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INFLUENCE OF SODIUM INTAKE ON EXCHANGEABLE SODIUM IN NORMAL HUMAN SUBJECTS *

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Several methods for determining exchangeable sodium in human subjects by using the gamma-ray emitter Na^{22} (half-life 2.6 years) in conjunction with measurements of body radioactivity have previously been described (1–3). With these methods, it is possible to make repeated exchangeable sodium determinations over a period of several weeks or months after giving a single tracer dose of the radioisotope. Sodium metabolism can thus be studied in a way that has certain advantages over conventional metabolic balance techniques in that sodium losses from all sources are accounted for and the results obtained reflect specifically changes in the active sodium pool.

For the determination of exchangeable sodium, a 24- to 48-hour period is usually allowed for exchange of the tracer sodium with body sodium in adult subjects, but some observations have suggested that there is significant continuing exchange after this interval (1, 4–7). The fraction of body sodium not exchanged in 24 to 48 hours is estimated at 30% of total body sodium and is thought to consist mostly of sodium in bone (4, 5, 8–11). If these observations are correct, they would seriously limit the interpretation of long-term exchangeable sodium determinations after a single Na^{22} injection, for this slow exchange would result in a continually increasing calculated exchangeable sodium, and it would be difficult at any given time to determine how much of a measured increase in exchangeable sodium was due to the continuing internal exchange and how much to an actual increase in body sodium. Furthermore, if our interest is in the active sodium pool, that is, that part of body sodium available for relatively rapid metabolic accommodations, it would be erroneous to represent this pool by an exchangeable sodium value which included sodium that had taken several days to equilibrate with the tracer.

In the present report, Na^{22} and a body radioactivity counter have been employed for repeated exchangeable sodium determinations in five normal individuals, each given widely varied amounts of sodium over extended periods. The influence of changes in sodium intake on and the contribution of slowly exchanging body sodium to such exchangeable sodium values were evaluated.

METHODS

Experimental procedure. Five healthy men varying in age from 23 to 40 received iv tracer doses of Na^{22} (10 to 15 μc). Three of the subjects (B.E., L.M., and P.J.) were taking fixed low-sodium diets at the time of the injection, and the other two (B.B. and J.C.) were taking their normal diets with a variable sodium content and later were placed on fixed low-sodium diets. In three of the subjects (P.J., B.B., and J.C.), the fixed low-sodium diet consisted of a liquid synthetic preparation that provided 2 mEq of sodium per day or less.[1] The low-sodium diet for the other two subjects (B.E. and L.M.) was a hospital low-sodium diet supplying an average of 20 mEq of sodium per day. The period of fixed low-sodium intake was followed in each subject by a period of fixed relatively high-sodium intake. During the period of high intake, two of the subjects (P.J. and B.B.) took their daily sodium load of 200 mEq orally in the first

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[1] The major component of the diet for J.C. and B.B. was kindly supplied as Product 3060-1-A by Mead Johnson & Co., Evansville, Ind. The synthetic diet for P.J. was generously furnished by Dr. Jacob Lemann, Jr.; its major constituents were soybean flour, corn oil, and glucose.

TABLE I

Body weight; sodium intake, output, and serum concentration; serum and body Na^{22} values; and exchangeable sodium determinations in Subject P.J.

Day	Wt	Na intake	Urine Na output	Serum Na	Serum Na^{22}	Body retention, percentage of dose	Na_e
	kg	*mEq*	*mEq*	*mEq/L*	*percentage of dose/L*	%	*mEq*
1	80.5	1	18.3	143	4.355	99.42	3,260
2	80.1	1	5.8	137		99.61	
3	79.6	1	4.3			97.63	
4	79.6	1	2.6	136	4.224	97.61	3,140
5	79.5	1	1.3			98.33	
6	79.4	1	1.6	137	4.302	96.43	3,070
7	79.3	1	0.9			96.16	
8	79.1	1	0.6	136		96.57	
9	78.9	1	3.2	138	4.470	95.92	2,960
10	78.1	1	3.9	139		95.31	
11	77.7	1	4.1			94.53	
12	77.5	1	2.7	138	4.341	96.21	3,060
13	77.1	1	2.2	138		96.58	
14	77.1	1	1.6	138		94.38	
15	77.2	1	0.4	140	4.194	94.55	3,160
16	77.3	1	0.5	138		93.95	
17	77.2	1	0.4	137	4.258	93.24	3,000
18	77.1	1	0.4			92.53	
19	77.0	1	0.4	138	4.266	92.75	3,000
20	77.0	200	1.3	145	4.140	90.82	3,180
21	78.3	200	5.7	141	3.803	91.36	3,390
22	78.8	200	36.6	150	3.921	91.09	3,480
23	79.6	200	82.8	145	3.378	89.04	3,820
24	79.5	200	206			91.51	
25	79.2	200	213	145	3.111	77.14	3,600
26	79.0	200	254	149	2.905	73.95	3,790
27		ad lib	376				
28		ad lib	497				
29	79.0	ad lib	353	146	2.265	53.77	3,470
30		ad lib	314			48.51	
31		ad lib	347			45.54	
32	77.6	ad lib	267			40.69	
33	77.7	ad lib	243	144	1.652	38.42	3,350
34	77.6	ad lib	269			34.65	
35	77.3	ad lib	285			31.89	
36	77.0	ad lib	349	143	1.309	28.37	3,100
37	76.9	ad lib	266			26.06	
38	77.3	ad lib	212			24.14	
39	77.6	ad lib	184	144	1.008	23.13	3,300
40	77.2	ad lib	312			20.72	
41	77.3	ad lib	236	139	0.883	19.48	3,070
42	76.9	ad lib	192				
43	77.5	ad lib	176			16.55	
44	76.8	ad lib	244	134	0.693	15.08	2,920
45	77.1	ad lib	185				
46	76.5	ad lib	137			14.16	
47	77.4	ad lib	177	128	0.590	13.05	2,830
48	77.9	ad lib	205			12.57	
49	78.0	ad lib	189			11.91	
50	77.6	ad lib	171	142	0.477	10.88	3,240
51	77.0	ad lib	173				
52	77.4	ad lib	197				
53	77.5	ad lib	372			8.906	
54	77.7	ad lib	196	145	0.385	8.375	3,150
55	76.9	ad lib	186			7.957	
56	77.2	ad lib	434				
57	77.1	ad lib	222	144	0.294	7.013	3,430

