THEORETIC AND EXPERIMENTAL CONSIDERATIONS OF BIOLOGIC DECAY PERIODS: STUDIES IN MAN WITH THE USE OF Na^{22} [1]

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The rates of turnover of isotopes in organisms or isolated compartments of organisms are of considerable interest to general and human biologists. For obvious reasons, most studies of biologic decay of tracer materials have been conducted in small organisms or experimental animals. Through the kindness of Drs. A. L. Hughes and Martin Kamen of Washington University and Drs. M. Tuve and Dean Cowie of the Carnegie Institution in Washington, Na^{22} was obtained for certain experiments in man. Because of its long physical half-life (3 years), Na^{22} is the only isotope of sodium suitable for tracer studies which require relatively long periods of time. Although these studies were not designed primarily for observation of biologic decay periods in man, the data were suitable for analyses concerned with such problems both in normal man and in patients with chronic congestive heart failure or with the nephrotic syndrome of chronic glomerulonephritis. The rates of biologic decay were influenced by drugs and dietary factors studied in these experiments. Theoretic considerations, which are of some interest in tracer principles in general, were applied. It is the purpose of this presentation to summarize these data, which will be reported in more detail elsewhere (Burch, Threefoot and Reaser, 1948; Threefoot, Burch and Reaser, 1949; and Burch, Threefoot and Cronvich, 1949).

Materials and Methods

Twelve subjects were observed continuously for periods varying from 20 to 70 days. Four of these were normal, six had chronic congestive heart failure (2 slowly improving, 2 rapidly improving and 2 slowly becoming worse) and two had the nephrotic syndrome of chronic glomerulonephritis (see Table 1 for details).

Na^{22}, as NaCl in approximately 2 cc. of water, was administered intravenously to each subject. Doses of Na^{22} with an activity such that there were 17.7×10^6 disintegrations per minute (about 0.09 mc.) were administered to seven of the subjects, 12.5×10^6 (about 0.06 mc.) to three subjects, and 1×10^7 (about 0.05 mc.) to the other two subjects. The dosage was reduced as more sensitive counting equipment became available.

The urine was collected separately at each voiding, and at least daily blood samples were taken. The volume and radioactive count of each sample of urine were recorded so that the total elimination of radiosodium could be determined. Radioactive counts of blood serum were followed as an index of the concentration of radiosodium in the extracellular fluid.

Table 1. Clinical Data

Subject No.	Age in years	Sex	Wt., initial, in lbs.	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 25–30% normal; slowly improving
12	28	F	285.75	Renal function 25–30% normal

The aliquots of serum and urine were delivered as free falling drops from a calibrated micropipette to the surface of discs of filter paper. When dry, the paper discs were cemented to metal discs so that the quantity and geometric characteristics of each sample remained constant. The preparations were counted for five minutes, and the necessary corrections for background were made. Data were recorded as counts per minute per cubic centimeter of

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fluid. For purposes of comparison, all counts were corrected to correspond to an injection of 17.7×10^6 disintegrations per minute for each subject.

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

$$\%N_t = \left(1 - \frac{\sum_{s=1}^{t} k_s}{N_0}\right) \times 100,$$

where

N_0 = injected Na^{22}, in counts per minute,

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

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

Weights and fluid intake and output were recorded daily. The sodium intake was varied in some instances from *low* (1.7 gm. NaCl/day), to *regular* (8 gm. NaCl/day), to *high* (13.7 gm. NaCl/day), and the effect on the rate of excretion of radiosodium was noted. A mercurial diuretic[4] and other drugs frequently employed in the clinical management of congestive heart failure exerted some influence on the rate of excretion of the radiosodium in all subjects.

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

Subject No.	$C_{\frac{1}{2}}$	$U_{\frac{1}{2}}$	Days of continuous observation	Weight change, in lbs.
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

RESULTS

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

1. In the *control* subjects, who had no cardiovascular disease or edema, the serum concentration of Na^{22} decreased to half the initial level in an average of 13.3 days (Table 2 and Fig. 1). The rate of elimination of the isotope in the urine was such that one-half the Na^{22} administered would have been excreted in an average of 28.8 days. Normal subject No. 1 demonstrated the influence that intake of sodium chloride has upon the rate of elimination of Na^{22} (Fig. 1B); increase of the daily intake of NaCl from 1.7 gm. to 13.7 gm. resulted in a threefold increase in rate of decline of serum concentration of Na^{22}. Similar response was noted for rates of elimination in the urine (Fig. 3B).

2. The patients with *chronic congestive heart failure* responded differently from the controls, and their response was related in part to the state of failure.

(a) In two patients who were *slowly recovering* from heart failure, 40 and 42 days respectively were required for the serum concentration of Na^{22} to reach half the initial level (Table 2 and Fig. 2A)—approximately one-third the rate of the control subjects. The Na^{22} was excreted in the urine at a rate such that 60 and 72 days respectively would have been required for elimination of one-half the administered isotope (Table 2 and Fig. 3C)—essentially one-half the rate of the control subjects.

(b) The two patients who were *rapidly improving* required 13 and 28 days respectively for the serum concentration of Na^{22} to reach one-half the initial level (Table 2 and Fig. 2B). During the first few days of observation the rate of decrease in serum concentration of the isotope was relatively slow, but when recovery from the failure once began, the drop was rapid, and became more rapid in one patient than that observed in the control subjects. Rates of urinary excretion tended to parallel changes in concentration in the serum (Fig. 2B and 3D). These two patients eliminated Na^{22} more rapidly than the two who improved slowly.

(c) In two patients who *slowly became worse* there was a reduction of the serum concentration to one-half the initial level in an average of 24 and 30 days respectively (Table 2 and Fig. 2C). The mean rate of loss of Na^{22} in the urine was such that one-half the administered radiosodium would have been

[4] Mercuhydrin (sodium salt of methoxyoximercuripropylsuccinylurea with theophylline) furnished by courtesy of Lakeside Laboratories, Milwaukee.

excreted in 60 days (Table 2 and Fig. 3E). These patients required a longer period of time to excrete the Na^{22} than did the subjects discussed previously.

