STRONTIUM AND ITS RELATION TO CALCIUM METABOLISM

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Research Article

STRONTIUM AND ITS RELATION TO CALCIUM METABOLISM *

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Interest in strontium and its relation to calcium metabolism dates back over 20 years. At that time, radioactive calcium (Ca^r) was relatively unavailable. It was thought that radioactive strontium (Sr^r), which was more readily available and which can be detected more simply, might serve as a substitute tracer for Ca^r. Early experiments (1–3) confirmed this notion in a general way, and several investigators (4–7) have subsequently proceeded on the assumption that Sr behaves like Ca in the body. Although the urinary excretions of Sr and Ca were found to differ, it has been assumed or demonstrated that as far as the skeleton is concerned, differences in the biological behavior of Ca and Sr are small and perhaps negligible (4, 8–15).

Intrinsic interest in Sr was heightened when it was found to be an important product of fallout resulting from the explosion of nuclear devices in the atmosphere. Protection against Sr fallout depends on adequate knowledge of the metabolism of this nuclide, and in the last decade, a large number of studies have been published that deal with various aspects of Sr metabolism (16).

Clinical interest in Sr developed when Shorr and Carter (17) proposed treating patients with postmenopausal osteoporosis by giving them Sr supplements in the diet (18). Sr rickets has been known since the early work of Lehnerdt (19, 20) and has been studied subsequently (21).

To use Sr as a tracer for Ca requires detailed knowledge of the metabolism of these elements. Knowledge of Ca metabolism has progressed considerably in recent years, so that a formal analysis of the metabolic behavior of this element

is now possible. This is not true for Sr for several reasons. Sr occurs in the body in only very small quantities, and its concentration in various tissues is known with only moderate precision (22). Analytical techniques for precisely analyzing small quantities of Sr have been developed only recently (5, 7, 23). In contrast with Ca studies, Sr concentration in kinetic studies with Sr^r has generally not been expressed in terms of specific activity (units of radioactivity per unit of mass), the only valid independent parameter. Rather, investigators have used various devices for expressing their results. These have generally fallen into four categories: *1)* units of radioactivity per tissue (e.g., percentage of dose in liver); *2)* units of radioactivity per unit of Ca (e.g., percentage of dose per milligram of Ca); *3)* units of radioactivity per liter of plasma or per liter of plasma cleared per unit time (e.g., percentage of dose per liter of plasma); and *4)* the observed ratio, i.e., (Sr^r/Ca^r) tissue/(Sr^r/Ca^r) source, a measure of the relative extraction or concentration of Sr with respect to Ca (24).

The theoretical and practical difficulties inherent in any one of these modes of expressing results are apparent and will be discussed. We allude to them here to point out that what would appear to be the most direct experimental approach to compare Ca and Sr metabolism, i.e., a parallel study of Ca^r and Sr^r metabolism in the same individual, is also beset by the problem of expressing the results in equivalent terms.

This paper presents an analysis of findings obtained in parallel experiments, i.e., studies in which Ca^{45} and Sr^{85} were injected intravenously into the same individual before and after treatment thought to affect Ca metabolism. It proposes a method of expressing results that is independent of the scheme of either Ca or Sr metabolism, but that allows a quantitative comparison of the metabolic behavior of these nuclides. It will be shown that Sr is not a tracer

for Ca in a given individual, whether the analysis is general or restricted to what happens in bone. It will also be shown that this lack of parallelism in an individual may not apply to groups of patients. A preliminary account of this work has been given (25).

METHODS

Experimental. The experimental approach and mode of analysis of Ca metabolism have been described in detail (26–28). In brief, a patient was admitted to the metabolic ward on an analytically verified intake of Ca. Ca output in urine and feces was measured throughout the period of study. After a period of adjustment, which was never less than 5 to 6 days, a kinetic study was initiated. Ca^{45} and Sr^{85} were injected intravenously at the same time, and their output in urine and feces was measured for several days thereafter. Some time after completion of this first phase, treatment was begun in some patients, and the kinetic study was repeated several weeks later.

Table I summarizes the clinical data and treatment, as well as certain of the parameters of the Ca metabolism of the eight patients studied. For the four young patients with scoliosis, all of whom had been studied first while ambulatory, treatment consisted of immobilization in a plaster cast equipped with turnbuckles. Treatment of the three adult women with osteoporosis was 0.5 mg diethylstilbestrol daily by mouth.

Ca analysis of urine and of ash solutions of stool and diet was performed by precipitation as the oxalate and titration with perchloratoceric acid (29). Ca^{45} analysis was performed by counting precipitates of Ca oxalate in an automatic flow counter (27, 29). Sr^{85} activity was measured in a scintillation well-counter connected to an automated sample-changing device. The patients received approximately 5 μc of either nuclide per kinetic study.[1]

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[1] Radioisotopes were purchased under license from the Oak Ridge Installation administered for the U. S. Atomic Energy Commission, Oak Ridge, Tenn. In the early studies, Sr^{85} was also purchased from the Nuclear Science and Engineering Corporation, Pittsburgh, Pa.

