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THE BIOLOGIC DECAY PERIODS OF SODIUM IN NORMAL MAN, IN PATIENTS WITH CONGESTIVE HEART FAILURE, AND IN PATIENTS WITH THE NEPHROTIC SYNDROME AS DETERMINED BY Na^{22} AS THE TRACER

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A SUBSTANCE introduced into an organism tends to be eliminated exponentially, that is, the amount excreted is a fairly constant percentage of that which remains. Mathematically, the substance is never completely eliminated, and it is therefore preferable to measure the interval of time required to eliminate one-half the material introduced; this is known as the *biologic half-life period* of the substance. It is important to know this measurement for several reasons:

(1) The length of time required to *excrete* one-half an isotope or labeling substance introduced into an organism is equal to the time required to excrete one-half the total amount of the regular form of the substance already present in the organism. Therefore, a measurement of the biologic half-life period of the substance introduced indicates the total rate of turnover of the regular substance.

(2) Whenever radioelements are introduced into an organism, the *safety factor* is determined in part by the time interval of exposure of the organism to radiations from the radioelement. Radioelements with a long physical half-life, such as Na^{22} or C^{14}, will not decay rapidly enough to change their activity appreciably. The degree of their action upon the organism, on the other hand, is reduced as the radioelement is excreted. Therefore, from a knowledge of the biologic half-life period the duration of exposure of the organism to the radiations of the substance is known.

(3) *Safety measures* of public health importance are concerned with the biologic half-life period of radioelements, and these problems will assume greater import as radioelements are more widely employed.

(4) The biologic half-life period of a substance influences the *nature of the study* concerned with labeling by radioactive substances, such as the rate of collection of samples of biologic fluids, the time at which animals must be sacrificed, and clinical management of human subjects. For example, a radioelement with a relatively long biologic half-life period and a very short physical half-life is not suitable for tracer studies involving over-all turnover in the organism.

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(5) The biologic half-life period is an important factor in calculating *dosages* of radioelements to insure levels of counts which permit accuracy of measurements.

(6) The influence of *disease* upon the biologic half-life is significant from the point of view of understanding disease and of planning further investigations.

(7) This measurement is also valuable in clarifying problems related to *therapy*, characteristics of species in animals and plants, toxicology, and many other problems peculiar to individual experiments.

The wide variations in metabolic activity, diet, and general biologic processes affect the biologic half-life of radioelements considerably. This is true in health and particularly in disease. For this reason, values for the biologic half-life of a substance for a normal organism cannot be applied empirically to an abnormal one. For example, since the excretion of a substance varies with each subject and with the intake of that substance by the organism, any interpretation based upon an average biologic half-life period is only an approximation for some other subject with a different intake and a different biologic state.

During the course of the study of the rate of sodium turnover in normal human subjects and the influence of congestive heart failure on sodium excretion with a limited supply of long half-life radiosodium (Na^{22} with $t_{\frac{1}{2}}$ of three years), sufficient data were obtained to indicate the biologic half-life period of sodium in man. These help elucidate the influences of diet and drugs upon the biologic half-life in normal man as well as in patients with chronic congestive heart failure and in those with the nephrotic syndrome of chronic glomerulonephritis.

MATERIALS AND METHODS

In the studies with Na^{22} not designed primarily for measuring the biologic half-life period of sodium, twelve subjects were observed continuously for periods varying from twenty to seventy days. Four of these were normal subjects, six had chronic congestive heart failure (two were slowly improving, two rapidly improving, and two slowly becoming worse), and two patients had the nephrotic syndrome of chronic glomerulonephritis (see Table I for clinical details).

Na^{22}, as NaCl in approximately 2 c.c. of water, was administered intravenously to each subject. Doses with an activity such that there were 17,725,000 counts per minute (about .09 mc.) were administered to seven subjects (Nos. 2, 3, 4, 5, 6, 11, and 12), 12,500,000 counts per minute (about .06 mc.) to three subjects (Nos. 1, 7, and 9), and 10,000,000 counts per minute (about .05 mc.) to two subjects (Nos. 8 and 10). It was found that sufficiently high counts could be obtained by injection of smaller doses, necessitated by the limited supply of Na^{22}.

Each specimen of urine during the entire period of study was collected separately, and daily blood samples were taken. The volume of each urine specimen, and the radioactive count, were recorded so that total elimination of radiosodium could be determined. Counts of blood serum were followed as an index of radiosodium concentration in the extracellular fluid.