3. The two patients with the *nephrotic syndrome of chronic glomerulonephritis* had the slowest rates of Na^{22} excretion. Decrease in the serum concentration of Na^{22} was such that an average of 56 days would have been required to reach one-half the initial level (Table 2 and Fig. 2D). The rate of urinary excretion was also extremely slow in both patients; an average of 513 days would have been necessary to eliminate one-half the Na^{22} administered (Table 2 and Fig. 3F).

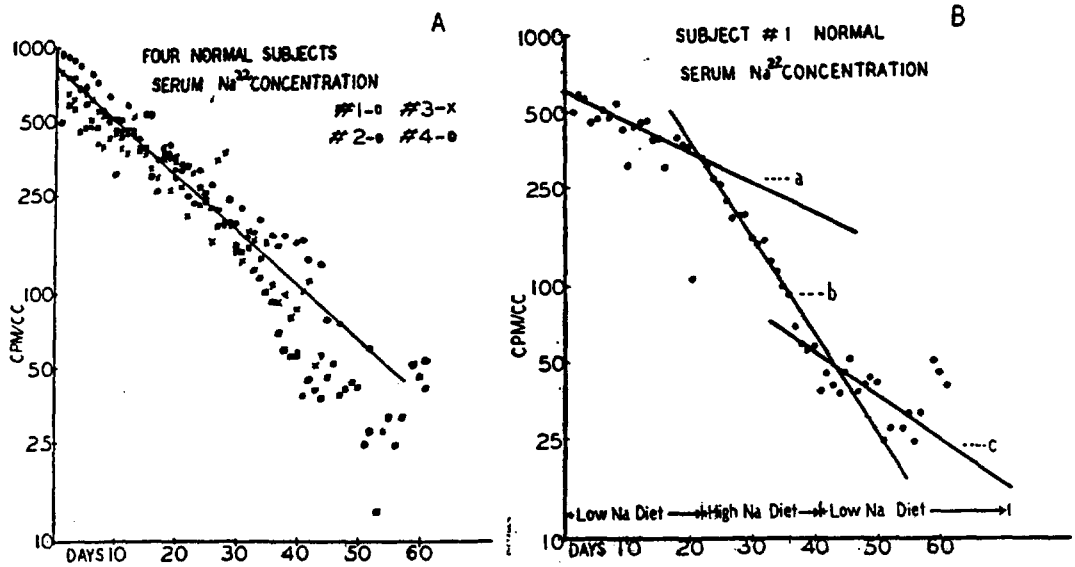

FIG. 1. Semilogarithmic graphs of relation of changes in serum concentration of Na^{22} (counts per minute per cubic centimeter) to time.

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* shows a change in rate of fall in serum concentration of Na^{22} with variations in sodium content of the diet, i.e. 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 25 days. At rate *b*, with a high sodium diet, half serum concentration was reached in 8 days, and at rate *c*, when a low sodium diet was resumed, half-concentration was reached in 18 days.

COMMENT

Morgan (1947) suggested the symbol "Te" for "the body elimination half-life"; this term might be satisfactory if the time required to eliminate one-half the radioactive material administered could be determined without too much difficulty. Unfortunately, this is not always easily accomplished in man, especially for sodium. Results showed considerable variations in man, influenced especially by disease, drugs, diet, previous physiologic state and many other factors. It is therefore possible to determine only approximately the time required to eliminate one-half the administered isotope. Because values obtained for sodium differed from those found for the urine, it was necessary to introduce new terms:

$B_{1/2}$ = *biologic half-life,* the time required to eliminate one-half the administered tracer substance from the body. This corresponds to the "Te" value of Morgan (1947).

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

$U_{1/2}$ = *urinary elimination one-half,* the time required to eliminate in the urine one-half of the tracer substance administered.

From the point of view of calculating safe dosages (Morgan, 1947), it is the $C_{1/2}$ that is important. However, $C_{1/2}$ measurements may not indicate rates of turnover or elimination from the body if the compartment for the tracer changes in size. Moreover, $C_{1/2}$ and $U_{1/2}$ will differ, since they are usually concerned with physiologic phenomena which are similar only under certain conditions. This problem will be discussed more fully later.

