Reprinted from JOURNAL OF APPLIED PHYSIOLOGY
Vol. 21, No. 1, January, 1966
*Printed in U.S.A.*

# Strontium and calcium skeletal discrimination determined by compartmental analysis[1]



**The Medical Research Center**

**Brookhaven National Laboratory**

**Upton, L. I., New York**

S. H. COHN, S. R. BOZZO, J. E. JESSEPH, C. CONSTANTINIDES, E. A. GUSMANO, AND J. S. ROBERTSON
*Medical Research Center, Brookhaven National Laboratory, Upton, Long Island, New York*

COHN, S. H., S. R. BOZZO, J. E. JESSEPH, C. CONSTANTINIDES, E. A. GUSMANO, AND J. S. ROBERTSON. *Strontium and calcium discrimination determined by compartmental analysis.* J. Appl. Physiol. 21(1): 67–72. 1966.—A multicompartmental-type analysis was used to describe metabolic data obtained in a double tracer experiment in man and to compare the quantitative differences in the values of the parameters obtained with Ca and Sr tracers. The compartmental sizes and transfer constants and their standard deviations were obtained with the NIH-OMR-SAAM program and an IBM-7094 computer. To obtain data beyond the 10-day period in which plasma activity could be measured, a whole-body counter and a collimated external detector were employed. The absolute values of the various parameters obtained with Sr were slightly lower than those obtained with Ca, but the Sr-derived values did reflect the Ca metabolism very well in terms of the assumed model for the 10-day data. The whole-body counter data collected over 30 days indicated differences in the whole-body and bone turnover of Sr and Ca, suggesting differences in resorption and long-term exchange of Ca compared with Sr which are not apparent in the 10-day study.

mineral metabolism; calcium and strontium kinetics; compartmental model for calcium and strontium; computer analysis of tracer kinetic data

As THERE IS no long-lived gamma-emitting radioisotope of calcium, a substitute is required. Because of the chemical similarity of calcium and strontium, radioactive Sr has commonly been used as a tracer in Ca metabolic studies. Notwithstanding the chemical similarity of Sr and Ca, physiological differences have been shown to exist, particularly in those processes which involve metabolic transfer across membranes. Ca is transferred preferentially to Sr in gastrointestinal absorption, renal excretion, lactation, and placental transfer (9). In-vitro studies (12, 14) have suggested that discrimination by skeletal tissue may also exist. Such discrimination in the transfer of Sr and Ca between plasma and bone or within bone, however, has not been conclusively demonstrated in vivo. It is the object of this study to determine whether discrimination between Sr and Ca by skeletal tissue does exist and, if so, to quantify the differences.

In addition to the interest in Sr as a tracer for Ca, there has been considerable attention to the metabolism of Sr per se. However, the metabolism of Sr in a biological system is described most effectively in terms of the comparative Sr and Ca kinetics for, while Sr metabolism is apparently not under direct homeostatic control, it nevertheless appears to be influenced by the Ca level. Differences in the kinetic behavior of the two elements reflect the basic physiological processes responsible for their differential movement in the body.

In the present study, multicompartmental analysis was used to describe the metabolic data so that quantitative differences in the values of the parameters could be used to compare the kinetics of Sr and Ca metabolism. A two-compartment model was previously formulated (unpublished data) to represent the kinetics of injected $Ca^{47}$ and applied in a study of parathyroid deficiency (6). The compartment sizes and transfer constants and their standard deviations were obtained with the NIH-OMR SAAM program using an IBM-7094 computer. The model was shown to have a high degree of uniqueness in its fit of the data. With this model and computer program, the data obtained with $Sr^{85}$ and $Ca^{47}$ simultaneously administered to a number of subjects were also analyzed. In order to obtain data beyond the 10-day period in which plasma activity can be measured, a whole-body counter was employed. In addition, a collimated detector was used to measure the activity in a bone compartment (knee) to provide further data on the turnover of the tracers.

