METABOLIC EFFECTS OF MARKED SODIUM RESTRICTION IN HYPERTENSIVE PATIENTS: CHANGES IN TOTAL EXCHANGEABLE SODIUM AND POTASSIUM¹

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(Submitted for publication February 16, 1954; accepted June 16, 1954)

It is important to understand the mechanism by which drastic sodium restriction effects a decrease in blood pressure in some patients with essential hypertension. It has been shown (1) that a decline in total exchangeable sodium (TENa) as measured with the isotope Na^{24} , is not correlated with a decline in blood pressure, and therefore simple "desalting" of the body can not account for the phenomenon. The important relationship which exists between sodium and potassium in most living species, both animal and plant, suggested the possibility that sodium restriction might be effective in lowering blood pressure through secondary effects on K. With the isotopes Na^{24} and K^{42} , nearly all of the body's Na and K pools can be measured (2, 3). Therefore, it is possible to quantitate accurately the effects of marked Na restriction upon these pools and to determine whether the effects of Na restriction on total exchangeable potassium (TEK) may be correlated with alterations in blood pressure. The present paper is a report of a study on 11 patients with essential hypertension who were given a basic low Na diet supplemented during the period of control observations with 10 grams (180 mEq.) of enteric coated NaCl per day. The removal of this added NaCl during the subsequent test period constituted the sole change in regimen. During both phases of the study after suitable periods for equilibration the effects on TENa, TEK, and blood pressure were studied.

PROCEDURE

Patients and clinical status

Eleven adult patients with essential hypertension were studied for a 3-month period on the metabolic wards of the Brookhaven National Laboratory Hospital. These people were admitted in two groups; one consisted of two males and four females from April to July (Group I), the

other of three males and two females from September to December (Group II), 1953. Since the primary purpose of this communication is not concerned with the clinical effects of sodium restriction which have been reported frequently in the past (4-6) itemized details of each patient's status relative to laboratory findings have been omitted from this report except as seemed pertinent. With the two exceptions noted below (patients M and R) all patients were of the type classed as benign essential hypertension. Urea clearances were normal in all, but variable degrees of albuminuria were present in some patients. Intravenous pyelograms were normal except in patient R as noted. Serum cholesterol, CO_2 , Cl, total protein, albumin and globulin, sodium and potassium were within normal limits in all patients. Electrocardiograms ranged from normal to variable degrees of left axis deviation and low or inverted T waves. (Tracings on patient R revealed classical evidence of acute myocardial infarction involving the anterior wall of the left ventricle during the two episodes described subsequently.) Heart size was shown by X-ray to vary from normal in some to moderate, diffuse enlargement in others. None gave past histories which suggested episodes of acute heart failure. Benzodioxane tests for pheochromocytoma were negative in all. Both males mentioned earlier had serious disease; M, age 53, had had a right hemiplegia six months prior to admission with residual weakness and spasticity. Upon admission, he was found to have mild diabetes mellitus as well, which was readily controlled by small doses of protamine zinc insulin. During his hospital stay, he had two transient cerebrovascular thromboses, from both of which return to previous level of function occurred in three to seven days. This patient's disease was obviously severe and about six weeks after his initial discharge he died from multiple cerebrovascular thromboses. Patient R, age 47, who had had angina on effort for several years, developed two mild coronary occlusions five and seven weeks after admission with uneventful recovery. He had had a chronic duodenal ulcer of more than 20 years duration which plagued both patient and staff during the study. By intravenous pyelogram he was shown to have a small asymptomatic calculus in each kidney, measuring 5 and 15 mm. in diameter, respectively; these were presumed to be secondary to the heavy alkali and milk ingestion for many years.

