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RATES OF SODIUM TURNOVER IN NORMAL SUBJECTS AND IN PATIENTS WITH CONGESTIVE HEART FAILURE

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THERE is a need for a study of the rate with which sodium escapes from the blood into the tissue spaces and urine of man, especially because of the present interest in the role of sodium in congestive heart failure and other types of edema. Although studies of sodium metabolism have been conducted in man by means of radiosodium,[1-4] these have not included a detailed tracing of the variations in sodium concentration in the blood, urine, and sweat. The rates of diffusion of sodium through the vascular wall have been determined for other animals[5, 6] but not for man. Furthermore, tracer studies in congestive heart failure with the use of radiosodium have not been conducted previously. These studies are concerned with such problems.

METHODS

The subjects were all patients at the Charity Hospital. For purposes of discussion, the subjects were divided into three groups: normal subjects, those with congestive heart failure, and miscellaneous subjects. Certain detailed information concerning them is given in Table I. The ten normal subjects were patients who had entered the hospital for observation but were clinically well when studied. The patients with congestive heart failure suffered with chronic congestive heart failure of Functional Class IV and were bedridden. All were under treatment and were improving.

Because of the 14.8-hour half life of the radioactive tracer, Na^{24}, and the uncertainty of delivery from the cyclotron laboratories it was not possible to keep patients without treatment in preparation for the experiments. The influence of various therapeutic measures and other details concerning congestive heart failure were evaluated in studies conducted with the use of the long-life sodium, Na^{22}.[7, 8] The results of those studies will appear from time to time elsewhere in a series of papers, one report[7] having been published.

All subjects were at least three hours postprandial. They were taken to the laboratory where ureteral catheters were placed‡ into the pelves of each kidney of the normal subjects. The first subjects studied received no drugs in preparation for the cystoscopy while the later ones received morphine

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TABLE I. CLINICAL DATA CONCERNING THE NEGRO SUBJECTS STUDIED*

SUBJECT	SEX	AGE	WT.	DIAGNOSIS	TREATMENT	Na^{23} IN URINE (MEQ./L.) MEAN	MAX.	MIN.	Na^{23} SPACE TIME OBSERVED (C.C.) 60 MIN.	90 MIN.
					Normal Subjects					
1	F	37	152	Rheumatoid arthritis	None	123	128	119	12180	-----
2	F	32	119	Rheumatoid arthritis	None	176 212	182 219	179 (lt.) 203 (rt.)	16598	-----
3	F	24	94	Pneumonitis	Vitamins	116 119	120 123	112 (rt.) 115 (lt.)	8587	-----
4	F	17	108	Syphilis	None	100	103	84	11689	11891
5	F	24	118	Anxiety neurosis	Na salicylates	144	149	139	11786	-----
6	F	48	110	Syphilis	None	88	91	85 (lt.)	11534	12508
7	F	23	146	Normal	None	185	192	187	9132	-----
8	F	32	100	Normal	None	209 194	216 201	202 (rt.) 187 (lt.)	6124	-----
9	F	19	92	Chronic bronchitis	None	216 209	223 216	208 (rt.) 202 (lt.)	10301	11198
10	F	34	130	Anxiety neurosis	None	263	272	254	8961	-----
Mean						163 157 (lt.) 188 (rt.)	171 163 (lt.) 195 (rt.)	157 154 (lt.) 181 (rt.)	10689	11866
Maximum							272	254	16598	12508
Minimum							91	84	6124	1198
					Subjects With Congestive Heart Failure					
1	F	66	121	Arteriosclerotic heart disease, congestive heart failure, syphilis, auricular fibrillation	Digitalis, salt-free diet	62	64	51	12747	16556
2	F	65	159	Hypertensive cardiovascular disease, congestive heart failure	NH_4Cl, salt-free diet, digitalis	132	13.7	12.8	12461	13559
3	F	36	129	Hypertensive cardiovascular disease, congestive heart failure	Salt-free diet, NH_4Cl, digitalis	162	16.7	15.6	17197	21186
5	F	46	125	Hypertensive cardiovascular disease, congestive heart failure	Digitalis, salt-free diet	52	53	50	10315	10220
6	F	53	122	Hypertensive cardiovascular disease, congestive heart failure	Digitalis, salt-free diet, Hg (occasionally)	119	123	115	17668	17762
7	M	32	137	Hypertensive cardiovascular disease, congestive heart failure	Salt-free diet, NH_4Cl, digitalis				10163	9259
8	F	59	181	Arteriosclerotic heart disease, congestive heart failure	Salt-free diet, NH_4Cl, digitalis	136	141	132	28624	-----
9	F	61	148	Arteriosclerotic heart disease, congestive heart failure		40	41	38	12895	16461

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TABLE 1—CONT'D

SUBJECT	SEX	AGE	WT.	DIAGNOSIS	TREATMENT	Na^{23} IN URINE (MEQ./L.) MEAN	MAX.	MIN.	Na^{23} SPACE TIME OBSERVED (C.C.) 60 MIN.	90 MIN.
10	F	67	140	Arteriosclerotic heart disease, congestive heart failure	Salt-free diet, digitalis, salyrgan, NH_4Cl	253	261	239	14674	16736
11	M	62	166	Hypertensive cardiovascular disease, congestive heart failure	NH_4Cl, digitalis, salt-free diet	100	103	98	9029	9970
Mean						87.9	90.7	83.5	14577	14634
Maximum						13.2	26.1	23.9	28624	21186
Minimum						25.3	13.7	12.8	9029	9259
Subjects With Miscellaneous Disease States										
1	F	41	151	Hypertensive cardiovascular disease, congestive heart failure, ovarian malignancy	NH_4Cl, digitoxin salt-free diet	31	32	30	25157	23474
2	F	27	110	Chronic active hemorrhagic nephritis	Low-salt diet				14535	15662
3	F	37	134	Sarcoidosis	Symptomatic	52	53	50	10899	10701
4	F	42	141	Hypertensive cardiovascular disease, pylonephritis vs. chronic active hemorrhagic nephritis	No diuretic or edema therapy	90	93	87	20833	20618
5	F	50	109	Phlebothrombosis of deep leg veins	No special therapy	25	26	24	10315	11561
6	F	36	173	Cold allergy, anxiety neurosis	None for edema, kidney	132	137	128 (rt.)	10096	1154
7	M	15	110	Chronic adhesive pericarditis	NH_4Cl, salt-free diet, paracentesis	26.5	27.4	25.6		
Mean						44.9	46.3	43.3	15306	15528
Maximum						90	93	87	25157	23474
Minimum						25	26	24	10096	10701

*The concentration of the sodium (Na^{23}) in the urine was determined on the basis of a normal blood sodium concentration. The "sodium space" was calculated on the basis of a state of equilibrium at the times indicated. The normal subjects were clinically well when studied; the diagnoses indicated were those made at the time of admission to the Charity Hospital for study.

sulfate, 15 mg., and atropine sulfate, 0.3 mg. subcutaneously thirty minutes before the cystoscopy. The results showed evidence of influence by the drugs used in preparation of the subjects for cystoscopy. The patients with congestive heart failure and two normal subjects had a small catheter passed only into the bladder. The patients with congestive heart failure were too ill to permit a cystoscopy to place catheters into the renal pelves. Bladder urine was about as informative as the pelvic urine.

After catheterization, a sample of urine was collected from each catheter and a sample of blood was collected simultaneously from the antecubital vein of one arm through a heparinized needle. The radioactive tracer, Na^{24} (0.5 to 2 c.c. of a neutral and hypotonic aqueous solution of NaCl), with an activity

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of 20,000,000 counts per minute (approximately 0.1 mc. or 0.04 r) was injected quickly into the antecubital vein of the opposite arm. Two cubic centimeter samples of blood were collected for serum studies as rapidly as possible, every five to ten seconds unless the needle became obstructed and necessitated a greater interval between collections. This rate of collection was followed for the first three minutes after the injection of the Na^{24}. The interval between collections was increased to thirty seconds for the next five minutes, increased again to every sixty or 120 seconds for the next ten minutes, and finally, to every three, five, or ten minutes for the remainder of the study, which lasted from sixty to one hundred eighty minutes. The urine samples were collected from each catheter in separate vials. For the first three minutes the interval between collections of the urine samples varied with the rate of urine flow, that is, long enough for four drops of urine to be collected. This usually required five to fifteen seconds. For the next five minutes collections were made at thirty-second intervals, etc., as for the blood samples. Attempts were made to collect the blood and urine samples at the same time in order to permit satisfactory comparisons. The volume of the urine samples was measured to determine the sodium (Na^{24}) clearances from collection to collection. The urine samples collected from the pelvis of each kidney were studied separately.