TABLE I

*Summary of clinical data and parameters of calcium metabolism**

Patient no.	Study no.	Age	Sex	Wt	Clinical diagnosis	Treatment	Ca pool	Ca intake	Fecal Ca output
		yrs		*kg*			*P mg*	*v_i mg/day*	*v_F mg/day*
3	B	17	M	76	Scoliosis and hyper-calciuria	None	6,098	1,159	862
	F					Immobilization, 9 mos	5,586	1,070	912
4	C	16	F	48	Scoliosis	None	4,566	961	826
	D					Immobilization, 2 wks	3,623	988	857
7	A	74	F	54	Osteo-porosis	None	3,086	791	707
	C					Estrogen, 2 wks	4,630	793	692
8	A	14	F	43	Scoliosis	None	3,968	786	483
	C					Immobilization, 6 wks	5,000	808	548
12	B	23	M	68	Scoliosis	None	4,785	1,461	1,229
	D					Immobilization, 3 wks	4,739	1,467	1,417
	F					Immobilization, 5 mos	5,780	1,221	1,028
13	A	65	F	66	Paget's disease	None	5,714	968	991
15	C	70	F	49	Osteo-porosis	Estrogen, 3 wks	2,565	557	516
20	B	58	F	59	Osteo-porosis(?)	None	2,165	344	349
	C					Estrogen, 3 wks	1,949	381	313

* All remaining parameters of the calcium metabolism of these patients may be calculated (26, 27) with the aid of P. v_i, v_F listed above and the rate constants shown in Table II.
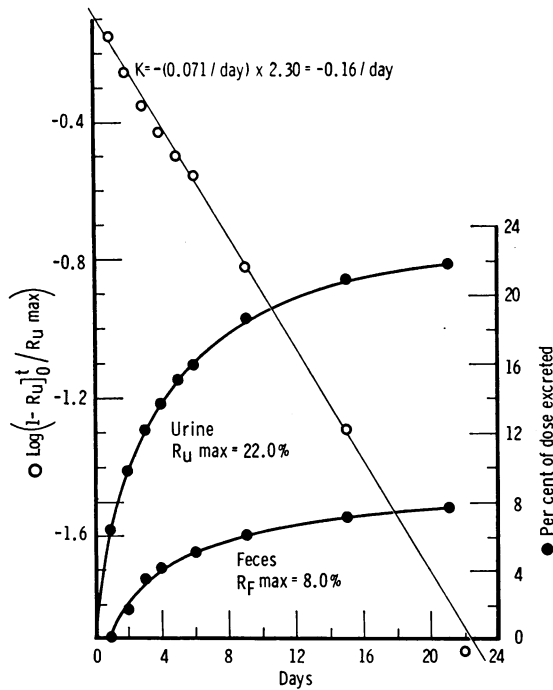
FIG. 1. CUMULATIVE EXCRETION OF Sr^{85} IN URINE AND FECES AND TIME–COURSE OF LOG $1 - (R_u]_0^t)/(R_{u_{max}})$ AFTER AN IV INJECTION OF Sr^{85} (Study 20B, Table II). $R_u]_0^t$ = cumulative radioactivity (percentage of injected dose) in urine. $R_{u_{max}}$ = maximal quantity (asymptote) excreted in urine. $R_{F_{max}}$ = maximal quantity (asymptote) excreted in feces.

Theoretical analysis. When high specific activity Sr^r is injected intravenously in human subjects, the time-course of the radioactivity in the blood between 0 and 7 days, expressed as counts per minute per milliliter of serum, can be described as a series of four exponential terms, the first three of which become negligible after 1 to 2 days (30). In other words, the monoexponential portion of the experimentally determined Sr disappearance curve is represented by

$$R_B = Ae^{-at}, \quad [1]$$

where R_B is concentration of Sr^r in blood (expressed as percentage of dose per liter of plasma), and A and a are positive numbers.

After an iv injection, a portion of the injected radioactivity is excreted in the urine and another portion in the stools. Let R_u = radioactivity in urine and R_F = radioactivity in feces. If the collection is extended long enough, e.g., ≥ 9 days, the amount of radioactivity circulating at that time becomes negligible and the amount of radioactivity excreted thereafter is small (Figure 1).

If it is assumed that essentially all Sr^r not recovered in either urine or feces is in the skeleton, one can write

$$R_{o+} = R_i - (R_u]_0^9 + R_F]_0^9) \quad [2]$$

where R_{o+} = the amount of radioactivity in the skeleton and R_i = the amount of injected radioactivity. (A more extended theoretical discussion of this approach is given by Aubert, Bronner, and Richelle [26].)

These experimental facts can correspond to two different systems (Figure 2). In the one system, there is a central pool with size remaining constant and specific activity decreasing with time. The other has no central pool of constant size, and the circulating mass decreases with time, the specific activity of the circulating mass remaining constant.

To establish one or the other hypothesis experimentally would require a formal study of Sr metabolism, i.e., measuring its concentration in accessible body compartments and fluids, its rate of ingestion in the food, and its rate of elimination in urine and feces. The analytical difficulties of measuring Sr chemically are well known, so that the task entailed in such a program is hardly justified if there is no intrinsic interest in Sr metabolism.