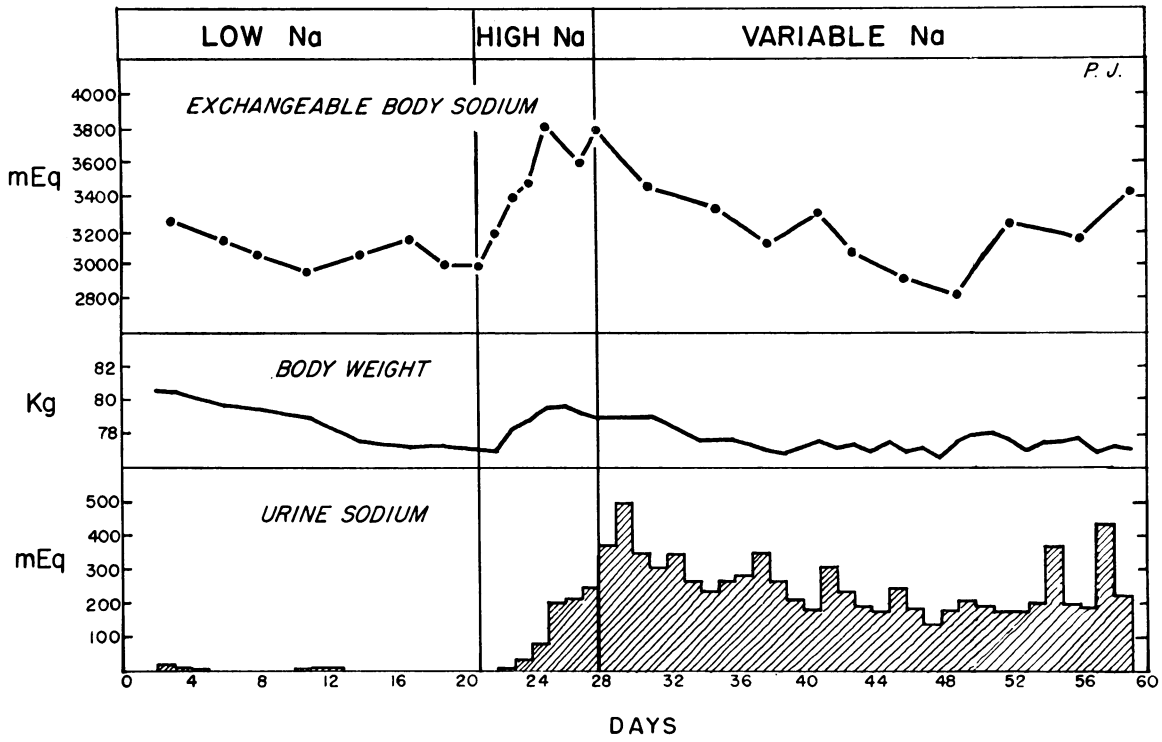


FIG. 1. EXCHANGEABLE SODIUM VALUES, BODY WEIGHT, AND URINE SODIUM PLOTTED AGAINST TIME. Salt loading in this subject was accomplished by the ingestion of NaCl tablets. At his own request, the subject was on a low-calorie diet during the first two dietary periods. Note that his weight at the end of the study (day 59) was 3.5 kg less, but his exchangeable sodium was slightly higher. This suggests the loss of sodium-free tissues, presumably mainly fat.

8 to 10 hours of each 24-hour period, and the other three (B.E., L.M., and J.C.) received their sodium load of 181 to 359 mEq per day intravenously in the form of 5% saline solution in the first 2 hours of each 24-hour period. After the period of high-sodium intake, each subject resumed his normal diet and was followed for an additional period on a variable sodium intake.

A study day ran from one morning to the next and ended with the patient fasting. Urine was collected each day for determination of 24-hour urine sodium excretion. One subject (P.J.) also collected all stools during the periods of fixed low- and fixed high-sodium intakes, and pooled stool specimens were analyzed for sodium content after nitric acid digestion. Venous blood samples were drawn, and body radioactivity measurements were made at the end of the study day.

Body radioactivity measurements. Body radioactivity measurements were made with the subject seated in a contour chair beneath the open end of a shielded sodium iodide crystal 4 inches in diameter by 4 inches in height. The center of the crystal was placed 50 cm from the midline of the body. The details and efficiency of this counting arrangement have been described elsewhere (3). Separate measurements of the radioactivity of the knee and the posterior aspect of the head were made with smaller sodium iodide crystals. At the knee, the collimation for the crystal was such that the Na^{22} radioactivity measured came from a limited area composed mainly of the bony structures (5). At the posterior aspect of the head (lower occipital area), there was less collimation, and radioactivity from a wider area containing cerebrospinal fluid and brain tissue as well as bone was measured.

