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SOME ASPECTS OF RENAL EXCRETION OF NA^{24} BY NORMAL SUBJECTS AND BY PATIENTS WITH CONGESTIVE HEART FAILURE*

G. E. Burch, M.D., S. A. Threefoot, M.D. and P. B. Reaser, M.D.

Department of Medicine, Tulane University School of Medicine, and Charity Hospital of Louisiana at New Orleans

Just as chemical and microchemical analyses of body fluids opened the way for unlimited investigation of human physiologic phenomena, so has the introduction of radioelements into biologic studies led to a new frontier of research beyond access of the usual quantitative chemical methods.

In the few years since the introduction of radioelements as tracers, it has been possible to conduct only pilot studies; these will of course suggest new avenues of approach and lead to more comprehensive investigation. The data are worthy of presentation, however, because they clarify a few heretofore unanswerable problems and because they may encourage more extensive studies.

Radiosodium was used as a tracer in normal human subjects and in patients with congestive heart failure. This approach has made it possible to determine the time of appearance of sodium in the urine after its intravenous and oral administration, the rate of clearance of the serum sodium by the kidneys, and the rate of sodium excretion by normal and diseased subjects. Since the studies herein reported were conducted with a relatively short half-life radiosodium, Na^{24} ($t_{\frac{1}{2}} = 14.8$ hrs.), it was not possible to make long-term observations of sodium excretion and metabolism. This was done, however, in other experiments with long half-life radiosodium, Na^{22} ($t_{\frac{1}{2}} = 3$ yrs.) (2, 3, 4). Data concerning rates of exchange between intra- and extravascular sodium in most of these subjects have already been published (1) and will therefore be omitted from this presentation.

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METHODS

Twenty-nine patients, twelve normal, ten with chronic congestive heart failure (Functional Class IV), and seven with miscellaneous diseases were studied (Table I). Eight of the normal subjects were cystoscoped and ureteral catheters were placed in the pelves of each kidney.† Urine was collected separately from each catheter. The patients with congestive heart failure were too ill to permit such a procedure, and consequently only bladder catheters were used.

Na^{24}, with an activity of 20,000,000 counts per minute (approximately 0.1 millicurie), was injected intravenously into an antecubital vein; three subjects received this same dose orally. Samples of blood were drawn as rapidly as possible from the antecubital vein of the opposite arm through a heparinized needle, and urine samples were collected as rapidly as the rate of urine flow would permit. The time interval between collections was usually 5 to 15 seconds. After several minutes of rapid collection the interval between samples was lengthened to 30 seconds, then 1 minute, 3 minutes, 5 minutes, and so on, so that for the last two-thirds of the 60-180 minute experiment, samples were collected every 10 minutes.

Attempts were made to collect urine and blood simultaneously to permit better comparisons. The volume of the urine samples was measured. The concentration of Na^{24} in all samples was expressed in counts per minute per cubic centimeter of biologic fluid. Corrections were made for background and decay. All dosages were reduced to the common value of 20,000,000 counts per minute per 100 pounds of body weight (1).

All experiments were done at least three hours postprandial. Because of the 14.8 hour half-life of the radioactive tracer, Na^{24}, and the uncertainty of delivery from the cyclotron

