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Strontium Metabolism and Strontium-Calcium Discrimination in Man. (23231)

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The need for a better understanding of the behavior of strontium in man has arisen because of development of nuclear weapons and potential applications of atomic energy. Radioactive strontium, disseminated worldwide, eventually finds its way into accessible calcium reservoirs of the biosphere (of which the human skeleton is one) and tends to attain steady state movement between such reservoirs. Information is needed to permit prediction of levels to be attained in the human population in terms of the amount falling out upon the earth or becoming incorporated in the diet. Since on a long-term basis the human burden will result from strontium contamination of dietary calcium, considerable advantage is gained by studying the comparative behavior of these two elements. Knowledge of the manner in which various physiological processes affect retention of strontium and calcium in the body may lead to ways in which the comparative retention can be modified at will. It is of practical importance to determine the extent to which the urine or blood levels can be used to estimate the body burden or over-all intake of radioactive strontium.

The world-wide distribution of strontium 90 has been reviewed by Libby(1) and Kulp *et al.*(2). The metabolism of strontium in laboratory and domestic animals has been extensively studied(3-6), and the behavior of intravenously injected strontium 85 in human subjects has been reported by Spencer *et al.*(7). Harrison *et al.*(8) have followed, in normal man, the course of stable strontium given in amounts (20 to 250 mg) that allowed analysis by radioactivation. These findings have been reviewed and compared with animal data by Comar and Wasserman(3).

The long-term problem is concerned with the behavior of essentially carrier-free radiostrontium ingested over an extended period with each meal. Therefore, in the present work, emphasis has been given to experiments that simulate this situation, rather than to the usual single parenteral dose-type experiment often employed in metabolic studies. Data are presented on the behavior of strontium 85 in man after single and daily feeding, and on the strontium-calcium discrimination as shown by daily feeding of strontium 85 and calcium 45 in double tracer studies.

Methods. These studies were done with chronically ill patients having leukemia or widespread malignant neoplasms. Carrier-free strontium 85 (cyclotron produced from rubidium; 65 day half life; no beta rays; 0.013 Mev X ray, 0.513 γ ray) and high specific activity calcium 45 were used. The levels of Sr 85 employed ranged from 5 to 20 microcuries for single dosage studies and from 1 to 3 microcuries per meal for the daily feeding experiments. In the double tracer studies, Ca 45 was given at about twice the microcurie amounts of Sr 85. The usual procedures for handling of samples and radioassay were employed(9) except as noted. The Sr 85 was counted with a well-scintillation crystal. Double counting was accomplished by scintillation measurement of the sample itself or of an aliquot of ash solution for Sr 85, and

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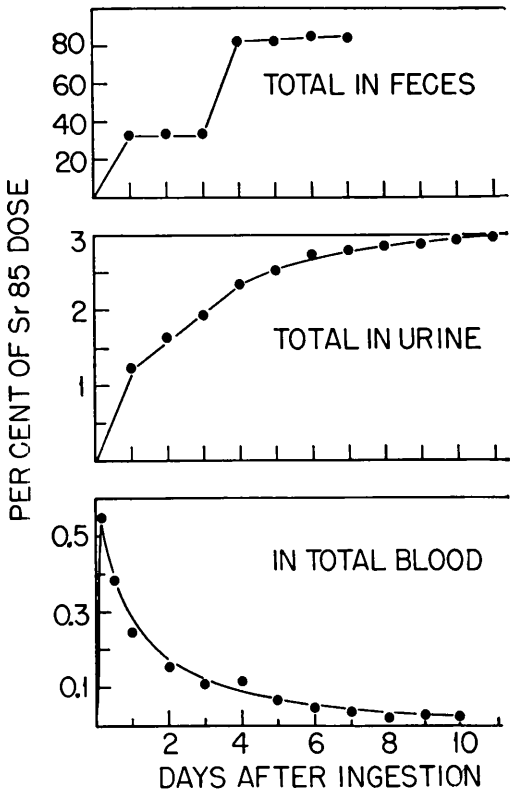

FIG. 1. Course of strontium 85 following a single ingestion (57-year-old woman with breast carcinoma and bone metastases, patient E).

conventional precipitation of calcium oxalate for beta counting of Ca 45. With this instrumentation and the relative amounts of the two radioisotopes in the samples, the Ca 45 did not contribute significantly to the scintillation counts, nor the Sr 85 to the beta counts.