Sample measurements. The Na^{22} radioactivities of serum and urine samples were determined in a standard sodium iodide well-counter. In one study where Na^{24} was measured in the presence of Na^{22} (Subject B.E.), a differential pulse height analyzer was used. Chemical sodium concentration of samples was measured by flame photometry.

Calculations. Exchangeable sodium was derived from the retention of Na^{22} determined from body radioactivity measurements, serum Na^{22} concentrations, and serum concentration of stable sodium. The formula employed was: *Exchangeable sodium = body Na^{22} retention (per cent) × serum sodium concentration (milliequivalents per liter)/serum Na^{22} concentration (per cent per liter)*, where Na^{22} retention in the body and Na^{22} concentration in the serum are expressed as percentages of the initial dose.

The body counter was calibrated for each patient by equating the measurement at 24 hours with Na^{22} retention at that time as determined from urinary excretion.

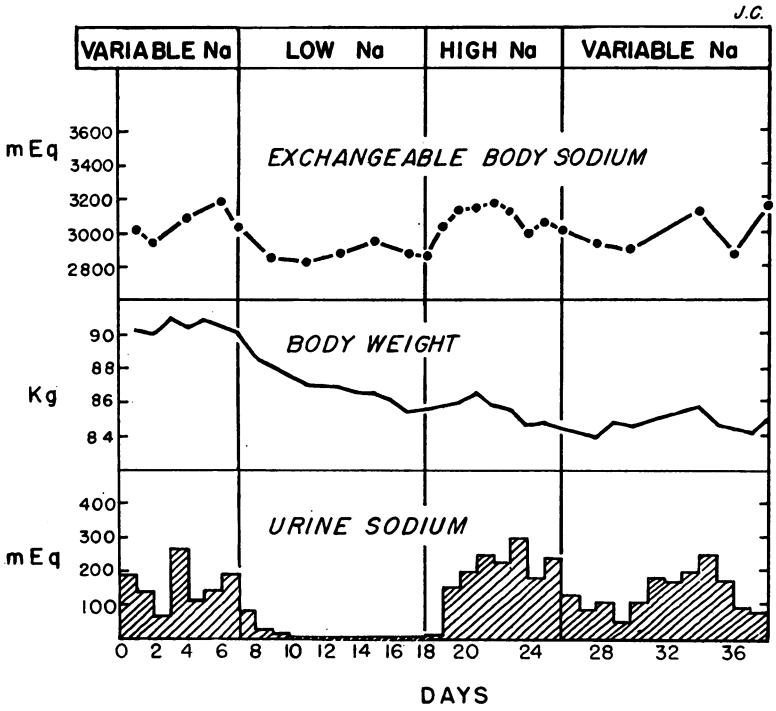


FIG. 2. EXCHANGEABLE SODIUM, BODY WEIGHT, AND URINE SODIUM PLOTTED AGAINST TIME. Sodium supplementation during the period of high-sodium intake was administered intravenously. Exchangeable sodium during this period gradually increased to a peak value and then fell off to intermediate levels. The subject was also on a low-calorie reducing diet and lost a total of 5.3 kg over the course of the study without a decrease in the final exchangeable sodium values as compared to the initial ones.

Long-term Na^{22} retention. In three subjects (P.J., B.B., and J.C.), measurements of body radioactivity due to Na^{22} were continued at intervals up to 2½ years after the initial injections with a more sensitive counting arrangement, consisting of an 8- × 4-inch NaI (Tl) crystal mounted in a steel room and connected to a multichannel pulse height analyzer.[2] The purpose of these measurements was to determine the residual amount of the tracer dose of Na^{22} and the long-term turnover of this residual.

RESULTS

Exchangeable sodium. The three subjects who were taking a fixed low-sodium diet at the start of their studies (B.E., L.M., and P.J.) showed relatively constant values for exchangeable sodium throughout the period of fixed low-sodium intake (Figure 1, Table I). The two subjects who started their studies on regular diets (B.B. and J.C.) showed varying exchangeable sodium values as long as they remained on their regular diets, but when they changed to the fixed low-sodium diets, their exchangeable sodium values decreased for the first few days, and then also remained relatively constant (Figure 2, Table II).

When each subject changed from a fixed low-sodium intake to a fixed high-sodium intake, there was a definite increase in his exchangeable sodium values. In two of the subjects (B.B. and J.C., Figure 2), there was a gradual increase to a peak value and then a fall-off to intermediate levels. In the other three subjects, there was no such clearly defined pattern. Despite this variation in exchangeable sodium values on the high-sodium intakes, there was a significant group increase in exchangeable sodium with increased sodium intake (Table III).

Values for exchangeable sodium during the final periods when the subjects resumed their normal diets again showed considerable variability; average values for this period were intermediate to the low- and high-sodium intake averages in three

[2] Radioactivity Center, Massachusetts Institute of Technology, Cambridge, Mass.

TABLE II

Body weight; sodium intake, output, and serum concentration; serum and body Na^{22} values; and exchangeable sodium determinations in Subject J.C.

