EXPERIMENTAL POTASSIUM DEPLETION IN NORMAL HUMAN SUBJECTS. I. RELATION OF IONIC INTAKES TO THE RENAL CONSERVATION OF POTASSIUM*

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(Submitted for publication June 3, 1958; accepted February 19, 1959)

When healthy human subjects ingest a diet deficient in potassium but not in calories and protein, the daily loss of potassium in the urine progressively decreases (1–7). Since the daily urinary loss often continues to exceed the daily intake (2, 3, 6), prompt and effective renal conservation of potassium has been questioned. Furthermore, the fecal excretion of the ion has been found to exceed the intake when the latter is low (2). But these studies do not indicate to what level the intake of potassium must fall before the renal excretion and the fecal excretion consistently exceed the intake and lead to a progressive deficit of the ion. Nor do these studies completely define the conditioning effects of intakes of other major ions on the excretion of potassium during varying degrees of potassium deprivation.

The aim of this paper is to report quantitative data describing the loss of potassium in the urine and feces of human subjects while ingesting low potassium diets and to discuss certain metabolic corollaries of the loss of potassium in urine and feces relevant to the physiological regulation of potassium excretion.

EXPERIMENTAL PROCEDURE AND METHODS

Human subjects. Fourteen balance studies were done in 11 volunteer male subjects (nine medical students and the authors). By the criteria of the medical history and physical examination every subject appeared to be in good health. However, Subject T. C. was subsequently shown by roentgen examination to have an asymptomatic duodenal ulcer.

The study design. The basic study plan consisted of a control period lasting three to eight days, and a potassium depletion period lasting six to 21 days. The duration of each study largely depended upon how long the subject could remain on the Metabolic Unit or tolerate the dietary restriction. During the control period a measured "normal diet" was ingested. Potassium depletion was studied at three levels of potassium intake: 25 to 27 mEq. per day, 14 to 16 mEq. per day, and less than 1 mEq. per day.

Experiments were designed to study, in the depletion period, the effect on urinary and fecal potassium loss of: *1*) a normal or high sodium intake throughout the entire study; *2*) ingestion of sodium and potassium with chloride or with chloride and bicarbonate in a ratio of 3:1; *3*) a low intake of 14 mEq. of sodium per day during the depletion period; and *4*) progressively increasing oral doses of KCl to more than 300 mEq. per day in the control period.

The renal conservation of potassium and sodium was compared in separate studies in which the intake of either ion averaged 15 mEq. per day.

Potassium skin loss was not measured in our subjects; such loss of potassium during normal potassium intakes amounts to about 4 mEq. per day (8, 9). No correction for skin loss was made.

Subjects were allowed normal activity in the hospital and medical school during the cool fall and winter months. Studies conducted during the warm spring and summer months took place in the air-conditioned Metabolic Unit or air-conditioned portions of the hospital. Balance periods lasted 24 hours, starting at 7 a.m. The subject was awakened at that time and voided urine immediately. He was then weighed, and blood was drawn. He was then given breakfast.

Urine and stool collection. Urine was voided into a screw-capped, wide-mouthed jar large enough to hold the 24 hour specimen, as well as a measured constant amount of mineral oil and chloroform or toluol. Urine was refrigerated between voidings. Feces were collected for periods from two to eight days according to the study plan. They were passed directly into tared, wax-impregnated cardboard containers which were kept covered and refrigerated when not in use.

The stools in the depletion periods of Subjects L. P., H. F., E. H.$_1$, E. H.$_2$, R. S.$_1$ and R. S.$_2$ were demarcated with either barium sulfate or charcoal.

* This study was aided by Grant H-340 of the National Heart Institute of the United States Public Health Service and by the C. Mahlon Kline Fund of the Department of Medicine, University of Pennsylvania, Philadelphia, Pa.

† Part of the work was done during Dr. Squires' tenure of a J. Allison Scott Fellowship, Department of Research Medicine, University of Pennsylvania, 1952–1953.

‡ Part of the work was done during Dr. Huth's tenure of a Life Insurance Medical Research Fund Postdoctoral Fellowship, 1952–1953.

A stool-marking agent, charcoal or carmine, was given to Subjects R. A., J. B., J. D., C. P. and J. M. on their arrival on the Metabolic Unit; stool preceding this marker was discarded. The ends of the control period and the depletion period were likewise marked. Two to six day intervals were also marked during the control and depletion periods in some studies. Stool data from only these subjects were used in estimating the daily decline of the measured constituents.

Blood was drawn with minimal stasis and clotting took place under oil at room temperature. Serum was separated anaerobically.

Dietary procedure. Water was allowed *ad libitum* and the amount drunk each day was recorded. Subjects ingested all the food given; when possible, food was eaten from the container in which it was prepared so that the juices and small fragments of food could be completely ingested. Metabolic diets were made up from the following food sources: *1*) weighed portions of previously analyzed foodstuff; *2*) commercial dialyzed milk preparations [Theralac®, Lonalac® (Mead Johnson formula L.P. 412)],[1] and fresh whole homogenized milk passed through a monobed ion exchange resin column (Amberlite MB-3)[2]; *3*) lactose; *4*) the addition of measured quantities of $NaHCO_3$, NaCl, KCl, Ca lactate and NH_4Cl when needed as supplements; and *5*) multivitamin supplements.

Subjects on diets containing about 25 mEq. potassium per day were given diets containing solid food. Those on lower potassium intakes consumed whole milk, lactose and vitamin supplemented diets. The total calories ingested were kept constant throughout each study. In a few cases nitrogen intake was reduced during the depletion period.

Specific methods, chemical determinations and calculations

Diet. Samples of homogenized, whole 24 hour diets were analyzed as well as individual samples of the foodstuff comprising this diet. Whole diet analysis was carried out periodically as a check on the summing of previous food analytical values. Agreement was satisfactory for Na, K and N; Cl was somewhat variable. Diets consisting only of treated whole milk were analyzed daily.

Foods were prepared for analysis by nitric acid digestion (10), except for samples analyzed for total nitrogen by the macro-Kjeldahl method.

Chemical determinations. Sodium and potassium were determined by means of a Barclay internal standard flame photometer by the method of Wallace, Holliday, Cushman and Elkinton (10), serum chloride by the method of Franco and Klein (11) and urine chloride by the method of Harvey as described by Peters and Van Slyke (12). Urinary ammonia was measured by the method of Folin and Bell (13). Urinary titratable acidity was measured by titrating an aliquot to pH 7.4 with 0.01 N sodium hydroxide using a Beckman pH meter to determine the endpoint, venous serum CO_2 by the method of Stadie and Van Slyke (14), urine CO_2 by the method of Peters and Van Slyke (12) and serum and urine creatinine by the method of Bonsnes and Taussky (15). Nitrogen was determined by the macro-Kjeldahl method (12). Finger blood pH and carbon dioxide content were determined by the method of Singer and Hastings (16).

Metabolic calculations, with the few exceptions noted in the Results, were performed as previously described (17).

[1] Mead Johnson formula L.P. 412 was kindly supplied by Dr. Warren Cox, Evansville, Ind.

[2] Amberlite MB-3 was obtained from Fisher Scientific Company, 633 Greenwich Street, New York 14, N. Y.

RESULTS

The observed data are recorded in Tables I to VIII.

