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Research Article

STRONTIUM^{85} AND CALCIUM^{45} METABOLISM IN MAN [1, 2]

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Preliminary reports were recently published from this laboratory on the metabolism of intravenously administered radiostrontium and on the effect of calcium upon strontium excretion in man (1, 2). The absorption, the digestive juice excretion and tissue retention have been studied following the oral and intravenous administration of Sr^{85}. Furthermore, the metabolism of orally administered radiostrontium has been compared with that of radiocalcium in the same patients (3, 4). These data form the basis of this communication.

MATERIALS AND METHODS

The six patients listed in Table I were studied on the Metabolic Research Ward. They were maintained on a controlled, analyzed, low calcium diet containing approximately 150 mg. calcium and 600 mg. phosphorus per day (5). Patient 4 received 520 mg. calcium as daily supplement in the form of calcium gluconate. The diet as well as the excreta were analyzed for nitrogen, calcium and phosphorus and the metabolic balances of these constituents were determined on six-day metabolic pools. The urinary calcium was determined daily, the serum calcium once weekly. At the start of each study the patients received at 8:30 a.m. a tracer dose (0.1 to 0.4 μc. per kg.) [4] of Sr^{85} as the chloride. The radioactive solution was administered *orally* with breakfast to insure proper mixing of the isotope with the food. At the conclusion of these studies which lasted 12 to 40 days a second tracer of Sr^{85} was administered *intravenously* to four of these patients in the fasting state. Sr^{85} chloride (0.1 to 0.4 μc. per kg.) was injected rapidly into the clamped distal portion of the tubing of an intravenous infusion set. After completion of the injection the clamp was released and the isotope solution was flushed rapidly into the vein with the infusion fluid of 5 per cent glucose in water. The intravenous studies lasted 14 to 16 days.

Sr^{85} is a carrier-free isotope [5] produced by bombardment of rubidium^{85}. It is a pure γ-emitter, its energy is 0.51 mev. and its half-life is 65 days. The radioactivity of duplicate samples of plasma, urine and stool was measured in a well-type scintillation counter. The stability of the counting arrangement was checked daily against a uranium standard. The statistical counting error varied: in the initial phases of the experiment sufficient counts were taken to keep the probable error within 2 per cent. In later phases, counting rates were lower, and it was not feasible to maintain this precision, so that counting errors as high as 5 per cent were incurred. Standards were prepared for each patient at the time of administration of the isotope by delivering the same dose into a volumetric flask; appropriate dilutions were then prepared for counting. The standards were counted along with each set of experimental samples, thereby correcting for the decay of the isotope.

The radioactivity was determined on 2 to 5 ml. of plasma obtained 5, 15 and 30 minutes and 1, 4, 8 and 24 hours after the ingestion or injection of the isotope. Thereafter, plasma was obtained every morning in the post-absorptive state during the first week of each study and 2 to 3 times per week thereafter. The plasma radioactivity was calculated for the total plasma volume which was determined for each patient using T-1824 dye (6). The urinary output was separated on the day of the isotope administration in fractions at 1, 4, 8 and 24 hours. On the subsequent days, the 24-hour urine output was collected. Aliquots of 2 to 5 ml. of urine were used for radio-assays. Each stool specimen was collected separately, water was added to obtain a homogeneous mixture in a Waring blendor. The weight of the homogenate was determined and aliquots of 4 to 5 gm. were assayed in the scintillation counter. Multiple analyses of such aliquots indicated homogeneous distribution of the isotope. Since the radioactivity of the stool specimens was high after the ingestion of the tracer, these specimens were counted in a bismuth cathode γ-counter. The radioactivity was determined on the total stool homogenate and on several water rinses of the Waring blendor using Marinelli beakers.

Two patients (2 and 6, Table I) also received an oral tracer of Ca^{45} prior to the administration of oral Sr^{85}. Radiocalcium was administered orally as the chloride

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[4] A higher tracer dose was given to the first two patients of this study (Patients 5 and 6, Table I), to insure sufficient counting accuracy of the specimens for approximately 40 days.