In several experiments samples of edema fluid were collected simultaneously through a puncture wound made through the skin near the ankle with an 18-gauge needle. The rates of collection approximated those for the blood and urine. Simultaneous collections of successive samples of ascitic and pleural fluid in subjects with congestive heart failure were made to study the change in concentration of Na^{24}.

One normal subject was placed in a hot and humid room (temperature, 48° C.; relative humidity, 45 per cent) free from drafts. After sweating had become profuse the procedure described above was followed except that the urine was collected at less frequent intervals while the blood and sweat samples were collected at the rapid rates stated previously. The sweat was collected by allowing the beads of sweat to roll into the opening of a tall narrow-mouthed vial which was promptly closed with a bakelite screw cap. Each sample of sweat consisted of about 0.1 cubic centimeter. These collections were continued for about thirty minutes, that is, until the subject and observers began to experience marked discomfort from the hot and humid environment.

The concentration of Na^{24} in all samples was expressed as counts per cubic centimeter per minute. Geiger-Muller counters* were used to determine radioactivities of the injections and the samples. Corrections were made for background counts and decay. The entire counting method had an over-all error of less than 3 per cent. All dosages of Na^{24} were reduced to the common value of 20,000,000 counts per minute per 100 pounds of weight.

RESULTS

Normal Subjects.—The results for the normal subjects are summarized in Figs. 1 to 6.

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Blood: It can be seen from Fig. 1 that the concentration of the Na^{24} rose rapidly in the *blood serum,* fluctuating in concentration for the first five to fifteen minutes and then becoming relatively constant for the remainder of the period of observation. The concentration of Na^{24} did not rise to levels as high as would be expected if all the Na^{24} remained in the blood stream. There was a tendency for the concentration of Na^{24} in the serum of most of the subjects to rise for the first ten to twenty minutes to levels higher than those reached during the final periods of the study and to show marked variations from subject to subject. There was a gradual decline in the serum concentration of Na^{24} in all subjects throughout the entire period of study even after a fairly stable state had been reached. The Na^{24} did not appear in the antecubital vein of the sampling arm until nineteen to twenty-three seconds after the radiosodium had been injected into the antecubital vein of the other arm, that is, by a time equal to the circulation time.

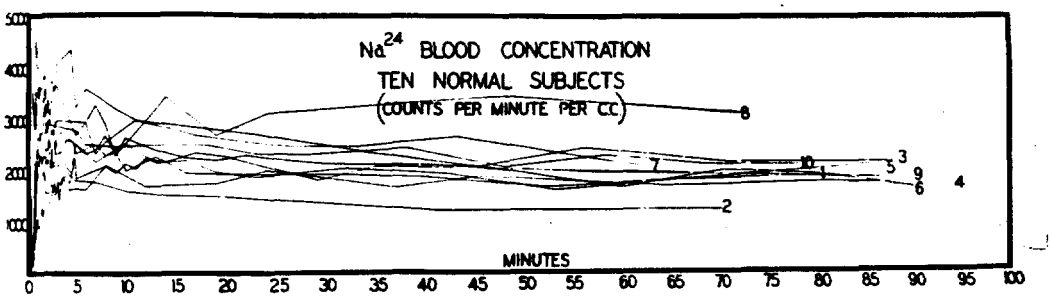

Fig. 1.—Variations in serum concentration of Na^{24} in ten normal subjects. There are considerable individual variations, especially during the first two to three minutes when the mixing of the injected radiosodium is occurring.

Because of the marked variations in concentration of Na^{24} in the serum of the subjects and because of the small number of subjects studied, it was impossible to obtain a composite tracing which properly depicted the rate of diffusion of sodium from the vascular bed (Fig. 1). Therefore, the data on a subject (Subject 6) were selected for analysis in the manner described by Gellhorn and co-workers;[5] all diffusion curves were drawn by inspection. These authors showed that the vascular bed of dogs could be considered to be composed of two separate areas through which the sodium ion diffuses at different rates. Area A_1 consists of an area through which the sodium diffuses at a very rapid rate, while A_2 represents another area through which the rate of diffusion is relatively slow. The same types of areas were observed in these studies in the normal and diseased man. Fig. 2 can be seen to represent a typical double exponential curve for the blood concentration. There was a *rapid rate* of escape of Na^{24} from the vascular bed and a *slow one.* The general expression obtained by Gellhorn and co-workers[5] for dogs, and found to apply to man in many of the subjects of this study, is

$$c_p - c_{eq} = a_1 e^{b_1 t} + a_2 e^{b_2 t} \qquad (1)$$

where c_p is plasma concentration of Na^{24} at time, t, c_{eq} is plasma concentra-

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tion at equilibrium, b_1 and b_2 are rates of diffusion from the vascular bed, and a_1 and a_2 are coefficients which depend upon the rates of movement and distribution of Na^{23} through areas A_1 and A_2 in the vascular bed. Since the diffusion of Na^{24} is determined by the diffusion of Na^{23}, the exponents b_1 and b_2 are expressions of the rates of diffusion of the total plasma sodium (Na^{23}) out of the vascular bed. Therefore, it is possible to consider the sodium of the plasma as being divided into three parts: one represented by a_1, which diffuses outward rapidly through area A_1; a second represented by a_2, which diffuses outward at a relatively slow rate through area A_2; and a third represented by c_{eq}, which remains in the plasma.

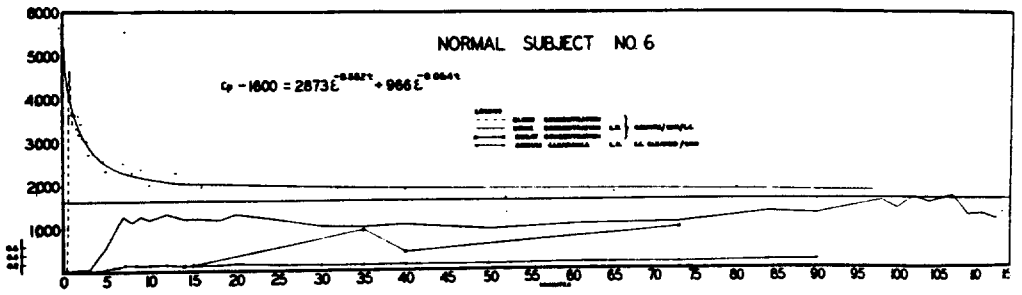

Fig. 2.—Variations in serum, urine, and sweat concentrations of Na^{24} and the Na^{24} clearance in normal Subject 6. The curve of blood concentration is a double exponential curve representing sodium diffusion, the equation of which is shown. *L.K.*, Left kidney.

To determine the rate of loss by diffusion of the total plasma sodium, the equation

$$\frac{-a_1b_1 - a_2b_2}{c_p} = R_p$$

is employed, where c_o is the extrapolated initial count per minute per cubic centimeter of the plasma.

The expression for radioactive sodium concentration in the plasma for Subject 6 (normal) was

$$c_p - 1600 = 2873\epsilon^{-0.582\,t} + 966\epsilon^{-0.0844\,t}. \qquad (2)$$

Thus 58 per cent of the rapidly diffusing sodium left the plasma per minute, and 6.4 per cent of the slowly diffusing sodium left the plasma per minute. Considering the sizes of these sodium compartments in the plasma, an average of 32 per cent of the total sodium in the plasma diffused out of the vascular bed per minute.

Furthermore, Merrell and associates[6] have shown that from the same data the rate of diffusion of sodium from the extravascular fluid* back into the plasma at equilibrium could be determined by the equation

$$R_e = R_p \frac{(1-q)}{q}$$

*The term extravascular sodium employed here probably is concerned predominantly with interstitial fluid sodium because of the relatively short duration of the studies. For that reason interstitial and extravascular sodium is considered essentially synonymous in these studies.

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where R_e = rate at which the extravascular sodium returns by diffusion into the plasma, R_p = rate of loss by diffusion of the total plasma sodium in the vascular bed, and $_q$ = total extravascular sodium. The values obtained for Subject 6 are shown in Table II. It is noted that about 32 per cent of the total sodium in the plasma diffused into the interstitial fluid per minute and that 13 per cent of the total sodium in the interstitial fluid returned by diffusion to the plasma per minute.

