and occasional electrocardiographic tracings and serum potassium determinations were normal. At the end of this time, a third evaluation of renal function revealed that all functions measured (C_{In} , C_{Cr} , C_{PAH} , T_{mPAH}) had increased substantially and were now within normal limits. A concentration test produced a maximum urine specific gravity of 1.025.

The final study of renal function listed in Table VI was carried out at the end of a two-week period of diarrhea, when the serum potassium was 3.0 mEq. per l. and the electrocardiogram showed marked changes in Q-T interval and T-waves consistent with hypokaliemia. C_{Cr} , C_{In} , and C_{PAH} were now roughly 30 per cent below their previously normal levels, but T_{mPAH} was essentially unchanged.

DISCUSSION

That excessive use of laxatives was the sole cause of the potassium depletion in these two women is not proven conclusively by these data, but the clear-cut history of diarrhea related to the chronic use of laxatives and the lack of evidence for any other mechanism make this conclusion highly probable. Furthermore, when R. S. was allowed to use laxatives again, balance study demonstrated loss of potassium in the diarrheal stools and a negative daily potassium balance (21). The concentration of potassium in stool water during this laxative-induced diarrhea was 50 to 55 mEq. per l., and the stools contained 2 to 4 per cent of solids.

The extraordinarily severe potassium deficits in these two women apparently developed gradually over a period of months or years without producing any striking symptoms or signs. This suggests that the rate at which potassium depletion develops is of importance in determining symptomatology. Although rapid loss of potassium from isolated perfused muscle will reduce contractility (22), it has been shown that the gradual production of potassium depletion in rats does not impair the muscular response to a tetanic stimulus (23) or reduce the animals' swimming ability (24). Further evidence that tissue may become acclimatized to potassium deficiency is provided by the "potassium paradox" of Libbrecht (25).

The important contribution of renal "leakage"

of potassium to the development of potassium depletion in man has been emphasized (26, 27). Although there are no observations on the efficiency of renal conservation of potassium early in the development of the potassium deficit in the two cases reported here, the data in R. S. demonstrate unequivocally that, with prolonged depletion, renal excretion of potassium may sometimes be reduced to extremely low levels despite normal urine volumes. In this patient the renal excretion of potassium during repair remained so low that her body fluids became temporarily surfeited with this ion and signs of potassium intoxication appeared in the electrocardiogram. This temporary failure in renal regulation may have been due in part to impairment of renal function.

The very close correlation between total exchangeable potassium and the potassium balance in patient A. B. is noteworthy. This observation implies that exchangeable potassium measured the metabolically active pool of potassium in the body, irrespective of whether it measured total body potassium.

The apparent discrepancy between the net balance of water and cations (Section D, above) could have resulted from excessive unmeasured skin losses of electrolytes or from other systematic errors in balance technique. However, in the absence of any evidence for such an explanation, it would appear likely that uptake of potassium was associated with a reduction in the osmotic activity of some intracellular constituent (28, 29). Total intracellular cation concentration (calculated on the assumptions that $[a]$ "chloride space" is equivalent to extracellular space, and $[b]$ intracellular calcium and magnesium did not change [29]) increased approximately 40 mEq. per l. in R. S., and 25 mEq. per l. in A. B. If the final tissue composition was normal, this would indicate a low intracellular cation concentration prior to treatment. Similar changes are regularly found in the muscles of potassium-deficient rats (29).

Restoration of tissue potassium was also accompanied by a large but transient retention of sodium, an observation similar to that made by Elkinon, Squires, and Crosley (30). Sodium retention may have been related to the reversible disturbances in renal function observed in the present patients. No explanation can be offered at present for the sustained retention of chloride

(Figures 3 and 4) and expansion of the "chloride space."

The absence of significant alkalosis in these patients despite a prolonged period of severe potassium depletion requires consideration. It has been suggested that the alkalosis usually present in potassium deficiency may be due, at least in part, to exchange of intracellular potassium for extracellular hydrogen ions (31, 32). The approximate equivalence of the sodium and potassium shifts listed in Table IV would suggest that no large transfers of hydrogen occurred in either of the present cases. However, the methodological errors inherent in these calculations (31) preclude close interpretation of the data. Further evidence against a shift of hydrogen ions from the cells can be deduced from the fact that the excretion of ammonium plus titratable acid decreased during the uptake of potassium. This is in contrast to the findings of Cooke and associates (32), who observed an increased excretion of ammonium and titratable acid during treatment of potassium-deficient, alkalotic rats. Interpretation of the present data is complicated by the possibility that previous loss of bicarbonate in the diarrheal stools may have affected the acid-base balance.

The observations of urinary excretion of ammonium and potassium depicted in Figures 5 and 6 show that, contrary to prevailing hypotheses (33), changes in ammonium excretion were independent of changes in urine pH. The rapid decline in urinary ammonium coincided with an increase in the excretion of potassium and sodium in both subjects. Such an inverse relationship between the urinary excretion of potassium and ammonium might be expected if renal ammonium production involves secretion of hydrogen ions (33) and if there is a competition between tubular secretion of hydrogen and potassium (34). However, the hypothesis of hydrogen-potassium competition would still fail to explain the apparent indifference of urine pH and titratable acidity to the large changes in potassium excretion.