Results. Single oral dosage. The course of Sr 85 following a single ingestion is illustrated in Fig. 1, which represents a study on a 57-year-old woman (E) with breast carcinoma and bone metastases. The total fecal excretion was about 86% of the ingested dose and, as shown, occurred within 4 days after ingestion. The total urinary loss was 3% with the highest excretion rate during the first day, a slower rate between 1 and 4 days, and a decreasing rate thereafter. The percentage of the dose in the total blood was calculated from blood concentrations by assuming a standard blood volume of 7.7% of the body weight. Of particular interest was that the peak concentration in the blood occurred at 4 hours or earlier after ingestion; this emphasizes the rapidity of absorption. A summary of excretions by several patients is presented in Table I. The effect of milk on increasing absorption has been discussed elsewhere(10). On the nonmilk diet the fecal excretion averaged 74% and the urinary excretion about 6%.

Daily oral dosage. Although it is theoretically possible to use single-dose data to calculate steady state levels resulting from daily ingestion, it was deemed advisable to obtain direct information. Two patients were given Sr 85 Cl_2 in water before each meal for 20 days. The over-all results are given in Table II; there is reasonable agreement between the excretion figures and those of the single dosage experiments as already presented. The time pattern is illustrated for patient F in Fig. 2. The percentage of the ingested dose retained in the body at each day was calculated by subtracting total excretion from total dose up to that day. It is of particular interest to note that the body burden of Sr 85 was

TABLE I. Fecal and Urinary Excretion of Single Dosages of Strontium 85.

Subject	Age	Sex	Diet	Condition	Feces % of dose	Urine % of dose
A	64	♂	Nonmilk	Generalized lymphosarcoma	86	1.8
A	64	♂	Milk		89	.7
B	68	♂	Nonmilk	Lymphoepithelioma	55	7.7
B	68	♂	Milk		35	.5
C	58	♂	Nonmilk	Generalized lymphosarcoma	59	7.8
C	58	♂	Milk		1	3.6
D	15	♀	Nonmilk	Brain tumor, medulloblastoma	84	11
D	15	♀	Milk		17	7.8
E	57	♀	Nonmilk	Breast carcinoma	86	3.0

still increasing up to the 20th day, even though a person of this age is probably in stable strontium balance(8). Thus it appears that there is a continuing net retention of ingested radiostrontium even at a time when plateau levels have been attained in the body fluids and presumably the exchangeable sites in the skeleton are saturated. A possible explanation is that unlabeled areas of bone are probably undergoing resorption at this time so that the corresponding accretion may result in net retention of radiostrontium but not of stable strontium. It will be important to determine for how long and at what rate the body burden increases after the start of ingestion by persons with fully developed skeletons. As expected, there was only a slight loss from the body after the dosage was stopped.

The feces curve, of course, reflects the irregular passage of the stool. The urinary excretion showed an upward trend with time but it is not possible to say whether a plateau level had been reached: the sharp drop after cessation of dosing emphasizes that urinary levels are primarily an indication of the previous day's intake rather than of the body burden. The plasma level showed a steady rise and a suggestion of a slight decrease before the dosing stopped, although this may not have been real.

Of particular interest is the blood picture as a function of time after the start of daily administration. Data from several patients are shown in Fig. 3. It is noted that 2 patients with leukemia showed a low blood level and attained a plateau within 5 or 6 days. A

TABLE II. Steady State Excretions and Plasma Levels of Strontium 85.