Sixteen free-falling drops of urine or serum from a calibrated micropipette were placed on filter paper disks fixed with rubber cement to metal disks so that the quantity and geometric characteristics of each sample remained constant. The samples were counted for

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TABLE I. CLINICAL DATA

SUBJECT NO.	AGE (YR.)	SEX	INITIAL WEIGHT (POUNDS)	DIAGNOSIS
		A. Normal or Control		
1	41	M	142.5	Obliterative pleuritis
2	16	F	134	Acute rheumatic fever
3	33	F	121	Esophageal peptic ulcer
4	39	F	123	Duodenal ulcer
		B. Congestive Heart Failure (Slowly Improving)		
5	47	F	153	Hypertension
6	48	F	162	Arterial hypertension
		C. Congestive Heart Failure (Rapidly Improving)		
7	63	M	131.5	Hypertension
8	47	F	134	Rheumatic heart disease (inactive); auricular fibrillation
		D. Congestive Heart Failure (Slowly Becoming Worse)		
9	46	M	155.5	Syphilitic aortic insufficiency
10	54	F	129.5	Hypertension
		E. Chronic Hemorrhagic Nephritis (Nephrotic Syndrome)		
11	15	F	138	Renal function 25 to 30 per cent normal; slowly improving
12	28	F	285.75	Renal function 25 to 30 per cent normal

five minutes with mica-window Geiger-Müller counters. Corrections for background were made, and the data were recorded in counts per minute per cubic centimeter of fluid. In order to compare the concentrations of radiosodium in the serum, all counts were corrected to correspond to an injected dose of 17,725,000 counts per minute for each subject. The range of error was plus-minus 3 per cent.

The urinary excretion of Na^{22} was expressed in terms of the percentage of injected Na^{22} which was not eliminated by the kidneys. This value, represented symbolically as $\%N_t$, was calculated from the equation

$$\%N_t = \left(1 - \frac{\sum_{s=1}^{t} k_s}{N_o}\right) \times 100$$

where

N_o = injected Na^{22} in counts per minute,

k_s = Na^{22} excreted in urine only during the sth day after injection, expressed in counts per minute,

$\%N_t$ = percentage of injected Na^{22} not excreted in urine by the end of the tth day after injection.

Weights and fluid intake and output were recorded daily for each subject. The sodium intake was varied in some instances from low (<1.7 Gm. NaCl per day), to regular (8 Gm. NaCl per day), to high (13.7 Gm. NaCl per day), and the effect on the rate of elimination of radiosodium was noted. Mercurial diuretics* and other drugs, used frequently in both the diseased and normal subjects, exerted some influence on the rate of excretion of the radiosodium.

*Mercuhydrin (sodium salt of methoxyoximercuripropylsuccinylurea with theophylline), furnished by courtesy of Lakeside Laboratories, Milwaukee, Wis.

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TABLE II. THE INDIVIDUAL AND MEAN $C_{1/2}$ AND $U_{1/2}$ VALUES FOR THE SUBJECTS STUDIED

SUBJECT NO.	$C_{1/2}$	$U_{1/2}$	DAYS OF CONTINUOUS OBSERVATION	WEIGHT CHANGE (POUNDS)
A. Normal or Control				
1	14	30	62	- 3.5
2	13	9	22	-14
3	12	42	45	-11
4	14	34	65	2.25
Mean	13.3	28.8	48.5	- 6.6
B. Congestive Heart Failure (Slowly Improving)				
5	40	60	35	-18
6	42	72	46	- 7
Mean	41	66	40.5	-12.5
C. Congestive Heart Failure (Rapidly Improving)				
7	13	26	62	-29
8	28	33	58	-17
Mean	20.5	29.5	60	-23
D. Congestive Heart Failure (Slowly Becoming Worse)				
9	24	72	68	17
10	30	48	58	- 5.5
Mean	27	60	63	5.75
E. Chronic Hemorrhagic Nephritis (Slowly Improving)				
11	58	660	45	15
12	54	366	71	-86
Mean	56	513	58	-35.5

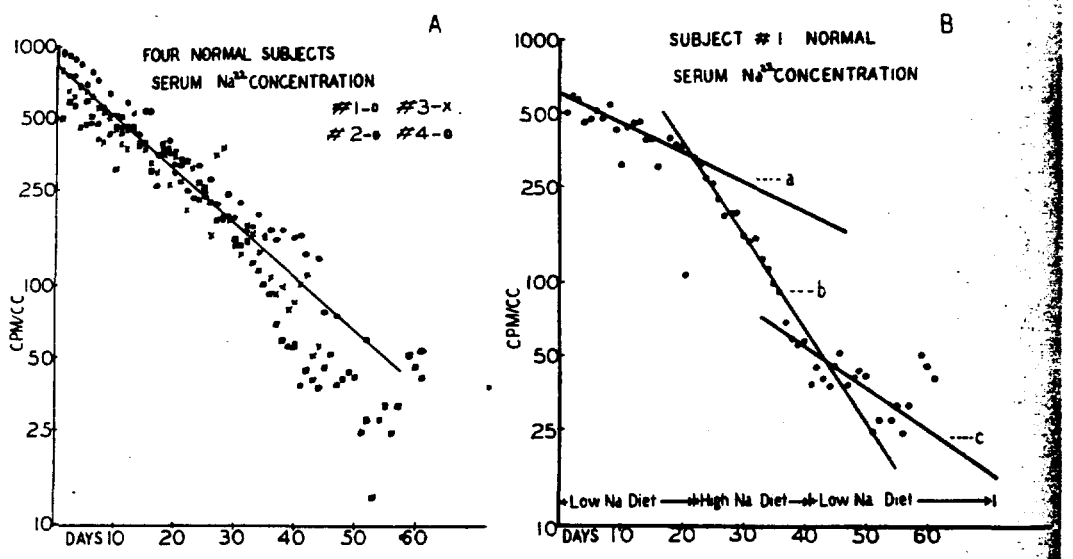

Fig. 1.—Semilogarithmic graphs of relation of changes in serum Na^{22} concentration (counts per minute per cubic centimeter) to time.