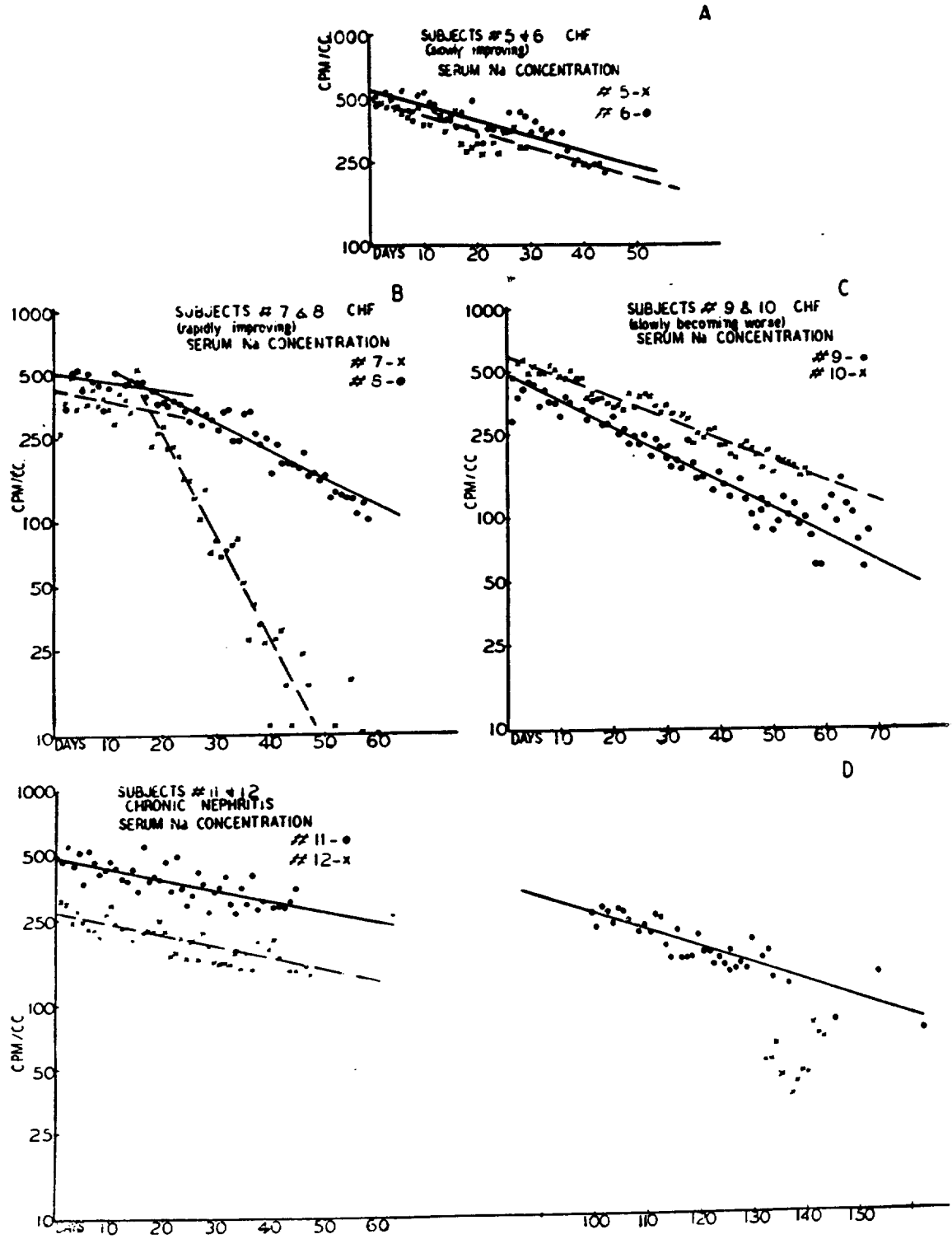

FIG. 2. Semilogarithmic graphs of changes in serum concentration of Na^{22} (counts per minute per cubic centimeter) as a function of the time for 6 patients with congestive heart failure and for 2 patients with the nephrotic syndrome of chronic glomerulonephritis.

A. *Two patients with congestive heart failure who were slowly improving. Patient No. 5* showed a mean rate of fall in serum concentration of Na^{22} such that half-concentration was reached in 40 days ($C_{1/2}$). For *Patient No. 6,* 42 days were

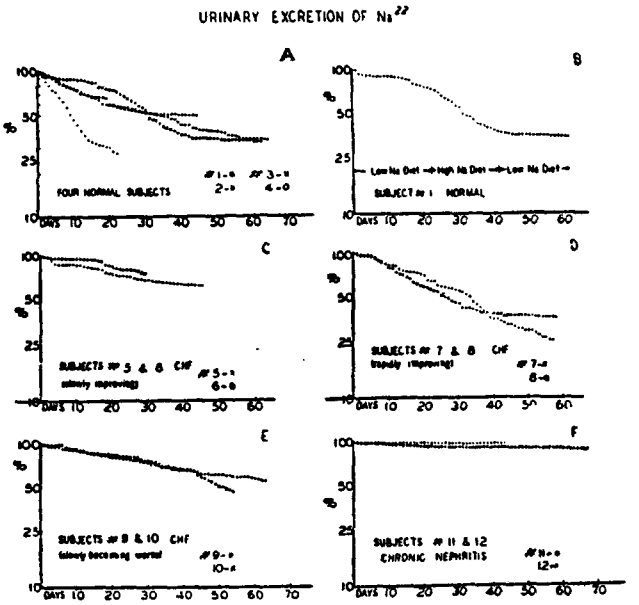

FIG. 3. Semilogarithmic graphs for all subjects showing the urinary excretion of Na^{22} (percentage of injected Na^{22} which was not eliminated by the urine). This value was obtained from the total counts of Na^{22} excreted daily through the urine. That for the first day was subtracted from the total 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 remained within the body plus that which was excreted by some other route, i.e., that Na^{22} which had 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, 28.8 days (mean value, $U_{1/2}$) would be required for the injected radiosodium to be excreted.

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 22 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 100 days ($U_{1/2}$). For the next 19 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 19 days. For the last 19 days of observation during a low sodium diet and administration of antidiuretics, the rate 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 30 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 2 patients being 66 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 be noted as in the other subjects. The mean time necessary for excretion of one-half the injected sodium through the urine was 60 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.

THEORETIC CONSIDERATIONS

More careful consideration of the $C_{1/2}$ data presented reveals the numerous difficulties which arise when an attempt is made to compare the values for the control subjects with those for the edematous patients. Certain factors are worthy of discussion. For example, the excretion of an isotope is related to the following phenomena:

1. There is daily reduction in concentration and/or total amount of the isotope within the body because of continuous excretion. Experimental results indicate that excretion is exponential in character.

2. Change in concentration of the tracer material results whenever the volume of the compartment of the tracer varies.

LEGEND FOR FIGURE 2—*continued*

required. 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 18 days, was such that half-concentration would have been reached in 6 days. *Patient No. 8* also showed two distinct rates of fall; the first, present for 18 days, was such that half-concentration would have been reached in 71 days, whereas with the second rate 24 days would have been necessary.

C. *Two patients with congestive heart failure who were slowly becoming worse.* For *Patient No. 9* the mean rate of fall in serum concentration of Na^{22} was such that half-concentration was reached in 24 days ($C_{1/2}$), and for *Patient No. 10* in 30 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 concentration of Na^{22} so that half-concentration would have been reached in 58 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 37 days, and *Patient No. 12* required 54 days.

3. Daily intake and elimination of the non-tracer form of the substance affects the behavior of the tracer form.

Although many other factors are concerned with the elimination of the tracer, only the foregoing three will be discussed since they deserve constant attention during experimentation. Any one of these may alter appreciably the concentration and rate of elimination of the tracer substance independent of the physicochemical process under observation.

It is advisable to define certain terms employed.