Renal potassium excretion during the potassium depletion period

The daily rate of renal potassium excretion on a given day varied with the level of oral sodium intake in the depletion period and with the difference between the oral potassium intake in the control and depletion periods. Higher than normal levels of oral sodium intake tended to increase the rate of potassium excretion and lower than normal oral sodium intake may have reduced the rate of renal potassium excretion during the potassium depletion period. When the oral potassium intake was raised to three or four times the normal level during the control period the rate of renal potassium excretion was initially increased in the depletion period.

The lower the oral potassium intake during depletion the lower the daily urinary potassium content. However, the urinary potassium loss continued to be greater than the oral potassium intake when the intake fell below 14 mEq. per day for up to 21 days in one study.

1. Subjects on normal intakes of sodium (130 mEq. per day). In the two subjects *ingesting 25 to 30 mEq. of potassium per day* (Subjects T. C. and C. $P._1$), the daily rate of urinary excretion of this ion, UV_K, fell to a level equivalent to the intake in four to seven days. In the two different experiments on the same subject (E. $H._1$ and E. $H._2$) *ingesting 14 mEq. of potassium per day*, UV_K fell to 25 and 35 mEq. per day, respectively, on the fourth day and further to 19 and 27 mEq. per day, respectively, on the eighth day; in the experiment of E. $H._2$ the nitrogen intake was lower. In two subjects, J. D. and C. $P._2$ (Figure 1), *ingesting less than 1 mEq. K per day*, the UV_K fell to around 13 to 15 mEq. on the fourth day and 9 mEq. on the eighth day. One of these, C. $P._2$, was maintained for a third week on

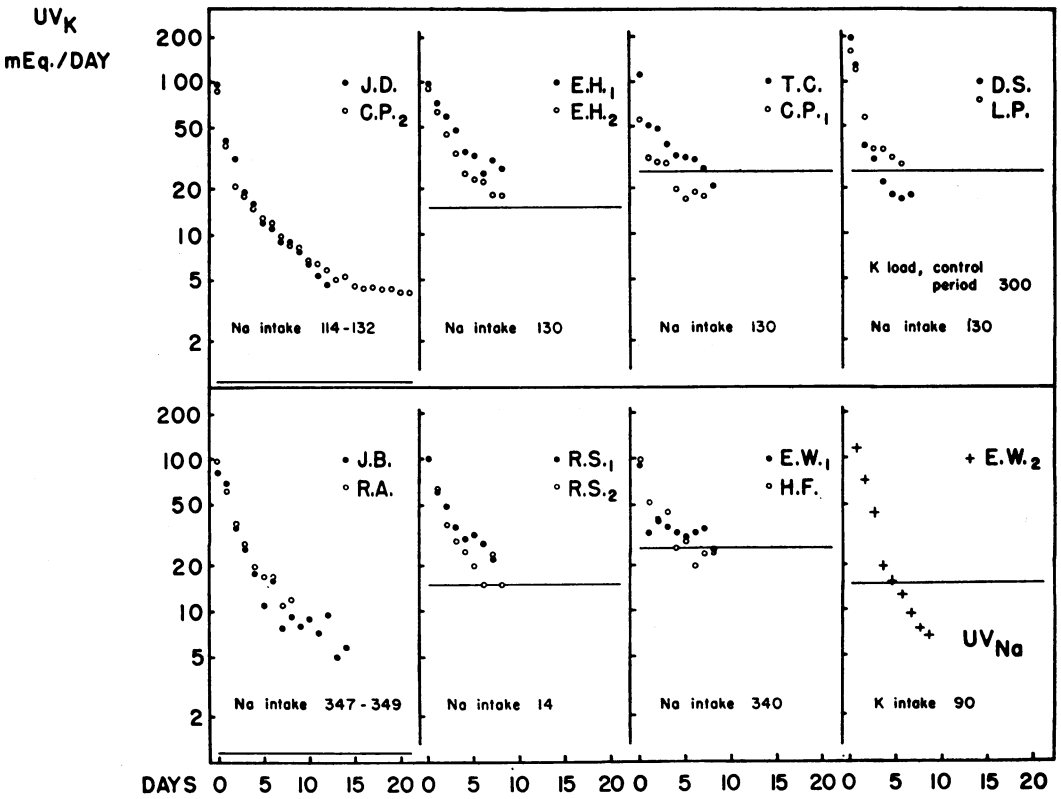

FIG. 1. THE DAILY URINARY EXCRETION OF POTASSIUM OR SODIUM DURING DEPLETION

The values plotted represent the daily urinary excretion of potassium in mEq., except for those of E. W.$_2$ which are for sodium. The first value of each curve represents the subject's average daily excretion during the control period. Depletion intake values are shown by the solid horizontal lines drawn across each graph (Na for E. W.$_2$, K for the rest). Intakes for J. D., C. P.$_2$, J. B. and R. A. were less than 1 mEq. per day. For additional detail on the diets and for discussion, see Table I and text.

potassium deprivation with further diminution of his UV_K to 4.2 mEq. per day. One of these two subjects, J. D., received bicarbonate and chloride in a ratio of 1:3 as the supplemental anions; no difference in the excretory pattern of potassium was observed. The total cumulative amount of potassium lost in the urine showed no relation to the level of potassium intake when compared on the seventh day of depletion. At the 25 to 30 mEq. per day level of intake of potassium Subject C. P.$_1$ lost 138 and Subject T. C. lost 263 mEq. of potassium. Ingesting approximately 14 mEq. of potassium per day, Subject E. H. lost 305 and 232 mEq. potassium during two separate studies. Subjects C. P.$_2$ and J. D. lost 128 and 143 mEq. potassium, respectively, while ingesting less than 1 mEq. potassium per day (Tables I and II).

2. High sodium intake (340 mEq. per day). In two subjects, J. B. and R. A., ingesting less than 1 mEq. K per day, the UV_K fell more slowly, reaching 20 mEq. per day on the fourth day and 10 mEq. on the eighth day (Figure 1). Although J. B. ingested bicarbonate and chloride in a ratio of 1:3 and R. A. ingested only chloride as the supplemental anion, the curve of UV_K was essentially the same in these two subjects.

3. Low sodium diet (14 mEq. per day). The ingestion of a low sodium intake (14 mEq. per day) (R. S.$_1$ and R. S.$_2$) with a potassium intake of 14 mEq. per day made no significant reduction in total urinary loss of potassium when compared to a subject in a normal sodium intake, E. H.$_1$ and E. H.$_2$ (Figure 1).

4. High potassium diet during the control period. In two subjects, D. S. and L. P. (Figure 1), ingesting 300 mEq. potassium per day during the control period and 25 mEq. per day during the

depletion period, the UV_K declined very rapidly from an average control level of approximately 280 mEq. per day to a level of 28 mEq. by the fourth day of depletion. The high initial takeoff of the UV_K curve resulted in a substantially higher urinary potassium loss during the first three days than for the subjects starting from normal levels.

5. Low sodium plus normal potassium intake. One subject, E. W.$_2$, was placed on a diet of 14 mEq. per day of sodium and 90 mEq. per day of potassium, following a control period, for comparison of rate of sodium conservation with a subject, R. S.$_2$, receiving only 14 mEq. per day of each ion. Decrease in excretion rate of sodium was more rapid than that of potassium for comparable levels of intake of the respective ions; the rate of sodium conservation was enhanced by concomitant deprivation of potassium (Figure 2).