[5] Produced by the Nuclear Science and Engineering Corporation, Pittsburgh, Pa.

TABLE I

Patients receiving Sr^{85} orally and intravenously

Patient number	Age	Sex	Diagnosis	Route of Sr^{85} administration	Duration of study *days*
1 H. R.	58	M	Carcinoma of lung. No bone metastases. Partial immobilization.	Oral Intravenous	13 15
2 I. B.	54	F	Carcinoma of uterus; lymphoma; osteoporosis. No bone metastases.	Oral Intravenous	12 14
3 B. H.	76	F	Senile osteoporosis	Oral Intravenous	14 16
4 H. B.	63	M	Paget's disease of bone	Oral Intravenous	12 14
5 S. M.	55	F	Carcinoma of breast. Bone metastases.	Oral	40
6 B. L.	72	M	Carcinoma of larynx. No bone metastases.	Oral	40

in isotonic saline with breakfast. The plasma levels, urinary and fecal excretions of Ca^{45} were followed in a manner similar to that outlined for Sr^{85}. The data on the Ca^{45}-metabolism of these two patients who were studied for 74 days and the techniques employed were previously published (7, 8).

RESULTS

The metabolism of an intravenously administered dose of Sr^{85} (plasma levels, urinary and fecal excretions) was described in a previous publication (2).

The plasma levels and urinary Sr^{85} excretions of two patients in the 24 hours following the oral administration of the tracer are listed in Table II.

Radioactivity was detected within 5 minutes in the plasma of B.L. and within 15 minutes of S.M. The Sr^{85} plasma level increased gradually, was highest 4 hours after ingestion of the tracer and declined thereafter. The rate of urinary excretion of Sr^{85} at 1, 4, 8 and 24 hours as well as the cumulative urinary strontium excretions are listed in Table II. The highest rate of Sr^{85} excretion per hour, 0.24 per cent of the dose, was noted between the 2nd and 4th hour in S.M. while it occurred between the 8th and 24th hour in B.L. at a level of 0.044 per cent of the dose. The cumulative urinary Sr^{85} excretion in the first 24 hours was 2.42 per cent and 0.90 per cent for the two patients, respectively.

TABLE II

Sr^{85} in plasma and urine following the ingestion of the tracer

Time interval after ingestion of Sr^{85}	S. M. Patient 5			B. L. Patient 6		
	Sr^{85}, % dose			Sr^{85}, % dose		
		Urine			Urine	
	Plasma*	Rate/hour	Cumulative	Plasma*	Rate/hour	Cumulative
5 minutes	0			0.035		
15 minutes	0.036			0.041		
30 minutes	0.081			0.18		
1 hour	0.48	0.04	0.04	0.28	0.002	0.002
2 hours	1.67	0.19	0.23	0.77	0.014	0.016
4 hours	1.85	0.24	0.70	1.60	0.029	0.074
8 hours	1.26	0.11	1.13	1.16	0.030	0.194
24 hours	0.80	0.08	2.42	0.74	0.044	0.904

* Calculated per total plasma volume. The plasma samples were obtained at the end of the indicated time intervals.