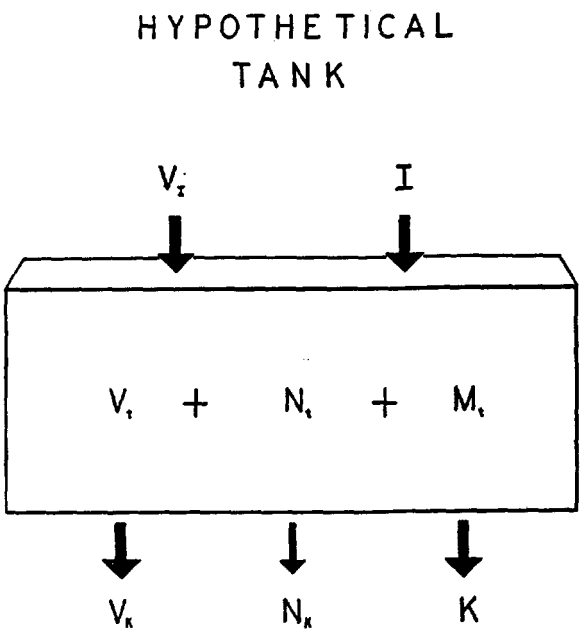

FIG. 4. Diagram of a "tank" or compartment containing Na^{23} in water in which the concentration of Na^{23} remains constant. Na^{24} as a tracer substance is added at an instant to "label" the Na^{23}. The Na^{23} and Na^{24} are always thoroughly mixed. To this tank more Na^{23} and water are being added continuously while Na^{23}, Na^{24} and water are constantly being removed. The problem is to determine the change in total quantity and concentration of the Na^{24} (the tracer substance) within the tank for various rates of intake and output of Na^{23} (the non-tracer substance). Man, or any organism or portion of an organism, may be compared to the tank. See text for details.

Elimination denotes any movement of the substance being studied from the compartment under observation.

Intake refers to any addition of the non-tracer substance to the compartment under study.

Volume of the compartment indicates the volume or space of that portion of the organism under study with the tracer. It is much more satisfactory to include in a compartment that portion of the organism which is physiologically (physically and chemically) homogenous. When a tracer, such as sodium, has several compartments with different rates of turnover, the problem becomes complex, especially if there are sudden changes.

With the use of these three terms, it is possible to apply the ideas presented hereafter to the organism as a whole or to any portion of the organism, even as small as a chromosome or gene.

The *problem* under consideration can best be approached through the aid of Fig. 4, which represents a tank. At time t this tank contains a compartment with a volume V_t, into which is dispersed a substance M_t, in solution or other state, to be observed. To this tank there is continuously being added more of the material which constitutes the dispersing compartment or medium, V_t, as well as more of the substance to be observed, I. Simultaneously, a certain amount of the dispersing medium V_K, and a certain amount of the substance under observation, K, are being removed continuously from the tank. If it is desired to trace this substance within the tank, then at a time $t = 0$ the known quantity of the tracer form, N, should be added to the tank. It is important to note that only a single addition of the tracer substance is made at one instant and that it rapidly becomes thoroughly mixed with the non-tracer.

1. If CN, the concentration of the tracer substance, is being observed in order to gain quantitative and/or qualitative information concerning the tracer substance, N, and the non-tracer form, M, then:
   (a) CN changes if there is escape of N from the tank and V does not change proportionally.
   (b) CN changes if N_K (the excretion rate of N) is zero, but V changes.
   (c) CN is dependent upon the relative variations in N_K and V. V, of course, depends upon the relative variations in V_I and V_K.

2. The total quantity of N within the tank at any given time varies with the rate of discharge of N from the tank.

3. The tank may be compared with any living organism such as man. Under biologic conditions further restrictions, such as isotonicity, must be imposed. For example, if the osmotic force of M within V is constant, then the variations in concentration of N and M and in the quantity of N, M and V will be determined by the relative intake and elimination of M and V.

When an analogy *between the tank and an organism* or any part of an organism is drawn, it is necessary to consider such factors as state of equilibrium, homogeneity of the compartment and substances under study, functional disturbances related to the problem and physiologic, physical and chemical peculiarities inherent in the substance being traced and in the compartment in which it resides. These and other matters will become evident as the discussion progresses.

It is possible to compare man with the tank in which M is sodium (Na^{23}), V is the sodium com-

partment, N is the tracer sodium (Na^{22}), I is the daily intake of Na^{23} in the diet, V_I is the daily intake of water, K, N_K and V_K are respectively the amounts of Na^{23}, Na^{22} and water eliminated daily. Isotonicity of the solution of M (Na^{23}) must be maintained. Therefore, CN (concentration of Na^{22} in the tank) will vary with the relative intake and output of V and, of course, with the relative values of I and K. In general, it is possible to disregard the mechanisms of metabolic processes within a compartment concerned with the sodium turnover when the compartment as a whole is considered.

For a more thorough understanding of the quantitative and qualitative nature of some of the important factors, unrelated to purely metabolic processes, which influence concentrations and total quantity of the tracer substance, certain interesting and essential equations were derived.

Mathematical Considerations

Another publication (Burch, Threefoot and Cronvich, 1949) contains a detailed discussion of the mathematical considerations. If a whole organism is considered as a tank, the mathematical theories outlined below will hold, regardless of the complex metabolic processes within the organism.

The equations may be applied to any types of tracer studies which satisfy the conditions imposed by the following essential assumptions. That these assumptions are reasonable is shown by the agreement of the theoretic and experimental data compared later in the presentation.

1. Tracer and non-tracer substances are uniformly mixed in the organism and are affected similarly by chemical and physical processes in the organism.
2. All of the tracer substance is added at time $t = 0$ and is rapidly mixed completely with the non-tracer substance.
3. Intake and discharge are continuous processes.
4. The changes in the quantity of the non-tracer substance and in the volume of its compartment vary exponentially. This is a physiologic variation which has been observed in our studies.
5. The solution of certain non-tracer substances, such as sodium, is assumed to be isotonic.