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TABLE I

SUMMARY OF CLINICAL DATA AND OF RESULTS FROM TWENTY-NINE NEGRO SUBJECTS STUDIED

Subject	Sex	Age	Wt.	Diagnosis	Treatment	Time of Appearance in the Urine (min. and sec.)	Total Counts of Na^{24} Excreted in 90 Min. (counts/min.)	Total Urine Volume Excreted in 90 Min. (counts/min.)	Average Rate of Urine Flow in c.c./min.	Average Na^{24} Clearance in c.c. Serum Cleared/Unit
					NORMAL					
1	F	37	152	Rheumatoid arthritis	None	10:15 (bladder)	39,107 (total)	33.4 (bladder)	.37 (bladder)	.22 (bladder)
2	F	32	119	Rheumatoid arthritis	None	3:15 (left) 2:20 (right)	10,938 (left) 40,872 (right) 51,810 (total)	13.8 (left) 38.0 (right) 51.8 (total)	.55 (left) .41 (right) .96 (total)	.11 (left) .15 (right) .26 (total)
3	F	24	94	Pneumonitis	Vitamins	4:55 (left) 4:09 (right)				
4	F	17	108	Syphilis	None	5:30 (bladder)				
5	F	24	118	Anxiety neurosis	Sodium Salicylates	1:08 (bladder)	56,135 (total)	37.6 (bladder)	.42 (bladder)	.45 (bladder)
6	F	48	110	Syphilis	None	4:03 (left)	32,052 (left) 32,052 (total)	65.1 (left) 33.0 (right) 98.1 (total)	.72 (left) .72 (total)	.29 (left) .29 (total)
7	F	23	146	Normal	None	1:35 (left) 1:35 (right)	89,387 (left) 66,345 (right) 155,732 (total)	31.6 (left) 71.2 (right) 102.8 (total)	.60 (left) 1.34 (right) 1.94 (total)	1.17 (left) .94 (right) 2.11 (total)
8	F	32	100	Normal	None	2:50 (left) 4:00 (right)				
9	F	19	92	Chronic bronchitis	None	2:35 (left) 5:47 (right)				
10	F	34	130	Anxiety neurosis	None	4:35 (left)				
11	F	33	93	Normal	Sulfadiazine. Low residue diet.	5:55 (left) 4:35 (right)				
13	F	17	105	Syphilis	None	3:20 (bladder)				
	Mean					3:43 (left) 3:44 (right) 3:44 (left and right) 5:03 (bladder)	44,126 (left) 53,609 (right) 48,868 (per kidney) 66,967 (total)	36.8 (left) 47.4 (right) 42.1 (per kidney) 64.7 (total)	.62 (left) .88 (right) .75 (per kidney) .88 (total)	.52 (left) .55 (right) .54 (per kidney) .66 (total)
					MISCELLANEOUS					
1	F	41	151	Hypertensive cardiovascular disease, congestive heart failure, ovarian malignancy	NH_4Cl Digitoxin Salt-free diet	21:14 (bladder)	2,056 (total)	13.0 (bladder)	.11 (bladder)	.03 (bladder)
2	F	27	110	Chronic active hemorrhagic nephritis	Low salt diet		34,560 (total)	120.0 (bladder)	1.35 (bladder)	