A, Four subjects without cardiovascular disease. The mean rate of fall in concentration was such that half-concentration was reached in 13.3 days ($C_{1/2}$).

B, Normal Subject No. 1, showing a change in rate of fall in concentration with variations in sodium content of the diet, low sodium diet (1.7 Gm. NaCl daily) and high sodium diet (13.7 Gm. NaCl daily). At rate *a*, with low sodium diet, serum concentration reached half the initial value in twenty-five days. At rate *b*, with a high sodium diet, half serum concentration was reached in eight days, and at rate *c*, when a low sodium diet was resumed, half-concentration was reached in eighteen days.

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RESULTS

Results are summarized in Table II and in Figs. 1, 2, 3, 4, and 5.

1. Controls.—In the four control subjects who had no disturbance in the cardiovascular system and no edema, the serum concentration of Na^{22} dropped to half the initial level in an average of 13.3 days, the extremes being twelve and fourteen days (Table II and Figs. 1 and 4). The rate of elimination of the isotope in the urine was such that one-half of the Na^{22} administered would have been excreted in an average of 28.8 days, with a range of nine and forty-two days (Table II and Figs. 3 and 4). Subject No. 1 demonstrated the influence which intake of sodium chloride has on the rate of elimination of Na^{22} from the body (Figs. 1, *B* and 3, *B*). The rate of decline in serum concentration whereby one-half the initial concentration was reached in twenty-five days when the patient was given 1.7 Gm. of available sodium chloride increased to a rate whereby one-half the initial concentration was attained in eight days (three times as rapid) when 13.7 Gm. of available chloride was allowed, and then changed again to a reduced rate of eighteen days when the patient again received 1.7 Gm. available sodium chloride (Fig. 1, *B*). Similar response was noted for rates of elimination in the urine (Fig. 3, *B*).

2. Patients With Chronic Congestive Heart Failure.—

(a) Patients Slowly Improving: In two patients who were slowly recovering from congestive heart failure forty and forty-two days were required for the serum concentration of Na^{22} to reach one-half the initial level (Table II and Figs. 2, *A* and 4). These patients required about three times as many days as the control subjects for reduction of serum concentration of Na^{22} to half the initial level. The Na^{22} was excreted in the urine at such a rate that sixty and seventy-two days would have been required to excrete one-half the administered Na^{22} (Table II and Figs. 3, *C* and 4). The rate of excretion of Na^{22} in the urine of the control subjects was more than twice as rapid as in the patients with heart failure.

(b) Patients Rapidly Improving: The two patients with chronic congestive heart failure who improved rapidly required an average of 20.5 days (extremes, thirteen and twenty-eight days) for the serum concentration of Na^{22} to reach one-half the initial level (Table II and Figs. 2, *B* and 4). The mean rate of excretion of Na^{22} was 29.5 days, the extremes being twenty-six and thirty-three days (Table II and Figs. 3, *D* and 4). Although the average rate of decline in the serum concentration in Patient No. 7 was thirteen days, once improvement began, the rate of decline exceeded that of the control subjects. Initially the rate of decrease in blood concentration of Na^{22} was such that half concentration would have been reached in fifty-five days. During rapid improvement, however, this level was attained in six days, a rate more rapid even than that of the control subject on a high sodium intake. The rates of elimination of Na^{22} in the urine of this patient tended to parallel changes in concentration in the serum (Figs. 2, *B* and 3, *D*). Patient No. 8 also showed two rates of decline in serum concentration of Na^{22} (seventy-one and twenty-four days respectively required to reach

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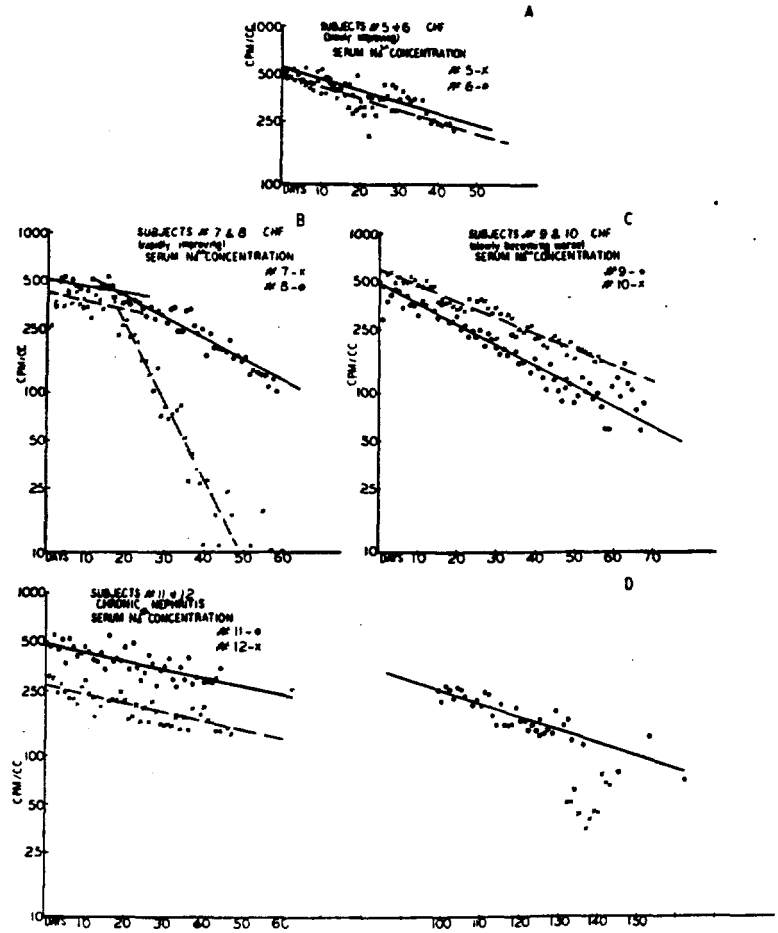