Three conditions were then analyzed (Burch, Threefoot and Cronvich, 1949). The equations for each are as follows:

Symbols

M_t = time
t = quantity of non-tracer substance in organism at time t
M_o = quantity of non-tracer substance in organism initially
I = quantity of non-tracer substance taken into organism per unit time
G = net quantity of non-tracer substance gained by organism per unit time (negative G = loss)
K = quantity of non-tracer substance eliminated from organism per unit time
D = total amount of non-tracer substance when quantity in organism is increasing
a = fraction of non-tracer substance in organism eliminated from organism at any time t—an expression of the rate of elimination
α = fraction of difference between maximum of the non-tracer substance to be reached and amount present at time t—an expression of the rate of accumulation
N_t = quantity of tracer substance in organism at time t
N_o = quantity of tracer substance in organism initially
V_t = volume of compartment under study at time t
V_o = initial volume of compartment under study
CM = concentration of non-tracer substance in organism
CN_t = concentration of tracer substance in organism at time t
CN_o = concentration of tracer substance in organism initially

Condition 1: Where G is negative or organism or tank is in a negative balance for Na^{23}

$$N_t = N_0 \mathcal{E}^{I(1-e^{\alpha t})/\alpha M_0} \mathcal{E}^{-at} \tag{1}$$

$$CN_t = CN_0 \mathcal{E}^{I(1-e^{\alpha t})/\alpha M_0}. \tag{2}$$

Condition 2: Where G is positive or organism or tank is in a positive balance for Na^{23}.

$$N_t = N_0[M_0^{-1+I/(M_0+D)\alpha}] \cdot [M_0+D(1-\mathcal{E}^{-\alpha t})]^{1-I/(M_0+D)\alpha} \cdot \mathcal{E}^{-It/M_0+D)} \tag{3}$$

$$CN_t = CN_0[M_0^{I/(M_0+D)\alpha}] \cdot [M_0+D(1-\mathcal{E}^{-\alpha t})]^{-I/(M_0+D)\alpha} \cdot \mathcal{E}^{-It/(M_0+D)} \tag{4}$$

Condition 3: Where $G=0$, or the intake of non-tracer substance is equal to the output for Na^{23}.

$$N_t = N_0 \mathcal{E}^{-It/M_0} \tag{5}$$

$$CN_t = CN_0 \mathcal{E}^{-It/M_0} \tag{6}$$

Note: $\mathcal{E}$ = Base of natural log.

The equations were applied to certain theoretic but clinically compatible situations concerned with the study of sodium following a single injection of Na^{22} in man with and without chronic congestive heart failure and generalized edema.

Application 1.—A man with generalized edema such that his total Na^{23} mass is 121.4 grams and ex-

tracellular fluid 34,000 grams, his edema is progressively disappearing, and he finally reaches the sodium (Na^{23}) and extracellular fluid mass for a 70 kilogram man (50 and 14,000 grams respectively).

For a better understanding of the influence of the rates of intake and output of the non-tracer upon the concentration and total content of the tracer, the rate of intake of the non-tracer substance and the rate with which the subject became edema-free were varied. Fig. 5 shows the theoretic progressive

large total elimination of Na^{22}. This is to be expected, since water is being lost simultaneously at a rate which maintains isotonicity of the Na^{23}.

(b) Differences in the rates of elimination of Na^{23} from the subject are accompanied by less change in the concentration of the Na^{22} in the extracellular fluid than in total quantity of Na^{22} present within those fluids. Similarly, this is reasonable because water is being eliminated with the Na^{23} to maintain isotonicity.

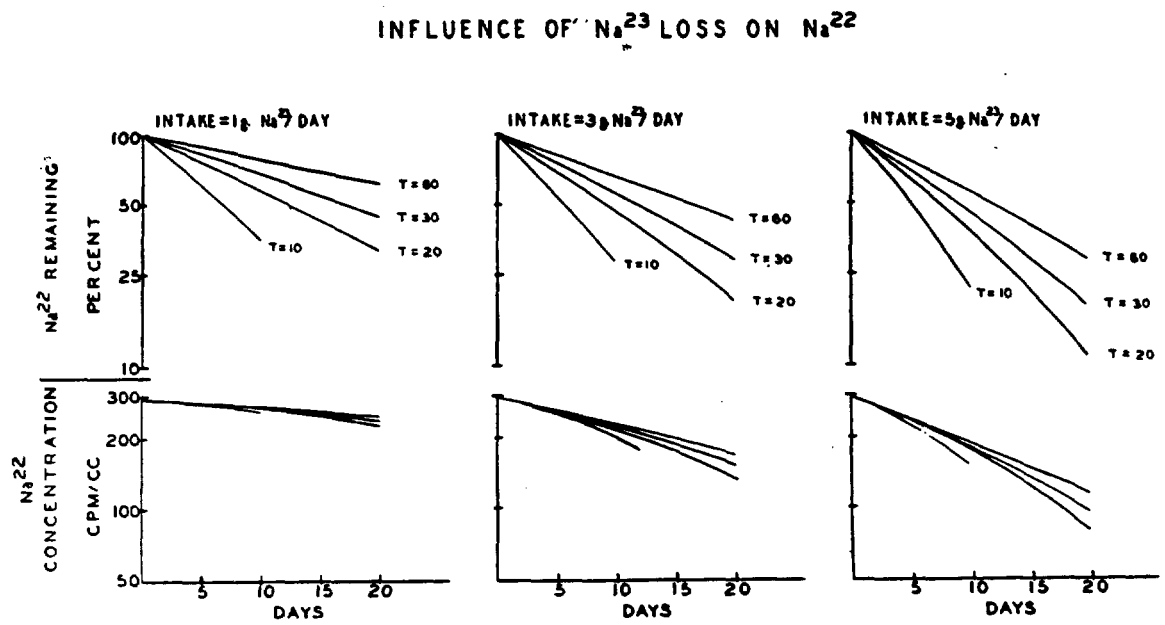

FIG. 5. Semilogarithmic graph showing the influence of the net loss of Na^{23} and the Na^{22} content of the "body" after administration of a single dose of the tracer. The influence of the rate of Na^{23} intake upon the Na^{22} is indicated. "T" denotes the time in days required for an *edematous individual* with a total of 121.4 grams of Na^{23} in the body to become edema-free and for the Na^{23} content to be reduced to 50 grams. The upper family of curves shows the time variations in the percentage of the initial Na^{23} remaining in the body, and the lower family of curves indicates the time variations in concentration of the Na^{23}. The T values follow the same order for the lower family of curves as indicated for the upper ones. For the curve showing rapid rate of Na^{23} loss or rapid rate of elimination of edema (T = 10 days), the patient reached the edema-free state in 10 days and the curve therefore does not extend as far on the abscissa as those for the other rates. It is interesting to note that the curves are *not straight lines*. For convenience the other curves were not continued beyond 20 days; if they were extended until the subject became edema-free, the amount of Na^{23} remaining in the body would be progressively less as the value of T increased.