Patient	F	G
Age	47 yr	28 yr
Sex	♀	♂
Disease	Ovarian carcinoma	Granulocytic leukemia
Duration of feeding	20 days	20 days
% of dose in feces at steady state	60	60
% of dose in urine at steady state	8.8	3.2
% of daily dose in plasma at steady state	3.9	1.0

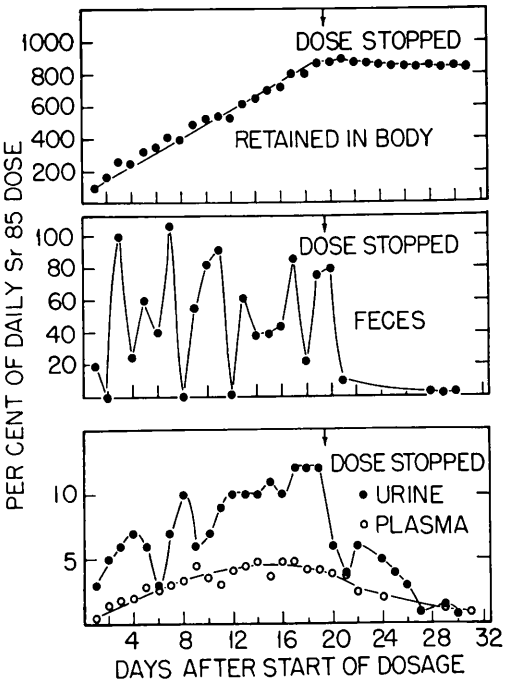

FIG. 2. Course of strontium 85 following ingestion with each meal (47-year-old woman with ovarian carcinoma, patient F).

patient with an osteolytic lesion demonstrated a steep slope during the first 6 days. Patients with ovarian carcinoma were intermediate in terms of both slope and level whereas the few points on a 9-year-old boy with cerebellar medulloblastoma indicated that a plateau had been reached by the fourth day.

Tissue distribution. Tissue samples were available from some of the patients at autopsy at varying times after the metabolism experiments. The concentrations of Sr 85 calculated as percentage of dose per kilo of tissue are presented in Table III. Definite interpretations are difficult because of the differing experimental conditions; however, the general levels are of interest and it is clear that the behavior of the Sr 85 is at least qualitatively similar to that in animals. From the blood value of patient H at 8 hours after injection, it is inferred that there is the usual blood disappearance curve. At a few hours after injection it is noted that the blood, kidney, spleen, thyroid, bones, and bone marrow were about the same level, whereas the other tissues were much lower. At the longer

TABLE III. Tissue Distribution of Sr 85 in Human Subjects. (Values calculated as % of dose per kilo fresh wt.)

	Patient, age (years), disease			
	H	I	C	G
	73	47	58	28
	Myeloma	Ovarian cystadenocarcinoma	Generalized lymphosarcoma	Leukemia
Admin. and time schedule	Intraven., died 8 hr after dosage	Intrav., died 17 days after dosage	2 equal oral doses 32 and 19 days before death	Oral with each meal for 19 days, died 40 days after last dose
Blood	2.7	.36		
Muscle	.67	.14	.011	.15
Heart		.19		.12
Lung		.63	.35	.54
Colon	.29	.44	.021	.44
Liver	.79	.26		
Kidney	1.6	.36	.19	.24
Spleen	1.1	.29	.52	1.0
Thyroid	1.6	1.7		1.1
Adrenal		.32		
Pancreas	.70	.41		.19
Rib	2.2	8.3	.22	
Femur shaft	1.0	4.2	.29	2.3
Medullary bone				
sternum		1.3	.33	1.8
vertebra	4.0	5.4	.80	1.3
ilium	3.7	8.7		4.1

time intervals there was generally the pattern of high bone values and lower blood and soft-tissue values; for example, concentrations in the femur shaft ranged from 15 to 30 times those of muscle.