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3	F	37	134	Sarcoidosis	Symptomatic	10:50 (bladder)	30,067 (total)	46.2 (bladder)	.51 (bladder)	.13 (bladder)
4	F	42	141	Hypertensive cardiovascular disease pylonephritis vs. chronic active hemorrhagic nephritis	No diuretic or edema therapy	5:35 (bladder)	39,217 (total)	94.6 (bladder)	1.04 (bladder)	.59 (bladder)
5	F	50	109	Phlebothrombosis of deep leg veins	No special therapy	4:35 (bladder)	20,591 (total)	48.4 (bladder)	.52 (bladder)	.11 (bladder)
6	F	36	173	Cold allergy, anxiety neurosis	None for edema, kidney		2,592 (left) 7,001 (right) 9,593 (total)	1.3 (left) 3.9 (right) 5.2 (total)	.02 (left) .05 (right) .07 (total)	.19 (left) .53 (right) .72 (total)
8	F	34	149	Hypertensive cardiovascular disease congestive heart failure, syphilis, hemiplegia	Digitoxin Salt-free diet	23:55 (oral)				
	Mean					10:34 (intravenous)	22,681 (total)	54.6 (total)	.60 (total)	.32 (total)
					CONGESTIVE HEART FAILURE					
1	F	66	121	Arteriosclerotic heart disease, congestive heart failure, syphilis, auricular fibrillation	Digitalis Salt-free diet	18:29 (bladder)	2,613 (total)	10.3 (bladder)	.12 (bladder)	.03 (bladder)
2	F	65	159	Hypertensive cardiovascular disease, congestive heart failure	Digitalis Salt-free diet NH_4Cl	27:11 (bladder)	1,862 (total)	17.6 (bladder)	.19 (bladder)	.01 (bladder)
3	F	36	129	Hypertensive cardiovascular disease, congestive heart failure	Digitalis Salt-free diet NH_4Cl	30:12 (bladder)	3,720 (total)	21.1 (bladder)	.27 (bladder)	.04 (bladder)
5	F	46	125	Hypertensive cardiovascular disease, congestive heart failure	Digitalis Salt-free diet	18:33 (bladder)	35,976 (total)	79.9 (bladder)	.85 (bladder)	.21 (bladder)
6	F	53	122	Hypertensive cardiovascular disease, congestive heart failure	Digitalis Salt-free diet Salyrgan (occasionally)	5:55 (bladder)	14,910 (total)	25.8 (bladder)	.29 (bladder)	.18 (bladder)
7	M	32	137	Hypertensive cardiovascular disease, congestive heart failure	Digitalis NH_4Cl	44:00 (oral)				
8	F	59	181	Arteriosclerotic heart disease, congestive heart failure	Digitalis Salt-free diet NH_4Cl	12:00 (bladder)	32,480 (total)	28.1 (bladder)	.47 (bladder)	.33 (bladder)
9	F	61	148	Arteriosclerotic heart disease, congestive heart failure		11:00 (bladder)	8,746 (total)	23.5 (bladder)	.26 (bladder)	.09 (bladder)
10	F	67	140	Arteriosclerotic heart disease, congestive heart failure	Digitalis Salt-free diet NH_4Cl Salyrgan	6:17 (bladder)				
11	M	62	166	Hypertensive cardiovascular disease, congestive heart failure	Digitalis Salt-free diet 1 day NH_4Cl	30:00 (oral)				
	Mean					16:12 (intravenous) 37:00 (oral)	14,330 (total)	29.5 (total)	.35 (total)	.13 (total)

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laboratories, it was not possible to withhold treatment of the patients in preparation for the experiments.

RESULTS

Results are summarized in Table I and in Figures 1, 2, 3, 4, and 5. In some instances the data are not complete because the rate of urinary flow was not recorded in the earlier studies.

1. *Time of Appearance of Na^{24} in the urine* (*Fig. 1*).—Of the eight normal subjects with ureteral catheters in place, the earliest time of

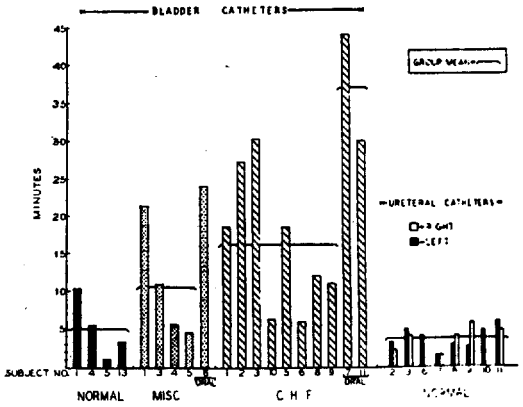

FIG. 1.—Graph showing time of appearance of radiosodium (Na^{24}) in the urine after intravenous and oral administration to normal subjects, to patients with chronic congestive heart failure and to patients with miscellaneous diseases.

appearance of sodium in the urine after intravenous injection was 1.5 minutes, the latest 5.9 minutes. The mean time of appearance of sodium in the urine from the kidneys which began excreting Na^{24} first was 3 minutes, and from the kidneys which began excreting Na^{24} the latest was 4.2 minutes. The mean time of appearance of Na^{24} from the left kidneys was 3.7 minutes and from the right 3.7 minutes.

In four normal subjects in whom urine was collected by means of *urethral* catheters, appearance time of radiosodium after intravenous injection varied from 1.1 minute to 10.3 minutes, with a mean of 5 minutes. In four of the subjects in the miscellaneous group who received intravenous Na^{24}, the time of appearance of the isotope in the bladder urine ranged from 4.5 minutes to 21.2 minutes, with a mean of 10.5 minutes. In eight patients with congestive heart failure who received Na^{24} intravenously, the time of appearance of the radiosodium varied from 5.9 to 30.2 minutes, the average being 16.2 minutes.