change in total content and concentration in the extracellular fluid of Na^{22}, the tracer, for rates of excretion which would make the subject free of edema in 10, 20, 30 and 60 days when the daily intake of the non-tracer (Na^{23}) was 1, 3 or 5 grams.

This figure shows:

(a) When the intake of Na^{23} remains constant, its rate of elimination so influences the Na^{22} in the extracellular fluid that determination of the concentration of Na^{22} in the blood serum alone cannot serve as an index of the amount of Na^{22} still remaining in the body; a small decrease in the concentration of Na^{22} is associated with a relatively

(c) The rate of intake of Na^{23} has a greater influence upon the change in concentration of Na^{22} in the extracellular fluid than does the rate of elimination of the edema (Fig. 6). A greater intake of Na^{23} results in a more rapid rate of elimination of Na^{22} as well as in a sharper rate of decline in concentration of Na^{22} in the extracellular fluids. This effect of Na^{23} intake upon Na^{22} must exist, because the rate of elimination of the former must increase in order to produce the edema-free state at the given time. Since the movement of Na^{22} is determined by the movement of Na^{23}, then a greater intake with resulting increased elimination of Na^{23},

effects an increased rate of elimination of Na^{22}.

(d) Elimination of Na^{22} under the circumstances described is not a simple exponential phenomenon.

(e) It is evident from the equations and from Fig. 5 and Fig. 6 that when a subject is losing edema, the rate of excretion of Na^{23} greatly influences the Na^{22} content of the body, since the volume of the extracellular fluid decreases at a rate which insures isotonicity. The rate of intake of Na^{23} is important because of its effect upon its own rate of elimination.

(f) When a subject is progressively excreting the non-tracer substance under the conditions defined, the rate of change in *total amount* of the tracer substance retained is greater than the rate of change in *concentration* of the tracer. This is true because the volume of the compartment of the tracer and non-tracer substances is diminishing progressively as the Na^{22} is being eliminated.

(g) The concentration of Na^{23} in the extracellular fluids is constant, a necessary condition since isotonicity is essential for life. Concentration of Na^{22}, however, is not constant, because Na^{22} is

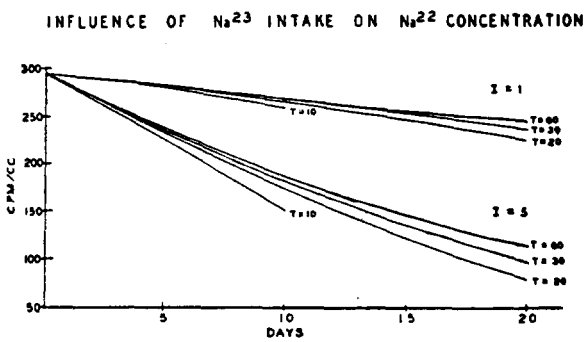

FIG. 6. The concentration curves of Fig. 5 drawn on ordinary cartesian coordinate paper for the intakes of 1 gram and 5 grams daily respectively. Note the greater change in concentration when the intake of Na^{23} is increased.

gradually being eliminated from the body without any associated continuous addition.

Application 2.—A man free of edema and weighing 70 kilograms, whose total sodium (Na^{23}) and extracellular fluid masses are 50 and 14,000 grams respectively and in whom edema is progressively developing until his sodium and extracellular fluid masses reach 121.4 and 34,000 grams respectively.

Figure 7 summarizes the theoretic changes in concentration and total content of the tracer (Na^{22}) in the extracellular fluids as influenced by various rates of development of the edematous state and by rates of intake of the non-tracer (Na^{23}). The calculations from which these curves were drawn yielded the following facts:

(a) A subject cannot acquire edema and accumulate sodium at a rate faster than the intake, except where special consideration must be given to storage depots and local shifts.

(b) When Na^{23} is being accumulated during progressive formation of edema, the rate of decrease in concentration of Na^{22} exceeds the rate of change in total content of the tracer within the body. This is to be expected, since the concentration of Na^{22}

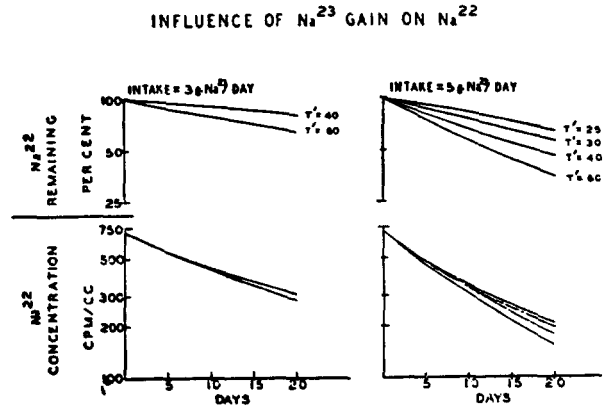

FIG. 7. Semilogarithmic graph showing the influence of the *net gain* of Na^{23} on the Na^{22} content of the "body" after administration of a single dose of the tracer. The influence of the rate of Na^{23} intake upon the Na^{22} is indicated. T′ denotes the time in days required for the total sodium of a *non-edematous* individual to increase from 50 grams to 121.4 grams, when an arbitrary maximum of edema is reached. The labeling scheme is the same as in Fig. 5. Each curve is not a straight line, for obvious reasons. Values of T′ smaller than those shown could not be analyzed under the conditions of the calculations (see text). Note the inverse relationship in the order on the ordinate positions of the curves for the respective T and T′ values of this figure and that of Fig. 5.

is being reduced because of *two* factors acting simultaneously:

(1) Accumulation of the fluid of edema, which produces a dilution of the Na^{22} and

(2) Continuous elimination of Na^{22}.