Experimental program

The patients remained ambulatory throughout their stay except during studies or intercurrent illnesses. Upon

¹ This work was carried out under the auspices of the Atomic Energy Commission.

admission, each patient was placed on a basic diet calculated to yield about 6 mEq. sodium per day (analysis of 18 separate diets yielded a mean value of 5.7 mEq. with S.D. ± 1.4); because of this restriction the daily protein intake averaged approximately 55 grams. In Group I, protein supplement, although allowed, was not required to be eaten; associated with this, members of the group lost variable and often significant amounts of weight. Since previous work (7) had shown that the levels of protein in the diet had no effect upon blood pressure, weight loss seemed unimportant. In view of the changes in TENa and TEK, subsequently calculated to be present, it was thought necessary in the future to control the factor of weight loss as well. Therefore, members of the second group were required to consume a total of 1.5 grams of protein per Kg. per day through low Na protein supplements with Lesofac² or Lonalac®; on this regimen, the weights remained within narrow limits, with the maximal change recorded being a gain of 4.0 Kg. in patient B. Salt-free or salt-poor carbohydrates and fats were given in amounts sufficient to satisfy caloric needs. The diets were calculated to contain 30 to 100 mEq. of potassium per day and this was confirmed by analyses. The first five to six weeks served as the control period; therefore, during these first weeks 10 grams (180 mEq.) of sodium chloride in enteric coated capsules were administered daily to each patient in divided doses, an amount which is regarded as being within the average of American intakes (8). At the termination of the control observations, the sole change in the regimen was the omission of the added NaCl, so that the effects of this restriction alone could be studied. At intervals before and after this sharp decrease in NaCl intake, TENa and TEK were measured as well as other studies appropriate for evaluation of clinical status.

METHODS

Blood pressure, urine and blood collections; sodium and potassium analyses

Blood pressures were measured six mornings a week by one of the authors under standard conditions; namely, after breakfast with a minimum bed rest of half an hour before the readings were made. Systolic and diastolic pressures were recorded as the first appearance and total disappearance of sound respectively as recommended by a committee of the American Heart Association (9). All urines in each 24-hour period were pooled, the volumes measured, aliquots removed, and then preserved with 1 per cent HCl for subsequent chemical analysis of sodium and potassium with a Perkin-Elmer Model 52A flame photometer, with a lithium internal standard. The volume of the urine samples used for analysis ranged from 1 to 40 ml. depending upon the concentration of Na or K in the specimen. Blood samples were removed without stasis, mixed in heparin tubes and centrifuged within 5 to 10 minutes. With care in handling the samples visible

hemolysis was not seen. From the plasma so obtained, 1 ml. samples were analyzed in duplicate with the flame photometer in the fashion used for urine.

Total exchangeable sodium (TENa)

TENa was determined by an isotope dilution technique with the procedure essentially as described earlier (1). The isotope $\text{Na}^{24}\text{CO}_3$ was obtained from the Brookhaven National Laboratory reactor, sterilized, then prepared for administration by diluting with 5 per cent dextrose; of this each patient received about 100 μc (containing approximately .06 mEq. Na^{24}) intravenously from a calibrated 100 ml. buret over a 7- to 10-minute period. Plasma samples were always taken at 5, 7, and 24 hours in the first group and at 24 and 26 hours in the second group; the final 24- and 26-hour specimens were always collected with the patients in the fasting state. Thus, in Group I the value for final exchangeable sodium represented the corrected 24-hour figure and was in all instances a reasonable extension of the values found earlier. In Group II, the final figure was the mean of the 24- and 26-hour values at both of which times presumably the maximal value for TENa had been reached. Based on the data of Edelman, James, Baden, and Moore (2) it is highly improbable that a much longer period of equilibration would have affected the values for TENa obtained here. During the low sodium phase of these and related studies, correction for Na^{24} excretion in the urine was found to be negligible whereas during the high sodium phase the average 24-hour excretion was 6.3 per cent (range 3.2 to 10.0 per cent) of the injected dose.

Radioactivity was measured with a Texaco well-type Geiger counter and standard scaler; 5 ml. liquid samples were counted until at least 10,000 counts above background were recorded in duplicate on specimens of blood, urine, and standards. During the low sodium phase, however, urines were counted only long enough to demonstrate that the specific activity was not significantly above background. Correction for decay was made by counting at precisely spaced intervals *seriatim* Standard No. 1, Sample No. 1, Sample No. 2, Standard No. 2 with the counting intervals so arranged that the average of the times of counting samples and standards were at the same mid-point in time, with decay corrections having been made automatically thereby.