## METHODS

*Subjects.* Seven male subjects ranging in age from 53 to 80 years of age received doses of $Sr^{85}$ and $Ca^{47}$ simultaneously. All of the subjects received a physical examination as well as essential laboratory and X-ray studies

Received for publication 19 April 1965.
[1] This research was supported by the US Atomic Energy Commission.

TABLE 1. *Clinical description of experimental subjects*

| Subj | Age, yr | Weight, kg | Significant Lesions | Abnormal Laboratory Findings | Other Pertinent Data |
|---|---|---|---|---|---|
| 1 | 80 | 48.5 | Mild pulmonary emphysema; old MI | | |
| 2 | 76 | 52.7 | Right hemiparesis, partial (CVA); ambulatory | | |
| 3 | 79 | 69.1 | AsHD, mild, compensated | | ? Mild Paget's disease, pelvis only |
| 4 | 69 | 74.5 | AsHD, mild, compensated | Slight increased urinary $PO_4^-$ | ? Paget's disease, right ilium |
| 5 | 63 | 50.4 | AsHD, mild, compensated | | Substernal goiter (euthyroid) |
| 8 | 53 | 90.4 | Idiopathic epilepsy, seizure-free | Weakly reactive STS; treated | |
| 10 | 77 | 67.7 | Minimal right hemiparesis, fully ambulatory, AsHD, minimal, compensated | | Minimal osteoporosis |

MI = myocardial infarct, CVA = cerebrovascular accident, AsHD = arteriosclerotic heart disease, STS = serological test for syphilis.

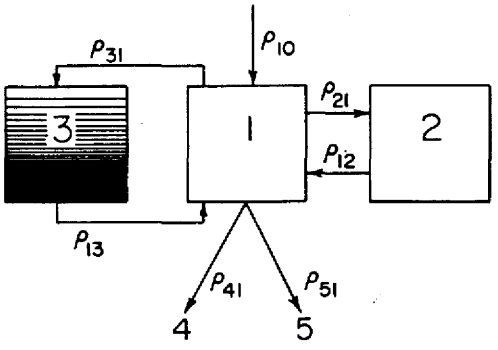


FIG. 1. Compartmental model of calcium kinetics. Compartments are designated as follows: 1, physiological pool of calcium in isotopic equilibrium within 1 hr (plasma-extracellular-intracellular); 2, physiological pool of calcium in isotopic equilibrium within 3 days (exchangeable bone); 3, calcium in "deep bone" or very slowly exchanging bone. The transfer constants, $\rho$, are designated as follows: $\rho_{10}$ = calcium intake rate, $\rho_{12}$ = Ca flow rate into compartment 1 from exchangeable bone, $\rho_{21}$ = Ca flow rate into exchangeable bone from compartment 1, $\rho_{13}$ = rate of resorption and slow exchange from bone, $\rho_{31}$ = rate of accretion into bone, $\rho_{41}$ = urinary calcium excretion rate, $\rho_{51}$ = fecal calcium excretion rate.

3-135-64

prior to the study. The subjects were in good health and ambulatory. They were admitted to the metabolic ward of the hospital, but allowed complete freedom of movement. A brief clinical description of these subjects is presented in Table 1.

*Diet.* Subjects were placed on a constant diet of 800 mg/day of Ca and 1,220 mg/day of P, before and during the study.

*Blood chemistry.* Plasma Ca levels were measured on each subject before and during the study and were found always to be in the normal range.

*Radioisotopes.* $Ca^{47}Cl_2$ (20 $\mu$c) with a specific activity of 140 mc/g and $Sr^{85}Cl_2$ (15 $\mu$c) carrier free were administered intravenously and simultaneously to each subject.

*Radiochemical assay.* The concentration of $Ca^{47}$ and $Sr^{85}$ in 24-hr urine and stool samples was measured daily for 10 days. The entire 24-hr urine and stool samples were placed in tin cans, filled with water, sealed, and counted under an 8 inch x 4 inch NaI detector in the whole-body counter connected to a 400-channel pulse-height analyzer.