Reduction in the total content of Na^{22} within the body results from excretion only.

(c) Intake of Na^{23}, and of course its output, has a greater influence on the concentration and total content of Na^{22} within the body than does the rate of development of the edema.

Application 3.—A man whose electrolyte and water balances are stationary.

In this situation, in which the quantity of Na^{23} in the body remains constant and in which the extracellular fluid remains isotonic, the rate of elimination of Na^{23} becomes all important. The rate of intake exerts its influence upon excretion; when G is equal to zero, then intake and output must be equal.

Results of the calculations, shown in Fig. 8, indicate that:

(a) The greater the elimination and of course the intake of Na^{23}, the greater the rate of elimination of Na^{22}. This is tenable because the movement of the non-tracer substance governs the movement of the tracer.

(b) When G is equal to zero, the influence of intake and output on the concentration of the tracer is identical with that in the total content.

(c) When G is equal to zero and the tracer substance is not fixed in the organism in any manner, $B_{1/2}$ and $C_{1/2}$ are equal. These parameters are equal to $U_{1/2}$ if the elimination is entirely in the urine.

(d) When G is equal to zero, the decay curves for concentration and for total quantity of the tracer remaining in the organism are simple exponential curves which are straight parallel lines when plotted on semilogarithmic paper.

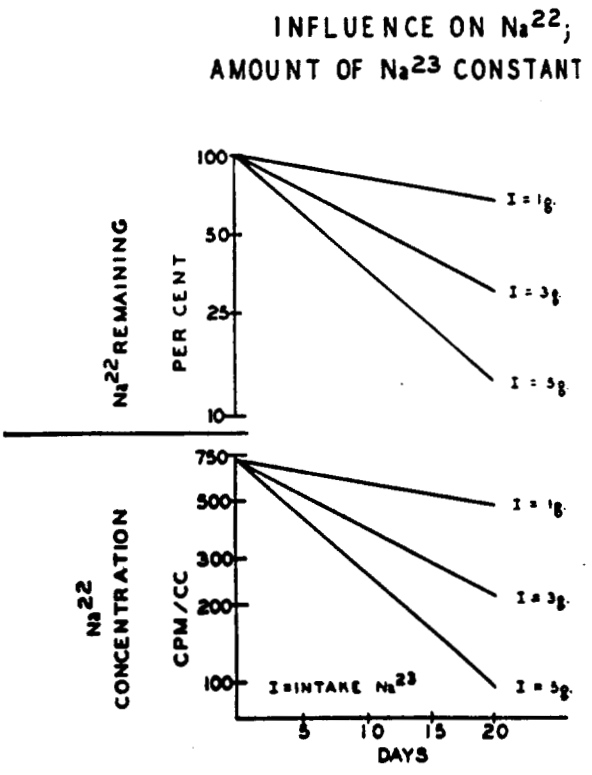

FIG. 8. Semilogarithmic graph showing the influence of *no change in the total* Na^{23} upon the Na^{22} content of the "body" after administration of a single dose of the tracer. Although the total amount of Na^{23} does not change, Na^{23} is being taken into the body and also being eliminated at rates of 1, 3 and 5 grams daily. These curves are all *straight lines*, for obvious reasons.

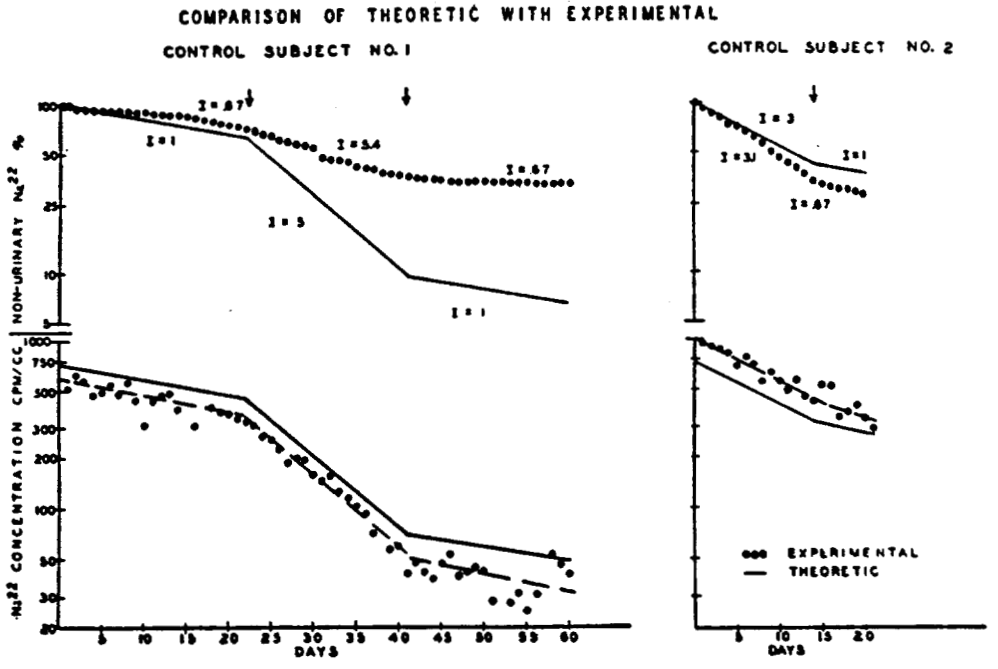

FIG. 9. Comparison of the theoretic curves of the concentration of Na^{22} and total content of Na^{23} in the body of a normal man with data obtained experimentally in 2 normal subjects. The nonurinary Na^{22} is that not excreted in the urine and is represented as percentage of total Na^{22} injected intravenously into the subject at a single dose. For the theoretic curve it represents the percentage of the total Na^{22} which is not excreted and therefore remains within the body. Values for intake of Na^{23} selected for the theoretic curves were those which approximated the dietary intake in the subjects studied. The theoretic and experimental curves agree: discrepancies between the nonurinary Na^{22} curves are due to failure to collect all excretion from the subjects studied experimentally. The experiments were designed for urinary collections alone.