Strontium-calcium discrimination. Double tracer procedures and rationale for estimation of strontium-calcium discrimination in rats have been described(4). The same methods have been used with human subjects except that Sr 85 was employed instead of Sr 89. Terminology and equations are as follows:

Strontium-Calcium Observed Ratio (OR)

$$OR_{sample\text{-}precursor} = \frac{\text{Sr/Ca of sample}}{\text{Sr/Ca of precursor}} \quad (1)$$

Strontium-Calcium Discrimination Factor (DF)

$$DF_{absorptive} = \frac{100 - \%\ \text{Sr 85 in feces}}{100 - \%\ \text{Ca 45 in feces}} \quad (2)$$

$$DF_{urinary} = \frac{OR_{body\text{-}diet}}{DF_{absorptive}} \quad (3)$$

Since the major route of exposure of the human population is via milk (at least in the Western countries), the following experiments were done by giving Sr 85 and Ca 45 in milk with each meal for 5 to 20 days. A summary of results on 4 patients is presented in Table IV. The most important observation was the $OR_{blood\text{-}diet}$ and the extent to which this value reflected the $OR_{body\text{-}diet}$. In the interests of brevity the data are not presented, but in the first 3 patients it was noted that the $OR_{blood\text{-}diet}$ on the second day of feeding and thereafter was not significantly different from average values after feeding for 15 to 20 days. Therefore it was felt that 4 to 5 days of daily feeding is adequate for this type of experiment.

With patient J complete collections of excreta were made and the $OR_{retained\text{-}diet}$ was calculated by difference between dose and excretion. In agreement with previous studies on rats(4), the $OR_{retained\text{-}diet}$ was slightly higher than the $OR_{blood\text{-}diet}$. The $OR_{retained\text{-}diet}$ should represent the ratio in the skeleton. Patient L died about one month after the last dosage and samples of rib and femur were analyzed to give $OR_{bone\text{-}diet}$ values. It has been shown that the $OR_{bone\text{-}diet}$ value after a single dose tends to decrease with time(2)

TABLE IV. Summary of Strontium-Calcium Discrimination in Human Subjects as Shown by Double Tracer Method.

	Patient, age, sex and disease			
	J 73 yr, ♀ Primary tumor unknown	K 38 yr, ♀ Ovarian carcinoma	L 25 yr, ♂ Chronic granulocytic leukemia	M 9 yr, ♂ Cerebellar medulloblastoma
Days on test	11	15	12	6
$OR_{blood-diet}$	.62	.50	.52	.52
$OR_{retained-diet}$	.75			
$OR_{bone-diet}$			.53	
$OR_{urine-diet}$	1.8	1.6	2.2	
% total excretion*				
Ca 45 in urine	1.8			
Sr 85 " "	3.1			
Ca 45 in feces	36			
Sr 85 " "	50			
$DF_{absorptive}$	.78			
$DF_{urinary}$	.87			
% daily dose/ml plasma†				
Ca 45	.0014	.0013	.00042	.0015
Sr 85	.00085	.00061	.00021	.0008
% daily dose in total blood†				
Ca 45	2.9	2.5	.96	1.4
Sr 85	1.8	1.2	.48	.72
% daily dose in urine/day†				
Ca 45	1.4	1.7	.10	
Sr 85	2.6	2.7	.23	

* $\frac{\text{Total in excreta}}{\text{Total ingested}} \times 100$. † At steady state.

and this seems to fit with the values of $OR_{blood-diet}$ and $OR_{bone-diet}$ for this patient. The $DF_{absorptive}$ and $DF_{urinary}$ values of 0.78 and 0.87, respectively, are in agreement with values obtained for rats on a milk diet(4). The levels in blood and urine are in fair agreement between patients except for the low values from patient L with leukemia. It may be coincidental but it should be noted that patient G (Table II), also with leukemia, showed a lower plasma and urine level. The general plasma and urine levels were also in agreement with those reported in Table II.