TABLE II. PROPORTION OF SODIUM DIFFUSION IN FOUR HUMAN SUBJECTS

	NORMAL SUBJECT	CONGESTIVE HEART FAILURE SUBJECT		MISCELLANEOUS SUBJECT
	6	3	1	5
Proportion of total sodium in interstitial fluid	0.70	0.89	0.90	0.65
Proportion of total plasma sodium diffusing out of vascular bed per minute	0.32	0.63	0.54	0.35
Proportion of total interstitial fluid sodium diffusing into the vascular bed per minute	0.13	0.08	0.06	0.18

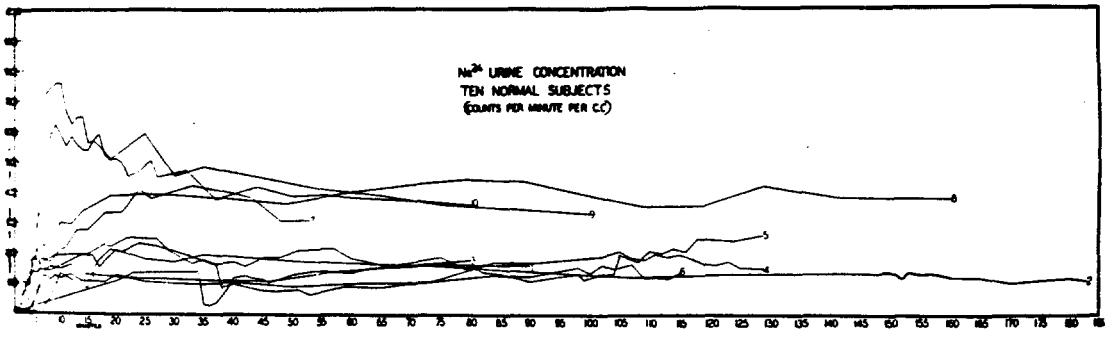

Fig. 3.—Variations in urine concentrations of Na^{24} in ten normal subjects.

Urine: The concentration of radioactive sodium in the urine exceeded that in the blood serum in three subjects (Fig. 3). In most cases the blood and urine concentrations were essentially equal, although the urine concentration was definitely lower in Subject 6. The urine concentration varied much more than did the blood concentration after the initial few minutes following the injection.

Sodium Clearance: The sodium clearances for five normal subjects are shown in Figs. 4, 5, and 6. Na^{24} clearances were employed in these analyses since they integrated volume of urine flow and blood and urine concentrations. The exact significance of these values for a substance like sodium is not known. They do make certain comparisons feasible. These values were calculated in a manner similar to that used for the urea clearance.

The equation for the calculation is

$$Na^{24} \text{ clearance} = \frac{Na_u^{24}\ U_v}{Na_b^{24}} \qquad (3)$$

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Fig. 4.—Variations in Na^{24} clearance in five normal subjects. Since the movement of Na^{24} around the body is determined by the movement of Na^{22}, these curves represent rates of Na^{22} clearance once equilibrium has been reached.

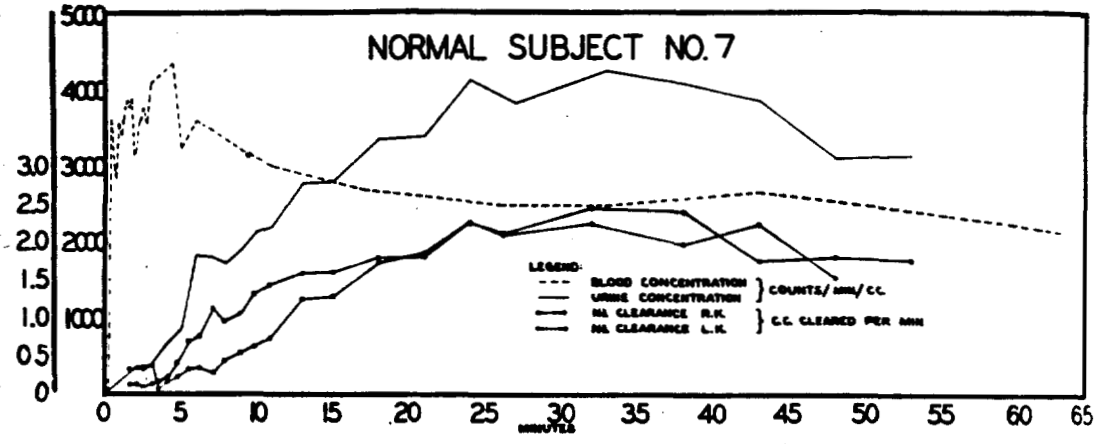

Fig. 5.—Variations in serum and urine concentration (left kidney) of Na^{24}, and Na^{24} clearance for both kidneys separately in one subject. Note the marked variations in serum concentration during the first three minutes. The serum concentration then settled down to a diffusion type of curve as shown for normal Subject 6 (Fig. 2). The mixing phenomenon was relatively poor for the first three minutes in Subject 7, but early and adequate for Subject 6. Such chance variations are to be expected. Note the concordant and only occasional discordant relationship of the Na^{24} clearances in the urines of the right and left kidneys.

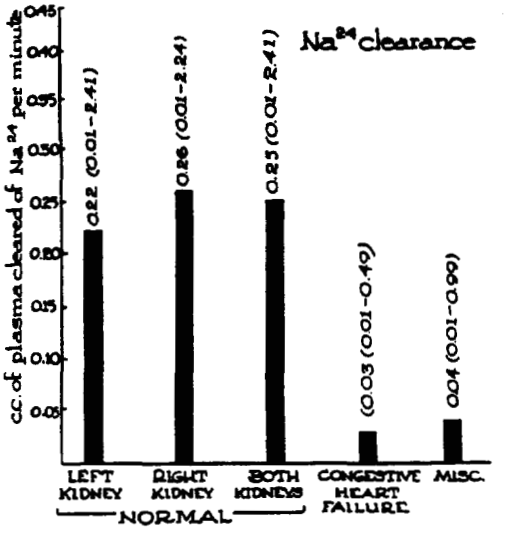

Fig. 6.—The average and extreme (within parentheses) values for Na^{24} clearance in the three groups of subjects. It is necessary to remember that the patients with congestive heart failure were on a slow sodium diet.

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where Na_u^{24} = counts per cubic centimeter of urine, Na_b^{24} = counts per cubic centimeter of blood, and U_v = volume of urine flow per minute.

Except for Subject 7 the rates of Na^{24} clearance were fairly constant and of essentially the same magnitude. They tended to average 0.22 c.c. of blood cleared per minute per kidney but were high for Subject 7, reaching a level of about 2.4 c.c. of blood cleared of Na^{24} per minute for both kidneys. Figs. 4, 5, and 6 show the quantitative and qualitative variations in the clearances for both kidneys observed separately and simultaneously.

Comment: The levels of Na^{24} concentration in the blood serum should have reached values of about 10,000 counts per minute per cubic centimeter if all of the injected materials had remained in the blood. Instead, the concentrations actually reached averaged about 2,500 counts per minute per cubic centimeter, with the maximum being 4,600. The average curve for the normal subject shows a tendency for the concentration of Na^{24} in the blood to reach the final concentration level rapidly and not to exceed it appreciably. This indicates the very rapid rate of diffusion of sodium from the blood. In fact, the diffusion is so rapid that the circulation of the blood is too slow to permit adequate mixing before a considerable amount of diffusion occurs. The relatively marked variations in Na^{24} concentration in the blood observed during the first few minutes of the study are due in a large part to inadequate mixing. Adequate mixing does not appear to be completed in some subjects before ten minutes have elapsed (Fig. 1). As stated previously, the marked variations in the rates of mixing of the blood made it impossible to determine the average diffusion rates for the normal subjects as a group. From the analysis of the data of Subject 6 it was found that sodium diffused across the vascular bed at two separate rates. This diffusion outward resulted in a loss per minute of about 0.6 of the rapidly diffusing and of about 0.06 of the slowly diffusing plasma sodium. The average rate of diffusion of sodium from the vascular bed was 32 per cent of the total plasma sodium per minute. This is equal to about 4,000 Gm. of sodium per day for a man weighing 70 kilograms. These results are remarkably similar to those observed in dogs by Gellhorn and associates.[5] It is interesting to note that if the Cl ion tends to follow the Na ion during its diffusion, this would entail a diffusion of about 10,000 Gm. of NaCl out of the vascular bed of the average man per day. The amount of sodium returning is, of course, the same. Thus there is a diffusion of about fifty pounds of NaCl back and forth through the capillary wall per day in a man weighing 70 kilograms.