Fig. 2.—Semilogarithmic graphs of changes in serum Na^{22} concentration (counts per minute per cubic centimeter) as a function of the time for six patients with congestive heart failure and two patients with the nephrotic syndrome of chronic glomerulonephritis.

A, Two patients with congestive heart failure who were slowly improving. Patient No. 5 showed a mean rate of fall in serum Na^{22} concentration so that half-concentration was reached in forty days ($C_{1/2}$). Patient No. 6 showed a mean rate of fall in concentration so that half-concentration was reached in forty-two days. It may be noted on the graphs that for each of these patients several rates of change existed, although only the mean rate is shown by the straight line.

B, Two patients with congestive heart failure who were rapidly improving. Patient No. 7 showed two distinct rates of fall in serum Na^{22} concentration. The first rate, maintained for eighteen days, was such that half-concentration would have been reached in six days. *Patient No. 8* also showed two distinct rates of fall in serum Na^{22} concentrations. The first rate, present for eighteen days, was such that half-concentration would have been reached in seventy-one days, whereas with the second rate twenty-four days would have been necessary.

C, Two patients with congestive heart failure who were slowly becoming worse. Patient No. 9 showed a mean rate of fall in serum Na^{22} concentration so that half-concentration was reached in twenty-four days ($C_{1/2}$). *Patient No. 10* showed a mean rate of fall in concentration so that half-concentration was reached in thirty days. Several rates of change in concentration may be noted, although only the mean rate for each patient is indicated by the straight line.

D, Two patients with the nephrotic syndrome of chronic glomerulonephritis. Both of these patients were discharged from the hospital and later readmitted for continuation of the studies. On the first admission *Patient No. 11* showed a mean rate of fall in serum Na^{22} concentration so that half-concentration would have been reached in fifty-eight days ($C_{1/2}$). During the second period of study this patient showed a mean rate of fall in concentration so that half-concentration would have been reached in thirty-seven days, and *Patient No. 12* required fifty-four days.

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half-concentration) and at least two rates of elimination of Na^{22} in the urine (Figs. 2, *B* and 3, *D*). These two patients eliminated Na^{22} more rapidly than the two patients who were improving slowly.

(c) Patients Slowly Becoming Worse: Two patients gradually became clinically worse throughout the period of study. The serum concentration of Na^{22} was reduced to one-half the initial value in an average of twenty-seven days, the extremes being twenty-four and thirty days (Table II and Figs. 2, *C* and 4). The mean rate of loss of Na^{22} in the urine was such that one-half the administered Na^{22} would have been excreted in sixty days, with extremes being forty-eight and seventy-two days (Table II and Fig. 3, *E*). These patients required a longer period of time to excrete the Na^{22} than did the control subjects or the patients with congestive heart failure who were rapidly improving, but essentially the same time was necessary in patients who were slowly improving.

3. Patients With the Nephrotic Syndrome of Chronic Glomerulonephritis.— The two patients with the nephrotic syndrome showed the slowest rates of elimination of Na^{22}. The decline in the serum concentration of Na^{22} was such that an average of fifty-six days (extremes, fifty-four and fifty-eight) would have been required for the serum level to reach one-half the initial value (Table II and Figs. 2, *D* and 4). The rate of Na^{22} excretion in the urine was extremely slow in both patients: an average of 513 days would have been necessary to eliminate one-half the Na^{22} administered (Table II and Fig. 3, *F*). The control subjects exhibited a rate of decline in the serum concentration of Na^{22} more than four times as rapid as in these patients, and the rate of urinary elimination was ten to twenty times as rapid (Table II and Fig. 4).

DISCUSSION

Morgan[1] suggested the symbol "Te" for "the body elimination half-life." This term is satisfactory if the time required to eliminate one-half the radioactive material administered can be determined without too much difficulty. Unfortunately, this is not easily accomplished in man, especially for sodium. Results indicate that there are considerable variations in normal as well as in diseased man. Because of these wide variations from moment to moment and because of differing conditions of environment, diet, physical activity, severity, stage and course of disease, therapy, previous physiologic state, and many other factors, it is possible to obtain only an approximation of the time required to eliminate one-half the radioactive material administered. Furthermore, values observed for changes in blood concentration differ from those for elimination in the urine (Table II, Figs. 1 to 4). It is, therefore, preferable to indicate in the symbol for the half-elimination time the method by which the value was obtained. It is suggested that the following symbols be employed in the discussion of rates of elimination:

$B_{1/2}$ — *biologic half-life,* that is the time required to eliminate one-half the administered tracer substance from the body. This corresponds to the "Te" value of Morgan.