It is possible, however, to analyze experimental results of Sr metabolism and to compare them with those of Ca metabolism regardless of which scheme of analysis, with or without pool of constant size, is chosen for Sr. This is done by characterizing each of the three routes of loss by a rate constant k, which is defined independently of the scheme of analysis chosen.

In the *system with a central pool of constant size* (26), the rates of loss from the pool, v_u for the urine, v_f for the endogenous fecal loss, and v_{o+} for the skeleton, are considered constant during the experimental period.

Let P = the mass of the pool, and M_u, M_f, M_{o+} = the corresponding amounts lost from the pool to urine, feces,
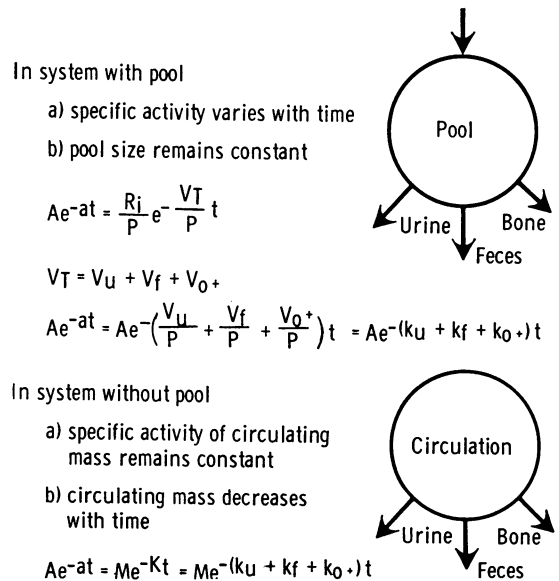

FIG. 2. TWO DIFFERENT SYSTEMS, BOTH OF WHICH CAN BE REPRESENTED BY A MONOEXPONENTIAL DECREASE OF PLASMA RADIOACTIVITY, EXPRESSED IN UNITS OF RADIOACTIVITY PER UNIT VOLUME OF PLASMA.

and bone during time t. The rates are then defined as follows:

$$v_u = \frac{dM_u}{dt} = -k_uP, \qquad [3a]$$

$$v_f = \frac{dM_f}{dt} = -k_fP, \qquad [3b]$$

and

$$v_{o+} = \frac{dM_{o+}}{dt} = -k_{o+}P, \qquad [3c]$$

where the various k's have the usual definition of a rate constant (1/time). Inasmuch as P is constant, the various rates v are necessarily constant as well.

When a radioactive tracer is introduced in such a system, the time-course of the disappearance curve can be expressed by a relationship like Equation 1,

$$R_{sB} = \frac{R_i}{P} e^{-(v_T/P)t}, \qquad [4]$$

where R_{sB} = the specific activity of the element in the serum, R_i = the amount of injected radioactivity, and P = the pool size. v_T = the sum of the component losses from the pool,

$$v_T = v_u + v_f + v_{o+}. \qquad [5]$$

By combining Equations 4, 5, and 3, a to c, one obtains the relationship

$$R_{sB} = \frac{R_i}{P} e^{-(k_u+k_f+k_{o+})t}, \qquad [6]$$

which expresses Equation 4 in terms of the rate constants. Equation 6 can also be written as

$$R_{sB} = \frac{R_i}{P} e^{-Kt}, \qquad [7]$$

where

$$K = k_u + k_p + k_{o+}. \qquad [8]$$

In the system without a central pool of constant size, the amounts, in mass, excreted in urine and feces and deposited in time dt are proportional to the circulating mass M which varies in size with time. One therefore writes:

$$\frac{dM_u}{dt} = -k_uM, \qquad [9a]$$

$$\frac{dM_f}{dt} = -k_fM, \qquad [9b]$$

and

$$\frac{dM_{o+}}{dt} = -k_{o+}M. \qquad [9c]$$

These equations are identical with Equations 3, a to c, except that v_u, v_f, and v_{o+} can be defined only as instantaneous and no longer as average rates, because M is a continuous function of time.

As urine, feces, and the skeleton are the only routes of loss, one can write:

$$dM_u + dM_f + dM_{o+} = dM, \qquad [10]$$

where dM is the total amount lost from the system in time dt. By combining Equations 9, a to c, and 10, one obtains

$$\frac{dM}{dt} = -(k_u + k_f + k_{o+})M. \qquad [11]$$

Integration of Equation 11 yields

$$M = M^0e^{-(k_u+k_f+k_{o+})t}, \qquad [12]$$

where M^0 = the mass at $t = 0$, and M is the mass circulating at time t.

If M^0 at $t = 0$ is labeled with a tracer R_i (the amount of radioactivity injected), the specific activity (R_{sB}) at $t = 0$, expressed as percentage of injected dose per unit mass, is given by

$$R_{sB} = \frac{R_i}{M^0}. \qquad [13]$$

In a system without central pool of constant size, this specific activity remains constant throughout the experiment. By combining Equations 12 and 13, one obtains the amount of radioactivity, R, circulating at time t:

$$R = \frac{R_i}{M^0} M^0e^{-(k_u+k_f+k_{o+})t} = R_ie^{-(k_u+k_f+k_{o+})t}. \qquad [14]$$

If R_B is the amount of circulating radioactivity per unit of plasma volume, the time-course of this parameter can be expressed in terms of Equation 14 as follows:

$$R_B = \frac{R}{L} = \frac{R_i}{L} e^{-(k_u+k_f+k_{o+})t} = \frac{R_i}{L} e^{-Kt}, \qquad [15]$$

where L = total apparent volume of distribution of the circulating mass (units of plasma volume) and K is defined by Equation 8.