General Discussion

The theoretic data presented indicate the complexities incident to an attempt to study rates of turnover from observations on the concentration within a compartment. This is particularly true in diseased states. For example, the changing size of the compartment for sodium in the subjects with generalized edema certainly makes it difficult to compare the rates of turnover in the normal subjects with those in the patients with congestive heart failure, if the serum concentration for Na^{22} is to be followed. When a patient is losing edema, $B_{1/2}$ would be smaller (the rate of elimination greater) than $C_{1/2}$ would suggest, whereas in a subject whose edema is increasing, $B_{1/2}$ would exceed that indicated by the change in serum concentration. When the state of the edema is constant or the size of the compartment is not changing, then $B_{1/2}$ could be obtained from the serum concentration, provided, of course, there were no shifts in the sodium among the various compartments. Therefore, caution should be employed whenever $C_{1/2}$ values are interpreted as evidence for $B_{1/2}$.

The great influence of the rates of intake and output of the non-tracer substance upon the elimination of the tracer substance renders necessary the consideration of diet, drugs and other measures which influence the movement of the non-tracer substance. Obviously, under most circumstances only an average $B_{1/2}$, $C_{1/2}$ or $U_{1/2}$ can be determined. In the case of sodium the custom of eating three meals will have its influence upon these parameters during the day. Such variations from absolute equilibrium and smoothness of intake may be inconsequential for most biologic purposes, but for others it can have considerable significance.

Measurements of various biologic decay rates are relatively simple for elements, but they become more difficult when molecules or more complex substances are being traced. In special circumstances, however, such as use of N^{15} to trace the life of the erythrocyte, the problem appears to be simplified by the complex structural and peculiar biologic nature of the erythrocyte. On the other hand, Fe^{59} and certainly P^{32} have metabolic characteristics which do not lend themselves as well to the tracing of the life of the human erythrocyte.

In spite of the many complex physicochemical processes and other problems involved in the metabolism of sodium, the experimental data obtained for the change in serum concentration of Na^{22} in normal man with varying intakes of sodium agree well with the theoretic calculations based on the equations presented previously (Fig. 9). Lack of agreement between $U_{1/2}$ and the theoretic $B_{1/2}$ is due to failure to measure directly all of the Na^{22} eliminated; only the Na^{22} excreted in the urine was determined. Experiments carefully designed for the quantitative measurement of the $B_{1/2}$ should be conducted.

Values of $C_{1/2}$ and $U_{1/2}$ obtained for the subjects with chronic congestive heart failure and with the nephrotic syndrome of chronic glomerulonephritis are significant biologically and must be interpreted cautiously when compared with those parameters determined in the normal subjects or when considered with respect to $B_{1/2}$ implications. The radiobiologic significance from the point of view of safety, public health precautions, and calculation of dosage is self-evident. The values also have biochemical and physiologic significance related to sodium metabolism, rate of sodium turnover, and the better understanding of states of generalized edema.

More extensive details of these studies, including the influence of drugs and certain procedures, will appear in papers to be published elsewhere.

Summary

Rates of elimination of sodium were studied with Na^{22} in normal man and in subjects with chronic congestive heart failure or with the nephrotic syndrome of chronic glomerulonephritis. Clinical phases of the diseases varied in these patients.

The nature of the experiments made it impossible to determine directly the true biologic half-life period ($B_{1/2}$) for sodium. It was necessary to introduce new terms for biologic decay periods, such as $C_{1/2}$ (the time required for the tracer to reach one-half the initial concentration in the compartment under study), $U_{1/2}$ (the time required to eliminate one-half of the tracer material by way of the urine) and $E_{1/2}$ (the time required to eliminate one-half of the tracer substance administered). The $C_{1/2}$ values were obviously less than the $U_{1/2}$ values. In the control subjects $C_{1/2}$ could not have differed appreciably from $B_{1/2}$, whereas in the diseased subjects these parameters were dissimilar.

$C_{1/2}$ for the subjects with congestive failure was about three times greater and for the subjects with the nephrotic syndrome about five times greater than that for the controls. $U_{1/2}$ was increased to a greater extent by these diseases; $C_{1/2}$ and $U_{1/2}$ varied with the state of the diseases, dietary intake of sodium, and administration of drugs. Direct comparisons of the $C_{1/2}$ values in the edematous subjects with those of the control cannot be made when the quantity of edema fluid is varying because of the influence of change in the volume of the compartment upon the concentration of the tracer.

Equations have been derived which make it possible to predict variations in concentration and total content of a tracer substance in a compartment for various rates of intake and output of the non-tracer substance and for variation in size of the tracer compartment. These theoretic considerations demonstrate the importance of considering the rate of intake of the non-tracer and variations in the volume of the tracer compartment when $C_{1/2}$ and

$B_{1/2}$ are being determined in biologic studies. Although the present investigations were chiefly concerned with sodium, the theoretic considerations are applicable to any type of tracer, organism, or compartment. The mathematical data may prove to be of value to others interested in this field of biologic research.

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Discussion

NOONAN: The data presented by Dr. Burch, showing the decreased rate of "turnover" of sodium in patients with congestive heart failure, are of great interest. Since increased "sodium space" and decreased urinary output of sodium both act to decrease sodium turnover, I should like to ask Dr. Burch if he has information concerning the relative importance of these two mechanisms involved in the slower replacement rate of body sodium in cardiac patients.

BURCH: These data do not indicate the relative importance of sodium space and renal function in the rate of turnover of sodium. As indicated in the paper, the studies, as planned, were not primarily directed at the many factors involved in sodium turnover, but merely indicate overall rates.