In the one patient of the miscellaneous group (Subject No. 8) who received Na^{24} orally, the sodium appeared in the urine collected from a urethral catheter in 23.9 minutes. For the two patients with congestive heart failure who received the radiosodium orally (Subjects 7 and 11) the appearance times were 30 and 44 minutes respectively.

2. *Total excretion of Na^{24} over a period of 90 minutes* (*Fig. 2*).—Since most of the experiments lasted at least 90 minutes, this period of time was chosen as a standard interval for comparison of total amounts of radiosodium excreted.

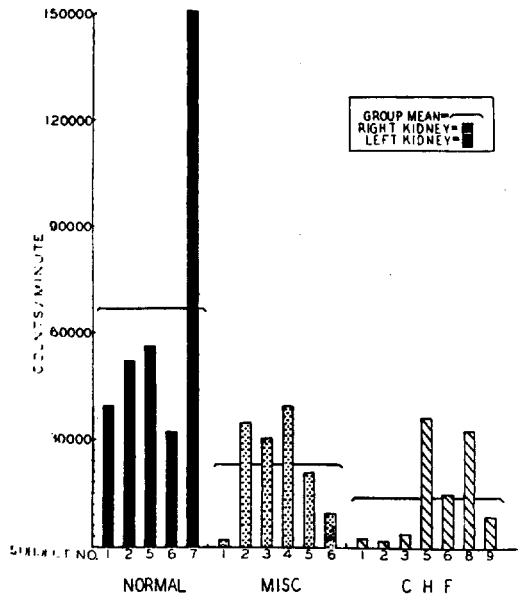

FIG. 2.—Graph showing the total counts per minute of Na^{24} excreted in 90 minutes for the three groups of subjects studied.

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The normal subjects in whom ureteral catheters were placed excreted from 11,000 CPM (counts per minute) to 90,000 CPM (a mean of 49,000 CPM) per kidney in 90 minutes. The total Na^{24} excretion by the normal subjects (by both kidneys) ranged from 32,000 CPM to 156,000 CPM, with a mean of 67,000. During the same length of time the miscellaneous subjects excreted a total of from 2,000 CPM to 39,000 CPM, the mean being 23,000. The patients with congestive heart failure excreted a mean total of 14,000 CPM, with extremes of 1,900 and 36,000 CPM.

3. *The total volume of urine excreted for the 90-minute period* (Fig. 3).—From each normal kidney it averaged 42.1 cc., with limits

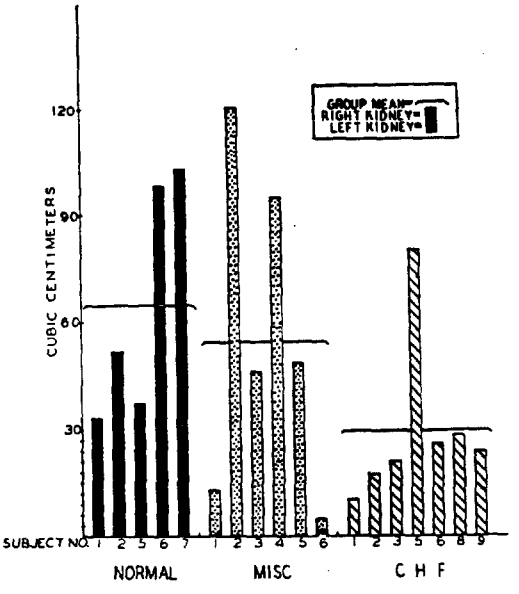

FIG. 3.—Graph showing the total volume of urine excreted in 90 minutes for the three groups of subjects studied.

of 13.8 cc. and 71.2 cc. The total urine volume excreted by the normal subjects in this period ranged from 33.4 cc. to 102.8 cc., with a mean of 64.7 cc. The miscellaneous group of subjects excreted from 5.2 cc. to 120 cc. and yielded a mean of 54.6 cc. During the same period the patients with congestive heart failure excreted a volume of urine which averaged 29.5 cc., with limits of 10.3 cc. and 79.9 cc.