$C_{1/2}$ — *concentration one-half,* that is the length of time required for the concentration of the tracer material in the body fluid or substance or

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URINARY EXCRETION OF Na^{22}

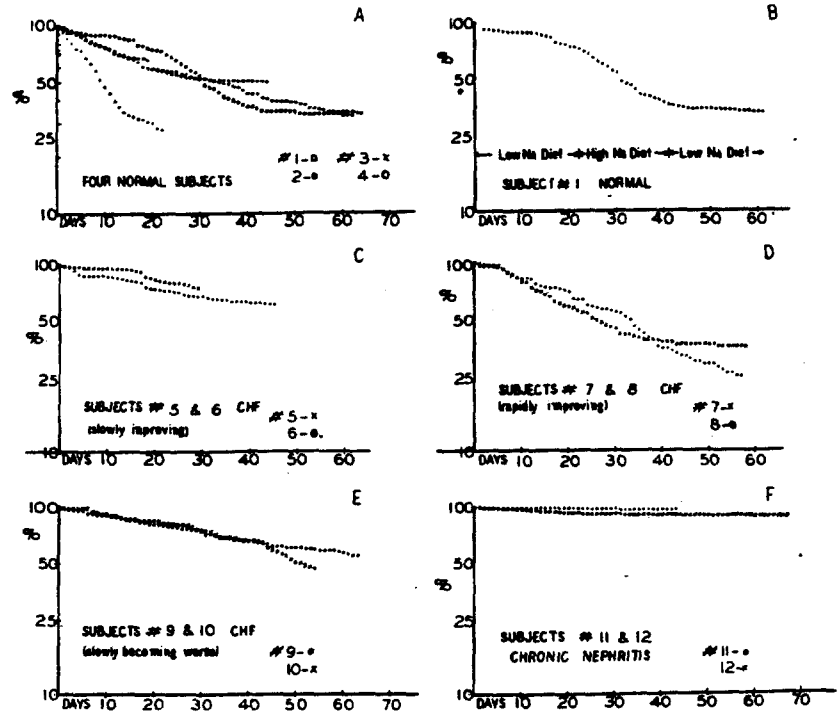

Fig. 3.—Semilogarithmic graphs for all subjects showing the urinary excretion of Na^{22} (percentage of injected Na^{22} which was not eliminated by the urine). This value was obtained from the total counts of Na^{22} excreted daily through the urine. That for the first day was subtracted from the total counts injected; the total for each successive day was subtracted serially. Each resultant was then expressed as a percentage of the total injected dose. These values represent that radiosodium which has remained within the body plus that which has been excreted by some other route, i.e., that Na^{22} which has not been eliminated in the urine. This also indicates the *rate* of excretion by way of the urine.

A, Four subjects without cardiovascular disease. If all the Na^{22} were eliminated in the urine, the day upon which one-half of the injected radiosodium would have been excreted (mean value, $U_{1/2}$).

B, Normal Subject No. 1 shows changes in rate of excretion of Na^{22} in the urine with changes in the sodium content of the diet. For twenty-two days during a low sodium diet the rate of elimination in the urine was such that one-half the sodium present in the body would have been eliminated in one hundred days ($U_{1/2}$). For the next nineteen days during a high sodium diet the rate of excretion increased, so that one-half the body sodium would have been excreted in the urine in nineteen days. For the last nineteen days of observation during a low sodium diet and administration of antidiuretics, the rate of urinary excretion of body sodium was such that 250 days would have been required for excretion of one-half the sodium present at the beginning of that period. Actually one-half the injected Na^{22} was excreted in thirty days.

C, Two patients with congestive heart failure who were slowly improving. Several different rates of excretion for each patient may be noted, the mean rate for the two patients being sixty-six days for excretion of half the Na^{22} injected.

D, Two patients with congestive heart failure who were rapidly improving. Several rates of excretion may be observed. The mean length of time required to excrete one-half the injected Na^{22} by the urine was 29.5 days ($U_{1/2}$).

E, Two patients with congestive heart failure who were slowly becoming worse. Changes in rate of excretion may me noted as in the other subjects. The mean time necessary for excretion of one-half the injected sodium through the urine was sixty days.

F, Two patients with the nephrotic syndrome of chronic glomerulonephritis. If sodium were excreted only by the urine, a mean of 513 days would have been required to excrete one-half the injected radiosodium.

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specific compartment to reach one-half the concentration existing at any time after equilibrium of distribution of the tracer has been reached. It is thus possible to speak of the $C_{1/2}$ for cerebrospinal fluid, $C_{1/2}$ for hepatic parenchyma, $C_{1/2}$ for blood serum.

$U_{1/2}$ — *urinary elimination one-half,* that is the length of time necessary to eliminate in the urine one-half the tracer material administered.