It is generally agreed that the rapid diffusion of sodium is into the interstitial fluid.[5] The slower diffusion must take place into bone,[2, 9] cerebrospinal fluid,[10] chambers of the eye,[10] and other structures of the body which allow relatively slow rates of sodium exchange. It is also important to know the rate of diffusion of water across the vascular bed. Merrell and co-workers[6] observed that 1.46 of the plasma water diffused out into the tissues of the guinea pig per minute. Since comparable values were obtained for the rates of diffusion of sodium in guinea pigs, dogs, and man, it is likely that the rates of diffusion of water should be similar. If the same rates are applied for man as were

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found in the guinea pig, then about 6,300 liters of water per day diffuses out of the vascular bed of a man weighing 70 kilograms. It is obvious from the diffusion rates for sodium and water that water diffuses more rapidly. Not only has this been observed for the body as a whole, but for isolated tissues as well. Kinsey and associates[10, 11] found this to be true for the vitreous body and aqueous humor of the eye of the rabbit. It has also been noted for the cerebrospinal fluid.[12]

Although the Na^{24} concentration in the blood serum reached a level free from marked fluctuations within a few minutes, the concentrations progressively decreased and did not reach a state of equilibrium by the end of two hours, even though corrections were made for loss of Na^{24} in the urine. These findings, therefore, indicate that the Na^{24} rapidly reaches equilibrium with the interstitial fluid. This represents the greatest portion of the Na^{24} injected. Then for several hours there is a gradual passage of the Na^{24} into bone, spinal fluid, vitreous body, aqueous humor, and similar sodium compartments.[9-11] Therefore, studies which require a complete state of equilibrium with radiosodium for all structures of the body must be conducted several hours after the injection of the tracer. The measurement of the sodium compartment of the body cannot be measured properly until the tracer has reached a state of equilibrium for all structures of the body. For that reason any estimate of the sodium compartment with the use of Na^{24} in the studies reported here is subject to error and therefore has limited significance.

The urine concentration of Na^{24} varied considerably from subject to subject. These differences must be related, in part, to the sodium intake preceding the experiments. The cause of the delay in the appearance of the Na^{24} in the urine is unknown. It must be due partly to the time required for the urine to flow from the glomerulus to the outlet of the catheter. However, this requires only about thirty seconds. The delay might be due in part to diffusion from the blood into Bowman's capsule, but the rapid appearance of Na^{24} in the sweat and the rapid diffusion into the interstitial fluid tends to eliminate such a delay as an important factor. The effect of pooling of urine in the pelves of the kidneys could not be evaluated.

Although the data are not shown for both kidneys separately, for all subjects the rates of excretion of Na^{24} were essentially the same for both kidneys. Although there were periods when the rates of excretion and Na^{24} concentration showed discordant relationships, the behavior was so similar as to make it unnecessary to report the data for both kidneys separately. Subject 7 (Fig. 5) exemplified the individual kidney relationships. Since the Na^{24} clearances are reported for only one kidney, the total clearances are essentially twice that shown for one kidney.

Although the concentration of Na^{24} in the urine varied quite markedly (Fig. 3), the rate of Na^{24} clearance was fairly constant. This indicates that when the volume of urine flow was great, the concentration of Na^{24} in the urine was proportionately low and vice versa.

Subjects With Congestive Heart Failure.—The results obtained in the subjects with congestive heart failure are summarized in Figs. 6 to 11.

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Blood: There was a tendency for the concentration of Na^{24} in the blood serum to reach a higher level in the subjects with congestive heart failure than in the normal subjects (Fig. 7). Marked fluctuations were noted for the first ten to twenty minutes; then a stable level was reached. The injected Na^{24}

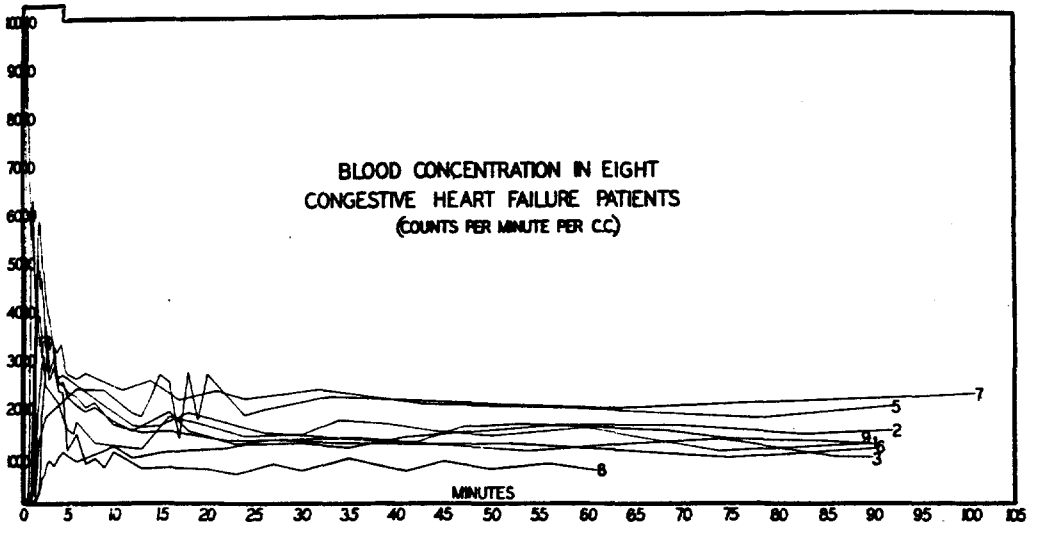

Fig. 7.—Variations in serum concentration of Na^{24} in eight patients with congestive heart failure. If the presence of a diffusion type of sodium curve indicates adequate and early mixing of the injected radiosodium, then mixing appears to have developed more quickly in these persons than in the normal ones.

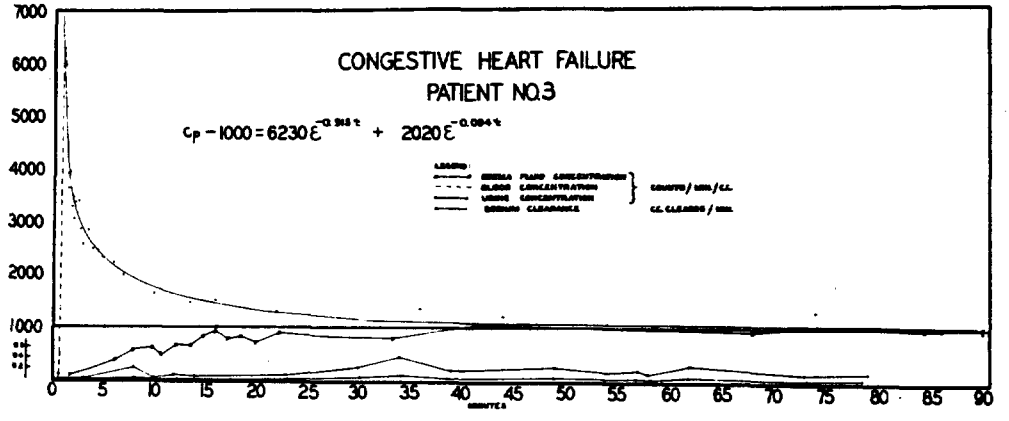

Fig. 8.—Variations in serum, urine, and edema fluid concentration and Na^{24} clearance in Patient 3 with chronic congestive heart failure. The serum concentration curve is a typical double exponential diffusion curve, the equation of which is shown. Note the fairly rapid increase in concentration of Na^{24} in the edema fluid to a level equal to that in the serum.

appeared in the antecubital vein of the sampling arm a few seconds later than in the normal subjects. Like the normal subjects, the patients with congestive heart failure showed such wide variations in the serum concentrations of Na^{24} that it was impossible to calculate a satisfactory average diffusion pattern for the Na^{24}. Some individuals, however, presented typical diffusion curves with

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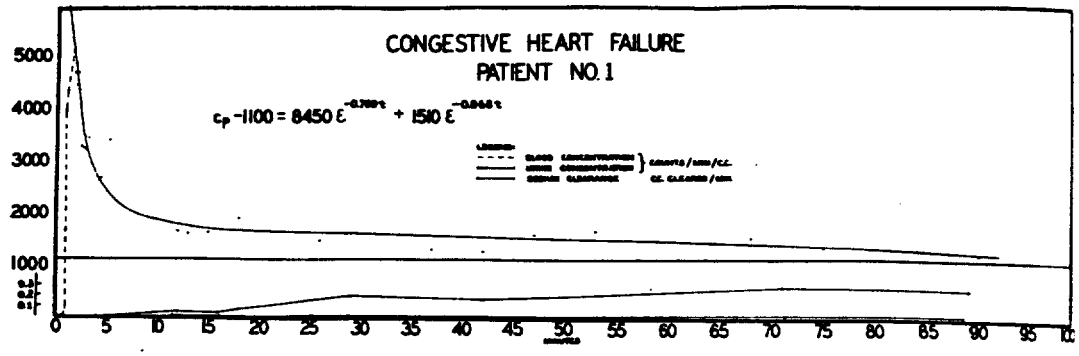

Fig. 9.—Variations in serum and urine concentration of Na^{24} and Na^{24} clearance in Subject 1 with congestive heart failure. The equation for the sodium diffusion curve is shown.