4. *The average rate of urinary flow* (*Fig. 4*).—From each kidney of the normal subjects it varied from 0.41 cc. to 1.34 cc. per minute,

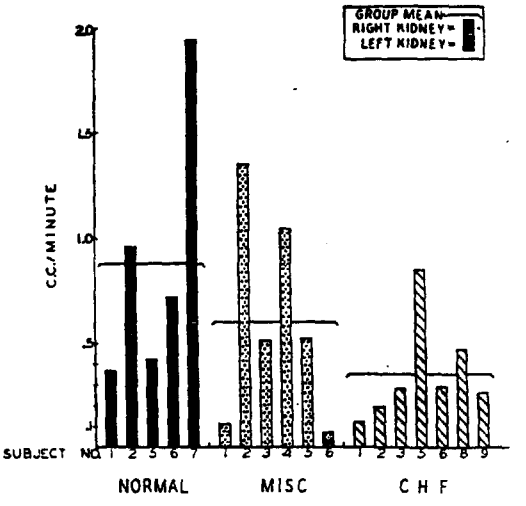

FIG. 4.—Graph showing the average rates of urine flow for each of the subjects studied.

the mean being 0.8. The mean total flow of urine for both kidneys of the normal subjects ranged from 0.37 cc. to 1.94 cc. per minute, the mean being 0.88. For the miscellaneous subjects the range was 0.07 to 1.35 cc. per minute (mean 0.60). The patients with congestive heart failure had rates varying from 0.12 to 0.85 (mean 0.35).

5. *Clearance of Na^{24}* (*Fig. 5*).—The average Na^{24} clearance for each catheterized kidney ranged from 0.11 cc. of serum cleared of Na^{24} per minute to 1.17 cc. (mean of 0.54). For both kidneys of the normal subjects, the range of Na^{24} clearance was from 0.22 cc. to 2.11 cc. per minute (mean of 0.66). The average clearance for the miscellaneous patients extended from 0.03 to 0.72 (mean of 0.32). The patients with congestive heart failure showed average clearances varying from 0.01 to 0.33 cc. per minute (mean of 0.13).

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The clearance values were obtained from the equation:

$$Na^{24} \text{ clearance} = \frac{Na_u^{24}\, U_v}{Na_s^{24}}$$

where: Na^{24} = counts per minute per cubic centimeter of urine,

Na_s^{24} = counts per minute per cubic centimeter of serum,

U_v = cc. per minute of urinary flow.

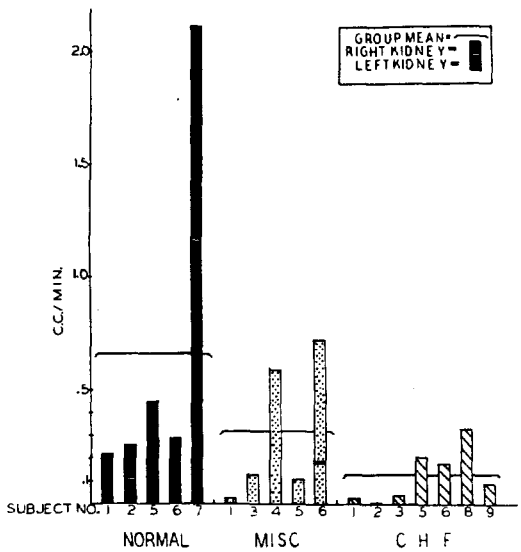

FIG. 5.—Graph showing the average Na^{24} clearance for each subject studied.