5012706

The plasma concentration of the isotopes was measured at 0.5 and 4 hr and at daily intervals for 10 days. Plasma samples were counted in a NaI well-type detector connected to a 400-channel pulse-height analyzer. Both $Ca^{47}$ and $Sr^{85}$ concentrations are expressed per 10 liters of plasma (1 g Ca).

The whole-body retention of $Ca^{47}$ and $Sr^{85}$ was measured initially at 4 hr after administration (100% administered dose) and then at daily intervals in the Brookhaven whole-body counter (7). In addition, the concentration of these tracers in both knees was measured at the same intervals, with a 3-inch collimated NaI detector.

It was found advantageous to process the large amount of data collected in this study automatically. The output of the analyzer was recorded on paper punch tape and later transferred to magnetic tape for the IBM-7094. The gamma spectral data were analyzed manually initially, but later in the study the spectral stripping was performed by a computer.

*Compartment model.* The mathematical bases of compartment theory and its application to biological systems analysis have been extensively reviewed (10, 13). The kinetics involved in a multicompartment model can be briefly expressed by the following set of first-order linear differential equations:

$$f_i(t) = \sum_{j=1}^{n} \lambda_{ij} f_j(t) \qquad (i = 1, \cdots, n) \qquad (1)$$

where:

$f_i(t)$ represents a function, such as specific activity
$\lambda_{ij}$ are the transition probabilities per unit time from $j$th into the $i$th compartment

$$\lambda_{ii} = -\sum_{\substack{k=0 \\ k \neq i}}^{n} \lambda_{ki} \qquad (2)$$

$\lambda_{0i}$ represents loss from $i$th compartment to outside

For the mathematical analysis, the usual steady-state assumptions are made. These include the following: 1) the volumes of the compartments and the concentrations

TABLE 2. *Comparative calcium and strontium parameters*

| Subj | Isotope | Compartment Sizes, g | | | Transfer Constants, g/d | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 1 + 2 | Urine $\rho_{41}$ | Feces $\rho_{51}$ | Accretion $\rho_{31}$ | $\rho_{21}$, 12 |
| 1 | Ca | 2.40±.38 | 2.30±.37 | 4.70±.24 | .072±.004 | .230±.014 | .356±.036 | 1.89±.30 |
| | Sr | 2.30±.25 | 2.24±.27 | 4.54±.16 | .280±.011 | .250±.011 | .358±.026 | 1.92±.23 |
| 2 | Ca | 1.38±.30 | 2.50±.75 | 3.88±.19 | .064±.006 | .088±.011 | .330±.033 | 4.35±1.31 |
| | Sr | 1.05±1.19 | 2.01±3.31 | 3.06±.76 | .180±.065 | .102±.037 | .262±.083 | 4.07±6.08 |
| 3 | Ca | 1.71±.29 | 1.79±.34 | 3.50±.18 | .186±.015 | .176±.016 | .474±.062 | 2.12±.40 |
| | Sr | 2.76±.57 | 3.73±.71 | 6.49±.39 | .607±.041 | .591±.043 | .337±.067 | 2.27±.43 |
| 4 | Ca | 2.07±.31 | 3.52±.39 | 5.59±.17 | .129±.006 | .149±.012 | .434±.056 | 2.18±.24 |
| | Sr | 1.92±.17 | 1.87±.14 | 3.79±.10 | .349±.010 | .216±.007 | .172±.023 | 1.22±.09 |
| 5 | Ca | 2.28±.27 | 5.01±.30 | 7.29±.15 | .061±.002 | .147±.007 | .428±.059 | 2.26±.14 |
| | Sr | 2.04±.34 | 2.39±.35 | 4.43±.18 | .131±.006 | .090±.005 | .441±.038 | 1.54±.23 |
| 8 | Ca | 2.76±1.32 | 1.85±1.46 | 4.61±.69 | .015±.002 | .173±.026 | .370±.067 | 3.94±3.11 |
| | Sr | 2.58±.32 | 3.75±.62 | 6.33±.34 | .129±.007 | .245±.013 | .349±.034 | 3.82±.63 |
| 10 | Ca | 1.47±.32 | 2.11±.53 | 3.58±.14 | .050±.004 | .108±.009 | .221±.027 | 3.17±.79 |
| | Sr | 1.10±.55 | 1.97±1.23 | 3.07±.25 | .172±.025 | .134±.019 | .172±.026 | 3.30±2.01 |
| $\bar{x} \pm \sigma_m$ | Ca | 1.94±.17 | 2.81±.45 | 4.75±.52 | .065±.017 | .146±.017 | .353±.034 | 2.51±.30 |
| | Sr | 2.07±.22 | 2.54±.30 | 4.61±.52 | .242±.057 | .208±.052 | .289±.041 | 2.18±.38 |