From the point of view of *safety*[1] it is actually the $C_{1/2}$ that is important. Since the $C_{1/2}$ and $U_{1/2}$ are sometimes extremely different, particularly in abnormal states (Table II, Figs. 2, 3, and 4), the $U_{1/2}$ value is of little assistance in calculation of dosages and may result in error. $B_{1/2}$ is certainly important but is not easily determined in man, especially for sodium. Such a determination would require measuring all of the radiosodium excreted by *all* avenues for long periods in a great many persons under varying conditions of diet, environment, disease, and therapy; this is a tremendous task. With the present state of knowledge of radioelements and biologic influences of radioactivity, $C_{1/2}$ and $U_{1/2}$ furnish important data of useful physiologic nature. The possibilities of variations in $B_{1/2}$, $C_{1/2}$, and $U_{1/2}$ are discussed in a second paper,[2] and various mechanisms by which they may differ considerably are suggested.

In all subjects studied, $C_{1/2}$ was less than $U_{1/2}$ except in Control Subject No. 2. Careful analysis of the data failed to suggest a rational explanation for this discrepancy. $U_{1/2}$ is expected to be greater than $C_{1/2}$, since sodium is eliminated by avenues other than the urine, such as sweat, tears, sputum, feces, vomitus, and other body fluids. "Binding" of sodium in cells and onto cells, proteins, and other complex molecules can account in part for these differences. These factors should be studied in experiments designed to determine the $B_{1/2}$; the present experiments, however, were planned for other purposes, and it was not possible to make these measurements. They were satisfactory for determining the $C_{1/2}$ and $U_{1/2}$ in the subjects observed.

The $C_{1/2}$ and $B_{1/2}$ would be expected to be identical in subjects in whom the size of the sodium compartment fails to change, and this is more likely to occur in normal than in diseased subjects. This is probably true for Control Subject No. 1, who was apparently normal in every respect. This was true clinically for Subject No. 2 except that she had fever with arthralgia three weeks before initiation of the studies. Control Subjects Nos. 3 and 4, who suffered from dyspepsia from time to time and experienced vomiting occasionally, were not truly normal but could be considered so for practical purposes.

It is obvious from the values obtained for $C_{1/2}$ and $U_{1/2}$ that Na^{24} is not suitable for measuring these parameters or for measuring $B_{1/2}$. Na^{22}, on the other hand, is excellent for such purposes. Although the supply of Na^{22} was limited, a relatively large number of subjects was observed for long periods of time. If the $C_{1/2}$ values approximate the $B_{1/2}$, the physical half-life period (three years) of Na^{22} is of little value in safety considerations for the subject, because the radiosodium is excreted long before sufficient physical decay can occur, that is, for biologic purposes, Na^{22} may be considered stable. Na^{24}, on the other hand, rapidly decays to levels of radioactivity too low for accurate measurements of biologic decay periods.

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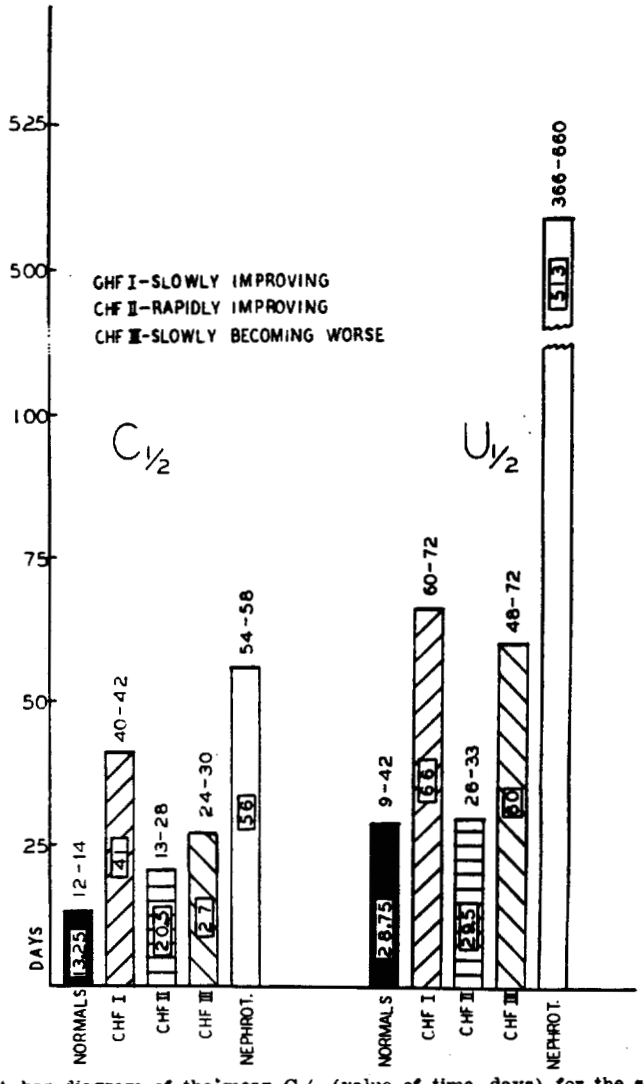

Fig. 4.—A bar diagram of the mean $C_{1/2}$ (value of time, days) for the serum Na^{22} concentration to reach one-half the initial equilibrium concentration ($C_{1/2}$), and the mean time for one-half the injected Na^{22} to be excreted in the urine ($U_{1/2}$). The mean value for each group is enclosed in the column and the extremes are indicated above the column.