Total exchangeable potassium (TEK)

TEK was measured by an isotope dilution technique (3). Approximately 100 to 150 μc K^{42}CO_3 obtained from the Brookhaven reactor (containing about .04 mEq. K^{42}) were administered by the same technique used for estimation of exchangeable sodium. In Group I, all urines were pooled up to 37 hours with spot specimens collected after an overnight fast at 38, 40, and 42 hours, at which times probably 95 per cent of the total body potassium is in equilibration with K^{42} (3). The average specific activity of these three samples, corrected for loss of the isotope in urine, was used to calculate total exchangeable potassium. The average excretion of the administered K^{42} at 40 hours in 34 consecutive determinations was 5.5

² Obtained through the courtesy of Wyeth Laboratories, Philadelphia, Pennsylvania.

per cent (range 1.2 to 8.7 per cent) and did not change during either phase of the present study. In Group II, the period allowed for equilibration was an average of 20 hours with all urine pooled up to 17 hours and spot samples collected under fasting conditions at 18, 20, and 22 hours. In no instance did it appear that equilibration had failed to occur in these times as manifested by a regular increase in TEK. If these 20-hour determinations underestimated the exchangeable K slightly relative to the 40-hour values (3), since each patient was his own control, the final relative values during high and low Na would not be affected. A cation exchange resin of the sulfonic type (Amberlite IR-120) was used to concentrate the urine potassium and thereby enhance the counting rate approximately eight-fold. Counting was done with a Harshaw scintillation crystal using a special input amplifier designed at the Brookhaven Laboratory and an Atomic Scaler (Model 1050A). Three ml. liquid samples of standard and sample were counted in the fashion described for Na²⁴ using the same technique for decay correction.

Statistical analyses of significance

The total exchangeable sodium values were calculated from the following data: serum sodium concentration,

the volume and counting rate of the isotopic solution administered with correction for the amount excreted where this was significant, and the counting rate of serum at the time of equilibration. Serum sodium determinations in duplicate were reproducible within 0.5 mEq., which amounts to less than a 0.4 per cent difference. Recovery experiments in which standard saline solutions were added to plasma gave maximal errors of 1 per cent; therefore, an error of 1 per cent has been allowed. The infusion fluid was administered in a 100 ml. buret, calibrated to contain 100.14 ml.; this correction has been disregarded. In this series, the average counting rate of infusion fluid and serum were 5000 and 2500 counts per minute (cpm), with total counts on duplicate samples averaging 27,500, and 25,000, respectively. The coefficient of variation calculated from standard deviation is respectively, .0063 and .0060 (10). Because of local conditions (both a reactor and 2.5 billion electron volt proton accelerator within 1.5 miles) background averaged 400 cpm, with a total of about 70,000 background counts per study. The coefficient of variation here amounts to .0040 and has been included in the calculation of total error. The final cumulative error has been calculated from the formula $\sigma^2 = \sqrt{\sigma_1^2 + \sigma_2^2} \dots$ (11) where σ equals cumula-

TABLE Ia
Data on Patients with Significant Declines in both Systolic and Diastolic Pressures

Pt.	Blood Pressure (Mean & S.D.)				Days before (-) or after (+) Na Restriction	Body Weight (Kg)			Exchangeable Sodium Data					Exchangeable Potassium Data				
	Syst.	p	Diast.	p		Admission	Study	Δ Admission	Total (meq)	Per Kg (meq/Kg)	Difference from Preceding Study x			Total (meq)	Per Kg (meq/Kg)	Difference from Preceding Study x		
											Δ Days	Δ Wt. (kg)	Δ TENa (meq)			Δ Days	Δ Wt. (Kg)	Δ TEK (meq)
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
C 939 (#2420)	162 (10)		111 (9)		-35 -28 -21 -12 -8	71.7	70.5 70.4 69.7 69.7	-1.2 -1.3 -2.0 -2.0	2531 2443	35.9 35.1				2558 2391	36.3 34.3	9	-0.7	-167
I	130 (6)	<.01	94 (6)	<.01	+19 +27 +39 +47 +51		69.0 68.7 68.6 68.2 68.0	-2.7 -3.0 -3.1 -3.5 -3.7	2320 2359	33.8 34.7	35	-1.0	-123	2253 2284 2320	32.7 33.3 34.0	31 20 8	-0.7 -0.4 -0.4	-138 +29 +36
A 642 (#2455)	159 (9)		97 (6)		-42 -19 -16 -12 -9	82.4	81.4 82.2 81.4 81.9	-1.0 -0.2 -1.0 -0.5	3127 3207	38.4 39.1	3	+0.8	+80	2879 2935	35.4 35.8	3	+0.5	+56
II	133 (14)	<.01	89 (7)	<.01	+30 +37 +40 +44 +46 +53		81.0 81.3 81.5 81.9 81.5 81.5	-1.4 -1.1 -0.9 -0.5 -0.9 -0.9	2922 2922 2968	36.1 36.1 36.5	46 10 6	-1.2 +0.5 0.0	-285 0 +46	3248 3231 3021	40.0 39.5 37.1	46 7 9	-0.6 +0.6 -0.4	+313 -17 -201
Non #45 (#2472)	218 (14)		135 (8)		-42 -19 -16 -12 -9	83.1	82.1 82.2 81.7 81.9	-1.0 -0.9 -1.4 -1.2	3190 3075	38.9 37.4	3	+0.1	-115	2844 2860	34.8 34.9	3	+0.2	+16
II	199 (15)	<.01	124 (8)	<.01	+30 +37 +40 +44 +46 +53		82.5 83.3 83.3 83.5 83.4 83.9	-0.6 +0.2 +0.2 +0.4 +0.3 +0.8	2974 3057 3057 2991	36.0 36.7 36.7 35.9	46 10 6	+0.3 +0.8 +0.1	-101 +83 -66	3329 3223 2962	40.0 38.6 35.3	46 7 9	+1.4 +0.2 +0.4	+469 -106 -261