Equation 15 is of the same type as Equation 7 and is identical with the experimentally derived Equation 1. In both Equation 7 and Equation 15, the apparent volume of distribution, L, is constant, but in the former the circulating mass is constant as well. It is easy to convert pool size in Equation 7 to volume of distribution by dividing P by plasma concentration expressed as mass per volume. Two methods can be utilized to calculate the rate constants, depending on whether or not the time-course of the plasma radioactivity is known.

When the time-course of the plasma radioactivity is known, in counts per minute per liter of plasma, the mono-exponential portion of the curve is extrapolated to $t = 0$, and K and L are calculated (26); k_u and k_f are then derived as follows:

$$R_u]_{t_1}{}^{t_2} = k_uL \int_{t_1}^{t_2} R_B dt \qquad [16]$$

and

$$R_F]_{t_1}{}^{t_2} = k_fL \int_{t_1}^{t_2} R_B dt. \qquad [17]$$

Equation 8 is used to derive k_{o+}.

If the amount of radioactivity injected into the experimental subject is too small to yield a reliable plasma disappearance curve, the cumulative urinary output of radioactivity may be used instead. Substitution of Equation 15 in Equation 16 yields

$$R_u]_o{}^t = k_uL \frac{R_i}{L} (1 - e^{-Kt}) = k_uR_i(1 - e^{-Kt}). \qquad [18]$$

When t is sufficiently long, 9 days in the case of Sr^r, e^{-Kt} becomes negligible and $R_u]_o{}^t \rightarrow R_{u_{max}}$. $R_{u_{max}}$ is given by the equation

$$R_{u_{max}} = k_u R_i. \qquad [19]$$

By combining Equations 18 and 19, one can write:

$$R_u]_o{}^t = R_{u_{max}}(1 - e^{Kt}). \qquad [20]$$

By rewriting Equation 20 in terms of logarithms, one can solve for K as follows:

$$\ln\left(1 - \frac{R_u]_o{}^t}{R_{u_{max}}}\right) = - Kt. \qquad [21]$$

The measurement of the daily output of radioactivity in the urine for 9 or more days permits determining R_u and $R_{u_{max}}$; this in turn permits calculating K; k_u may then be derived from the relationship

$$k_u = K \frac{R_{u_{max}}}{R_i}. \qquad [22]$$

In order to obtain k_f, one writes an equation similar to Equation 22 for $R_{F_{max}}$. Equation 8 is used to calculate k_{o+}. Figure 1 illustrates this method of calculation. It has been used in this report to derive the values for Table II.

It follows from what has been said that the time-course of the concentration of Sr^r in the plasma may reflect two entirely different metabolic schemes, one with and one without a central pool of constant size (Figure 2).

Eisenberg and Gordan (7) injected stable Sr into a variety of patients and observed a monoexponential decrease of the plasma Sr concentration after 1 to 2 days. Hence their data can be analyzed according to the system without a Sr pool of constant size. Eisenberg and Gordan treated their data as if the stable Sr they injected were a tracer of Ca, just as other workers have used Sr^r as a Ca tracer. This assumption is without experimental verification.

The use of rate constants avoids the need for making such assumptions and has the following advantages. The rate constants are identical, whichever of the two possible schemes is true for Sr; they can be calculated without reference to the metabolism of any other element, particularly Ca; and they can be compared formally and without any theoretical restriction to similar rate constants calculated for Ca.

RESULTS

Table II lists the results of parallel intravenous experiments where Ca^{45} and Sr^{85} were injected simultaneously. Table III lists the values for the same experiments, but expressed as percentages of injected dose. Multiplying K for a given study in Table II by the corresponding values for percentage of dose in Table III