Excretion of sodium and other constituents in the urine

Urinary *sodium* excretion tended to decrease during the first three to four days of the period of potassium depletion and then returned to approximately the intake level of sodium. Urinary *chloride* excretion fell abruptly in the same period of K depletion, reflecting the decrease in ingested supplements of potassium chloride. *Phosphate* exhibited no significant variation in excretion. Urinary *nitrogen* excretion for the most part reflected the nitrogen intake. In two of the subjects on less than 1 mEq. potassium

TABLE I

Metabolic data on Subject C. P.$_2$ (normal Na^+ intake)—Intake and urinary output of water, electrolytes, creatinine and nitrogen*

Day	Urine Vol.	pH	S.G.	Na	K	NH_4^+	T.A.	Cl	PO_4	CO_2	N	Cr
	ml.			*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mMoles*	*Gm.*	*mg.*
Control period												
1 C	2,645	5.38	1.010	143	88	66	41	206	37	3.7	16.7	1,706
2 C	2,985	5.00	1.009	161	100	81	50	261	40	2.9	18.4	1,716
3 C	2,540	5.00	1.011	132	100	85	57	225	47	2.8	18.8	1,753
4 C	2,240	4.90	1.011	118	92	85	55	207	44	2.3	19.2	1,769
5 C	2,750	4.88	1.009	122	95	92	53	229	40	2.8	19.1	1,760
Depletion period												
1 D	2,710	5.07	1.008	81	39	90	54	115	47	2.8	18.6	1,748
2 D	2,240	5.30	1.008	53	21	96	49	78	45	2.3	18.0	1,741
3 D	2,680	5.70	1.007	72	18	94	38	90	44	3.1	17.7	1,762
4 D	2,625	5.85	1.006	70	15	90	33	89	38	3.3	16.5	1,752
5 D	2,420	5.80	1.007	78	13	92	35	91	39	3.4	16.5	1,724
6 D	2,560	5.98	1.007	84	12	96	37	112	46	4.5	17.5	1,713
7 D	2,550	6.00	1.007	95	9.8	88	33	107	42	4.3	16.3	1,670
8 D	2,770	6.03	1.006	102	8.7	93	36	109	46	4.7	17.0	1,745
9 D	2,730	6.07	1.006	97	8.4	98	34	114	44	4.9	16.8	1,740
10 D	2,480	6.15	1.005	88	6.7	94	30	107	43	4.6	16.3	1,736
11 D	2,940	6.28	1.006	100	6.6	97	27	111	43	6.0	16.6	1,639
12 D	2,510	6.22	1.006	95	5.9	93	28	109	40	5.5	15.3	1,807
13 D	2,435	6.29	1.007	87	5.1	98	28	103	44	5.7	15.6	1,778
14 D	2,570	6.27	1.007	85	5.4	94	29	99	44	6.4	16.2	1,773
15 D	2,825	6.30	1.006	103	4.7	93	29	112	47	7.1	16.8	1,730
16 D	2,670	6.30	1.006	80	4.5	89	29	96	44	6.0	16.1	1,675
17 D	2,860	6.33	1.006	92	4.5	95	27	109	44	7.6	16.7	1,745
18 D	3,100	6.42	1.005	104	4.4	95	23	117	43	9.3	16.1	1,682
19 D	2,850	6.40	1.006	111	4.4	97	26	126	46	8.3	16.7	1,746
20 D	2,630	6.45	1.006	81	4.2	92	22	94	42	7.7	15.1	1,710
21 D	2,570	6.45	1.007	88	4.2	92	23	97	43	7.6	15.8	1,709

* The daily average and the extremes of variation of the analyzed dietary components in the control period were: water, 3,800 ml.; Na (mean) 131, range, 129 to 133 mEq.; K, 108 mEq.; Cl, 232 mEq.; and N (mean) 16.9, range, 16.3 to 17.0 Gm. The figures for the depletion period were: water, 3,952, range 3,800 to 4,000 ml.; Na (mean) 124, range, 114 to 130 mEq.; K < 1 mEq.; Cl, 125 mEq.; and N (mean) 16.4, range, 16.1 to 16.7 Gm. In Tables I through IV where the daily range of variation is not given for the mineral constituents, the content in the milk of the diet was too small for accurate analysis; therefore, the amount of the substance added to the diet was virtually the total amount ingested. Where no variation is given for the fluid volume, the daily intake was constant for that period.

TABLE II

Metabolic data on Subject J. D. (normal Na^+ intake, Cl^- : HCO_3^- = 3 : 1)—Intake and urinary output of water, electrolytes, creatinine and nitrogen*

Day	Vol.	pH	S.G.	Urine Na	Urine K	Urine NH_4^+	Urine T.A.	Urine Cl	Urine N	Urine Cr
	ml.			*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*mg.*
Control period										
1 C	2,400	5.78	1.010	123	82	46	28	158	16.8	2,196
2 C	2,770	6.28	1.011	142	118	43	24	205	20.0	2,126
3 C	2,500	5.87	1.010	112	86	43	29	133	20.1	2,156
4 C	2,390	6.07	1.010	93	112	38	25	134	19.3	2,103
5 C	2,810	6.55	1.009	165	100	34	13	179	19.0	2,158
Depletion period										
1 D	2,800	5.92	1.006	87	42	42	32	70	17.6	2,016
2 D	2,068	5.98	1.010	90	32	41	28	64	17.1	2,135
3 D	2,475	6.00	1.009	125	19	41	28	77	17.7	2,104
4 D	3,005	6.35	1.006	152	16	41	22	103	18.4	2,080
5 D	2,395	6.10	1.007	112	12	45	25	75	16.8	2,018
6 D	2,260	6.10	1.008	113	11	45	22	74	17.3	2,062
7 D	2,560	6.26	1.007	122	9	47	21	81	16.8	2,067
8 D	2,450	6.25	1.007	123	9	50	22	80	16.8	2,070
9 D	2,720	6.30	1.006	132	7.7	51	19	87	16.4	1,945
10 D	2,550	6.32	1.009	152	6.5	47	20	98	17.1	2,020
11 D	2,690	6.43	1.008	131	5.4	47	18	85	17.7	2,030
12 D	2,350	6.34	1.008	118	4.7	49	22	72	16.3	1,986

* The daily average and the extremes of variation of the analyzed dietary components in the control period were: water, 3,800 ml.; Na (mean) 128, range, 127 to 129 mEq.; K, 108 mEq.; Cl, 174 mEq.; HCO_3, 58 mEq.; and N (mean) 16.9, range, 16.9 to 17.0 Gm. The figures for the depletion period were: water, 3,800 ml.; Na (mean) 130, range, 129 to 132 mEq.; K < 1 mEq.; Cl, 94 mEq.; HCO_3, 31 mEq.; and N (mean) 16.8, range, 16.3 to 17.4 Gm.

per day intake, C. P.$_2$ and R. A. (Tables I and III), the nitrogen excretion decreased in relation to the nitrogen intake.

The excretion of *creatinine* showed no significant trend during the experiments.