Although the subjects were followed for as many as sixty consecutive days, the $C_{1/2}$ or $U_{1/2}$ values often exceeded this period considerably, so that it was necessary to extrapolate the observed curves to obtain the values of $C_{1/2}$ and $U_{1/2}$ recorded. This was true for only two of the $C_{1/2}$ determinations and for seven of the $U_{1/2}$. Therefore, all the values of $C_{1/2}$ and $U_{1/2}$ actually indicated the rates of change that existed only for the days observed.

A number of factors other than excretion can alter the $C_{1/2}$. As mentioned previously, a fixation of sodium to cells or protein and other large molecules will reduce the sodium content of the serum and the Na^{22} concentration. Fixa-

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tion or binding of the tracer can result in a state such that $C_{1/2}$ cannot be equal to $B_{1/2}$. Another important factor is a discrepancy in water intake and output, particularly in states of edema. When more water is taken in than is excreted,

RELATION OF DIET TO CHANGES IN RATES OF EXCRETION AND OF DECREASE IN SERUM CONCENTRATION OF Na^{22}

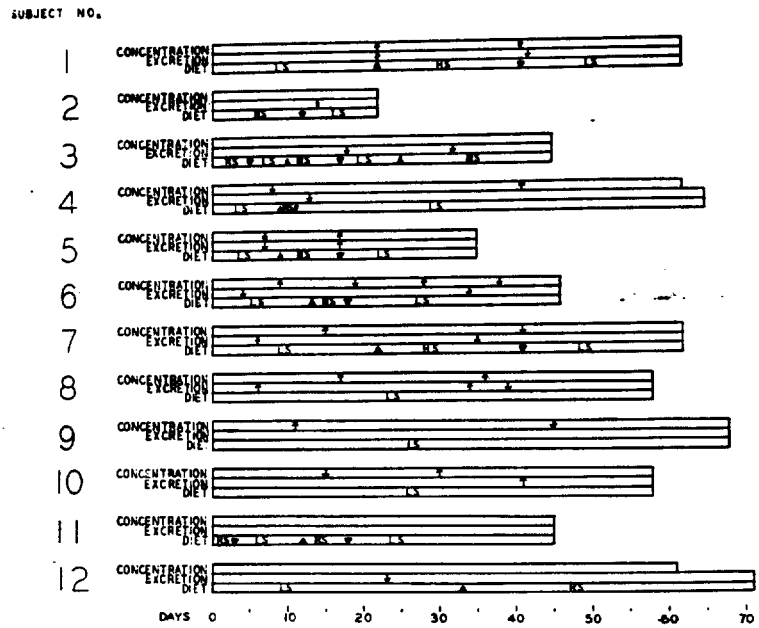

Fig. 5.—The relationship of change in sodium content of the diet and change in the rate of decrease of serum Na^{22} concentration and change in the rate of urinary excretion of Na^{22} for each subject. Sodium content of the diet is indicated by *HS* (high sodium, 13.7 Gm. NaCl daily), *LS* (low sodium, less than 1.7 Gm. NaCl daily), *RS* (regular sodium intake, 8 Gm. daily). Changes in rates are denoted by arrows; ↑ indicates a more rapid rate of change in serum Na^{22} concentration or rate of urinary excretion; ↓ indicates a reduction in either rate. Time is recorded as days of observation. High correlation of change in diet and change in rate may be noted in Subject No. 1, but poor correlation exists in the others (see text).

then the Na^{22} content of the body fluids will be diluted, and the serum Na^{22} concentration will be diminished. If Na^{22} counts for the serum had been employed alone in the interpretations, the rate of excretion of Na^{22} so obtained would have been inaccurate. In fact, if the sodium excretion fell almost to zero in a man who rapidly became edematous shortly after administration of a tracer dose of Na^{22} and if the edema were sufficiently severe to double the volume of the sodium compartment of the body, then the Na^{22} concentration in the serum would be reduced to one-half the initial value. Thus the subject might attain a $C_{1/2}$ value without excreting any sodium, but such a value would certainly differ greatly from the $B_{1/2}$. This dilution phenomenon was noted in some of the edematous patients studied (Subjects No. 9, 11, and 12).

If the reverse situation occurs, that is if an intensely edematous subject loses water more rapidly than sodium, then an actual rise in the serum concentration of Na^{22} and therefore in the $C_{1/2}$ time would ensue. Here, too, the

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$C_{1/2}$ and $B_{1/2}$ values would differ. It is obvious then, that the $C_{1/2}$ and $B_{1/2}$ values cannot be accepted as similar, particularly in subjects with edematous states.