TABLE II

Rate constants for strontium and calcium in simultaneous human studies*

Patient no.	Study no.	K_{total}			k_{urine}			k_{feces}			k_{bone}		
		Sr	Ca	Sr/Ca	Sr	Ca	Sr/Ca	Sr	Ca	Sr/Ca	Sr	Ca	Sr/Ca
3	B	0.39	0.27	1.4	0.20	0.055	3.6	0.027	0.031	0.9	0.16	0.18	0.9
	F	0.34	0.26	1.3	0.14	0.062	2.2	0.017	0.012	1.4	0.19	0.19	1.0
4	C	0.48	0.23	2.1	0.24	0.042	5.7	0.048	0.035	1.4	0.20	0.17	1.2
	D	0.48	0.33	1.5	0.29	0.069	4.2	0.062	0.060	1.0	0.13	0.20	0.7
7	A	0.39	0.26	1.5	0.051	0.021	2.4	0.043	0.045	1.0	0.30	0.19	1.6
	C	0.32	0.23	1.4	0.022	0.016	1.4	0.051	0.026	2.0	0.28	0.19	1.5
8	A	0.39	0.36	1.1	0.16	0.050	3.1	0.066	0.050	1.3	0.17	0.26	0.6
	C	0.37	0.30	1.2	0.22	0.090	2.4	0.022	0.033	0.7	0.13	0.18	0.7
12	B	0.23	0.24	1.0	0.044	0.017	2.6	0.025	0.029	0.9	0.16	0.19	0.8
	D	0.30	0.24	1.3	0.11	0.038	2.8	0.042	0.043	1.0	0.15	0.16	0.9
	F	0.28	0.24	1.2	0.064	0.012	5.3	0.042	0.034	1.2	0.17	0.19	0.9
13	A	0.23	0.30	0.8	0.051	0.033	1.5	0.025	0.021	1.2	0.15	0.26	0.6
15	C	0.23	0.19	1.2	0.076	0.032	2.4	0.041	0.051	0.8	0.11	0.11	1.0
20	B	0.16	0.17	0.9	0.032	0.027	1.2	0.011	0.031	0.4	0.12	0.12	1.0
	C	0.30	0.18	1.7	0.090	0.026	3.5	0.045	0.030	1.5	0.17	0.11	1.5
Mean		0.326	0.253	1.31	0.119	0.039	2.95	0.0378	0.0354	1.11	0.173	0.180	0.99

* Values for rate constants in days^{-1}.

TABLE III

Distribution of percentage of injected dose*

Patient no.	Study no.	Urine			Feces			Bone		
		Sr	Ca	Sr/Ca	Sr	Ca	Sr/Ca	Sr	Ca	Sr/Ca
3	B	52	20	2.6	7	11	0.6	41	68	0.6
	F	40	24	1.7	5	5	1.0	55	72	0.8
4	C	49	18	2.7	10	15	0.7	41	67	0.6
	D	60	21	2.9	13	19	0.7	27	60	0.45
7	A	13	8	1.6	11	18	0.6	76	74	1.0
	C	7	5	1.4	16	11	1.5	77	84	0.9
8	A	40	14	2.9	17	14	1.2	43	72	0.6
	C	59	30	2.0	6	11	0.5	35	59	0.6
12	B	19	7	2.7	11	12	0.9	70	81	0.9
	D	36	16	2.3	14	18	0.8	50	66	0.8
	F	23	5	4.6	15	14	1.1	62	81	0.8
13	A	22	11	2.0	11	7	1.6	67	82	0.8
15	C	33	17	1.9	18	27	0.7	49	56	0.9
20	B	20	21	1.0	7	16	0.4	73	63	1.2
	C	30	16	1.9	15	18	0.8	55	67	0.8
Mean		34	16	2.1	12	14	0.9	55	70	0.8

* The values reported are maximal values calculated from cumulative excretion measurements. Bone uptake = 100 − (urinary + fecal excretion).

will yield the fractional rate constants, k_u, k_f, and k_{o+}, shown in Table II.

Table II shows that the most consistent differences between rate constants were observed for k_{urine}. The $k_{u_{Sr}}$ was always larger than the $k_{u_{Ca}}$, their ratio varying from 1.2 to 5.7, with a mean of 2.95. Moreover, this ratio varied for a given patient. K_{total} also was rarely the same for the two nuclides, the ratio of $K_{total\ Sr}/K_{total\ Ca}$ varying from 0.8 to 2.1, with a mean of 1.31. This ratio, too, appeared to vary unpredictably in a given patient and between patients. The rate constant for Ca and Sr in feces varied rather less, the ratio of $k_{feces\ Sr}/k_{feces\ Ca}$ averaging 1.11, with a range of 0.4 to 2.0. Finally, differences between rate constants were smallest for k_{bone}, the mean ratio of $k_{bone\ Sr}/k_{bone\ Ca}$ equaling 0.99. But even here, this ratio varied from patient to patient and was not consistent in a given patient.

DISCUSSION

To appreciate the meaning of the differences and similarities of the values of the rate constants set out in Table II requires an analysis of the errors inherent in them. Each of the values reported in Tables II and III is subject to two types of errors: *1*) that due to the experimental analysis and *2*) that due to the method of analyzing the data.

Errors due to experimental analysis. The experimental values reported in Table III, i.e., the percentage of the dose recovered in urine and feces, are derived from duplicate analyses that differed from their mean by approximately ± 5%. Hence the percentage of dose in bone, which is the difference between the injected dose and that recovered in the excreta, has a relative error of ± 2% in the case of Ca and of ± 4% in the case of Sr[2]. The error of the Sr/Ca ratios

[2] If the experimental error is ± 5%, the absolute error for the mean urine excretion of Ca^{45} (Table III) is 0.80 (0.05 × 16) and for fecal excretion of Ca^{45} 0.70 (0.05 × 14). The error for the total excretion is therefore 1.5, which necessarily is the same absolute error for the percentage of dose in bone [100 − (14 + 16)]. Hence the relative error for the percentage of dose in bone is ± 2% (1.5 × 100)/70. The same reasoning applies for Sr, except that the total percentage of the dose excreted in urine and feces is 48; hence, the relative error for bone is larger.

in Table III is about double that of the component values making up the ratio.