Roman numerals I and II in column 1 refer to patient group I (April - July) or group II (Sept. - Dec. '53).

Mean blood pressures were calculated from the values measured during the last 10 days of control and low Na periods respectively.

Figures in parentheses are standard deviations from the mean.

p (column 3 and 5) = probability level calculated by Fishers "t-test" method.

Dark figures in column 10 and 15 represent values which differ from those preceding by more than 3 S.D.

x = Values are intervals (Δ) in days and changes (Δ) in weight and TE_{Na} or TE_K respectively, found in the successive studies reported in this paper.

TABLE Ib
Data on Patients with Significant Decline in Only Systolic or Diastolic Pressures

TABLE 1b																							
Data on Patients with Significant Decline in Only Systolic or Diastolic Pressures																							
Pt.	Blood Pressure (Mean & S.D.)				Days before (-) or after (+) Na Restriction	Body Weight (Kg)			Exchangeable Sodium Data					Exchangeable Potassium Data									
	Syst.	p	Diast.	p		Admission	Study	Δ	Total (meq)	Per Kg (meq/Kg)	Difference from Preceding Study x			Total (meq)	Per Kg (meq/Kg)	Difference from Preceding Study x							
											Δ Days	Δ Wt. (kg)	Δ TENa (meq)			Δ Days	Δ Wt. (kg)	Δ TEK (meq)					
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19					
E 246 (#5274)	185 (10)		104 (7)		-35 -28 -21 -12 -8	56.8	56.3 55.8 55.2 55.0	-0.5 -1.0 -1.6 -1.8	1900 1925	33.7 35.0				1867 1983	33.5 35.9	9	-0.6	+116					
					I		157 (10)	<.01	98 (8)	<.2	+19 +27 +39 +47 +51	53.7 53.0 53.2 52.4 52.7	-3.1 -3.8 -3.6 -4.4 -4.1	1747 1801	33.0 34.2	35 24	-2.0 -0.3	-178 +54	1926 1807 1793	35.9 34.0 34.2	31 20 8	-1.5 -0.5 -0.8	+57 -119 -14
											P 272 (#5424)	182 (17)		83 (6)		-37 -30 -21 -16	58.1	58.1 57.4 57.3 57.2	0.0 -0.7 -0.8 -0.9	2288 2366	39.4 41.4		
I	146 (11)	<.01	76 (7)	<.05	+10 +19 +31 +38 +43 +75 +78	53.3 53.2 53.2 53.1 52.8 53.6 53.6	-4.8 -4.9 -4.9 -5.0 -5.3 -4.6 -4.5	1977 2193 1957	37.1 41.5 36.5	36 24 32						-4.0 -0.4 +0.8	-389 +216 -236	1496 1539 1642	28.1 28.9 30.9	31 21 7	-4.0 -0.1 -0.1	-109 +43 +103	
					I	165 (12)	<.01	80 (8)	<.4>.3	-18 -20						54.6 54.5	-3.5 -3.6	2287	41.9	22	+1.0	+330	1433 1439
B 269 (#5504)	201 (14)		95 (11)							-42 -19 -16 -12 -9	62.2	62.6 64.9 65.3 65.4	+0.4 +2.7 +3.1 +3.2	2331 2332	37.2 35.9	3	+2.3	+1	1833 1880	28.1 28.4	3	+0.1	+47
					II	178 (11)	<.01	89 (9)	<.2>.1	+30 +37 +40 +44 +46 +53	65.6 65.8 65.7 66.2 65.9 65.9	+3.4 +3.6 +3.5 +4.0 +3.7 +3.7	2184 2232 2187	33.3 33.9 33.3	46 10 6	+0.7 +0.1 +0.2	-148 +48 -45	2023 1905 1812	30.8 28.8 27.5	46 7 9	+0.4 +0.4 -0.3	+143 -118 -93	
										L 242 (#5458)	172 (18)		101 (4)		-42 -19 -16 -12 -9	73.1	72.8 73.8 72.8 73.8	-0.3 +0.7 -0.3 +0.7	3002 3023	41.2 41.0	3	+1.0	+21
II	162 (15)	<.2>.1	83 (11)	<.01	+30 +37 +40 +44 +46 +53	72.3 72.0 71.7 71.7 60.6 71.6	-0.8 -1.1 -1.4 -1.4 -2.5 -1.5	2639 2708 2657	36.5 37.8 37.6						46 10 3	-1.5 -0.6 -1.1	-384 +69 -51	3259 3178 3063	45.3 44.3 42.8	46 7 9	-1.8 -0.3 -0.1	+212 -81 -115	