The sum of the equivalents of *titratable acid*

TABLE III

Metabolic data on Subject R. A. (high Na^+ intake)—Intake and urinary output of water, electrolytes, creatinine and nitrogen*

Day	Vol.	pH	S.G.	Urine Na	Urine K	Urine NH_4^+	Urine T.A.	Urine Cl	Urine N	Urine Cr
	ml.			*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*mg.*
Control period										
1 C	1,145	5.98	1.024	245	91	37	29	293	13.7	2,072
2 C	1,990	5.40	1.015	306	104	54	31	406	15.4	1,945
3 C	1,570	5.20	1.024	310	98	70	56	395	17.0	2,084
4 C	1,735	5.15	1.021	343	116	73	55	450	18.2	2,104
5 C	1,625	5.20	1.019	285	109	68	49	381	17.0	2,125
6 C	1,315	5.22	1.024	265	99	76	51	368	17.5	2,035
Depletion period										
1 D	1,420	5.40	1.019	224	63	71	47	291	15.5	1,860
2 D	1,875	5.55	1.019	235	38	74	47	269	16.1	1,973
3 D	1,615	5.62	1.015	235	28	80	44	258	17.5	2,249
4 D	1,645	5.61	1.013	233	20	65	31	255	14.1	1,968
5 D	1,940	5.63	1.023	191	17	61	33	203	13.6	1,828
6 D	1,360	5.90	1.021	268	17	74	38	274	16.1	2,360
7 D	2,205	6.21	1,012	321	11	60	25	339	13.0	1,725
8 D	1,525	6.03	1.014	232	12	61	28	236	12.9	1,731

* The daily average and the extremes of variation of the analyzed dietary components in the control period were: water (mean) 4,057, range, 3,840 to 4,250 ml.; Na (mean) 348, range, 347 to 349 mEq.; K, 110 mEq.; Cl, 454 mEq.; and Na (mean) 16.9, range, 16.5 to 16.9 Gm. The figures for the depletion period were: water (mean) 3,875, range, 3,800 to 4,050 ml.; Na (mean) 348, range, 347 to 349 mEq.; K < 1 mEq.; Cl, 345 mEq.; and N (mean) 16.3, range, 16.3 to 16.9 Gm.

and *ammonium ion* excreted by the kidney per 24 hours depended upon whether the subject had a portion of the total cations ingested with bicarbonate ions or almost entirely with chloride ions. In Subjects C. P.$_2$ and R. A., where the total cations ingested were associated almost entirely with chloride ions, the excretion of titratable acid plus ammonium ions was increased during the control periods and decreased during the potassium depletion periods (Tables I and III, Figure 3). In Subjects J. D. and J. B., where the total cations ingested were associated with bicarbonate and chloride ions in a ratio of 1:3, there was no consistent change in titratable acidity plus ammonium ion excretion during either the control or depletion periods (Tables II and IV, Figure 3). Both the titratable acid and ammonia increased in the urine during the control periods when bicarbonate was not added to the diet, Subjects C. P.$_2$ and R. A. (Figure 3). But in all four subjects the daily excretion of titratable acid decreased and urinary pH rose in the depletion period.

The urinary carbon dioxide and bicarbonate increased during the potassium depletion in Subject C. P.$_2$ (Table I).

Fecal excretion

These data from the subjects ingesting less than 1 mEq. potassium per day are presented in Table V.

The percentage of stool *solids* per stool collection period remained fairly constant for each individual except one (J. B.); there was, however, a wide variation in solids among the various subjects (8 to 34 per cent). The grams of *nitrogen* per 100 Gm. stool solids increased in three of these subjects and decreased in one. The amount

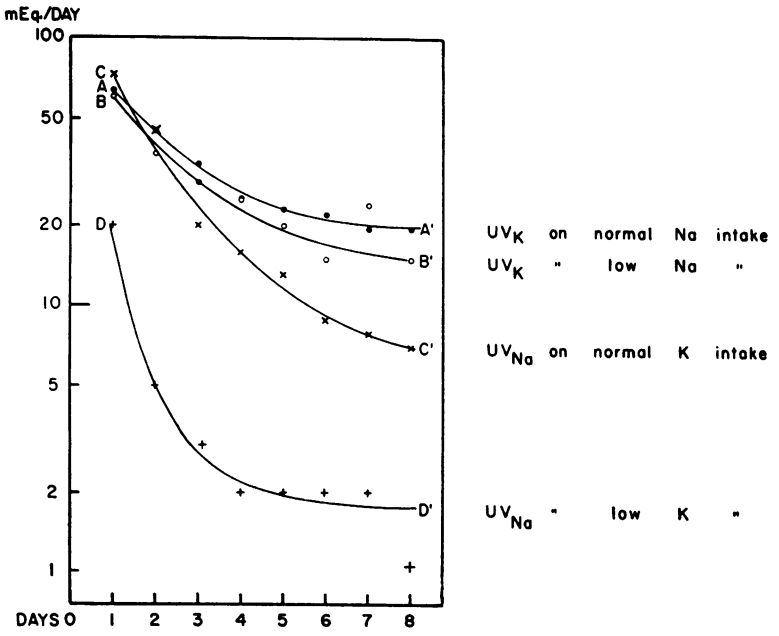

FIG. 2. THE RENAL CONSERVATION OF POTASSIUM AND SODIUM

The excretion rates of potassium are plotted against time for two subjects receiving 14 mEq. per day of potassium; one, E. H.$_2$, with a normal intake of sodium of 130 mEq. per day (curve A–A^1) and one, R. S.$_2$, with a low intake of sodium of 14 mEq. per day (curve B–B^1).

The excretion rates of sodium are plotted against time for two subjects receiving 14 mEq. per day of sodium; one, E. W.$_2$, with a normal intake of potassium of 90 mEq. per day (curve C–C^1) and one, R. S.$_2$, with a low intake of potassium of 14 mEq. per day (curve D–D^1).

This graph indicates that the rate of decline of urinary sodium was clearly more rapid than that of potassium under comparable reduction of intake of the respective ions. Sodium excretions were comparable on Day 0.

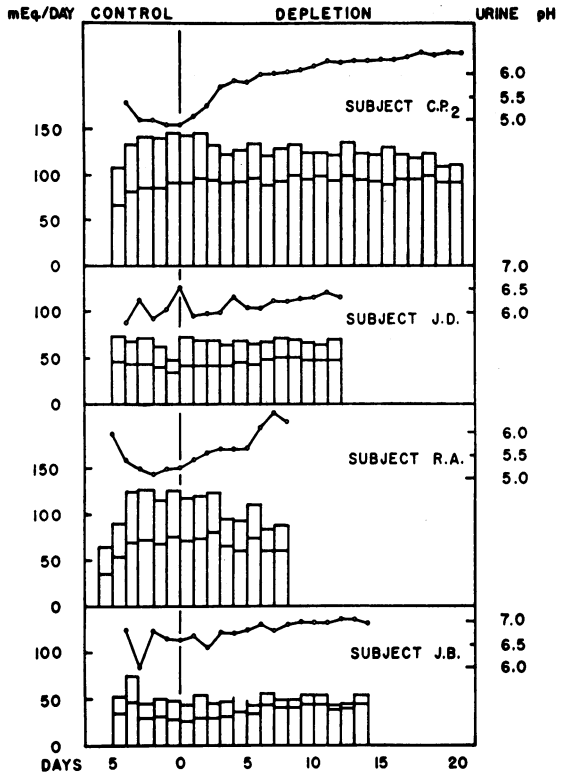

FIG. 3. THE DAILY EXCRETION OF AMMONIUM ION PLUS TITRATABLE ACIDITY AND THE DAILY URINE pH

Ammonium ion excretion is indicated by the lower portions and the titratable acid by the upper portions of the bars. The dots indicate the pH of the total 24 hour urine volume. Subjects C. P.$_2$ and J. D. received normal intakes of sodium (130 mEq. per day); Subjects R. A. and J. B. received high sodium intakes (340 mEq. per day). Subjects C. P.$_2$ and R. A. ingested only chloride as the supplemental anion and Subjects J. D. and J. B. received bicarbonate and chloride in a ratio of 1:3 as the supplemental anions.