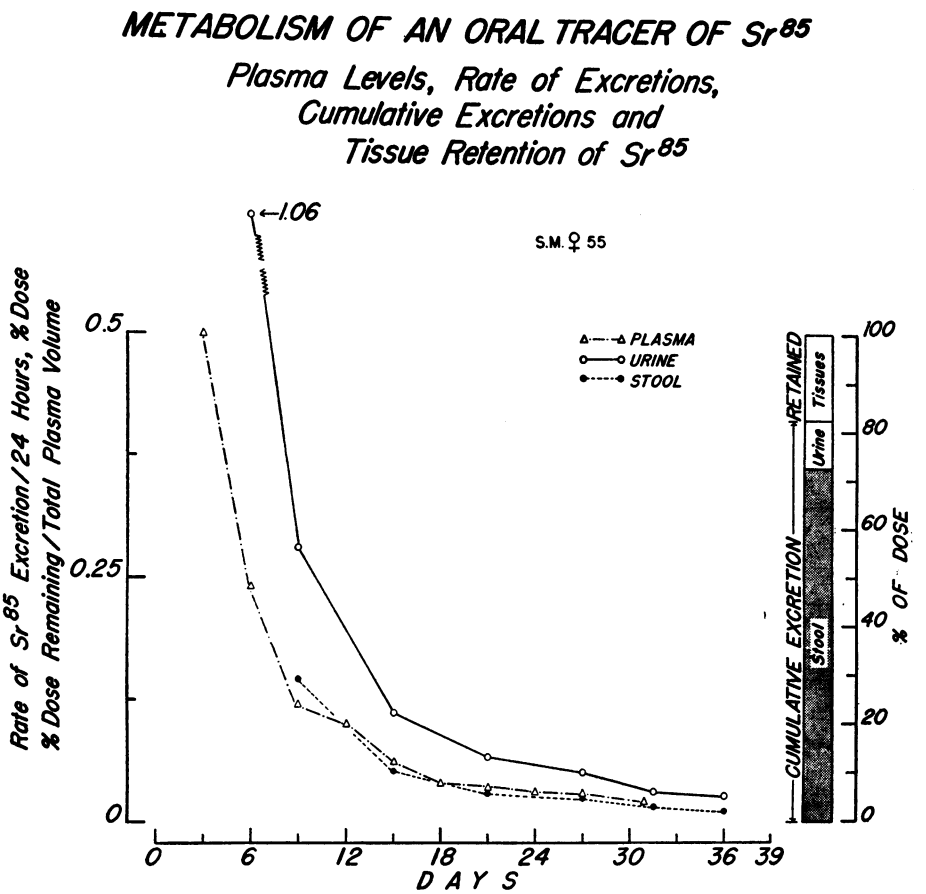

FIG. 1. RATES OF URINARY AND FECAL Sr^{85} EXCRETION PER DAY FOR EACH SIX-DAY METABOLIC PERIOD PLOTTED AT THE MID-POINT

One and six hundredths per cent Sr^{85} was excreted in the urine in the first six days of the study.

Figure 1 illustrates the metabolism of an orally administered tracer dose of Sr^{85} over a period of 39 days (Patient 5, Tables I and II). The plasma levels and rate of urinary Sr^{85} excretions declined after the fourth hour with time. The stool radioactivity was initially very high due to the presence of the unabsorbed dose; 70.7 per cent of the dose was contained in the stool by the fourth day of the study; a total of 71.2 per cent was excreted in six days. These values were too high to be included in the figure. After the passage of the unabsorbed fraction of the dose, the stool radioactivity declined gradually. The rate of urinary Sr^{85} excretion remained higher than the plasma level throughout the entire study. The bar-graph shows the total excretion and tissue retention by 39 days of the study: 72.7 per cent of the dose passed in the stool, 9.5 per cent in the urine. Less than 0.02 per cent remained in the plasma so that only approximately 18 per cent of the dose was retained in the tissues, in contrast to the much higher retention following the intravenous tracer (2).

The results of a 12-day study of 4 patients who received Sr^{85} orally and intravenously are listed in Table III. The urinary excretion differed greatly from patient to patient and ranged from 57.2 to 14.2 per cent of the administered dose after the intravenous injection of the tracer. The excretion was lowest in Patient 4 who had Paget's disease of the bone. The Sr^{85} content of the stool also varied but to a lesser extent, from 14.2 to 6.5 per cent and was lowest in the patient with Paget's disease. The total excretions of Sr^{85} in urine