Values are means ± standard deviation of value ($\sigma_n$). $\bar{x}$ = mean, $\sigma_m$ = standard error of sample. Compartment 1 = plasma, extracellular, intracellular Ca space; compartment 2 = exchangeable bone. $\rho_{31}$ = accretion—flow into bone, $\rho_{41}$ = urinary Ca excretion, $\rho_{51}$ = fecal (endogenous) Ca excretion, $\rho_{21}$ = flow into exchangeable bone, $\rho_{12}$ = flow from exchangeable bone into compartment 1.

of the substances being traced remain constant during the experiment; 2) the rates of transfer of the substance being traced, between compartments, and into and out of the system, are constant during the experiment; 3) intracompartmental mixing is rapid.

The solution of the equations describing the linear two-compartment open model (shown in Fig. 1) gives parameter values which fit the observed data and therefore the model appears to be consistent with the data. Compartment 1 is assumed to consist of plasma-extracellular space and intracellular space of soft tissue and possibly some exchangeable bone. Since compartment 1 achieves equilibrium in 30 min, the above-mentioned subcompartments are lumped together in the model. Compartment 2 comes into equilibrium within 2–3 days and is assumed to consist largely of rapidly exchanging bone. Activity is transferred from compartment 1 to compartment 2 ($\rho_{21}$) and is lost to "slowly exchanging" bone ($\rho_{31}$), and to the outside via urinary excretion ($\rho_{41}$) and endogenous fecal excretion ($\rho_{51}$). Although in the model the slowly exchanging bone (compartment 3) is illustrated as feeding back ($\rho_{13}$) into compartment 1, in the short-term study (10 days) described here, compartment 3 is treated as an irreversible open compartment similar to the urine and feces compartments ($\rho_{13} = 0$). The tracer is presumed to move slowly through this compartment until it reaches the resorption sites in significant quantity. Thus the 10-day data were insufficient to derive this feedback function for either Ca or Sr. Thus compartment 3 is illustrated in Fig. 1 as a series of subcompartments or as an infinitely expanding compartment. Longer term data are required to obtain the resorption or slow-exchange rate from bone.

*Computer analysis.* The solution of the model parameters, i.e., compartment sizes and transfer constants, was performed on an IBM-7094 with the NIH-OMR SAAM program (2–4). Once the initial estimates are provided, the program solves the required differential equations by an iterative procedure. The program computes a set of values for the parameters that give the best least-squares fit of the data to the model. The least-squares solution gives values of the parameters and their standard deviations as well. Since only the plasma data are expressed in absolute values, it is necessary to determine a proportionality constant ($k$) for each set of data. The computation of these constants ($k$) is also included in the computer solution.

In the computer solution, the whole-body counter data and the knee data are handled by a summer. The summer develops a linear combination of the data of the various compartments to fit the whole-body and knee data. In the summation of the whole-body counter data, the three compartments were weighted equally by a fixed factor, designated sigma. In analysis of the knee data, the sigmas for each compartment were independent and determined by the computer. A more detailed explanation of this aspect of the computer program was presented in an earlier study (unpublished data).