Urinary pH rose and titratable acidity decreased during the depletion period in all subjects; excretion of ammonium ion was either unchanged or increased.

of *potassium* per unit stool solids (mEq. per 100 Gm.) decreased in every subject; nevertheless, the fecal loss of this ion accounted for from 11 to 59 per cent of the total loss in these subjects on the very low intake of potassium (Table VI). The amount of *sodium* per unit stool solids was increased in three of the four subjects and was unchanged in the other; this increase in stool sodium was not related to an increase in oral intake of the ion. There was no remarkable or consistent change in the fecal chloride excretion among the various subjects.

Total balances of electrolytes and nitrogen

These data are presented in Table VII.

1. Potassium. On normal intakes of sodium during the depletion period the negative balance of potassium tended to become greater the lower the level of potassium intake. When compared at the end of seven days of potassium depletion, Subject C. P.$_1$ lost 66 and Subject T. C. 165 mEq. of potassium while ingesting between 25 and 30 mEq. potassium per day; Subject E. H. ingesting approximately 14 mEq. of potassium per day lost 235 and 189 mEq. potassium during two separate studies; and at the lowest level of intake, less than 1 mEq. potassium per day, Subject C. P.$_2$ lost 260 and Subject J. D. lost 192 mEq. of potassium. The largest negative potassium balance, −502 mEq., was in one of the subjects in the last group, C. P.$_2$, who was maintained on less than 1 mEq. per day for three weeks. For the entire 26 days of the study in this patient the total potassium balance was −6.5 mEq. per Kg. of body weight; the balance of potassium "in excess of nitrogen" was −4.5 mEq. per Kg.

High intake of potassium in the control period led to a greater loss during the depletion period in both Subjects D. S. and L. P., but resulted in a greater final depletion only in L. P. since in D. S. potassium was retained initially in the control period.

2. Sodium. The sodium balances were positive consistently during the depletion periods except when the sodium intake was restricted to 14 mEq. per day.

3. Chloride. The chloride balance tended to be positive when the balance of sodium was strongly positive. The balance of chloride was most accurately determined in the subjects on the diet of resin-treated milk containing less than 1 mEq. per day of K. This was due to the fact that the resin treatment removed virtually all of the chloride: The amount of chloride put in the milk diet could be more accurately measured than that in the natural foodstuffs.

4. Nitrogen. Urinary nitrogen excretion for the most part reflected the nitrogen intake; however, in Subjects C. P. and R. A. (Tables I and III, respectively) the UV_N appeared to decline somewhat. This observation could not be accounted for by a decrease in nitrogen intake.

TABLE IV

Metabolic data on Subject J. B. (high Na^+ intake, Cl^- : HCO_3^- = 3 : 1)—Intake and urinary output of water, electrolytes, creatinine and nitrogen*

Day	Vol.	pH	S.G.	Urine Na	Urine K	Urine NH_4^+	Urine T.A.	Urine Cl	Urine N	Urine Cr
	ml.			*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*mg.*
Control period										
1 C	3,850	6.80	1.007	263	77	35	16	263	15.6	1,940
2 C	1,420	5.98	1.018	233	44	47	29	231	15.6	2,130
3 C	2,840	6.78	1.012	355	95	30	16	337	18.6	2,002
4 C	2,610	6.60	1.012	326	75	31	19	298	16.5	2,010
5 C	2,600	6.58	1.013	365	121	28	20	360	17.0	2,048
Depletion period										
1 D	2,680	6.68	1.011	252	70	26	17	216	16.5	1,896
2 D	2,060	6.42	1.011	231	36	30	24	170	16.9	1,921
3 D	2,440	6.75	1.012	264	26	29	16	183	17.5	2,007
4 D	2,600	6.72	1.011	305	19	31	16	233	16.8	1,970
5 D	2,590	6.80	1.010	303	11	36		220	17.2	2,040
6 D	2,500	6.92	1.010	300	16	34	9	233	14.9	1,781
7 D	2,210	6.80	1.012	272	7.8	43	13	199	17.0	2,127
8 D	2,580	6.90	1.009	323	9.3	41	9	246	16.1	1,980
9 D	2,740	6.97	1.009	305	8.0	41	9	231	16.6	1,939
10 D	2,630	6.96	1.009	322	8.9	44	10	247	17.5	2,157
11 D	2,560	6.97	1.009	252	7.4	44	9	194	16.2	1,984
12 D	2,370	7.07	1.009	307	9.7	38	5	229	14.9	2,015
13 D	2,520	7.06	1.009	301	5.0	39	5	209	16.4	1,909
14 D	2,760	6.94	1.009	360	5.8	45	9	277	16.1	1,980

* The daily average and the extremes of variation of the analyzed dietary components for the control period were: fluid volume (mean) 3,837, range, 3,699 to 4,000 ml.; Na (mean) 312, range, 168 to 348 mEq. (Na^+ intake increased stepwise during control period); K (mean) 98, range, 55 to 109 mEq. (K^+ intake too low on the first day due to dietary error); Cl (mean) 303, range, 161 to 339 mEq.; HCO_3 (mean) 101, range, 54 to 113 mEq.; and N (mean) 16.8, range, 16.3 to 17.2 Gm. The figures for the depletion period were: fluid volume 3,800 ml.; Na (mean) 348, range, 347 to 349 mEq.; K < 1 mEq.; Cl, 259 mEq.; HCO_3, 86 mEq.; and N (mean) 16.5, range, 15.6 to 17.3 Gm.

Concentrations of electrolytes in serum

The concentration of potassium in serum fell progressively during the depletion period in all experiments, reaching the lowest value of 2.8 mEq. per L. in the subject on the lowest intake of K for the longest period, C. P.$_2$ (Table VIII). There were no apparent trends in the daily serum concentrations of sodium, chloride or creatinine. The venous CO_2 content rose slightly in Subjects C. P.$_2$ and R. A. but remained within normal limits.

Acid-base changes in "arterialized" finger capillary blood

Periodic samples of "arterialized" finger capillary blood showed no major changes in the whole blood pH, CO_2 content or "buffer base" (Table VIII).

DISCUSSION

Our data indicate that subjects ingesting an adequate diet containing at least 25 mEq. of potassium per day are unlikely to develop potassium depletion greater than 250 mEq. as the result of urinary potassium loss alone. This is probably also true for intakes of 14 mEq. per day. At both levels of intake the urinary potassium daily loss had reached or almost reached the intake levels within the duration of these studies (Figure 1). At the extremely low intake of 1 mEq. per day, however, the decline in the urinary loss was very slow in the last five days of a 21 day study (C. P.$_2$) as shown in Figure 4. Therefore, under the circumstance of prolonged and practically complete deprivation of potassium, the urinary loss, while not more than about 3 mEq. above the intake, could reasonably be expected to continue to add significantly to the deficit of the ion.