The values set out in Table II are not only subject to the analytical errors detailed above, but also to the error involved in deriving K. In all cases, the numerical value of K was derived by the method of least squares applied to the excretion values obtained in the period of 2 to 6 days following injection of the isotopes; the uncertainty attaching to each is about $\pm 5\%$.

By adding this error to the error inherent in the percentage of dose excreted and in bone, one can estimate the over-all experimental error of a given rate constant to be

	Ca	Sr
k_u	$\pm 10\%$	$\pm 10\%$
k_f	$\pm 10\%$	$\pm 10\%$
k_{o+}	$\pm 7\%$	$\pm 9\%$

Errors due to the method of analyzing the data. To compare the corresponding rate constants between patients, the error due to the method of calculation must be taken into account as well. The method used was of the same type described elsewhere as the "simplified method" (26, 28).

In this method, the behavior of the system is described by a single exponential term, and losses from the system prior to homogenization are not taken into account. As compared to the general method, based on the complete, multitermed equation, the simplified method overestimates P and v_T and therefore v_{o+} and v_{o-}. The degree of overestimation varies in direct proportion to the magnitude of P and v_T, but cannot be predicted unless both the simplified and general methods have been applied to the same study. Since this was not done here, we shall generalize a particular case.

In a patient whose true Ca pool was 6.5 g, but whose Ca pool by the simplified method was 9.2 g (28), we can calculate that by using the simplified instead of the generalized method, K would be underestimated by 15%, k_u by 40%, k_f by 20%, and k_{o+} by 9%. Although none of our patients had Ca pools as large as 9.2 g (by the simplified method), it may be prudent to consider errors of this magnitude as outside limits.

To compare the rate constant of a given patient with that of another subject, the error due to the use of the simplified method (which always underestimates the true value) must therefore

be added to the error due to the experimental analysis.

Because Sr metabolism may be formally described in a manner identical with that used for Ca metabolism, the errors inherent in the analysis of Sr metabolism are the same as for Ca metabolism. Hence, combining the experimental with the method error, one arrives at the following error range for the constants:

	Ca	Sr
K	-5% to $+20\%$	-5% to $+20\%$
k_u	-10% to $+50\%$	-10% to $+50\%$
k_f	-10% to $+30\%$	-10% to $+30\%$
k_{o+}	-7% to $+11\%$	-9% to $+13\%$

With the ratios of the rate constants, however, the error due to the use of the simplified instead of the general method cancels, being identical and in the same direction for both elements, if the experiment is done in the same patient. Hence, the ratios of the rate constants are in error only by approximately the sum of the over-all experimental errors of each rate constant, i.e., $K_{Sr}/K_{Ca} = \pm 10\%$, $k_{u_{Sr}}/k_{u_{Ca}} = \pm 20\%$, $k_{f_{Sr}}/k_{f_{Ca}} = \pm 20\%$, and $k_{o+_{Sr}}/k_{o+_{Ca}} = \pm 16\%$.

A comparison of the various rate constants listed in Table II indicates that the mean values of the different constants vary from one process to the other, both for Ca and Sr. Also, these mean values fall within a relatively large range (Table II). With the exception of the rate constants for urine, the ranges of the other constants are similar for Ca and Sr, and their mean values are relatively close to one another.

The question that arises first is whether or not, in a group of subjects as widely different in terms of Ca metabolism as that studied here, the various rate constants for Ca fall outside the range of the combined error, i.e., over-all experimental error and mode of analysis. By applying the error range calculated above to the mean values of the rate constants of the group, one obtains the following ranges: $K_{Ca} = 0.240$ to 0.303 $(0.253 - 5\%$ to $0.253 + 20\%)$; $k_{u_{Ca}} = 0.035$ to 0.058; $k_{f_{Ca}} = 0.031$ to 0.045; and $k_{o+_{Ca}} = 0.168$ to 2.200.

A comparison of these with the actual values shown in Table II indicates that 7 of the values for K exceed these limits (studies 4C, 4D, 7C, 8A, 15C, 20B, and 20C). Similarly, 11 of the 15 values are outside these limits for k_u, 8 are

outside the limits for k_f, and 6 are outside the limits for k_{o+}. Hence, we are dealing with variations in the rate constants that are outside of the limits of the experimental error, and the group can be used for a comparison of the metabolic behavior of Sr and Ca. Indeed, it would be meaningless to attempt to compare these in individuals whose rate constants for Ca did not differ significantly.

A similar calculation applied to the rate constants of Sr indicates that 9 of the 15 values for K_{Sr} are outside the error range, 12 are outside the error range of k_u, 9 outside the error range of k_f, and 9 outside the error range of k_{o+}.

When the mean values of the various rate constants were compared, K_{Ca} was found to differ significantly from K_{Sr} (p = 0.02), as did $k_{u_{Ca}}$ from $k_{u_{Sr}}$ (p < 0.01). Neither $k_{f_{Ca}}$ nor k_{o+Ca} differed significantly from $k_{f_{Sr}}$ and k_{o+Sr}, respectively.