and stool in 12 days and the percentage of the administered dose retained in the body are listed for each patient in the respective columns. The lower half of Table III lists the results obtained in the same patients following the oral administration of Sr^{85}. The cumulative urinary excretions in 12 days were much lower than following the intravenous dose, the lowest, 2.9 per cent, was again noted in Patient 4. An average of 80 per cent of the dose (78.3 to 82.5 per cent) was contained in the stool. Due to the high strontium content of the stool, the total Sr^{85} excretion was higher and the remaining tissue retention considerably lower after the oral than the intravenously administered tracer dose. Approximately four to six times as much Sr^{85} was retained after the intravenous than after the oral dose. The first patient retained only 6.2 per cent of the oral dose after 12 days.

TABLE III

EXCRETION AND RETENTION OF Sr^{85} 12 DAYS FOLLOWING AN I.V. AND ORAL TRACER DOSE

	INTRAVENOUS Sr^{85}, % OF ADMINISTERED DOSE			
	CASE 1	CASE 2	CASE 3	CASE 4
URINE	57.2	35.3	31.6	14.2
STOOL	10.4	12.7	14.2	6.5
TOTAL EXCRETION	67.6	48.0	45.8	20.7
RETAINED	32.4	52.0	54.2	79.3
	ORAL			
URINE	14.8	8.8	8.4	2.9
STOOL	79.0	82.5	78.3	81.5
TOTAL EXCRETION	93.8	91.3	86.7	84.4
RETAINED	6.2	8.7	13.3	15.6

Calculation of endogenous fecal strontium

Following the intravenous dose, the stool radioactivity is of endogenous origin, *i.e.*, Sr^{85} excreted with the digestive juices into the gastrointestinal tract minus the fraction which is reabsorbed. However, following the *oral* dose, the radioactivity of the stool is of exogenous and of endogenous origin, the former being the unabsorbed Sr^{85}. Knowing the endogenous fecal strontium from the intravenous dose, the exogenous or unabsorbed fraction of the total stool radioactivity following the *oral* dose can be calculated. In this calculation it is assumed that the pattern of excretion of strontium with the digestive juices is the same whether the tracer is injected intravenously or absorbed from the gastrointestinal tract. The validity of this assumption has been proven for radiocalcium in studies performed on animals (9, 10) and in man (11).

Example. Twelve and seven tenths per cent of the intravenously administered dose of Sr^{85} was excreted in the stool of Patient 2 (Table III) *i.e.*, endogenous fecal strontium. Let x be the percentage of the oral dose which was absorbed and y the remainder which passes unabsorbed. Following the oral dose the total stool strontium of this patient was 82.5 per cent, consisting of this unabsorbed fraction y plus the endogenous fecal strontium which is 12.7 per cent of the absorbed fraction x, or 0.127 x. Therefore,

$$x + y = 100\%$$
$$0.127x + y = 82.5$$

Therefore

$$x = 20$$
$$y = 80$$

It follows that of the 82.5 per cent radioactivity contained in the stool 80 per cent is the unabsorbed tracer while the endogenous fecal strontium is 2.5 per cent, and 20 per cent is the absorbed dose. The other three patients absorbed 23.4, 25.4, and 19.8 per cent of the administered dose, respectively.

The endogenous fecal strontium of the 4 patients ranged from 1.3 to 3.5 per cent (Table IV). The lowest value was obtained in the patient with Paget's disease of the bone.

Comparison of the metabolism of intravenously and orally administered Sr^{85}

The data are summarized for 12 days and are listed in Table IV. As shown in Column 2, 25.4 to 19.8 per cent of the oral dose was absorbed. The total excretion—urinary and endogenous fecal strontium—ranged from 17.2 to 4.2 per cent (Column 3). By expressing these total excretions in per cent of the absorbed oral dose, the figures listed in the left half of Column 4 were obtained: 74 to 21 per cent of the absorbed oral dose was excreted. The good agreement between these figures and those obtained following the intravenous dose is evident. However, it should be