See bottom of Table 1a for details.

□ = Days after Na added second time.

// = Weight may be erroneous since weights on days preceding and following were 64.5 and 64.9 Kg respectively.

See bottom of Table Ia for details.

□ = Days after Na added second time.

// = Weight may be erroneous since weights on days preceding and following were 64.5 and 64.9 Kg respectively.

tive error, and $\sigma_1, \sigma_2, \dots$ etc. denote individual analytical errors. Using this formula, the average standard deviation of the entire procedure was .014, equivalent to about 40 mEq. for a 70-Kg. adult. This calculated value subsequently proved to be in substantial agreement with that found in 29 consecutive determinations on six patients in which the mean difference of duplicate values for TENa obtained at equilibrium, namely 24 and 26 hours, was 40.4 mEq., uncorrected for weight. The value for TEK was based on primary data similar to those used for sodium, but the standard deviation of the counts among the three urine samples has also been included, the value amounting to 3.8 per cent. Based on average rates of 10,000, 1440 and 220 cpm for infusion fluid, urine samples, and background total counts of 20,000, 12,000 and 30,000, respectively, the coefficients of variance are .0092, .0070 and

.0058. A value of .01 has been given to the chemical analysis for K on the basis of analytical data similar to those obtained for sodium. The cumulative error of these five values becomes .041, equivalent to about 80 mEq. for a 60-Kg. female (12) and 130 mEq. for a 70-Kg. male (3). Standard deviations of blood pressures were calculated from the mean of readings obtained during the final 10 days of both the high (control) and low (test) sodium phases. Fisher's "t" test was used as a criterion of significance between the mean values so found, with $p = < .01$.

OBSERVATIONS

The results of these studies are summarized in Tables Ia, Ib, and Ic in which the data are listed and divided among those subjects with a fall in

TABLE Ic
Data on Patients with Significant Decline in neither Systolic nor Diastolic Pressures

TABLE Ic

Data on Patients with Significant Decline in neither Systolic nor Diastolic Pressures