A glance at the biologic decay curves reveals considerable fluctuation in the serum concentration of Na^{22}. These fluctuations are partially due to technical variations but in greater part are attributable to changes produced by phenomena described in the preceding paragraph. Furthermore, some of the variations are the result of responses to drugs and other pharmacologic reactions. The responses to such materials as desoxycorticosterone acetate, mercurial diuretic, sodium chloride and water intake, betahypophamine, and ammonium chloride were studied. These substances definitely influenced the $C_{1/2}$, $U_{1/2}$, and $B_{1/2}$ of the subjects. In some instances these correlations were difficult to interpret, whereas in others they were easy. For example, in Subject No. 1, the $C_{1/2}$ and $U_{1/2}$ were influenced significantly by the sodium intake in the diet, a correlation made possible by allowing mainly dietary sodium to vary (Figs. 1, *B* and 3, *B*). When the subject was on a low sodium chloride diet (1.7 Gm. of available NaCl), $C_{1/2}$ and $U_{1/2}$ were definitely longer than during the interval when he was receiving relatively large quantities of sodium (13.7 Gm. of available NaCl). For example, initially while on a low sodium intake, $C_{1/2}$ and $U_{1/2}$ values were twenty-five and one hundred days respectively; on high sodium intake they were reduced to eight and nineteen days, and when a low sodium intake was resumed, the $C_{1/2}$ and $U_{1/2}$ values lengthened to eighteen and two hundred and fifty days respectively. The correlations were impressive and, of course, predictable. Most subjects, however, failed to show a definite relationship between $C_{1/2}$ and $U_{1/2}$ and sodium intake (Fig. 5). This failure is related to other factors, such as drugs, water intake, and the like, which influence $C_{1/2}$ and $U_{1/2}$.

Another obvious factor of importance to consider when measuring the $C_{1/2}$ and $B_{1/2}$ in edematous subjects is that concerned with the mechanical removal of fluids from various compartments of the body. For example, if large quantities of ascitic fluid or pleural fluid are removed from a subject at equilibrium and containing Na^{22}, $B_{1/2}$ will be changed without changing $C_{1/2}$. This factor may become significant in a subject who is receiving repeated paracenteses. Proper considerations can be made for such factors.

Extremely edematous subjects who rapidly improve may excrete sodium at a rate considerably greater than that observed in the normal subject under the same therapeutic regimen. This phenomenon was noted for Subject No. 7, who had severe chronic congestive heart failure with anasarca. Diuresis was intense and prolonged, and during this period the $C_{1/2}$ and $U_{1/2}$ were six and twenty-two days respectively. The $C_{1/2}$ was shorter than that observed for the control subjects, even when sodium intake was high. Obviously, the subject was excreting the fluid of edema and Na^{22} at a rapid rate, with the Na^{22} elimination out of proportion to the water. This resulted in a relatively short $C_{1/2}$. At the same time the $B_{1/2}$ period would have to be short.

The results demonstrate reduction of sodium excretion in patients with chronic congestive heart failure and chronic glomerulonephritis of the nephrotic type. The mean $C_{1/2}$ periods were several times longer for these diseased sub-

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jects than for the controls. There were periods of improvement, however, for patients with congestive heart failure when $C_{1/2}$ and $U_{1/2}$ were shortened. These observations indicate the importance of considering the abnormal state in calculation of safety doses of radiosodium. It is essential that such variations of $B_{1/2}$ be known for any type of radioelement.

It is relatively easy to determine $C_{1/2}$ and $U_{1/2}$ for a radioelement, whereas for a labeled compound or even a simple molecule it is much more difficult. The labeling isotope is being "turned over" in the molecule of the labeled substance, and the substance itself is always in the process of breakdown and partial or complete resynthesis. Sometimes it is even possible to label complex structures to trace their $B_{1/2}$, a parameter difficult to evaluate even for elements. This is well exemplified by the measurement of the $B_{1/2}$ period of erythrocytes with N^{15}.[3] Fe^{59} is not as satisfactory as N^{15}, and P^{32} is even less satisfactory as a tracer isotope because it does not remain within the erythrocytes throughout their life. Proper consideration must be given such problems in determination of the $C_{1/2}$, $U_{1/2}$, or $B_{1/2}$ periods.

SUMMARY

Rates of elimination of sodium were studied with Na^{22} as a tracer in normal man and in man suffering from chronic congestive heart failure or from chronic glomerulonephritis of the nephrotic type.

Because of the nature of the experiments, the true biologic half-life period ($B_{1/2}$) was not measured directly. Instead, the time necessary to reduce the serum concentration to one-half the initial level after the establishment of equilibrium ($C_{1/2}$) and the time required to eliminate one-half the injected Na^{22} in the urine ($U_{1/2}$) were determined. $C_{1/2}$ values obtained were usually less than the $U_{1/2}$ ones. $C_{1/2}$ in the control subjects most probably was equal to $B_{1/2}$, but this was not likely to be true for the abnormal subjects. $C_{1/2}$ and $U_{1/2}$ varied considerably with normal physiologic phenomena and with such abnormal states as congestive heart failure, nephrosis, and with administration of drugs, and sodium and water intake. For example, a diet low in salt appeared to lengthen the time of $C_{1/2}$ and $U_{1/2}$, whereas a diet high in salt was shown to shorten them.

$C_{1/2}$ was increased about threefold in patients with chronic congestive heart failure and about fivefold in the presence of the nephrotic syndrome. $U_{1/2}$ was increased to an even greater extent by these diseases and was influenced by the progress of the process. When the diseases were aggravated and fluid of edema was accumulating, the influence of dilution modified the $C_{1/2}$.

The importance of these observations and the relative general significance of $B_{1/2}$, $C_{1/2}$, and $U_{1/2}$ periods in the biologic application of radioelements, particularly radiosodium, have been discussed.

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