Day	Wt	Na intake	Urine Na output	Serum Na	Serum Na^{22}	Body retention, percentage of dose	Na_e
	kg	*mEq*	*mEq*	*mEq/L*	*percentage of dose/L*	%	*mEq*
1	90.2	ad lib	185	139	4.291	93.68	3,030
2	90.0	ad lib	136	136	4.141	89.80	2,950
3	90.8	ad lib	64.9			87.84	
4	90.4	ad lib	265	136	3.659	83.15	3,090
5	90.8	ad lib	114			79.33	
6	90.5	ad lib	143	142	3.410	76.26	3,180
7	90.0	ad lib	193	138	3.232	71.22	3,040
8	88.5	1	79.5			69.72	
9	88.0	1	24.8	139	3.286	67.58	2,860
10	87.5	1	14.4			67.09	
11	87.0	1	4.04	139	3.323	67.37	2,820
12	86.9	1	4.52			66.94	
13	86.8	1	2.32	138	3.140	65.43	2,880
14	86.5	1	1.95			65.51	
15	86.3	1	2.31	142	3.166	65.84	2,950
16	86.0	1	1.47			64.95	
17	85.4	1	3.17	144	3.267	65.24	2,880
18	85.6	1	2.59	141	3.190	64.96	2,870
19	85.8	245	14.4	145	3.116	65.33	3,040
20	86.0	228	157	140	2.786	62.51	3,140
21	86.5	218	204	144	2.674	58.47	3,150
22	85.8	238	252	141	2.429	54.82	3,180
23	85.5	229	235	141	2.279	50.51	3,130
24	84.6	240	302	141	2.169	45.96	2,990
25	84.8	257	186	142	2.029	43.72	3,060
26	84.4	236	240	141	1.904	40.73	3,020
27	84.3	ad lib	132			38.31	
28	84.0	ad lib	91.2	140	1.763	37.01	2,940
29	84.8	ad lib	113			35.83	
30	84.6	ad lib	55	139	1.682	35.13	2,900
31		ad lib	113				
32		ad lib	181				
33		ad lib	174				
34	85.8	ad lib	202	141	1.277	28.31	3,130
35	84.8	ad lib	248			26.27	
36	84.4	ad lib	177	138	1.179	24.55	2,870
37	84.3	ad lib	95.1			24.15	
38	84.9	ad lib	82.5	142	1.051	23.56	3,180

TABLE III

Changes in serum sodium concentration and exchangeable sodium with increased sodium intake

Subject	Low-sodium period			High-sodium period				
	Na intake	Serum Na ± SD	Na_e ± SD	Na intake	Serum Na ± SD	Na_e ± SD	Δ Serum Na*	Δ Na_e†
	mEq	*mEq/L*	*mEq*	*mEq*	*mEq/L*	*mEq*	*mEq/L*	*mEq*
L.M.	20	141.9 ± 1.62 [9]‡	3,247 ± 29.2 [9]	181	145.0 ± 2.77 [7]	3,481 ± 34.0 [7]	+3.1	+234
B.E.	20	140.9 ± 1.25 [8]	2,635 ± 32.6 [8]	358	140.5 ± 1.69 [8]	2,830 ± 30.0 [8]	−0.4	+195
B.B.	1	140.1 ± 1.58 [7]	3,452 ± 140 [6]§	200	138.8 ± 1.64 [5]	3,616 ± 107 [5]	−1.3	+164
J.C.	2	140.5 ± 2.28 [6]	2,876 ± 27.9 [6]	236	141.8 ± 1.73 [8]	3,089 ± 25.2 [8]	+1.3	+213
P.J.	1	138.1 ± 1.73 [14]	3,081 ± 57.7 [8]	200	145.8 ± 1.21 [6]	3,543 ± 1.13 [6]	+7.7	+462

* Group change is insignificant (p greater than 0.2), according to paired *t* test (12).
† Group difference significant (p less than 0.01).
‡ Numbers in brackets refer to number of determinations.
§ Exchangeable sodium value for first day omitted from calculated mean.