Pt.	Blood Pressure (Mean & S.D.)				Days Before (-) or after (+) Na Restriction	Body Weight (Kg)			Exchangeable Sodium Data					Exchangeable Potassium Data					
	Syst.	P	Diast.	P		Admission	Study	Δ Admission	Total (meq)	Per Kg. (meq/Kg)	Difference from Preceding Study x			Total (meq)	Per Kg. (meq/Kg)	Difference from Preceding Study x			
											Δ Days	Δ Wt. (kg)	Δ TEKa (meq)			Δ Days	Δ Wt. (Kg)	Δ TEK (meq)	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Mor 653 (#283)	195 (9)		118 (10)		-35 -28 -8 -2	64.1	64.1 63.2 63.5	0.0 -0.9 -0.6	2681 2758	41.8 43.6	20	-0.9	+77	2280* 1784	35.9* 28.1				
I	192 (9)	<.5	115 (8)	<.5	+19 +27 +39 +47 +51		62.1 63.0 62.2 62.2 61.8	-2.0 -1.1 -1.9 -1.9 -2.3	2406 2256 2188	41.4 36.3 35.2	35 24	-0.2 -1.2	-152 +65	2049 2256 2188	33.0 36.3 35.2	21 20 8	-1.4 -0.8 0.0	-231 +207 -68	
R 648 (#303)	173 (14)		101 (6)		-35 -28 -21 -12 -8	92.7	88.2 87.4 86.0 84.4	-4.5 -5.3 -6.7 -8.3	3022 2738	34.3 32.4	20	-3.8	-284	4011 4042	45.9 47.0	9	-1.4	+31	
I	166 (13)	<.3	98 (8)	<.4	+27 +39 +47 +51		80.4 82.4 81.2 80.6	-12.3 -10.3 -11.5 -12.1	2862 2992	35.6 37.1	35 24	-4.0 +0.2	+124 +130	3505 3554	42.5 43.8	51 8	-3.6 -1.2	-537 +49	
U 920 (#348)	202 (13)		120 (8)		-35 -26 -22 -7 -1	44.4	46.7 45.7 45.4 44.7	+2.3 +1.3 +1.0 +0.3	2180 2073	47.7 45.4	15	-0.3	-107	2269 1633	48.6 36.5	25	-2.0	-636	
I	189 (13)	<.05	113 (9)	<.1	+13 +25 +30 +36		44.6 45.5 45.9 45.7	+0.2 +1.1 +1.5 +1.3	1956 2057	43.9 45.1	20 23	-0.8 +1.1	-117 +101	2183 2192	48.0 47.8	26 5	+0.8 +0.4	-86⑥ +9	
S 953 (#6268)	196 (33)		90 (11)		-42 -19 -16 -12 -9	51.5	51.6 52.0 52.2 51.8	+0.1 +0.5 +0.7 +0.3	1997 1845	38.3 35.5	3	+0.4	-132	1631 1570	31.3 30.3	3	-0.4	-61	
II	186 (19)	<.5>.4	88 (8)	<.5	+30 +37 +40 +44 +46 +53		52.9 52.2 52.3 52.7 52.7 53.2	+1.4 +0.7 +0.8 +1.2 +1.2 +1.7	1862 1806 1811	35.2 34.5 34.4	46 10 6	+0.9 -0.6 +0.4	+17 -56 +5	1706 1749 1657	32.7 33.2 31.1	46 7 9	+0.4 +0.5 +0.5	+136 +43 -92	

See bottom of Table Ia for details.

* = Only two urine specimens available. Because of poor checks, both values have been included, although the low value is more likely erroneous.

= This value so far out of line with other R² studies on this patient that it has not been used in calculations.

⑥ = Represents the difference between the first and third R² studies.

See bottom of Table Ia for details.

* = Only two urine specimens available. Because of poor checks, both values have been included, although the low value is more likely erroneous.

† = This value so far out of line with other R^{42} studies on this patient that it has not been used in calculations.

⑥ = Represents the difference between the first and third R^{42} studies.

both, either, or neither systolic and diastolic pressures, respectively. Statistically significant declines in both systolic and diastolic pressures were shown by 3 of the 11 patients following this degree of sodium restriction, a fraction that approximates our experience with a similar diet during the past six years, as well as the experience of others (13-15). Eight of these patients had a decrease in TENa of 3 S.D. or more during the low Na phase and were divided without relation to the effects on blood pressure. This was noted earlier (1).