In the first day of depletion, however, the drop in potassium intake is a more significant factor in determining the contribution of the urinary potassium loss to the depletion. Those subjects loaded with potassium during the control period,

TABLE V

Analysis of average daily stool values

Subject	Stool collection: Period	Stool collection: Duration	Total weight	Total solids	Na	K	Cl	N	K/Na ratio
		days	*Gm.*	*Gm.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	
C. P.$_2$	Control period								
	I	2	525	71.0	13.2	40.3	4.9	3.6	3.1
	II	3	175	30.1	2.6	22.2	1.8	1.4	8.5
	Depletion period								
	I	3	193	36.5	4.3	24.9	1.8	1.6	5.8
	II	3	155	27.6	7.2	15.9	1.5	1.8	2.2
	III	3	207	38.3	13.4	16.3	2.1	1.8	1.2
	IV	3	173	30.2	9.0	14.1	1.5	1.6	1.6
	V	3	168	31.4	7.8	12.0	1.4	1.6	1.5
	VI	3	174	29.8	8.0	9.5	1.2	1.5	1.2
	VII	3	164	31.9	7.6	11.4	1.0	1.7	1.5
J. D.	Control period								
	I	2	103	31	0.9	15.5	0.5	1.05	17.2
	II	3	77	22	0.7	12.5	0.3	0.70	17.9
	Depletion period								
	I	3	52	16	1.1	8.1	0.3	0.49	7.4
	II	3	66	21	3.0	9.2	0.3	0.63	3.1
	III	3	60	18	4.0	5.7	0.5	0.59	1.4
R. A	Control period								
	I	4	106	8.2	7.0	8.8	2.5	1.15	1.26
	II	2	110	8.8	4.5	14.0	5.0	1.10	3.11
	Depletion period								
	I	6	53	5.0	2.5	3.3	0.2	0.80	1.32
	II	2	52	3.6	2.5	2.5	0.5	0.70	1.00
J. B.	Control period								
	I	2	117	17	2.5	18.2	1.4	0.80	7.3
	II	3	68	29	1.7	7.8	0.6	0.38	4.6
	Depletion period								
	I	3	72	26	4.7	8.6	0.6	0.60	1.8
	II	3	40	13	2.8	4.0	4.0	0.35	1.4
	III	2	79	26	7.4	5.8	5.8	0.75	0.78
	IV	2	44	17	4.7	3.8	3.8	0.55	0.81
	V	4	39	12	3.1	2.6	3.8	0.50	0.84

D. S. and L. P., lost, respectively, 129 and 127 mEq. in the urine on the first depletion day as contrasted with losses of 29 to 52 mEq. in the other subjects on a comparable depletion intake (25 mEq. per day). However, despite the greater urinary loss on the first day in these subjects

TABLE VI

Per cent of total potassium loss and per cent solids in stools during potassium depletion period

Subject	Period duration	Urine K	Stool K	Total K loss	K loss in stool	Stool solids
	days	*mEq.*	*mEq.*	*mEq.*	%	%
Normal sodium intake						
C. P.$_2$	21	216	307	523	59	19
J. D.	12	174	86	260	33	31
High sodium intake						
R. A.	8	206	25	231	11	8
J. B.	14	270	67	307	22	34

TABLE VII

Summary of balance data

Subject	Control period						Depletion period									
	Period duration	Change in wt.	Balance				Period duration	Change in wt.	Final wt.	Total period balance					7th depletion day values	
			K	Na	Cl	N				K	K^{1}*	Na	Cl	N	Cumulative UV_K	Cumulative balance K / K^{1}*
	days	*Kg.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*days*	*Kg.*	*Kg.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*Gm.*	*mEq.*	*mEq.* / *mEq.*
<1 mEq. K/day depletion diets																
Normal Na intake																
C. P.₂	5	−1.31	−79	− 55	− 17	−19.8	21	−2.75	76.8	−502	−399	+889	+408	−36.8	128	−260 / −226
J. D. (HCO_3)†	5	−1.40	−27	+ 2	+ 59	−14.7	12	−2.68	85.8	−248	−218	+ 67	+157	−10.8	143	−192 / −175
Oral Na loading in control and depletion periods (350 mEq./day)																
R. A.	6	−1.81	−21	+298	+411	− 9.2	8	−0.85	88.6	−225	−244	+825	+660	+ 6.7	188	−207 / −223
J. B. (HCO_3)†	4	−1.02	+16	+ 12	− 57	− 1.3	14	−0.60	84.3	−293	−278	+716	+553	− 5.3	235	−235 / −229
14 to 16 mEq. K/day depletion diets																
Normal NaCl intake																
E. H.₁	3	−1.0	−31	− 93	−167	±	8	−0.50	70.4	−251	−217	+232	+102	−12.2	305	−235 / −205
E. H.₂	4	+0.1	−69	− 64	−104	− 2.0	8	−1.20	70.0	−206	−196	+202	+ 69	− 3.7	232	−189 / −180
Low NaCl intake during depletion period																
R. S.₁	3	−1.21	+44	− 84	−171	+ 2.9	7	−1.78	73.0	−176	−100	− 12	−100	−27.2	258	−176 / −100
R. S.₂	4	−0.14	−96	+ 12	− 14	− 0.3	8	−1.19	72.5	−183	−153	− 57	−123	−10.7	210	−167 / −141
25–27 mEq. K/day depletion diets																
Normal Na intake																
T. C.	3	−2.1	−38	+ 18	− 93	− 6.0	8	−0.70	85.9	−172	−162	+130	− 17	− 3.4	138	−165 / −155
C. P.₁	6	−1.3	−74	+103	+ 68	−12.8	7	−0.80	74.3	− 66	− 46	+195	+215	− 7.1	263	− 66 / − 46
Oral K loading in control period (300 mEq. K/day)																
D. S.	7	−0.3	+79	+ 90	− 11	+14.3	7	±	67.7	−208	−253	+ 44	− 74	+16.2	275	−208 / −253
L. P.	7	−0.9	+ 8	+ 19	− 85	− 4.6	6	−1.00	69.1	−244	−238	+289	+ 74	− 2.2		
Oral NaCl loading in control and depletion periods (340 mEq. Na/day)																
E. W.₁	7	±	−25	+ 37	− 71	+13.7	8	+0.30	67.5	−158	−197	+296	+323	+13.8	240	−146 / −180
H. F.	7	−2.1	−53	+116	− 87	−13.2	8	−0.60	84.2	− 79	− 60	+475	+324	− 6.7	256	− 97 / − 81

* K^{1} is potassium balance corrected for the nitrogen balance, assuming that 1 Gm. N = 2.8 mEq. K.

† Cl : HCO_3 intake ratio = 3 : 1.