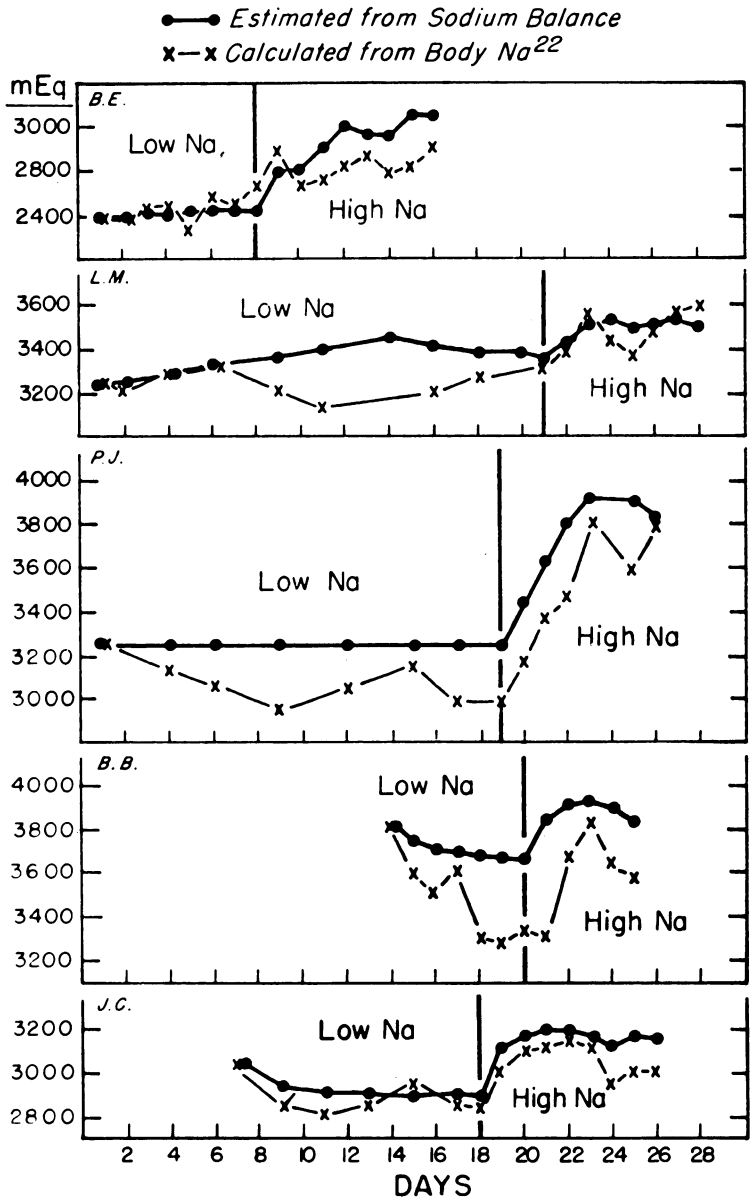


FIG. 3. EXCHANGEABLE SODIUM VALUES CALCULATED FROM SERUM SPECIFIC ACTIVITY AND BODY-COUNTING DATA COMPARED WITH THOSE ESTIMATED FROM SODIUM BALANCE. The latter values were obtained from the value calculated for exchangeable sodium at the end of the first day of low-sodium intake, corrected for each subsequent day for the sodium balance determined from intake and urinary excretion.

subjects (L.M., P.J., and J.C.) and greater than the fixed high-sodium intake averages in the other two subjects (B.E. and B.B.).

Body weights. There were no significant changes in body weights for the group as a whole in going from low-sodium periods to high-sodium periods, perhaps because caloric intake was not regulated to energy requirements. Two subjects, in fact, were placed on low-calorie diets because they wished to lose weight. However, body weights usually decreased when the subjects were placed on fixed low-sodium diets and usually in-

creased when they were changed to fixed high-sodium diets. It is worth noting that the two subjects on low-calorie diets lost totals of 3.5 kg (P.J.) and 5.3 kg (J.C.) without a significant difference in exchangeable sodium at the beginning and end of the studies.

Serum sodium concentration. The increase in serum sodium concentration for the group in going from a low-sodium intake to a high-sodium intake was not significant (Table III). The three subjects (P.J., L.M., and J.C.) who showed an increase in serum sodium concentration also showed the greatest increase in average exchangeable sodium between the low-sodium and high-sodium periods. The calculated values for exchangeable sodium are dependent on the serum sodium values, but the validity of these observations is supported by the fact that these subjects had been on the low-sodium diets for the longest intervals (11 or more days) before changing to a high-sodium intake.

Sodium balance. Daily 24-hour urine sodium excretions fell gradually to low levels, remained relatively constant when the subjects were placed on fixed low-sodium diets, and then gradually increased again after the institution of the fixed high-sodium intakes. A negative sodium balance, as determined from the urinary excretion, tended to coincide with a fall in measured exchangeable sodium, while a positive balance coincided with an increase.

A curve of estimated exchangeable sodium values can be constructed for the periods of fixed sodium intake by beginning with the value for