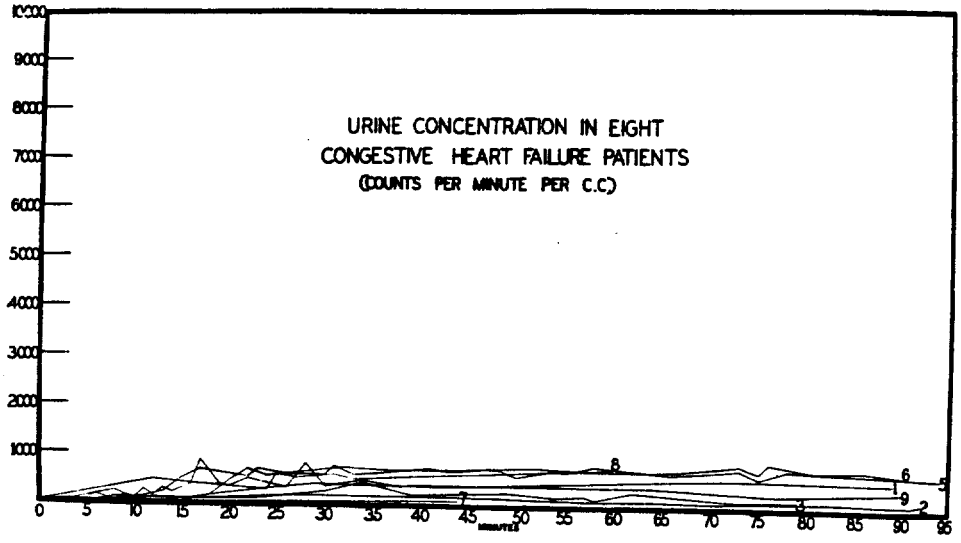

Fig. 10.—Variations in urine concentration of Na^{24} in eight patients with congestive heart failure and a low sodium diet. Compare these values with those for the normal (Fig. 3).

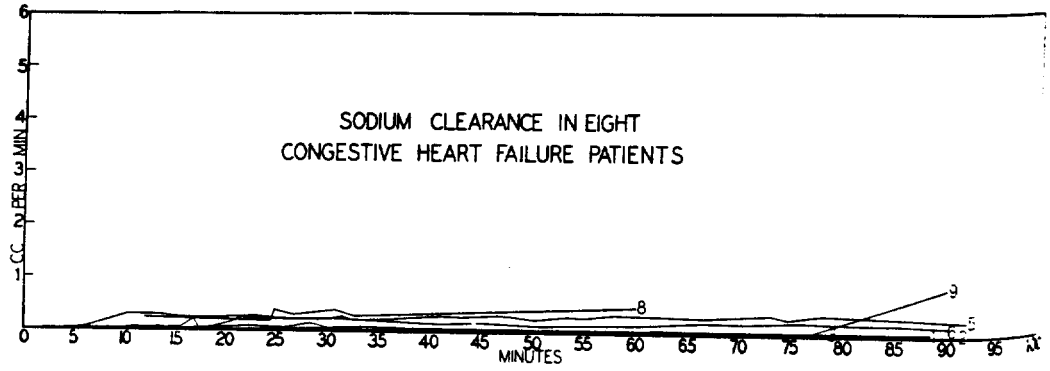

Fig. 11.—Variations in Na^{24} clearance in eight patients with congestive heart failure and a low sodium diet. Compare these values with those for the normal (Figs. 4 and 6).

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both rapid and slow rates of diffusion of sodium from the blood plasma (Fig. 8). The equation for the diffusion curve of Fig. 8 was found to be:

$$c_p - 1000 = 6230e^{-0.915\,t} + 2015e^{-0.094\,t}. \quad (4)$$

This indicates that 0.915 of the plasma sodium which diffuses at the rapid rate escaped from the vascular bed into the interstitial spaces per minute, and 0.094 of the plasma sodium which diffuses at the slow rate escaped from the vascular bed per minute. Because of the rapid rate of diffusion in Subject 3, another patient (Subject 1) with congestive heart failure was similarly studied (Fig. 9). The curve for this patient had the following equation:

$$c_p - 1100 = 8450e^{-0.700\,t} + 1510e^{-0.068\,t}. \quad (5)$$

The diffusion rates in this subject were about the same as for the normal subject, although still more rapid.

From Table II it can be seen that 54 and 63 per cent of the total plasma sodium diffused out of the vascular bed per minute as average rates in Subjects 1 and 3, respectively. Simultaneously 6 and 8 per cent of the total interstitial fluid sodium diffused back into the plasma per minute in the respective patients.

Urine: The urine was collected from the bladder and not directly from the renal pelves as in the normal subjects. The results are summarized by Figs. 8, 9, and 10. The Na^{24} did not appear in the urine until four to five minutes after injection except in one patient (Fig. 10). The concentration of Na^{24} rose more slowly and the concentration levels reached were much lower than in the normal subjects. Considerable fluctuations were observed during the initial twenty to thirty minutes of study, followed by a stable level with minor variations of essentially the same degree as those encountered in the normal subjects.

Sodium Clearance: The sodium clearances of the patients with congestive heart failure with therapy are summarized in Figs. 6, 8, 9, and 11. The rates by which the blood was cleared of sodium were considerably lower than those observed for the normal subjects. These clearance values for both kidneys were about 0.03 c.c. per minute, the quantitative and qualitative variations being shown in Fig. 11. The clearance values approached zero in some subjects (Subjects 1, 2, and 3).

Edema Fluid: It was possible to follow the appearance of Na^{24} in the edema fluid of most of the patients with congestive heart failure. The results of the study of the edema fluid of Subject 3 are shown in Fig. 8.

Comment: The rapid and slow rates of diffusion of sodium from the vascular bed of the patients with congestive heart failure were higher than those observed in the normal subject. Obviously, it is not possible to conclude that such a difference is characteristic of congestive heart failure. Too few subjects were studied and too many factors are concerned with the escape of the sodium ion into the tissues for one to conclude that a greater rate of transcapillary diffusion is at work in all patients with congestive heart failure. The problem of mixing of the blood and the general inefficiency of the circula-

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tion are important in congestive heart failure. Furthermore, it is necessary to bear in mind that all of the patients with congestive heart failure were receiving therapy. One aspect of the therapy (ammonium chloride and mercurial diuretics) was intended to make the kidneys excrete more sodium, while another phase of the therapy (dietary restriction of sodium) resulted in a decreased rate of renal excretion of sodium. The influence of these factors on the data obtained is unknown, but they were most probably great enough to make it impossible to evaluate the role of uncomplicated congestive heart failure on transcapillary diffusion of sodium. Gellhorn and associates[5] found the rates of transcapillary diffusion in dogs in shock, with and without treatment, were 50 per cent of those of normal dogs. Of course, the disturbances in hemodynamics are quite different in shock and in chronic congestive heart failure without shock.

Nevertheless, the more rapid rate of diffusion of sodium across the vascular wall in congestive heart failure than in the normal condition can be explained by the fact that there is a greater quantity of total amount of extracellular fluid and, therefore, of sodium in the edematous patients. Inspection of Table II shows that the part of the total extracellular fluid sodium of the patient with congestive failure diffusing back into the vascular bed per minute is about 50 per cent of that of the normal. The total quantity of sodium concerned, however, is greater than normal. Since the same quantity of sodium returns to the circulation as leaves it per unit time and since the increase in blood volume is not proportional to the increase in volume of the interstitial fluid, it is necessary that the plasma sodium diffuse more rapidly than in the normal subject in order to maintain a state of equilibrium. Thus the sodium of the interstitial fluid of the normal subject is turned over twice as rapidly as in the patients with congestive heart failure, whereas the sodium of the plasma of the latter patients is turned over twice as rapidly as that of the normal.