Yet when an attempt was made to develop regression equations for each pair of rate constants, no significant function was derived for any pair, whether or not the mean values differed significantly.

The failure to find a correlation for any pair of rate constants might be due to too great a dispersion resulting from the experimental errors. The probable error range for each ratio of rate constants was therefore calculated by use of the error range listed above: K_{Sr}/K_{Ca} = 1.18 to 1.44 (1.31 − 10% to 1.31 + 10%); $k_{u_{Sr}}/k_{u_{Ca}}$ = 2.36 to 3.54; $k_{f_{Sr}}/k_{f_{Ca}}$ = 0.89 to 1.33; and k_{o+Sr}/k_{o+Ca} = 0.83 to 1.15.

A comparison of the values listed in Table II for the ratio K_{Sr}/K_{Ca} with the above range reveals that 8 of the 15 values fall outside of the limit (studies 4C, 4D, 7A, 8A, 12B, 13A, 20B, and 20C). Similarly, 8 of the ratios $k_{u_{Sr}}/k_{u_{Ca}}$, 7 of the ratios $k_{f_{Sr}}/k_{f_{Ca}}$, and 9 of the ratios k_{o+Sr}/k_{o+Ca} fall outside of the limits. In other words, approximately half of the ratios of the rate constants fall outside of the experimental error. One may therefore conclude that the failure to find a regression function in any pair is not due solely to the dispersion owing to the experimental error and that none of the metabolic processes of Ca and Sr discussed here can be considered equivalent, i.e., the ratios of the rate constants do not only vary within the limits of error of their mean.

It is nevertheless surprising that as far as fecal excretion and bone uptake are concerned, the two elements seem directly equivalent. This is due to the fact that for an unknown reason the range of variation of the corresponding rate constants for either element is similar. Also, the rate constant for a given patient appears as if placed within this range by chance. Hence, the corresponding ratios of an individual patient's rate constants may differ considerably from the group mean that approximates unity.

SUMMARY AND CONCLUSIONS

1. In order to compare Sr and Ca metabolism in man without at the same time assuming any metabolic relationship between these elements, it was necessary to develop a set of parameters that have the same formal significance for each element. Present knowledge of Sr metabolism is as yet inadequate to permit affirming whether or not this element behaves in the body as if there were a central pool of constant size. Ca, on the other hand, is known to have such a central pool. To avoid making any assumption concerning such a pool in the presentation of our data, we have chosen to express each of the body processes (over-all loss, urinary excretion, fecal excretion, and bone uptake) in terms of its characteristic rate constant. This constant is independent of the real scheme of Sr metabolism. It has the drawback of being much less explicit for a given process than would be a true rate, expressed in units of mass per unit time. It is the only one, however, that allows describing Sr metabolism and comparing it with Ca metabolism.

2. A comparison of the Sr and Ca rate constants of the various processes in 15 studies done on 8 patients whose Ca metabolism differed widely revealed that these elements were not equivalent in any of these processes. In other words, in neither over-all loss, nor urinary excretion, nor fecal excretion, nor bone uptake was it possible to establish a ratio of the corresponding rate constants that varied only within the limits of error of the mean ratio.

3. It was not possible to establish a significant correlation (by means of regression functions)

between the corresponding rate constants calculated for each element.

4. Whereas the mean values of the total (K) and urinary rate constants (k_u) of Sr differed significantly from the corresponding Ca constants, the fecal (k_f) and bone (k_{o+}) rate constants of the two elements did not so differ. Values for individual patients of these latter two rate constants appear as if distributed by chance within the experimental range, with the result that the mean ratios of the rate constants of the two elements, $k_{f_{Sr}}/k_{f_{Ca}}$ and $k_{o+_{Sr}}/k_{o+_{Ca}}$, approach unity.

5. These findings are interpreted to mean that, qualitatively, both Sr and Ca follow the same metabolic pathways, and quantitatively, the use of Sr as a tracer for Ca in a given individual leads only to an approximation of the true value, the degree of error varying unpredictably for a particular case. Whereas all of the parameters of Ca metabolism can be evaluated in terms of unit mass and unit mass per unit time by the combined use of the Ca balance and Ca^r, the use of Sr in studies of Ca metabolism can yield information only in terms of an apparent circulating volume (expressed, for example, in liters of serum) and of rate constants (K, k_u, k_f, k_{o+}). Sr may be used as a tracer for Ca to measure the mean bone formation rate in groups of individuals whose Ca metabolism is disparate.