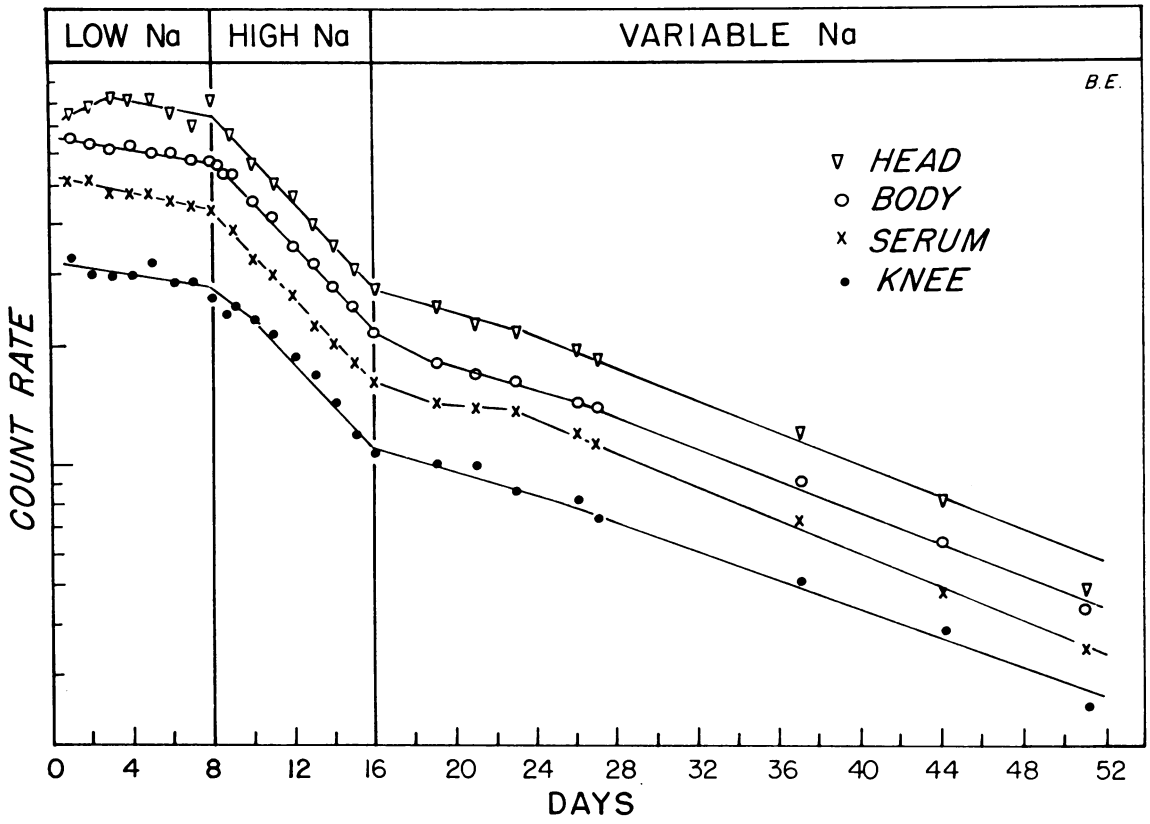
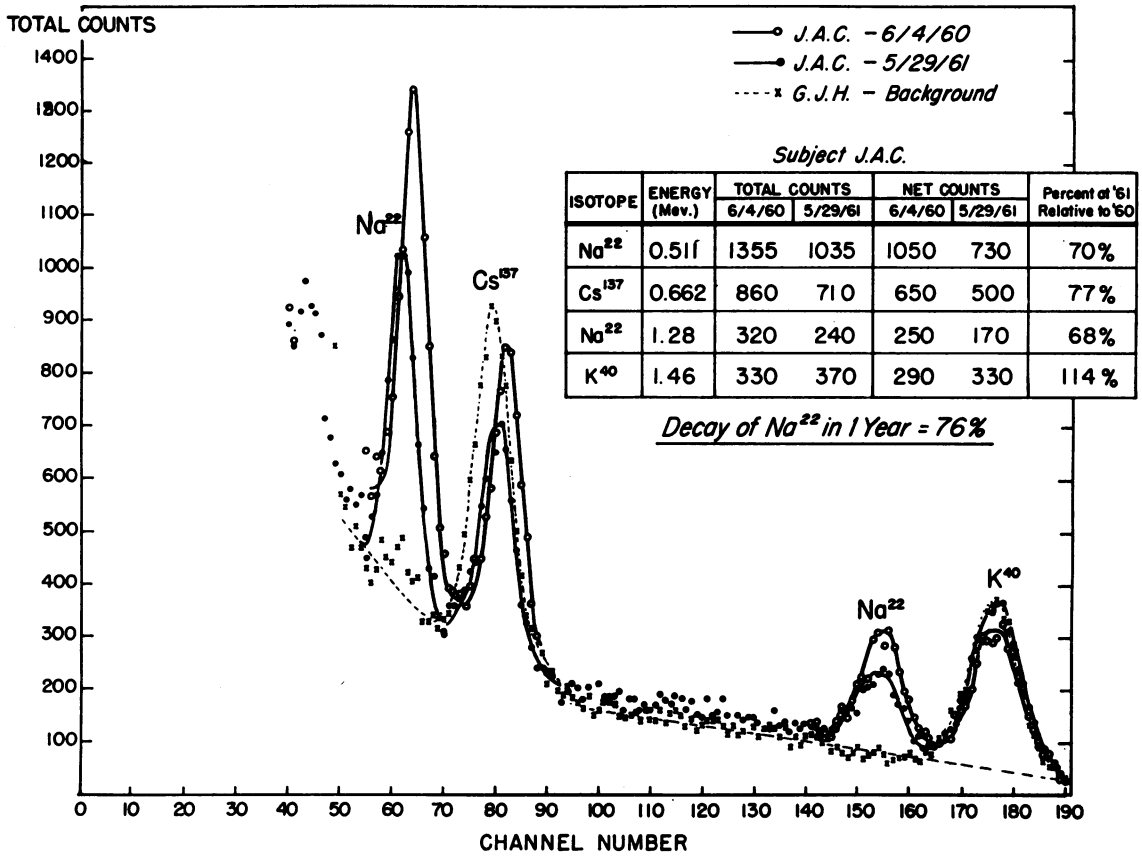


FIG. 4. REPRESENTATIVE SET OF RADIOACTIVITY MEASUREMENTS OBTAINED BY THE BODY COUNTER AND BY COUNTERS CLOSE TO THE HEAD AND THE KNEE. The curve of serum radioactivity is also included. The count rates are plotted on a logarithmic scale against time; the actual count rates were multiplied or divided by some arbitrary factors to bring all curves close together for better comparison. This example shows the prolonged equilibration time of the head, but not that of the knee as seen in other cases; it was chosen because of the long follow-up (51 days). After the initial period of equilibration, the curves are roughly parallel throughout. There is no evidence for continued slow penetration of Na^{22} into the bone of knee or head.



ISOTOPE	ENERGY (Mev.)	TOTAL COUNTS 6/4/60	TOTAL COUNTS 5/29/61	NET COUNTS 6/4/60	NET COUNTS 5/29/61	Percent of '61 Relative to '60
Na^{22}	0.511	1355	1035	1050	730	70%
Cs^{137}	0.662	860	710	650	500	77%
Na^{22}	1.28	320	240	250	170	68%
K^{40}	1.46	330	370	290	330	114%

FIG. 5. GAMMA-RAY SPECTRA OBTAINED IN IRON ROOM AT 15 AND 27 MONTHS AFTER ADMINISTRATION OF TRACER DOSE OF NA^{22} TO SUBJECT J.C. Measurements of body radioactivity of Subject G.J.H., who had not received Na^{22}, were obtained to serve as body background radioactivity in areas of Na^{22} photopeaks. The 1.28 Mev Na^{22} peak activity was approximately one-half that of the 1.46 Mev K^{40} peak activity on 6/4/60. Also shown are the 0.511 Mev Na^{22} photopeak and an adventitious 0.622 Mev Cs^{137} photopeak. With the K^{40} photopeak as a standard, the decrease in Na^{22} photopeak activities during the following year was approximately one-third.

calculated exchangeable sodium at the end of the first day of fixed intake and then correcting on each subsequent day for the sodium balance as determined from intake and urinary excretion. In Figure 3, the curve determined by the above method and the curve calculated from serum specific activity and body radioactivity are shown for each of the subjects. The curves show similar trends in each case; however, there is more variation in the day-to-day values calculated from serum specific activity and body radioactivity, and these values are usually lower than the balance values for the same day.