The rise in the concentration of Na^{24} in the edema fluid (Fig. 8) is an index of the rate of diffusion of normal sodium, Na^{23}, into edema fluid from the vascular bed. This rate is relatively high when the quantity of the edema fluid is considered. The concentration of the Na^{24} in the edema fluid reached that in the plasma, remaining near the plasma level thereafter. The duration of the rising periods of the Na^{24} concentration in the edema fluid is further support of the relatively long period of time required for a state of sodium equilibrium to be reached when tracer studies are done. This is particularly true when certain abnormal states are under observation.

Miscellaneous Subjects.—

Blood and Urine Concentrations and Sodium Clearance: The results are summarized in Figs. 12 to 15. The nature of the variations in Na^{24} concentration in the blood and urine and Na^{24} clearances was essentially the same as for the normal subjects and those with congestive heart failure, differences being determined by the underlying disease state. For example, Subject 1 suffered with congestive failure due to essential hypertension and was under treatment

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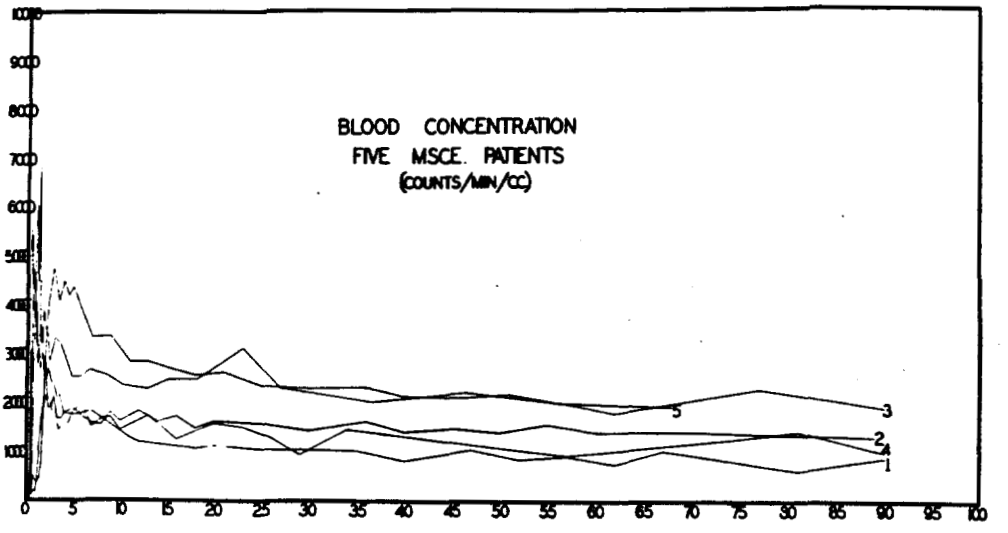

Fig. 12.—Variations in serum concentration in five patients with miscellaneous disease states (Table I).

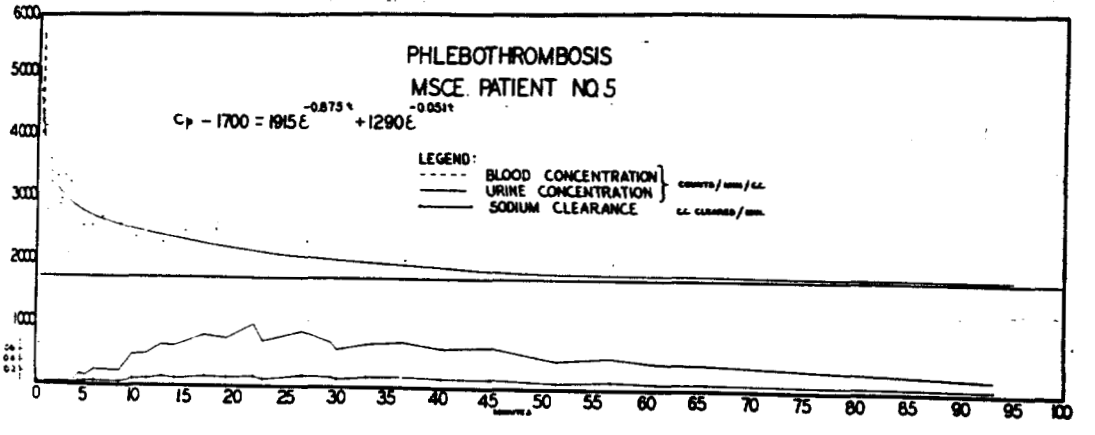

Fig. 13.—Variations in serum concentration, urine concentration, and Na^{24} clearance in a patient with chronic phlebothrombosis of both legs and moderate chronic edema. The diffusion curve for sodium and its equation are shown.

for the heart failure. She also had a fairly extensive ovarian malignancy. The variations in Na^{24} concentration in the blood and urine and in the sodium clearances were similar to those described for the group of patients with uncomplicated congestive heart failure under treatment. The patients with phlebothrombosis and sarcoidosis were not found to show any special characteristic behavior.

Subject 5 with phlebothrombosis was selected for analysis of the diffusion rates of sodium because the edema was limited to the two lower extremities and because the data were suitable for such an analysis. The curve (Fig. 13) representing variations in the serum concentration of Na^{24} is similar to that,

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of the normal subject and the subjects with congestive heart failure. The curve of the serum concentration may be expressed as

$$c_p - 1700 = 1915e^{-0.875\,t} + 1290e^{-0.051\,t}, \qquad (6)$$

that is, 0.875 of the plasma sodium which diffuses through area A_1 left the blood per minute, while 0.051 of the plasma sodium which diffuses through A_2 left the blood per minute.

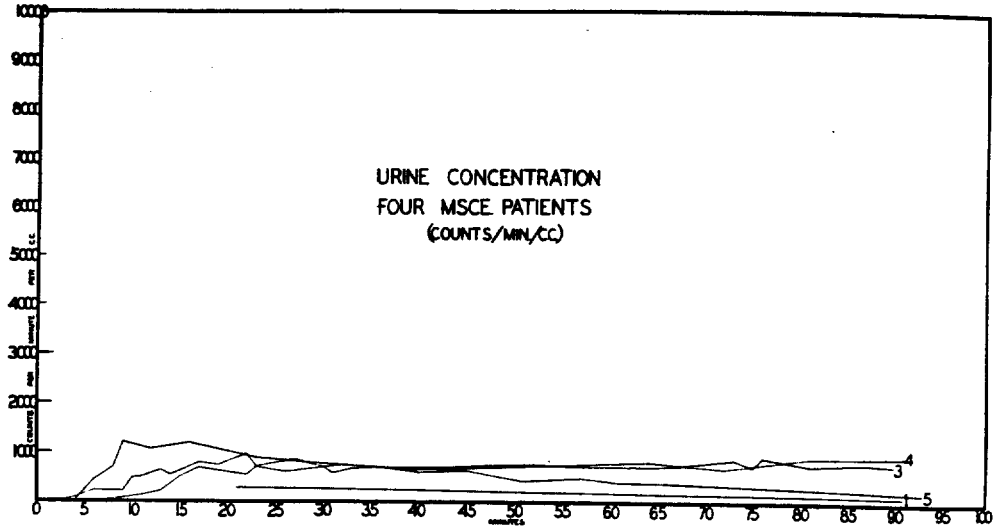

Fig. 14.—Variations in urine concentration of Na^{24} in four patients with miscellaneous disease states.

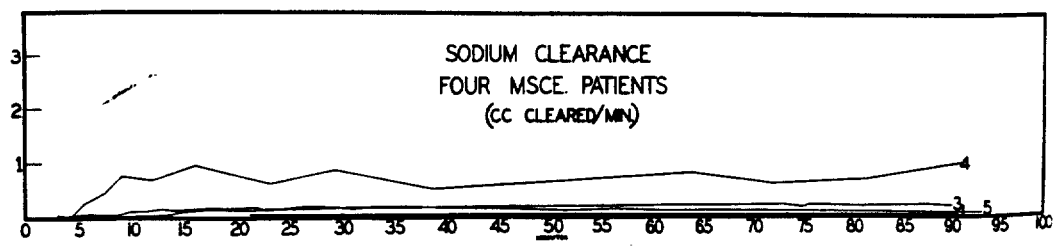

Fig. 15.—Variations in Na^{24} clearance in four patients with miscellaneous disease states. Compare these values with those of the other two groups of subjects (Figs. 4, 6, and 11).

Comment: Fever and other systemic influences from infection, malignancy, or sarcoidosis did not present any detectable influences on the diffusion of sodium through the vascular bed. The rate of excretion through the kidneys, however, might conceivably be influenced by renal damage as well as by therapy. The rates of sodium diffusion were too high to permit minor variations to manifest themselves sufficiently for detection.