TABLE IV

METABOLISM OF ORAL AND INTRAVENOUS Sr^{85}
A 12 DAY STUDY

CASE No.	ABSORPTION OF ORAL Sr^{85} % OF DOSE	EXCRETION OF % DOSE Sr^{85}			COMPARISON OF EXCRETION OF Sr^{85} % OF ABSORBED DOSE AFTER	
		URINE	STOOL ENDOGENOUS	TOTAL	Sr^{85}, ORAL	Sr^{85}, I.V.
1	23.4	14.8	2.4	17.2	74	68
2	20.0	8.8	2.5	11.3	56	48
3	25.4	8.4	3.5	12.0	48	46
4	19.8	2.9	1.3	4.2	21	21

emphasized that the calculation of the endogenous fecal strontium following the oral tracer dose is based on the assumption that the pattern of excretion of strontium with the digestive juices is similar following the intravenous or oral administration of the tracer (see above).

Comparison of calcium and strontium metabolism

The metabolism of calcium and strontium was compared in two patients (2 and 6, Table I). Although the isotopes were not administered simultaneously, the experimental conditions of the studies were comparable. Figure 2 illustrates the study of one of these patients (Patient 2). The plasma level of Ca^{45} was higher than that of Sr^{85} throughout the study, whereas the urinary excretion of Ca^{45} was lower than that of Sr^{85}. The bargraphs illustrate the balance of these two tracers in 12 days: considerably less strontium than calcium remained in the tissues principally

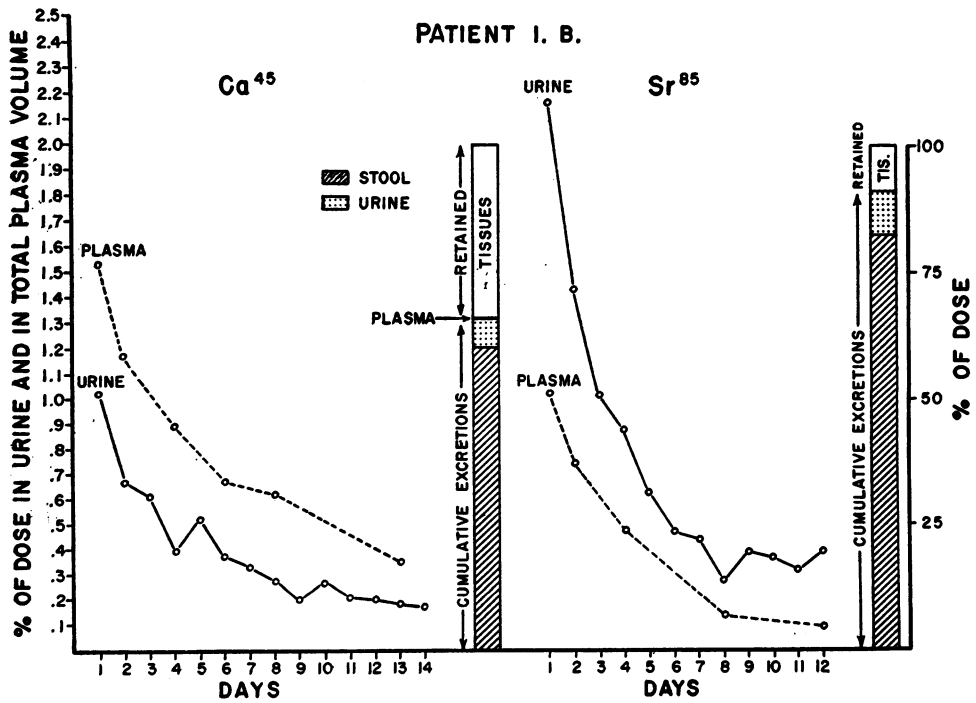

FIG. 2. METABOLISM OF Ca^{45} AND Sr^{85} FOLLOWING A SINGLE ORAL DOSE OF THE TRACERS

due to the higher fecal content and in part due to the higher urinary excretion of strontium.