Head and knee radioactivity measurements. Figure 4 shows a representative set of curves for radioactivity as recorded by the body counter and by the counters at the head and at the knee, together with the curve for serum radioactivity. As might be anticipated, times for equilibration of the Na^{22} recorded by the counters at the head in this subject and in both the head and knee in others are prolonged as compared with the time for equilibrium recorded by the body counter and in the serum samples. After equilibration, however, all the curves are parallel throughout the rest of the study periods.

Na^{24} study. On day 71 of the study in subject B.E., an exchangeable sodium value was determined from the Na^{22} data in the usual manner. A tracer dose of Na^{24} was then administered intravenously, and urine was collected for the next 24 hours while the patient took approxi-

TABLE IV

*Peak ratios of Na^{22} relative to K^{40}**

Subject	Na^{22} gamma rays	Date of measurement 6/4/60	5/29/61	6/1/62
	Mev	%	%	%
J.C.	0.51	100	61	42
	1.28	100	60	40
P.J.	0.51	100	55	50
	1.28	100	63	39
B.B.	0.51	100	58	33
	1.28	100	41	31

* Na^{22} to K^{40} ratios are given for both Na^{22} annihilation radiation (0.51 Mev) and for the Na^{22} gamma ray (1.28 Mev). The average of all data yields an effective half-life of about 1.3 years. Correcting for physical half-life (2.6 years) yields a biological half-life of approximately 2.6 years. At 15 to 19 months after the tracer doses of Na^{22}, heights of the Na^{22} 1.28 Mev photopeak and the K^{40} 1.46 Mev photopeak in the gamma-ray spectra were approximately the same in all subjects. If we assume a body burden for K^{40} of 0.12 μc and a gamma-ray abundance for Na^{22} ten times that for K^{40}, this indicated a retention of approximately 0.1% of the initial dose of Na^{22}. The ratio of the Na^{22} photopeaks to the K^{40} photopeak on 6/4/60 was taken as 100% for comparison with the Na^{22}:K^{40} photopeak ratios obtained at yearly intervals thereafter.

mately the same diet as during the previous day. At the end of the 24 hours, an exchangeable sodium value was determined from the serum specific activity of Na^{24} and body retention of that isotope, as indicated by urine data. The exchangeable sodium value determined from Na^{22} 71 days after its administration was 2,920 mEq, and the value determined the next day from Na^{24}, just 24 hours after its administration, was 2,910 mEq.

Long-term Na^{22} retention. Initial measurements in the steel counting-room were made 15 to 19 months after injection of the Na^{22} doses. The gamma-ray spectra that were obtained at this time showed a retention of Na^{22} that was less than the naturally occurring K^{40} in all three subjects. Subsequent determinations expressed as percentages of this initial Na^{22}:K^{40} ratio showed a markedly prolonged biological half-time, averaging approximately 2.6 years, as compared to an 11- to 15-day half-time for fall-off of serum Na^{22} activity in the same patients on their normal diets (Figure 5, Table IV).

DISCUSSION

Several lines of evidence bear upon the question of whether or not there is a later significant penetration of the Na^{22} tracer into that fraction of body sodium that has not equilibrated in the first 24 to 48 hours. The first is found in the curves for exchangeable sodium in the three subjects who began their studies on fixed low-sodium diets. There is some variability in day-to-day values for exchangeable sodium, but for periods of 8 to 21 days, there is no definite trend toward an increase in values that would occur with continuing penetration of Na^{22} into a slowly exchanging sodium space.

The second line of evidence comes from the comparison of curves of Na^{22} radioactivity fall-off recorded at the knee and at the back of the head with the curve for fall-off recorded by the body radioactivity counter and with the curve for serum Na^{22} radioactivity fall-off. The radioactivity at knee and head increases for 24 to 48 hours after body and serum curves have leveled off, but after this the curves are parallel. If there were significant further exchange of the Na^{22} with the sodium in bone after the first few days, the curves at knee and head should have had a slower rate of fall-off during the rest of the study than the curves for body and serum. This failure to show further exchange is comparable to the work in dogs reported by Edelman, James, Baden, and Moore (9), who compared bone specific activities to serum specific activities, and found that approximately 45% of the bone sodium was readily exchangeable in the first 1 to 3 days and that the rest showed no tendency to exchange over the next 30 days.

The third line of evidence comes from inspection of the curves for exchangeable sodium predicted from balance data and the curves calculated from serum specific activity and body radioactivity (Figure 3). Continuing exchange of the tracer should result in calculated exchangeable sodium values increasingly larger than those estimated from the balance data; however, this is apparently not the case. Still further evidence comes from the comparison of the exchangeable sodium value calculated from the Na^{22} data on day 71 of the study in B.E. with the 24-hour value for exchangeable sodium calculated from the Na^{24} data on the next day. If there had been a continuing slow exchange of the Na^{22} over the previous 71 days, the exchangeable sodium value calculated from the Na^{22} should have been significantly greater than that calculated from the Na^{24}, but the values were almost identical. Similarly close correlations were obtained between exchangeable sodium calculated from Na^{22} on day

98 and from Na^{24} on day 99 in one edematous subject and on days 100 and 101 in another (13).

Other reports have indicated results contrary to the above, with exchangeable sodium values, or with sodium spaces continuing to increase for a period of a week or more (1, 4–7). In the studies that did not employ direct measurements of body radioactivity (4–6), these contradictory results can probably be attributed to incomplete assessment of body Na^{22} losses, either because of failure to measure extrarenal losses or because of incomplete collections. This would result in values for body Na^{22} retention progressively higher than the actual retention, and use of these in the calculation of exchangeable sodium would result in values for exchangeable sodium that are increasingly larger than the actual values. The studies that did employ measurements of body radioactivity differ from the present one in that the subjects were not placed on fixed sodium intakes. As discussed below, exchangeable sodium varies according to sodium intake, and therefore it is difficult to draw definitive conclusions from studies in which sodium intake was not controlled.