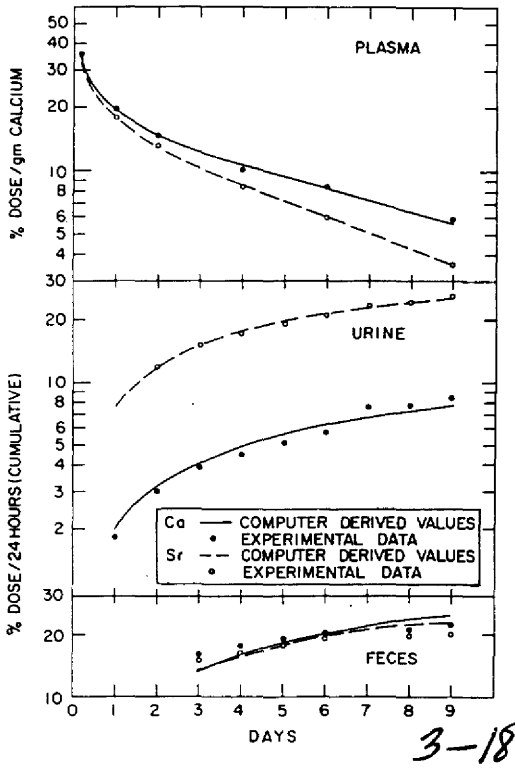


FIG. 2. IBM-7094 computer-derived fit to experimental plasma, feces, and urine data. ●, Ca experimental data point; ○, Sr experimental data point; ————, computer-derived curve for Ca; – – – –, computer-derived curve for Sr.

## RESULTS

The values of the transfer constants and compartment sizes of both Sr and Ca models obtained by the computer program are presented in Table 2. The standard deviations ($\sigma_n$) of each of these parameter values are also presented. The weighted mean of the seven subjects ($\bar{x}$) and the standard error of the mean ($\sigma_m$) are also shown in the table.

The computer-derived plasma and cumulative urinary and endogenous fecal excretion values for Ca and Sr are plotted along with the experimentally derived curves of a representative subject (*subject 1*) in Fig. 2. Whole-body counter data and knee data for Ca and Sr are plotted along with the computer-derived curves in Fig. 3. (The computer-derived values for both whole-body retention and knee retention represent the weighted summation of the tracers in all three compartments.)

The mean whole-body retention data for the seven subjects expressed as ratio of Sr/Ca over 30 days are shown in Fig. 4. The ratio falls rapidly due to the preferential excretion of Sr and reaches an approximate asymptote of 0.660 by 18 days. The level of both $Sr^{85}$ and $Ca^{47}$ in the knee can be expressed in the same manner as the whole-body retention data. The Sr/Ca ratio in the knees over 30 days, as shown in Fig. 4, also falls off rapidly and levels off at about 18 days but at a higher value than the whole-body data (0.730).

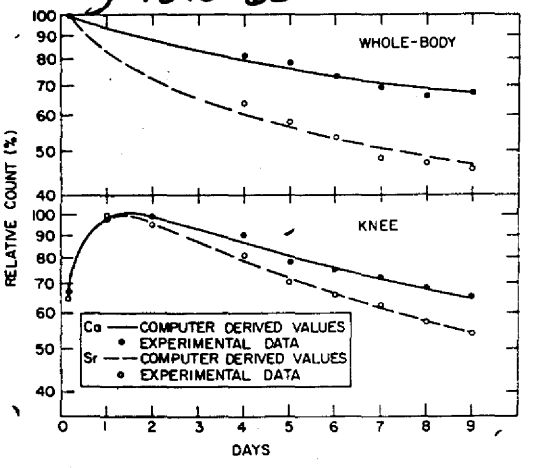


FIG. 3. IBM-7094 computer-derived fit to experimental whole-body counting and knee data. ●, Ca experimental data point; ○, Sr experimental data point; ————, computer-derived value for Ca; – – – –, computer-derived value for Sr.

## DISCUSSION

From the experimental data and the postulated general relationships of the variables, the computer calculated a set of values for the parameters which yielded a mean least-squares fit for the observed data. The fit of the model, thus obtained, to the experimental data for both Sr and Ca can be seen in Figs. 2 and 3. The "goodness of fit" of the model is measured by the random scatter of the data about the predicted values and the close correspondence between the observed data and the curve of computer-derived values. Quantitative examination of the variability of the observed data from calculated values indicates that the model represents both the Ca and Sr data very well. The model can be said to approximate both Ca and Sr metabolism and to be consistent with the biological data collected.