TABLE VIII

Analysis of blood and serum

Subject	Day	Whole blood*						Venous serum				
		pH	CO_2	pCO_2	Bb	Cell vol.	Hb	Na	K	Cl	CO_2	Creatinine
			mMoles/L.	*mm. Hg*	*mEq./L.*	%	*mMoles/L.*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mMoles/L.*	*mg. %*
C. $P._2$	C 5	7.39	21.7	42.0	48.5	46.5	9.20	140	4.1	104	26.1	1.10
	D 7	7.41	20.5	38.0	48.0	46.5	9.15	140	3.5	104	26.9	0.93
	D 12	7.42	20.6	38.0	48.0	44.0	9.00	140	3.3	104	28.0	1.20
	D 14	7.44	21.5	38.0	49.5	44.5	9.00	140	3.1	106	28.6	1.60
	D 16	7.41	21.1	39.0	48.0	43.0	8.65	140	3.1	104	30.6	1.10
	D 19	7.43	21.1	38.0	48.5	43.5	8.85	140	2.8	104	29.8	1.40
	D 21	7.43	21.1	38.0	49.0	44.0	8.95	141	2.8	107	29.6	0.90
J. D.	C 5	7.44	21.3	38.0	50.0	47.0	9.55	140	4.0	104	29.3	1.10
	D 6	7.42	21.0	38.0	48.5	45.5	9.25	140	3.9	102	28.8	0.93
	D 12	7.40	21.0	40.5	48.5	48.0	9.60	140	3.7	103	29.8	0.85
R. A.	C 3	7.38	18.4	37.0	45.5	47.0		138	4.0	105	23.1	1.20
	D 8	7.45	19.8	34.0	48.0	45.0		143	3.0	104	30.1	0.92
J. B.	C 5	7.44	22.1	38.5	50.0	43.0	8.65	139	4.2	105	31.2	0.90
	D 4	7.45	21.3	36.5	49.0	41.5	8.25	140	4.0	104	30.9	1.00
	D 8	7.43	20.9	36.5	47.5	40.0	7.85	140	3.5	104	31.0	1.70
	D 14	7.43	21.8	38.0	47.5	38.5	7.70	140	3.6	103	30.5	0.93

* Arterialized cutaneous whole blood (16). Normal values: pH 7.42 ± 0.04; CO_2 21.2 ± 2.6 mMoles per L.: BB (buffer base) 48.8 ± 3.8 mEq. per L.; pCO_2 37.6 ± 7.2 mm. Hg.

loaded with potassium in the control period, their urinary losses declined very rapidly. This impetus to renal conservation of potassium (the difference between control and depletion intakes) in the first day of depletion is shown clearly in Figure 5 where the decrement in intake corre-

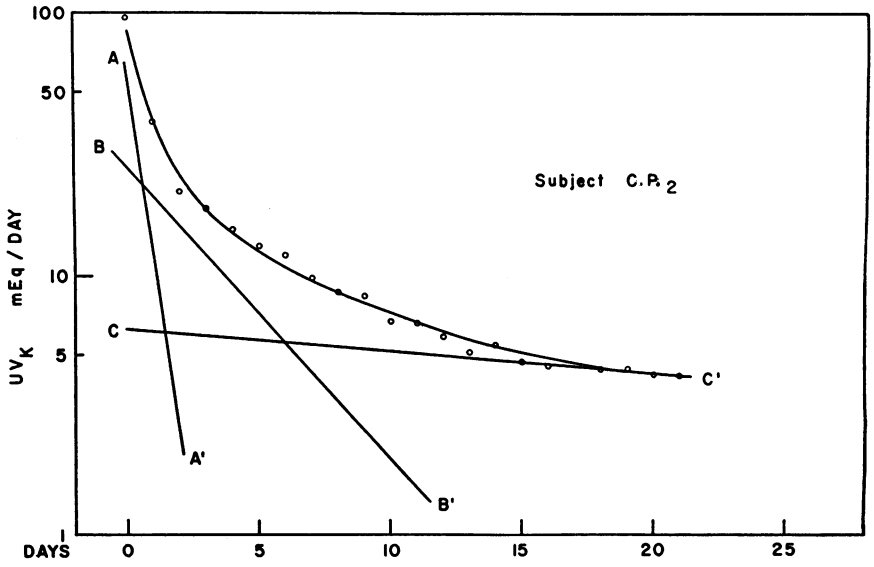

FIG. 4. THE RATES OF RENAL POTASSIUM EXCRETION DURING POTASSIUM DEPLETION

At least three exponential rates may be derived from the curve describing the daily urinary potassium excretion during potassium depletion (Subject C. $P._2$): A–A′ = (64) ($e^{-1.62d}$), B–B′ = (26) ($e^{-0.72d}$) and C–C′ = (6.3) ($e^{-0.019d}$). For further discussion, see text.

lates well with the estimated instantaneous rate of decline in urinary potassium at the end of the first day. This correlation becomes less certain at the end of the fourth depletion day and probably disappears by the end of the seventh day.

The decline in the urinary potassium content in the first three days of depletion was roughly comparable to that observed by Black and Milne (2) on similar potassium intakes.[3] However, the curve for urinary potassium could not be described by a single exponential function, as in their study. An analysis of the curve for the subject depleted for the longest period, C. P.$_2$, 21 days, showed that it could be reasonably well described as the sum of three exponential functions (Figure 4). This analysis does not necessarily imply the identification of three physiological functions in the body which determine urinary potassium content under the circumstances of the study, but it does serve as a convenient way to describe the shape of the curve.

The rate of renal potassium conservation was slower than that for sodium, as previously described (2). The improvement in potassium conservation during a simultaneous reduction in sodium intake is certainly small, if significant at all (Figure 2, curves A–A′ and B–B′). Sodium, however, appears to be conserved much more effectively during a simultaneous reduction in potassium intake (Figure 2, curves C–C′ and D–D′). These curves emphasize the greater effectiveness of renal conservation of sodium as compared to that for potassium.

No other attempts were made to study changes in renal function which might follow potassium depletion. Whatever impairment of concentrating power and resulting polyuria might have been found as described so well in rat studies by Hollander and associates (18) was obscured by the large fluid intakes required by the study

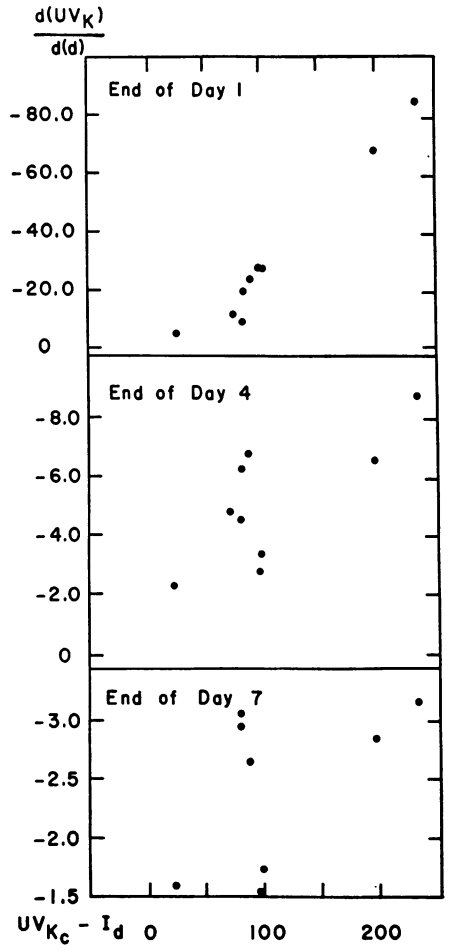

FIG. 5. THE DAILY RATE OF POTASSIUM EXCRETION DURING THE POTASSIUM DEPLETION PERIOD

The instantaneous rate of decline of urinary potassium excretion, $\frac{d\ (UV_K)}{d\ (days)}$, is plotted as a function of the average of the urinary potassium excretion for the last three days of the control period, UV_{Kc}, minus the potassium intake during the depletion period, I_d. The quantity $UV_{Kc} - I_d$ is taken as an index of the change in potassium load between the control and the depletion periods. The differential $\frac{d\ (UV_K)}{d\ (days)}$ was derived by differentiation of exponential curves fitted to the data of daily urinary potassium loss as in Figure 4. Any correlation existing between these two variables becomes less apparent the farther along in the depletion period the observation is made.