While continuing penetration of the Na^{22} tracer into a very slowly exchanging space does not significantly affect determinations of exchangeable sodium, measurements of body radioactivity over long intervals indicate that slow penetration of minute amounts of Na^{22} does occur. Measurements in the steel room indicate the persistence in the body of greater quantities of Na^{22} than would be expected from extrapolation of the disappearance slopes of serum radioactivity while the subjects were on normal diets; this persisting Na^{22} has a disappearance half-time measured in years, rather than in days. This prolonged retention of minute amounts of Na^{22} by human subjects also has been demonstrated by others (14–16). This very slowly exchanging sodium probably represents the incorporation of sodium into the internal structure of bone crystals, at a rate dependent upon the normal continuing process of bone resorption and deposition (17, 18). That part of bone sodium that exchanges within 24 hours, on the other hand, probably is the sodium that is merely absorbed on bone crystal surfaces (15, 17, 19, 20), or that displaces calcium ions from the surfaces of the crystal lattice.

The 24-hour equilibration time used in this present study in normal individuals may not always be adequate for patients with certain disease states. Such patients may well require 48 hours, 72 hours, or even slightly longer for equilibration (2, 21, 22). In a group of edematous patients in whom 48 hours was allowed for equilibration, evidence similar to that in normal subjects for lack of significant continuing exchange after this initial equilibration period was obtained (13, 23).

The mean values for exchangeable sodium during the periods of high-sodium intake were significantly higher for the group than the mean values during the low-sodium periods (Table III), even though final equilibrium following the change in sodium intake might not have been obtained. In three of the subjects, the agreement between the increase in sodium intake and the increase in exchangeable sodium was within 100 mEq. In one subject, B.E., who had some diarrhea during the period of high-sodium intake, the increase in sodium intake exceeded the mean increase in exchangeable sodium by 143 mEq, and in one subject, P.J., who was on a low-sodium intake before the high-sodium period for the longest interval, the increase in mean exchangeable sodium exceeded the increase in daily sodium intake by 263 mEq. In four of the five subjects, the increase in exchangeable sodium with an increase in sodium intake was about 200 mEq. More studies with a wide range of sodium intakes would be needed to substantiate this point, but this may be evidence that homeostatic mechanisms allow for relatively fixed net changes in exchangeable sodium and that, for most normal subjects at least, in going from a low- to a high-sodium intake, these changes are around 200 mEq.

The increase in body sodium with increased sodium intake is also confirmed by balance data. The curves for exchangeable sodium estimated from balance data and the calculated curves show similar trends in each subject (Figure 3). As noted above, the day-to-day values calculated from radioactivity measurements show more variability and tend to be lower. The lower values, however, may be closer to the true values, particularly in the later days of the studies, in that measurements of body radioactivity account for losses of sodium by nonrenal routes that are missed by the balance method. It is true that stool sodium losses by

one subject (P.J.) in whom collections were made totaled only 15 mEq over a 26-day period, but greater sodium losses may have occurred in Subject B.E. to account for the divergence between the balance curve and the body radioactivity curve during his period of high-sodium intake.

A change in exchangeable sodium with a change in sodium intake could be anticipated from previous studies (24). It is possible that the apparent magnitude of these changes may be due in part to incomplete mixing of the daily increments of stable sodium with the exchangeable sodium. This would give a falsely low serum specific activity which, in the subsequent calculations, would result in a falsely high exchangeable sodium. Equilibration of Na^{22} and Na^{24} with serum sodium is reasonably complete within 12 to 24 hours (10, 21, 25, 26). If we can assume that equilibration of stable sodium follows the same time course, the practice of giving the sodium supplements during the first part of each study day should have minimized this effect of increased sodium intake on the estimations of exchangeable sodium.

The magnitude and the pattern of the rises in exchangeable sodium when high sodium intakes followed sodium deprivation were probably due in part to the increased levels of circulatory aldosterone resulting from sodium restriction (27–32). One may speculate that the increases in exchangeable sodium to peak values over several days followed by a fall-off to intermediate values seen in at least two of the studies (J.C. and B.B., Figure 4) are indicative of levels of circulatory aldosterone that result in an "overcompensation" for the previous sodium deficit; then, as the levels of aldosterone fall, the excess sodium is excreted. A similar cyclical pattern with sodium loading has previously been reported (31).

It is not possible from the present data to determine the relative contribution of different body compartments to the sodium lost in going from the regular to the fixed low-sodium diets, nor the distribution among body compartments of the sodium gained in going from the fixed low- to the fixed high-sodium diets. On the basis of reported animal studies, however, it can be predicted that the extracellular fluid compartment would show the greatest changes followed by the exchangeable fraction of bone sodium (32–37).

SUMMARY

1. Long-term studies of sodium metabolism in five normal subjects were carried out by use of tracer doses of Na^{22} and measurement of body radioactivity to make repeated exchangeable sodium determinations.

2. Body sodium exchanging after the first 24 to 48 hours was not a significant fraction of the metabolically active sodium pool, nor did it interfere with long-term measurements of this pool by isotope dilution methods.

3. Exchangeable sodium was shown to vary directly with changes in sodium intake.

4. A small fraction of the tracer doses of Na^{22} was shown to have a prolonged biological half-life consistent with its incorporation within bone crystals.

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