Discussion. It is evident that the behavior of radiostrontium in man is not essentially different from that in animals. The major points include (a) rapid absorption from the gastrointestinal tract; (b) increased absorption and retention when milk is given simultaneously; (c) rapid removal from blood for deposition in bone and to a lesser extent excretion in the urine; (d) high retention of radiostrontium once it has been deposited in bone; and (e) preferential absorption of calcium and preferential urinary excretion of strontium. Under conditions of daily intake it is estimated that the plasma level would range from 0.0006 to 0.001% of the daily intake per ml. The daily urinary excretion is expected to range from about 1 to 10% of the daily intake, being variable between persons and reflecting primarily the previous day's ingestion.

The comparative behavior of the two elements in man is apparently similar to that in rats. There was preferential absorption of calcium from the gastrointestinal tract and preferential excretion of strontium in the urine. It can be inferred that there was little discrimination in movement between blood and bone (Table IV, patient L). This is in disagreement with the interpretations of Kulp *et al.*(2), based on single dosage studies.

It is of interest to consider the extent to which the results presented may apply to normal persons. There seems no doubt that the

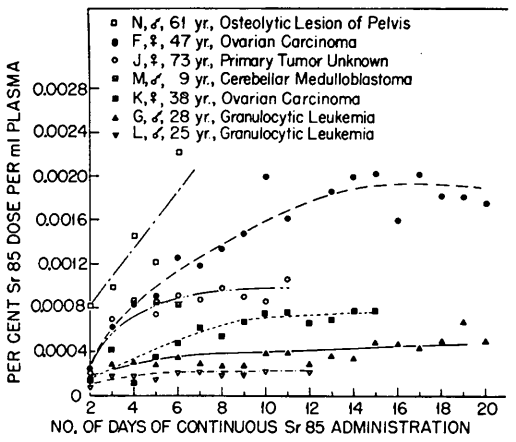

FIG. 3. Summary of plasma levels of strontium 85 following ingestion with meals over several days.

blood levels as presented in Fig. 3 indicate a dependence upon condition of the patient. The absorption values, however, are all quite similar to those reported by others(3). It is of special interest to note that similar discrimination values were obtained for patients with dissimilar conditions (leukemia *vs.* cerebellar medulloblastoma or ovarian tumor). Thus it might be reasonable to conclude that the disease condition, in these patients at least, affected the over-all behavior of calcium and strontium in the same way, if at all.

In evaluation of the discrimination that takes place against strontium in favor of calcium, we are proposing a factor of 2 for the calcium and strontium derived from dairy products, based on the data reported here. The discrimination is not known between calcium and strontium of plant origin as eaten by man. From experience with rats on a nonmilk diet, one might expect the discrimination in man on a nonmilk diet to be greater than 2, perhaps as high as 4. Some of the factors that may influence discrimination of nonmilk strontium and calcium are the presence of milk in the diet and the over-all level of dietary calcium; data are not yet available to permit estimates of the effect of such variables.

Summary. 1) These studies indicate that the behavior of radiostrontium in man is similar to that in animals. When ingested in water solution by adults, about 74% was excreted via the feces and 6% via the urine; the absorption occurred mainly within 4 hours after ingestion. Values are given for the plasma and urinary levels attained at steady state under conditions of ingestion with milk at each meal; these may be of use for monitoring purposes. 2) Two leukemia patients showed low plasma and urinary levels of radiostrontium whereas a patient with an osteolytic lesion showed a tendency towards high plasma levels. 3) When radiostrontium and radiocalcium were fed simultaneously in milk with each meal for several days there was a discrimination against strontium by a factor of about 2; this resulted almost equally from preferential absorption of calcium and preferential urinary excretion of strontium.

Note added in proof:

In recent studies with 4 patients on non-milk diets over periods up to 10 days, Dr. Daphne Papadopoulou in this laboratory observed a mean $OR_{blood\text{-}diet}$ value of 0.44 with a standard deviation of ± 0.05.

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