REFERENCES

1. Pecher, C. Biological investigations with radioactive calcium and strontium. Proc. Soc. exp. Biol. (N. Y.), 1941, 46, 86.
2. Pecher, C., and J. Pecher. Radio-calcium and radio-strontium metabolism in pregnant mice. Proc. Soc. exp. Biol. (N. Y.), 1941, 46, 91.
3. Greenberg, D. M. Studies in mineral metabolism with the aid of artificial radioactive isotopes. VIII. Tracer experiments with radioactive calcium and strontium on the mechanism of vitamin D action in rachitic rats. J. biol. Chem. 1945, 157, 99.
4. Jones, D. C., and D. H. Copp. Studies of bone metabolism with the aid of radioactive strontium. U. S. Atomic Energy Commission document no. 1962, 1948.
5. Fraser, R., M. Harrison, and K. Ibbertson. The rate of calcium turnover in bone. Measurement by a tracer test using stable strontium. Quart. J. Med. 1960, 29, 85.
6. Harrison, M., and Fraser, R. Bone metabolism in rats, studied with stable strontium. J. Endocr. 1960, 21, 191.
7. Eisenberg, E., and G. S. Gordan. Skeletal dynamics in man measured by nonradioactive strontium. J. clin. Invest. 1961, 40, 1809.
8. Bauer, G. C. H., A. Carlsson, and B. Lindquist. A comparative study on the metabolism of Sr^{90} and Ca^{45}. Acta physiol. scand. 1955. 35, 56.
9. Rich, C., J. Ensinck, and H. Fellows. The use of continuous infusions of calcium^{45} and strontium^{85} to study skeletal function. J. clin. Endocr. 1961, 21, 611.
10. Kulp, J. L., W. R. Eckelmann, and A. R. Schulert. Strontium^{90} in man. Science 1957, 125, 219.
11. Eckelmann, W. R., J. L. Kulp, and A. R. Schulert. Strontium^{90} in man, II. Science 1958, 127, 266.
12. Kulp, J. L., A. R. Schulert, and E. J. Hodges. Strontium-90 in man, III. Science 1959, 129, 1249.
13. Schulert, A. R., E. A. Peets, D. Laszlo, H. Spencer, M. Charles, and J. Samachson. Comparative metabolism of strontium and calcium in man. Int. J. appl. Radiat. 1959, 4, 144.
14. Dow, E. C., and J. B. Stanbury. Strontium and calcium metabolism in metabolic bone diseases. J. clin. Invest. 1960, 39, 885.
15. Wendeberg, B. Mineral metabolism of fractures of the tibia in man studied with external counting of Sr-85. Acta orthop. scand. 1961, suppl. 52.
16. Wasserman, R. H., and C. L. Comar. Annotated bibliography of strontium and calcium metabolism in man and animals. Misc. Pub. no. 821, Agricultural Research Service, U. S. Dept. of Agriculture, 1961.
17. Shorr, E., and A. C. Carter. The usefulness of strontium as an adjuvant to calcium in the remineralization of the skeleton in man. Bull. Hosp. Jt. Dis. (N. Y.) 1952, 13, 59.
18. McCaslin, F. E., Jr., and J. M. Janes. The effect of strontium lactate in the treatment of osteoporosis. Proc. Mayo Clin. 1959, 34, 329.
19. Lehnerdt, F. Zur Frage der Substitution des Calciums im Knochensystem durch Strontium. I. Beitr. path. Anat. 1909, 46, 468.
20. Lehnerdt, F. Zur Frage der Substitution des Calciums im Knochensystem durch Strontium. II. Mitteilung. Strontiumfütterung an säugende Tiere, der Einfluss des Strontiums auf das Knochensystem der gesäugten Jungen. Beitr. path. Anat. 1910, 47, 215.

21. Alexander, G. V., R. E. Nusbaum, and N. S. Mac-
Donald. The relative retention of strontium and
calcium in bone tissue. J. biol. Chem. 1956, 218,
911.

22. Widdowson, E. M., and J. W. T. Dickerson. Chemi-
cal composition of the body *in* Mineral Metabolism
—An Advanced Treatise, C. L. Comar and F.
Bronner, Eds. New York and London, Academic
Press, vol. 2A. In press.

23. Harrison, G. E. Estimation of strontium in biological
materials by means of a flame spectrophotometer.
Nature (Lond.) 1958, 182, 792.

24. Comar, C. L., R. H. Wasserman, and M. M. Nold.
Strontium-calcium discrimination factors in the rat.
Proc. Soc. exp. Biol. (N. Y.) 1956, 92, 859.

25. Bronner, F., J.-P. Aubert, and L. Richelle. Com-
parison of Ca and Sr metabolism in man. Fed.
Proc. 1962, 21, 78.

26. Aubert, J.-P., F. Bronner, and L. J. Richelle. Quanti-
tation of calcium metabolism. Theory. J. clin.
Invest. 1963, 42, 885.

27. Bronner, F., L. J. Richelle, P. D. Saville, J. A. Nicholas,
and J. R. Cobb. Quantitation of calcium metabo-
lism in postmenopausal osteoporosis and scoliosis.
J. clin. Invest. 1963, 42, 898.

28. Aubert, J.-P., and G. Milhaud. Méthode de mesure
des principales voies du métabolisme calcique chez
l'homme. Biochim. biophys. Acta (Amst.) 1960,
39, 122.

29. Bronner, F., R. S. Harris, C. J. Maletskos, and C. E.
Benda. Studies in calcium metabolism. Effect of
food phytates on calcium[45] uptake in children on
low-calcium breakfasts. J. Nutr. 1954, 54, 523.

30. Bauer, G. C. H., and R. D. Ray. Kinetics of stron-
tium metabolism in man. J. Bone Jt. Surg. 1958,
40A, 171.