The values obtained for TEK on all patients were in agreement with those reported for normal males (3) and females (12). Among the 11 patients limitation of Na was followed by a statistically significant change in TEK in only two sub-

jects, both males: Mon (Table Ia) and R (Table Ic). In the first instance there was an increase of 469 mEq. in TEK in association with a decline in blood pressure, and in the second there was a fall in TEK of 537 mEq. with no change in blood pressure. The remaining nine patients showed variable and modest responses in TEK which differed somewhat between the two groups. TEK in Group I was found to vary in minor degree about the control values, except for patient R as noted. By contrast, a fairly uniform reaction occurred in the members of Group II: 37 days after Na restriction TEK was elevated over control levels in all five patients. The increase exceeded 3 S.D. in only one patient (Mon, Table Ia) on a weight and sex basis, but the increases were all

FIG. 1. TENa and TEK before and after Na restriction in three patients

The vertical line on abscissa indicates day on which added Na (180 mEq.) was omitted from diet.

similar in magnitude (+136 to +469 mEq.). Recheck of TEK 44 and again 53 days after Na restriction revealed that the initial elevation was not permanent for by the 53rd day, the data obtained were in substantial agreement with those found during the control period. In Figure 1, the

values on several representative patients of Group II have been plotted against time from which it will be seen that the decline in TEK was gradual. This suggested that the initial elevation noted after Na restriction represented a physiologic response rather than a methodological aberration. Furthermore, from the characteristic urinary patterns shown in Figure 2, it may be seen that Na limitation had no apparent effect on K excretion. This confirms earlier observations (1). Repeated measurements were made of serum Na and K throughout the course of the study and showed no significant deviations during either phase of the regimen.

INTERPRETATION

In confirmation of earlier work (1), these studies indicate that sodium restriction does not act by simply "salting out" the organism since desalting, at least as measured by TENa, bore no relationship to the therapeutic effect in these patients. In view of the evidence (16) that in some patients TENa can decrease or increase unrelated to net balance of sodium, the possibility must be considered that TENa may not accurately mirror any desalting which does occur. However, calculation of the net sodium balance in this group by measurement of total urinary sodium assuming a daily stool output of 1.5 mEq. per day (1) and an intake of 6 mEq. per day, failed to show that in those with the greatest net loss, the most significant declines in blood pressure occurred.

It had been found earlier (1) in four patients subjected to a similar regimen that loss of exchangeable sodium uniformly exceeded the weight loss which should have occurred if the sodium came from extracellular fluid (ECF). Therefore, the hypothesis was proposed that failure to lose an equivalent amount of weight along with the sodium was due to a movement of water from an extracellular to an intracellular position. Analysis of the data from these 11 patients relative to this point is shown in detail in the accompanying table

FIG. 2. URINARY EXCRETION OF Na AND K before and after Na restriction

The second vertical line on patient P indicates point at which NaCl again was added to diet; this patient also received a total of 400 mgm. Cortisone, I.M., on 15 and 16 July, in association with studies not pertinent to the present paper. The studies on the group as a whole had been completed at this time; the effects on Na and K excretion are readily visible. Note that ordinates are logarithmic.

FIG. 2.

TABLE II

Comparison of determined TENa difference after Na restriction and theoretical Na equivalent of the weight change, assuming that all weight changes were due to variations in ECF associated with withdrawal or addition (P) of Na *

	Patient and No.	Δ Wt. (Kg.)	E.C.F. equiv. (A) (Kg. $\times 140$)	Δ TENa (B)	B-A
Group I	P 5424	-4.0	-560	-389	+171
		+1.0	+140	+330	+190
	U 5348	-0.8	-112	-117	-5
	C 5420	-1.0	-140	-123	+17
	E 5274	-2.0	-280	-178	+102
	M 5283	-0.2	-28	-152	-124
Group II	R 5303	-4.0	-560	+124	+684
	A 5455	-1.2	-168	-285	-117
	B 5504	+0.7	+98	-148	-246
	L 5458	-1.5	-210	-384	-174
	Mon 5472	+0.3	+42	-101	-143
	S 5268	+0.9	+126	+17	-109

* These values were obtained from the last TENa determination before, and the first TENa after, restriction of Na in the diet. The second value for patient P represents the difference between the last TENa before and the first TENa after, the re-addition of Na in the diet.

(Table II) which includes changes in weight and TENa recorded between the last measurement of TENa before Na restriction and the first such measurement after restriction (patient P includes a period of sodium restriction followed by one of sodium addition).