The transcapillary diffusion of sodium in these subjects indicated at least two rates, a rapid and a slow one. In the subject with phlebothrombosis the rates of diffusion through areas A_1 and A_2 were of the order encountered in the two patients with congestive heart failure. The patient with phlebothrombosis

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was receiving only bed rest; no therapy was directed at the edema specifically. Table II indicates the proportion of plasma and interstitial sodium diffusing through the vascular bed per minute.

Concretio Cordis and Marked Ascites: Miscellaneous Subject 7 had marked chronic cardiac tamponade with marked ascites and was receiving therapy for congestive heart failure. The therapy included the use of digitalis, mercurial diuretics, and a low sodium diet. He died at operation several days after this study and a thick fibrous sheet, which interfered markedly with diastolic filling of the heart, was found to encase the heart. He was studied in the manner previously described except that an 18-gauge needle was placed into the peritoneum so that samples of ascitic fluid could be collected at frequent intervals for study. The relative concentrations of Na^{24} in the blood and ascitic fluid are shown in Fig. 16. There was a very slow but definite rise in the Na^{24} concentration in the ascitic fluid. This rise was much slower than that observed in the urine or edema fluid of the other patients. The blood serum concentration of Na^{24} showed the usual variations.

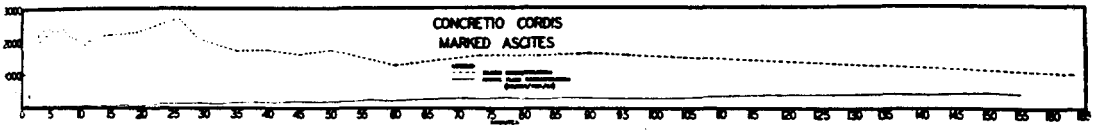

Fig. 16.—Variations in serum and ascitic fluid concentrations of Na^{24} in a patient with concretio cordis and marked ascites. Note the relatively slow increase in the Na^{24} concentration in the ascitic fluid as compared with that of the edema fluid of Subject 3 with congestive heart failure.

Comment: The relatively slow diffusion of Na^{24} into the ascitic fluid of this patient is probably due to the great mass of fluid through which the Na^{24} must diffuse, as well as a less rapid diffusion of sodium through the peritoneal membrane. The importance of the former factor is supported by the slow diffusion into the edema fluid. The tissues are richly supplied with capillaries which permit a larger area of contact with the interstitial fluid; that is, the ratio of area of capillary wall in contact with each unit volume of fluid is high. The capillary area of contact per unit volume of edema fluid is less and, therefore, a longer time is required for equilibrium to be established. In the case of the ascitic fluid the ratio of capillary wall per unit volume of fluid into which diffusion occurs is considerably less and, therefore, the slower diffusion and even longer time required for equilibrium to be established becomes evident. There is no doubt that the stirring of the edema fluid that occurs with breathing and movement of the body aids in increasing the rate with which the state of equilibrium is reached. These observations further support the evidence that several hours are required to reach equilibrium, especially in edema states, after radiosodium tracer studies are conducted.

Excretion of Na^{24} by the Sweat Glands: A normal subject (a 45-year-old white man) rested in a hot and humid air-conditioned room (temperature, 48° C.; relative humidity, 45 per cent). After the bladder was emptied he was studied in the same manner as described for the other subjects.

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Results: The results are summarized in Fig. 17. The Na^{24} appeared in the sweat in seventy-five seconds after the intravenous injection. The concentration of Na^{24} was greatest in the blood and least in the urine. The concentration in the sweat tended to follow that in the blood very closely. Unfortunately the subject could not remain very long in the hot and humid atmosphere; therefore, the experiment was stopped after only thirty minutes of observation. Another sample of urine and of blood, collected about forty minutes after the subject was removed from the hot room, showed no special change in Na^{24} concentration. Concentrations of Na^{24} in the urine, blood, and sweat of normal Subject 6 are shown in Fig. 2. Six samples of sweat were measured during the period of study.

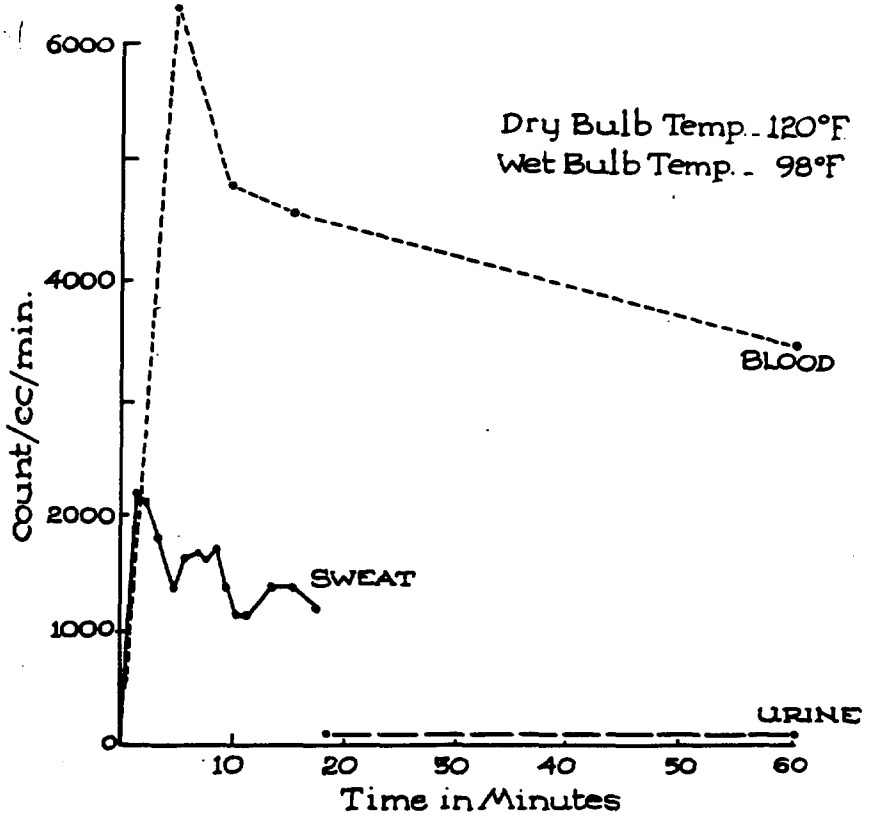

Fig. 17.—Variations in serum, sweat, and urine concentrations of Na^{24} in a normal subject who was in the process of profuse thermal sweating when the Na^{24} was injected intravenously.

Comment: These data show the rapid rate with which sodium reaches the sweat. When a correction is made for circulation time, sodium is found to diffuse from the plasma into the interstitial spaces, enter the cells of glomerulus of the sweat glands, be made into sweat, and delivered to the surface of the body in less than sixty seconds. Fig. 17 suggests many interesting concepts of integrations of urinary, sweat, and plasma sodium concentrations. Any

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comments based on one experiment would have little significance. More extensive studies will be described at a later date.

GENERAL DISCUSSION

The diffusion of sodium through the vascular bed in man behaves in a manner similar to that described by Gellhorn and associates for guinea pigs and dogs.[4-6] For comparison the vascular bed can be divided into at least two areas, A_1 and A_2, through which diffusion occurs at two very different rates. The more rapid rate of sodium exchange, through A_1, takes place between the plasma and the intercellular fluid. The slower rate of exchange, through A_2, occurs between the plasma and such fluids as that of the vitreous body, aqueous humor, cerebrospinal fluid, and probably the intracellular fluid. Inspection of the regression curves shown indicates a third main, and even slower, rate of diffusion which may occur between plasma and bone, dentin, and enamel.[5] This area of the vascular bed through which this occurs might be referred to as A_3. There is no doubt that there are *many* other differences in rates of diffusion of sodium between the plasma and other structures of the body, the number being limited by the sensitivity of the method of analysis. Under different states of salt intake, nutrition, glandular secretion, vasomotor function, and disease these rates are altered. For example, there is a different rate of diffusion into edema fluid (Fig. 8) from that into ascitic fluid (Fig. 16). A generalized edema state results, therefore, in two areas in the vascular bed with different rates of diffusion. At the present time it is much better to consider the vascular bed as having two main areas with diffusion at a rapid rate and at a slow rate, these being summations of many different rates of diffusion. It is necessary to remember that this may be an oversimplification of the problem and that with further study other rates will be defined.