[3] Black and Milne (2) measured the rate at which potassium conservation becomes effective by evaluating α in the following expression:

$$Q_t = Q_0 \times e^{-\alpha t}$$

in which Q_t is the potassium output on day t, and Q_0 is the initial potassium output. This equation for the data of Black and Milne is:

$$Q_t = 106 \times e^{-0.305t}$$

This equation for Subjects J. B. and R. A. is:

$$Q_t = 103 \times e^{-0.414t}$$

The value of α obtained for our subjects indicates a more rapid rate of potassium conservation compared to those of Black and Milne. This difference may not be significant. The αK of 0.414 obtained for our studies corresponds more closely to the αNa of 0.44 obtained by Black and Milne from a sodium conservation study (2).

design. No significant changes in creatinine clearance were found.

Although no direct information is provided by these studies on mechanisms regulating the loss of potassium in stools during reduced potassium intake, these data emphasize how important this route of loss was in the absence of diarrhea. Despite a tendency for conservation of potassium in the gut as well as in the kidney, the daily loss of between 2 and 25 mEq. of potassium in stools made stool loss a very substantial fraction of the total loss (Table VI). In Subject C. P.$_2$, for example, daily stool loss was about 10 mEq. when urinary potassium was only about 5 mEq. per day. A marked increase in the fluidity of the stool is associated with an increase in stool potassium content (19). In each subject there was little variation in the percentage of stool solids, but there was a considerable variation among subjects (Table V). This variation was not related, though, to the potassium content of these nondiarrheal stools and one can only conclude that a wide variation of stool potassium content can exist independently of fluidity in normal subjects.

Studies of Gardner, MacLachlan, Terry, McArthur and Butler (20) show that potassium deficiency may increase fecal loss of chloride in rats. Our human subjects did not show this phenomenon, but it must be conceded that the degree of their depletions were much smaller relative to body weight than were those of the rats. Perhaps the most surprising finding was the very modest degree of metabolic alkalosis which developed in any of these studies. The subject, C. P.$_2$, with the largest potassium deficit, 502 mEq. (351 mEq. when corrected for nitrogen balance), showed a rise in venous serum CO_2 content of only 3.5 mMoles per L. from a control level of 26.1 during his depletion period of 21 days. His arterial whole blood pH rose from 7.39 to only 7.43. Because in a previous study of experimental potassium depletion in man (2) more striking rises in serum CO_2 were noted when sodium loading accompanied the depletion (rises to 36.1 and 33.4 mEq. per L.), two of our subjects were given sodium loads of 350 mEq. per day. With potassium depletions comparable in degree to those of Black and Milne (2), one of the subjects (R. A.) developed a comparable rise in serum CO_2 (+7.0 mEq. per L.) but at a lower level (final CO_2, 30.1). The second subject (J. B.) showed not even a tendency toward metabolic alkalosis. The authors conclude that human subjects must show a great variability in susceptibility to metabolic alkalosis in the presence of a pure potassium depletion and agree with Moore and co-workers (21) that sodium loads must play a very significant part in the appearance of the alkalosis. A subsequent paper discusses the acid-base problem in experimental potassium depletion in greater detail (22).

A final comment must be made on the failure of the arterialized cutaneous blood total CO_2 values to parallel the venous serum CO_2 in Subjects C. P.$_2$ and R. A. (Table VIII). The authors do not believe that technical errors account for this failure but the only explanation they can offer is a speculative one. The red cell, in potassium depletion, may show a replacement of potassium lost by a sodium gain (23) like that shown by skeletal muscle (24). Gardner, MacLachlan and Berman have shown that this change in skeletal muscle composition is accompanied by a decrease in bicarbonate content (25). If a like change in red cell bicarbonate took place in the subjects under discussion, these decreases could have cancelled out or masked the rises in serum CO_2, inasmuch as the cutaneous blood analyses were done on whole blood.

SUMMARY AND CONCLUSIONS

Fourteen balance studies were done on 11 normal male subjects depleted of potassium by dietary deprivation of the ion. The basic study plan consisted of a control period lasting three to eight days and a succeeding depletion period lasting 6 to 21 days during which the potassium intake was set at one of three levels: 25 to 27, 14 to 16 or <1 mEq. per day. During the depletion period the effects of the following diet programs on the urinary and fecal potassium loss were observed: *1*) ingestion of a greatly augmented sodium intake through the entire study; *2*) ingestion of sodium and potassium entirely with chloride or with chloride and bicarbonate in a ratio of 3:1; *3*) ingestion of a low intake of sodium of 14 mEq. per day during the control period; and *4*) ingestion of a high intake of

potassium in excess of 300 mEq. per day during the control period.

The rate of *urinary excretion of potassium:* *1*) during the first few days of depletion varied directly with the difference between the urinary potassium of the control period and the potassium intake in the depletion period; *2*) varied directly with the level of potassium intake throughout the depletion period; but *3*) clearly exceeded the intake when the latter was 1 mEq. or less per day; *4*) declined at two or more exponential rates when the potassium intake was <1 mEq. per day; *5*) was increased by sodium loading at the lowest level of potassium intake; and *6*) was not affected by the association of chloride alone *versus* chloride plus bicarbonate with the total cation ingested.

Fecal potassium accounted for 11 to 59 per cent of the total loss of potassium when the intake of potassium was less than 1 mEq. per day. Cumulative negative *balances* of potassium varied with level of intake and duration of study reaching a maximum of −502 mEq. or 6.4 mEq. per Kg. in one subject on less than 1 mEq. per day for 21 days.

The rate of *urinary excretion of sodium* on a low sodium intake was diminished when the concomitant potassium intake was low. The rate of excretion of *titratable acid plus ammonium ion* remained essentially unchanged or decreased slightly during potassium depletion and the urine pH rose. *Urinary total CO_2 and bicarbonate* increased in the one subject in which it was measured and the calculated total excretion of hydrogen diminished relative to dietary intake.

Metabolic alkalosis was an inconstant finding and when present was of a minor degree.

It is concluded: *1*) that the degree of renal conservation of potassium *a*) is related to the degree of change in intake of the ion from predeprivation levels and to the duration of the deprivation, *b*) is diminished by an increased intake of sodium, and *c*) is less efficient than the renal conservation of sodium under conditions of comparable deprivation of the respective ions; *2*) that with prolonged deprivation of potassium the fecal loss of the ion, though absolutely decreasing, becomes a progressively larger factor in the development of the negative potassium balance; and *3*) that a marked degree of extracellular metabolic alkalosis is not an obligatory accompaniment to potassium depletion of the normal human subject.

ACKNOWLEDGMENTS

The authors wish to thank Dr. J. Russell Elkinton, Dr. J. R. Brobeck and Dr. F. C. Wood for their guidance and generous support during this study.

We are indebted to Mrs. Claire Tissari, Mrs. Dolores Bluemle, Mrs. Lidia Kosolapove, Mrs. Katherine Wishnevski and Mr. James Mitchell of the laboratory of the Chemical Section for most of the chemical analyses; to Mrs. Cynthia Henderson, Miss Helen Merton, Mrs. Patricia McCreary and the other members of the nursing staff of the Metabolic Unit; to Mrs. Marie Bunting, Miss Mary Demyan and Miss Nancy Sweeney for dietetic service, and to Dr. John Reinhold and the William Pepper Laboratory for technical advice and assistance in carrying out certain chemical procedures.

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