Table V shows the balances of Sr^{85} and Ca^{45} of a 12-day study. A considerably greater amount of strontium than calcium is contained in the stool of both patients; the urinary strontium is almost twice as high as the urinary calcium excretion in I.B. (Patient 2) and slightly higher in B.L. (Patient 6). The latter patient retained both tracers better than the former. The ratio of calcium to strontium retention is approximately 4:1 and 2.5:1, respectively.

The absorption of strontium and calcium of the two patients is also compared in this Table. The fecal excretions were corrected for endogenous fecal strontium and calcium in patient I.B., and for endogenous fecal calcium in patient B.L. No correction could be made for endogenous fecal strontium in this latter patient since he has not received Sr^{85} intravenously. However, the marked differences in absorption of the oral tracers can be readily seen: the absorption of both tracers is better in patient B.L., than in I.B., but only approximately half as much strontium as calcium is absorbed by each of the patients. Although less strontium than calcium is absorbed from the gastrointestinal tract, more strontium than calcium is excreted by the kidney as the figures of this Table indicate, the ratios being 4:1 and 2.5:1 for the two patients.

TABLE V

Comparison of strontium and calcium excretions (cumulative) and of the absorption of the orally administered tracers, % dose—A 12-day study

		I. B.		B. L.	
		Sr^{85}	Ca^{45}	Sr^{85}	Ca^{45}
Excretions	Stool	82.51	60.15	70.60	39.45
	Urine	8.79	4.49	3.82	3.05
	Total	91.30	64.64	74.42	42.50
Retention		8.70	35.36	25.58	57.50
Absorption		20	43	30	67
Per cent of *absorbed* dose excreted in urine		44	10	13	5

DISCUSSION

The metabolism and skeletal uptake of strontium in man have received increasing attention in recent years for Sr^{90}, a β-emitting isotope with a 28-year half life is one of the major potential hazards of nuclear fission. Because of the radiation characteristics, Sr^{90} could not be used for clinical investigation. Through the availability of Sr^{85}, a pure γ-emitter with a short half life, it became possible to investigate the metabolism and skeletal uptake of radiostrontium in man. Some of these results were recently published (1–4). The metabolism and skeletal uptake of radiostrontium were extensively studied in various species of *animals:* the isotope was fed or administered parenterally to young, adult and pregnant animals (12–15), the effect of various diets was investigated upon the metabolism of radioactive strontium (12, 14, 15) and the uptake in various parts of the skeleton was studied by radio-assay and autoradiographic techniques (12, 16, 17). Acute and chronic toxicity of radiostrontium were investigated (18–21). The metabolism and skeletal uptake of radioactive calcium and strontium were compared (16, 22–24) and the transport of these isotopes from maternal blood into the fetus was described (15, 22, 23).

Most of the metabolic data described in the experimental section agree well with those obtained in animals. For instance, the injected radiostrontium disappears rapidly from the blood stream (13, 15); the ingested tracer can be detected within a few minutes in the plasma, the radioactivity increases gradually, reaches a peak by 2 to 4 hours and declines slowly thereafter. Similar results were obtained with ingested radiocalcium (7, 8, 25). The major pathway of excretion of the *absorbed* radiostrontium is via the kidney, irrespective of the route of entry of the isotope. The maximum excretion takes place within 24 hours of the administration of the tracer by either route. The urinary excretion of radiostrontium varied from patient to patient. For instance, it was much higher in a patient who had carcinoma of the lung and was partially immobilized than in one with Paget's disease of the bone. The former excreted an average of 150 mg. calcium per 24 hours in the urine whereas the latter excreted only 30 mg. calcium per day. Similar observations on the correlation between the magnitude of urinary calcium and radiostrontium excretions were made on a large number of pa-

tients in our laboratory. These data indicate that the urinary strontium excretion reflects well the metabolic state of the skeleton. The rate of fecal losses of strontium via the digestive juice varies also but less than the urinary excretion so that the ratio of urinary to fecal loss was as high as 6:1 and as low as 2:1; this was mainly due to the differences in the rate of urinary strontium excretion. Under exceptional conditions such as in sprue syndrome or in patients with extensive osteoblastic metastases secondary to cancer of the prostate the urinary strontium excretion may be so low as to be exceeded by the endogenous fecal strontium.