The rate of the circulation in man is relatively slow when compared with that which would be desirable to insure adequate mixing for proper study of a substance which diffuses as rapidly as sodium. The mixing time in the average person is so long and the diffusion of sodium out of the blood vessels so rapid that in most cases data were obtained which did not lend themselves to detailed mathematical analysis. In some experiments, however, the mixing was rapid and adequate so that a mathematical analysis was possible. Several of these were selected for such a study. The period during the first minute after the injection was not suitable for proper study of diffusion because slow mixing and rapid diffusion complicated the diffusion pattern. The dashed lines in Figs. 2, 8, 9, and 13 show the rapid increase in the concentration of Na^{24} in the blood within the first minute or two after the injection of the radiosodium, during which time the regression curves are modified to an unknown extent. The remaining portion of the curves is a more accurate representation of the facts. There is no doubt that if there are any errors, such as those due to slow mixing, they are concerned with factors which tend to make the observed b_1, the rapid rate of diffusion of sodium, smaller than it actually is. The values for b_2, the slow rates of diffusion, are most probably near the

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true rate since mixing interferes little with the latter portions of the regression curves. Furthermore, since a state of equilibrium had not been fully reached by the end of ninety minutes, the equilibrium values, c_{eq} of equations (2) and (5), are not the true equilibrium values. Studies[8] with the long-life sodium, Na^{22}, in other subjects have shown the true c_{eq}, the equilibrium constant, to be near those employed in the regression curve formulas, however.

The coefficients, a_1 and a_2, of the various regression curves are dependent upon such factors as rates of diffusion, size of the areas A_1 and A_2, and the distribution of the sodium. Therefore, a_1 and a_2 can represent only roughly the degree of distribution of Na^{23} in the two compartments of the body, that is, the one which is concerned with a rapid rate of diffusion of sodium and the other with a slower rate. An index of the volume of the blood plasma should be c_o, the value of c_p at $t = 0$, but because of the difficulties introduced by slow mixing it is difficult to interpret.

The rates of diffusion appear to be quite variable among the individuals of all groups studied (Figs. 1 and 7). The rates of diffusion through areas A_1 and A_2 were definitely greater in the patients with congestive heart failure than in the normal subjects. Because of the marked variations and the relatively small number of subjects studied, it is not possible to be certain of the significance of these differences. However, as indicated previously, this is expected because of the greater absolute quantities of interstitial fluid and, therefore, of sodium in the patients with congestive heart failure. The turnover of the interstitial sodium in the patients with congestive heart failure is essentially half as rapid as in normal subjects, while the plasma sodium turnover is twice as rapid in the patients with congestive heart failure as that in the normal subjects.

The patients with congestive heart failure were too ill to permit the insertion of ureteral catheters into the pelves of the kidneys. A small urethral catheter was placed in the bladder instead. This resulted in a satisfactory study of Na^{24} excretion in the urine but did not present the advantage of studying each kidney separately. All sodium clearances for the patients with congestive heart failure represented total clearance, while those in the normal subjects represent unilateral clearance, or essentially one-half of the total clearance (Fig. 6). This should be remembered when examining the illustrations and when comparing the rates of clearance in the normal and abnormal subjects.

The radiosodium was excreted in essentially the same concentration and at the same rate by both kidneys. There was a tendency at times, however, for one kidney to excrete more rapidly than another, but this was varied throughout the period of study. Although the concentration of Na^{24} and the rate of sodium clearance tended to vary concordantly, there were sufficient variations to indicate differences in function between two contralateral normal kidneys. Although both are under the same general hormonal or chemical and nervous influences there were individual differences. Most of these differences must result from differences in intrinsic renal function. In some isolated instances these differences were considerable, although the excretion of Na^{24} usually differed very little in the two kidneys.

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The rate of sodium clearance was much slower in the patients with congestive heart failure than in the normal subjects. This is particularly significant when the rapid transcapillary diffusion rates are considered. It was impossible to evaluate the differences between the two groups of subjects because the patients with congestive heart failure were receiving treatment for the failure. This treatment included dietary restriction of sodium, a procedure normally associated with a decrease in renal excretion of sodium. Nevertheless, these differences are largely due to the congestive heart failure, as evidenced by previous studies[7] with Na^{22} and to the fact that three of the patients with a low sodium clearance had not been on sodium restriction for more than twenty-four hours before the study was begun. The long life of Na^{22} made it possible to control sodium intake, therapy, diet, and other factors in order to evaluate better the disturbances in sodium excretion in congestive heart failure. Unfortunately, this was not possible in these studies with Na^{24}.

Table I shows estimations of sodium space. A sodium space calculated within one or two hours after injection cannot be accurate. This is obvious from the preceding discussion of the rapid rate of diffusion of sodium and the relatively long time required for a state of equilibrium or "complete mixing" of the Na^{24} with all of the Na^{23} distributed through the body to occur. The inaccuracy of such a calculation is further indicated by Table I. The sodium space calculated from data at the sixtieth minute after injection of the Na^{24} was lower than that calculated at the ninetieth minute. Furthermore, radiosodium cannot be employed to measure extracellular water volume with any degree of accuracy because a fairly large portion of the body sodium is not in the extracellular water. The method becomes even more inaccurate in disease states, especially in those associated with edema. The values of sodium space presented in Table I are intended only to illustrate the possible error of such a calculation and not to present absolute values of sodium space. The lower equilibrium level, c_{eq}, for the patients with congestive heart failure and the larger values obtained for the estimated sodium space in these patients are quantitative evidence of the large edema fluid volume accompanying congestive heart failure.

The rapid rate and high concentrations with which Na^{24} appeared in sweat is further evidence in support of the rapid rate of diffusion of sodium across the vascular wall. The relationships of sodium in the sweat, urine, blood, and edema fluid are under study. The single study presented is not sufficient to warrant any definite physiologic conclusions, although many ideas are suggested.

Finally, it is important to note that the rapid rates of sodium and water diffusion and the tremendous quantities concerned make the problem of the mechanism of edema assume a different pattern. Sufficient evidence has not been gathered yet to make possible a proper appreciation of the role of the rapid and large turnover of sodium and water in edema formation. It is obvious that slight disturbances in sodium diffusion or excretion might result in a rapid and marked accumulation of edema fluid. These factors are now under observation.

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SUMMARY

Normal subjects, patients with congestive heart failure under treatment, and patients with other disease states were studied following a single intravenous injection of Na^{24} to learn the rate of diffusion of sodium through the vascular wall and its rate of excretion into the urine and sweat.

Sodium diffuses through the vascular wall with at least two rates, *rapid* and *slow*. These rates of diffusion of sodium in man are similar in quantity and quality to those described by Gellhorn and associates for guinea pigs and dogs. In a normal subject the average rate of diffusion indicated that about 32 per cent of the total plasma sodium diffused out of the blood every minute. This approaches a diffusion across the vascular wall equal to about 18 pounds of sodium or 50 pounds of sodium chloride per day.

The sodium that diffuses at a rapid rate is mainly concerned with an exchange between the plasma and interstitial fluid, while that which diffuses at the slow rate is probably concerned with exchanges between the plasma and such fluids as the vitreous body, aqueous humor, and cerebrospinal fluid. The regression curves observed suggest a possible third or slower rate of sodium diffusion such as might be expected for bone, dentin, and enamel already saturated with sodium.

The individual subjects in all groups showed a considerable spread in the blood and urine concentrations and rates of sodium cleared by the kidneys. The patients with congestive heart failure with treatment, including dietary restriction of sodium, showed a more rapid rate of sodium diffusion from the vascular bed than did the normal subjects. This was also true for a patient with phlebothrombosis receiving only bed rest therapeutically. The rate of turnover of the interstitial fluid sodium was 50 per cent as rapid in the patients with congestive heart failure as in the normal subject, while the plasma sodium of the patients with congestive heart failure turned over twice as rapidly as that of the normal subject.

The rapid rates of diffusion and the large quantities of sodium involved make it necessary to reconsider the role of sodium in edema formation. Relatively slight changes in the rates of sodium diffusion from the blood with a disturbance in its excretion in the urine might result in rapid and marked edema formation.

The rate of sodium clearance in the patients with congestive heart failure was considerably less than that in the normal subjects. These differences were not due entirely to a dietary restriction of sodium intake.

Simultaneous study of each kidney showed a tendency for the renal excretion of sodium to be similar bilaterally. There was sufficient qualitative and quantitative difference, however, to indicate intrinsic renal differences in the excretion of sodium. In some instances these differences were considerable.

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