The present data neither wholly confirm nor refute the hypothesis proposed above. It will be seen that the five patients in Group II are in agreement with the proposed interpretation in that weight loss fell short of equivalence with the decrease in TENa. But in Group I only patient M followed the same pattern although P, upon re-adding Na, gained less weight than would have been predicted from her increase in TENa, thereby suggesting that if the increase in TENa was associated with an increase in ECF, the necessary fluid came from intracellular water. The other five patients in this group were not in agreement with the hypothesis suggested. In two, decline in TENa and weight were virtually equivalent while the remaining three showed declines in TENa of less than the weight equivalence by 102 to 684 mEq. Na. It is of interest that the two groups differed by such an extent and it is not simply explained by the effects of weight loss with the relative absence of such loss in Group II versus the considerable loss in some members of Group I: patients U and

C in Group I lost insignificant amounts of weight, yet failed to lose more than an equivalent amount of sodium measured by TENa. Two of the five patients in Group II lost slightly greater amounts of weight than did U and C, yet had an associated decline in TENa of significantly greater equivalence. Parenthetically, a normal male that underwent the regimen in Group II, and who forms the subject of a separate report (16) behaved like the members of Group I rather than those in his own group; this suggested that changes in environmental temperature, diet, or unknown technical factors could not be called in to account for the difference between the groups. It seems at least as reasonable to interpret some of the changes in TENa as being fluctuations in the amount of body Na available for exchange with the isotope, presumably due to that in the reservoir contained in bone (17). Sjögren (18) made a similar suggestion after treating a patient with rheumatoid arthritis with 20 mg. DCA for 60 days and observing

FIG. 3. LACK OF CORRELATION BETWEEN CHANGES IN MEAN $\frac{(S+D)}{2}$ BLOOD PRESSURE AND CHANGE IN TEK

TABLE III
Summary of changes in blood pressure, TENa and TEK

Patient	Significant* decrease in B.P.		Significant decrease in TENa	Significant change (+ or -) in TEK
	Syst.	Diast.		
C	+	+	+	0
A	+	+	+	0
Mon	+	+	0	+
E	+	0	+	0
P	+	0	+	0
B	+	0	+	0
L	0	+	+	0
Mor	0	0	+	0
R	0	0	0	-
U	0	0	+	0
S	0	0	0	0

* Statistically significant.

an increase of 700 mEq. in TENa in the presence of a net Na loss of 330 mEq.

The data do not suggest that drastic limitation of Na intake acts by effects on K, at least as measured by TEK. The frank lack of correlation between blood pressure changes and TEK is shown in Figure 3. Further, as indicated in Table III, there seemed to be no relationship between changes in TEK, and those in TENa. The types of measurements used are, of course, relatively gross and it is possible that while no constant effect on K metabolism was found, fine changes were effected by the regimen but were obscured by the daily variations in K intake and the magnitude of the K pool. No explanation is presently available for the transient rise of TEK found in Group II and not in Group I. With Na restriction, it is known that K largely replaces Na as the dominant ion in sweat (5). It is therefore possible that the warm weather associated with the last half of the period in which Group I was studied could have led to K loss of considerable degree with resulting reflection upon TEK; and it is true that in this group as a whole, TEK declined slightly over control values.

The weight changes failed to account for variations in TENa as mentioned earlier; this was also true for TEK as indicated by data in columns 18 and 19, Tables Ia, Ib, and Ic. It is reasonable to suggest that here, too, the variability found is accounted for by changes due to the bone reservoir of K (17).

SUMMARY

1. A series of 11 patients with essential hypertension has been studied before and after restriction of Na intake to approximately 6 mEq. per day.

2. After restriction of Na intake, no correlations were found between changes in blood pressure and either total exchangeable sodium or potassium.

3. It was suggested that some of the variations which occurred in TENa and TEK were due to fluctuations in the amount of body sodium and potassium made available for exchange with the isotopes, presumably due to the reservoir of these elements contained in bone.

ACKNOWLEDGMENTS

We wish to thank Miss Ruth Sovocool, Mr. John Rusica, and Mrs. Miriam Brown for their invaluable technical assistance, and the Misses Susan Lamb and Norma Gillespie, dietitians, for supervision of the diets. The fine cooperation of the nurses, particularly Miss Josephine O'Connell, R.N. and Miss Rosemarie McCann, R.N., is acknowledged.

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