The standard deviations of the compartment sizes and transfer constants ($\sigma_n$) are functions of the individual datum points as specifically related in the equations of the model. The ability of the computer program to assess the standard deviation or precision of the model on the basis of the data being considered permits the comparison of the fit of Ca and Sr data to the model. The mean standard deviations ($\sigma_n$) (expressed as percentages) for the various calculated parameters of Ca and Sr were computed for the seven subjects considered here.

| Calculated Parameters | $Ca^{47}$ $\sigma_n$, % | $Sr^{85}$ $\sigma_n$, % |
|---|---|---|
| Compartment 1 | ±21.9 | ±19.4 |
| Compartment 2 | ±26.8 | ±21.5 |
| Compartment 1 + 2 | ±5.7 | ±4.9 |
| Accretion ($\rho_{21}$) | ±13.0 | ±14.7 |
| Urine ($\rho_{41}$) | ±8.0 | ±10.6 |
| Feces ($\rho_{51}$) | ±9.2 | ±11.0 |
| Flux ($\rho_{12,21}$) | ±26.8 | ±21.5 |

The size of compartments 1 and 2 and the transfer rate between them ($\rho_{12,21}$) are determined primarily from data obtained in the 1st day. Since only two plasma samples were taken in this interval, the above three

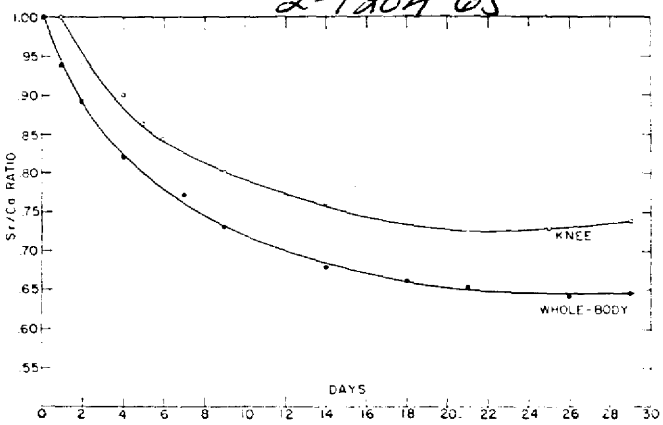


FIG. 4. Strontium/calcium ratio in whole body and knee (mean of seven subjects). The plotted values are expressed as the mean ratio of the percent of the administered doses of Sr over Ca in each individual subject.

values are poorly defined and the standard deviations are relatively large compared to the values of the other parameters.

The parameter values derived from the Sr data for each subject except for excretion are, with few exceptions, lower than those derived from the Ca data and the correlation is very high. The Sr values are lower than the Ca values by about the same percent as the statistical uncertainty in the individual measurements ($\sigma_n$). It is clear, therefore, that with less precise methods of analysis, the differences between the Sr and the Ca values are not readily discernible. For example, in a double tracer study on rats, Bauer and Carlsson (1) found that the accretion rate (A) and the exchange capacity (E) obtained with Ca and with Sr were not significantly different.. By the use of Bauer's analytical procedure, no significant differences could be found in the A and E values of six patients studied with $Sr^{85}$ and $Ca^{47}$, although an analogue computer solution of these data did suggest a smaller exchangeable pool for Sr as compared with Ca (8).

It is apparent that the spread in values for each parameter among the group is large. Statistical analysis of the grouped data indicated the absence of a significant difference between the means of the Ca and the Sr parameter values. Since the present study was limited to elderly males, a greater variability probably appears in the present results than would be expected in a younger group. The importance of extending these studies to a younger and more homogeneous population is manifest not only to establish more accurately the fine differences in the skeletal dynamics of Sr and Ca, but also to obtain data on this age group.