DISCUSSION

From these short-time turnover studies it was observed that the patients with chronic congestive heart failure did not excrete sodium as rapidly as the normal subjects. The mechanisms responsible for the reduced rate of sodium excretion in the urine are not understood. It is apparent, however, that the differences are not the result of low sodium intake, since one of the patients was on a low sodium diet for only 24 hours before initiation of the studies, and two patients were on a normal diet. Long-period observations (2, 3, 4) with Na^{22} support this. Diminished sodium excretion is probably the result of more complete reabsorption of sodium by the proximal tubules; this is not necessarily caused by abnormal function of the tubules but may be the result of a normal type of renal function such as is encountered when normal subjects are placed on a diet low in sodium (3 and 4). The data are inadequate to permit the formulation of a satisfactory theory to explain the sodium retention. The time of appearance of Na^{24} in the urine of the patients with congestive heart failure was more prolonged than in normal subjects, and the maximum concentration of Na^{24} in the urine was lower in the patients with the heart failure. The total Na^{24} excretion and fluid output for a given period of time was less than that of the normal subjects, and the sodium clearance for the diseased individuals was less. All of these observations indicate reduced excretion of sodium in congestive heart failure, in agreement with data obtained in long-term studies with Na^{22} (2, 3, 4).

The use of radiosodium made it possible to measure the time required for sodium to appear in the urine after its oral or intravenous administration without disturbance of the existing physiologic conditions, an observation which was not possible previously. The Na^{24} appeared in the urine of the normal subjects earlier than in the patients with congestive heart failure. It is difficult to explain the relatively long delay in its appearance in the urine of all subjects, even when samples were collected directly from the pelves of the kidneys. This is probably due in part to the circulation time of the blood and the time required for the urine to flow from the glomerulus to the renal pelvis and through the catheter. These two time factors are relatively short, approximately 20 seconds each, and together should not exceed one minute. Whether or not the additional delay is the result of pooling of urine in the pelvis near the orifices of the catheters remains unknown. It is interesting to speculate that a relatively large portion of the delay is due to the time required for the passage of the Na^{24} across the capillary walls, interstitial spaces and epithelium of Bowman's capsule; surely this must

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require some time. The influence of psychic phenomena precipitated by the pain of the venipuncture, resulting in momentary oliguria or even anuria, must be considered as a possible factor in this delay. This factor is not likely to explain the difference between the appearance time in the normal subjects and in the patients with congestive heart failure, however, as the mean time of appearance was three times greater in the latter group. The difference is more likely attributable to such factors as venous stasis, reduced renal blood flow and more complete tubular reabsorption of sodium.

It is noted in Figure 1 that the appearance time of the Na^{24} in urine of the normal subjects was not very much greater when urine was collected directly from the bladder than when it was obtained directly from the pelves of the kidneys. This observation suggests that the differences between the appearance times in the normal subjects and in those with heart failure were not the result of the method of collection.

The concentration of Na^{24} in the urine of the normal subjects was higher than in those with congestive heart failure (1). In no instance did this concentration exceed that in the serum of these patients. The normal subjects, on the other hand, showed considerable variations in Na^{24} concentration in the urine. The normal subjects at times presented urine concentrations which exceeded the serum levels. In some instances the levels of urine and serum concentration were essentially equal, whereas in others the urine concentration was lower. Since these subjects were on a normal diet with 8 grams of available sodium chloride but were permitted to add salt as desired, it was not possible to know the manner in which the level of sodium intake was responsible for the variations observed. High Na^{24} concentration in the urine is expected to be associated with a high sodium chloride intake and vice versa, if the cardiovascular and renal systems are normal. This was not necessarily true in congestive heart failure studied with Na^{22}.

SUMMARY

Excretion of radiosodium, Na^{24}, following intravenous administration of the isotope, was studied in twelve normal subjects, ten patients with chronic congestive heart failure, and seven patients with miscellaneous diseases.

The Na^{24} required about three times as long an interval to appear in the urine of the patients with congestive heart failure as in the normal subjects. In no instance did the concentration of Na^{24} in the urine of patients with congestive heart failure exceed that in the serum; in the normal subjects it varied over a wider range than in the patients with heart failure, and exceeded, equaled, or was less than that in the serum. The Na^{24} clearance in the patients with congestive heart failure was definitely less than that in the normal subjects.*

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