An alternative explanation is that ammonium may, under certain conditions, passively serve the demands of electroneutrality in the urine by acting as "available cation." According to this hypothesis the presence of increasing amounts of potassium ions in the tubular fluid would, if all other relevant factors were kept constant, reduce the stimu-

lus for release of ammonia by reducing the potential excess of urinary anions over cations. However, in view of the evidence presented here that potassium depletion impairs certain tubular functions, any interpretation of these data must be considered for the present as only tentative.

The unexpected discovery of fixed urine specific gravity in patient R. S. while she was potassium-depleted suggested that more detailed study of her renal function might be of interest. It was not until after balance studies had been completed and potassium balance restored that the clearances reported in Table V could be carried out. The changes in renal function in this patient were small but they suggested that glomerular and tubular function may have been impaired during the period of potassium depletion.

The more complete observations in patient A. B. who also initially exhibited isosthenuria indicated that there was marked impairment of glomerular and tubular function during potassium depletion which slowly returned to normal after treatment with potassium. Immediately after a second episode of diarrhea and potassium depletion renal function was found once more to be distinctly impaired.

Both patients had habitually ingested laxative mixtures containing aloin. Although this anthraquinone compound is said to cause renal damage in rabbits when administered subcutaneously in total doses of 0.2 to 2.25 gms. over a period of 1 to 40 days (35), the quantities of aloin ingested by these patients over a comparable period were far below this toxic level. Furthermore, humans are resistant to the nephrotoxic action of aloin because they excrete practically none of this substance in the urine when the drug is taken by mouth (36).

Disorders of fluid and electrolyte metabolism known to impair renal function, such as dehydration, sodium depletion, and alkalosis, were not present in these patients. The absence of any concomitant weight gain or retention of nitrogen suggests that the improvements in renal function cannot be ascribed to improved nutrition. Recent serial studies of another patient with severe chronic potassium depletion have also revealed reductions in glomerular and tubular function which were restored within six weeks by treatment with potassium (21). Although this patient's po-

tassium depletion was complicated by steatorrhea and malnutrition, there was no clinical change in these factors during the period of observation, and there were no other known disorders of water or electrolyte balance. The present data would therefore strongly suggest that potassium depletion may depress renal function.

Tubular dysfunction in these patients may be related to the observations of altered renal tubular morphology in potassium-deficient rats (37) and in patients dying with clinical evidences of potassium depletion (38, 39). The apparent changes in renal plasma flow could have been due in part to reductions in the tubular extraction of PAH such as occurred in patient A. B. (See Table VI.) In addition, plasma flow, as well as glomerular filtration, may have been affected by the expansion of the "chloride space" which occurred during uptake of potassium (Figures 3 and 4).

Renal dysfunction of the type reported here could account for certain phenomena associated with severe potassium depletion. Sodium retention (30, 40, 41), elevated blood nitrogen concentration (40), and reduced urea clearance (41) may be in part due to the reduction in glomerular filtration. Renal tubular damage could explain the isosthenuria in these and other cases of potassium depletion (38, 39, 42) as well as the polyuria in potassium-deficient dogs (43) and rats (44). The failure of the kidney in potassium depletion to adjust extracellular bicarbonate concentration (32) may also be related to the functional disorders reported here. Another interesting implication of these data is that potassium depletion may be responsible at least in part for the renal dysfunction found in many cases of alkalosis (30, 45).

SUMMARY AND CONCLUSIONS

Balance studies were carried out on two women who had gradually developed severe potassium depletion and hypokaliemia as the result of chronic diarrhea induced by overuse of laxatives. Neither of the patients had any overt neuromuscular symptoms or signs, and it was only through the discovery of T-wave changes in routine electrocardiograms that hypokaliemia was discovered. There were no other disturbances of serum electrolytes except for slight elevation of plasma bicarbonate in one patient. Red cell sodium, potassium and

phosphorus concentrations were normal. Renal excretion of potassium was very low.

When laxatives were withdrawn and the patients given normal oral intakes of potassium, each retained an amount of potassium roughly equivalent to one-half her total initial body potassium content (as estimated by K^{42} dilution), without significant retention of nitrogen or phosphorus. Changes in total exchangeable potassium were approximately equal to the actual potassium retention. In both instances potassium retention was accompanied by a large but transient retention of sodium. Internal balance calculations indicated that cellular uptake of potassium was approximately equal to the estimated loss of intracellular sodium and that total initial intracellular cation concentration was markedly reduced. Excretion of ammonium was relatively high initially and during correction of the potassium deficit ammonium diminished rapidly without significant change in urine pH or titratable acidity.

Ability to concentrate the urine was impaired in both patients prior to treatment, but was restored to normal after correction of the potassium deficit. Clearance studies begun immediately after treatment in the first patient revealed slight reductions in glomerular and tubular function. In the second patient glomerular and tubular functions were found to be markedly depressed prior to therapy. After correction of the potassium deficit there was a gradual return to normal of all functions in both patients. It is suggested that renal dysfunction may account for certain disturbances in water and electrolyte metabolism observed in potassium deficiency.

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