The mean urinary excretion rate of $Sr^{85}$ was approximately 3.7 times higher than that of the $Ca^{47}$, which is consistent with the known renal discrimination against Ca compared with Sr. The mean endogenous fecal excretion of $Sr^{85}$ was about 20 percent higher than that of $Ca^{47}$. The small systematic error in the fit of the fecal data (see Fig. 3) is probably due to the recycling of some of the tracer excreted into the gastrointestinal tract and to an error in the timing of the systematic collection of the stools. The data are insufficient to quantify this feedback from the gastrointestinal tract and it could not be included in the present model. The known gastrointestinal discrimination factor of two between Sr and Ca in this recycling may also account for some of the differences in the values between the Ca and the Sr data.

In a study of the comparative kinetics of Sr and Ca in man, Bronner et al. (5) measured the rate constants of the various processes independent of any model for Sr metabolism. Only the fecal excretion constant and the bone rate constant were found to be the same for Sr and Ca. The authors concluded that Sr, as a tracer for Ca, gives only approximate values, since Sr is expressed in terms of an apparent circulating plasma volume and not in units of mass as in the case of the Ca tracer. Since the present calculated values are based on the absolute concentration of Ca in compartment 1, to obtain the absolute Sr concentrations, a different proportionality constant would be required to determine the absolute levels of Sr based on the concentration of stable Sr in plasma. However, since it has not been demonstrated that the amount of stable Sr in plasma or bone is constant, it is more advantageous to continue to express Sr in terms of Ca because of the constancy of the Ca.

It is obvious that long-term retention data are required to determine differences in turnover and resorption of Sr and Ca. Unfortunately, because of the short half-life of $Ca^{47}$, this comparative study could only be carried out with sufficient accuracy for 30 days. Examination of the values for the Sr/Ca ratio for the whole-body retention obtained by whole-body counting over the 30-day period reveals the same patterns and absolute levels as previously noted (8). There is a rapid fall in the level of the ratio until an asymptote is reached at approximately 18 days and continuing to 30 days. The same pattern of Sr/Ca levels with time was found for the knee data except that the ratio leveled off at a higher value than for the whole-body retention data. This higher level may reflect the higher proportion of bone with its slower turnover of Ca in the knee field as compared to the whole-body detector's field, which includes a larger nonosseous component.

Since the Sr/Ca ratio does not continue to decrease progressively with time as a function of the differential renal discrimination, the turnover of Sr and Ca by bone must differ. The constancy of the Sr/Ca ratio after 18 days, assuming a constant renal discrimination against Sr, indicates that Sr must be returning to compartment 1 from bone less rapidly than Ca. Preceding this, in the period from 6 to 14 days, a similar leveling of the Sr/Ca ratio in urine observed in several patients (most noticeable in an osteoporotic patient) by Heaney (11) was interpreted to indicate preferential release of Sr from bone to plasma. The Sr enrichment of compartment 3 after 18 days due to the preferential retention of "bone-fixed" Sr is complicated by the differences in excretion of Sr and Ca and the presence of different sizes of non-

osseous pools. Nevertheless, the higher retention of Sr from 18 to 30 days indicates a slower turnover rate of Sr as compared to Ca, and probably reflects the different modes of binding and resorption of the two elements by bone.

To characterize the resorption or feedback differences between Sr and Ca, it is necessary to employ the model in analyzing the long-term (30-day) data. Unfortunately, attempts to fit the 30-day data for both Ca and Sr to the assumed two-compartment model have been unsuccessful to date. This lack of fit is probably due to the omission of a feedback from compartments 3 to 1 ($\rho_{13} = 0$) to simulate bone resorption or slow exchange. This feedback is not significant in the first 10 days, but must occur in the period 10–30 days. It would appear that the function describing this feedback is not a simple exponential function, but is related to the complex nature of compartment 3 itself. It would be most desirable to improve the model with this additional feedback loop simulating resorption in order to fit not only the 30-day data but also the longer term Sr data, as well as it now fits the 10-day data.

The present study demonstrates that while the absolute values of the parameters obtained with Sr do differ from those obtained with Ca, the differences are small and the Sr-derived values do reflect Ca metabolism quite well in terms of the model derived from the 10-day data. With the inclusion of the longer term data, it should be possible to improve the model and permit the quantification of the differences in the physiological parameters of resorption, slow exchange, and bone turnover as measured by Ca and Sr.

## APPENDIX

Definition of statistical terms in Table 2.

$$\bar{x} = \frac{\sum_{n=1}^{k} x_{(n)} \frac{1}{(\sigma_{(n)})^2 + \sigma_p^2}}{\sum_{n=1}^{k} \frac{1}{(\sigma_{(n)})^2 + \sigma_p^2}}$$

$$\sigma_p^2 = \frac{\sum_{n=1}^{k} (\bar{x} - x_{(n)})^2 \frac{1}{(\sigma_n)^2 + \sigma_p^2}}{\sum_{n=1}^{k} \frac{1}{(\sigma_{(n)})^2 + \sigma_p^2}}$$

$$\sigma_m = \frac{\sigma_p}{\sqrt{N - 1}}$$

$\sigma_n$ = standard deviation of individual values (as determined by computer)
$\sigma_p$ = standard deviation of population
$\sigma_m$ = standard error of sample mean

## REFERENCES


1. BAUER, G. C. H., AND A. CARLSSON. A comparative study on the metabolism of $Sr^{90}$ and $Ca^{45}$. *Acta Physiol. Scand.* 35: 56–66, 1955.
2. BERMAN, M. The formulation and testing of models. *Ann. N. Y. Acad. Sci.* 108: 182–194, 1963.
3. BERMAN, M., E. SHAHN, AND M. F. WEISS. The routine fitting of kinetic data to models: a mathematical formalism for digital computers. *Biophys. J.* 2: 275–287, 1962.
4. BERMAN, M., M. F. WEISS, AND E. SHAHN. Some formal approaches to the analysis of kinetic data in terms of linear compartmental systems. *Biophys. J.* 2: 289–316, 1962.
5. BRONNER, F., J. P. AUBERT, L. RICHELLE, P. D. SAVILLE, J. A. NICHOLAS, AND J. R. COBB. Strontium and its relation to Ca metabolism. *J. Clin. Invest.* 42: 1095–1104, 1963.
6. COHN, S. H., S. R. BOZZO, N. GLATSTEIN, C. CONSTANTINIDES, J. LITVAK, AND E. A. GUSMANO. Formulation of a compartmental model in a study of partial parathyroid deficiency. *Metab. Clin. Exptl.* 13: 1356–1368, 1964.
7. COHN, S. H., S. W. LIPPINCOTT, E. P. CRONKITE, AND P. G. REIZENSTEIN. Application of whole-body gamma spectrometry to clinical tracer studies. *Whole Body Counting*. Vienna: I.A.E.A. 1962, p. 469–480.
8. COHN, S. H., S. W. LIPPINCOTT, E. A. GUSMANO, AND J. S. ROBERTSON. Comparative kinetics of $Ca^{45}$ and $Sr^{85}$ in man. *Radiation Res.* 19: 104–119, 1963.
9. COMAR, C. L., AND R. H. WASSERMAN. Strontium. In: *Mineral Metabolism*, edited by C. L. Comar and F. Bronner. New York: Academic, 1964, vol. 2, part A, p. 523–572.
10. HART, H. E. (editor). Symposium on multi-compartment analysis of tracer experiments. *Ann. N. Y. Acad. Sci.* 108: 1–338, 1963.
11. HEANEY, R. P. Evaluation and interpretation of calcium-kinetic data in man. *Clin. Ortho.* 31: 153–183, 1964.
12. LIKINS, R. C., H. G. MCCANN, A. S. POSNER, AND D. B. SCOTT. Comparative fixation of calcium and strontium by synthetic hydroxyapatite. *J. Biol. Chem.* 235: 2152–2159, 1960.
13. ROBERTSON, J. S. Theory and use of tracers in determining transfer rates in biological systems. *Physiol. Rev.* 37: 133–154, 1957.
14. SAMACHSON, J., AND H. LEDERER. The uptake of $Ca^{45}$ and $Sr^{85}$ by bone *in vitro*. *Arch. Biochem. Biophys.* 88: 355–360, 1960.