Following the oral administration of radiostrontium the predominance of urinary over fecal strontium excretion is masked by the large fraction of *unabsorbed* radiostrontium of the stool. This predominance becomes apparent only if this unabsorbed fraction is subtracted from the total stool radioactivity and the endogenous fecal strontium is calculated. Approximately 80 per cent of the oral tracer passes unabsorbed. Comparison of the metabolism of ingested and parenterally administered radiostrontium revealed good agreement of the data.

Until recently only scanty information was available in the literature on the metabolism of stable strontium. Harrison, Raymond, and Tretheway reported on the study of five volunteers who were given 20 to 250 mg. Sr^{++} by the intravenous or oral route (26). These authors emphasize the differences between experiments performed with carrier amounts of strontium and tracer studies and feel that the latter are only of value as a means of assessing radiotoxicity. However, their data are in good agreement with those reported in this communication employing the radioactive tracer except that our studies have proven that significant amounts of strontium are carried with the digestive juices into the gastrointestinal tract. Also, the higher rate of urinary strontium excretion in the study of the English investigators may in part be due to the unphysiologic amounts of carrier strontium administered since enhancement of urinary strontium excretion was recently reported to occur following the administration of unphysiologic amounts of carrier calcium (1, 2). Furthermore, the high calcium intake and the high calcium clearance may also have contributed to the high urinary strontium excretion of their volunteers. McCance and Widdowson suggested that strontium behaves physiologically like calcium (27). Shorr and Carter studied metabolic balances in patients with osteoporosis receiving varying amounts of calcium and strontium supplements orally (28). They found that strontium is a valuable adjuvant in the remineralization of the skeleton of these patients.

However, no data are available on the direct comparison of the metabolism of radiostrontium and radiocalcium in man. Studies on the two patients reported here who received both tracers orally disclosed that major differences do exist. Radiocalcium was found to be more efficiently absorbed than radiostrontium and, in spite of the poor absorption of the latter, its renal clearance was significantly higher than that of calcium so that the remaining body load of strontium was only one-fourth to one-half of that of calcium. The data obtained in humans are in agreement with those obtained in animals by Comar, Whitney, and Lengeman (23) and by Bauer, Carlsson, and Lindquist (24). The latter investigators report that the body load of Sr^{90} in rats is significantly lower than of Ca^{45} due to the higher renal clearance, and higher gastrointestinal excretion of strontium. However, they claim that the skeleton *per se* cannot differentiate between calcium and strontium and the differences in skeletal uptake are secondary to the higher renal clearance. Harrison, Raymond and Tretheway believe that the absorption of calcium from the gastrointestinal tract of man is at least twice as great as that of strontium (26).

The studies carried out with radioactive or stable strontium indicate that strontium cannot be used as an accurate indicator for calcium metabolism. Its possible use as an investigative tool in physiologic and pathologic states of the skeleton of man is currently under investigation. These data, analyzing plasma disappearance rates, renal clearance and digestive juice losses of radiostrontium and of radiocalcium will be reported in a subsequent communication. Also, balances of intake and excretion do not provide information on the localization of the retained element. Therefore, human tissues obtained at autopsy have been radioassayed for calcium and strontium. Some of these data have been recently presented (29).

SUMMARY

1. The metabolism of an orally administered tracer of radiostrontium was studied in 6 patients and compared with that of an intravenous tracer in four. The metabolism of an orally administered tracer dose of radiocalcium and of radiostrontium was studied in two patients.

2. The main pathway of excretion of Sr^{85} is via the kidney irrespective of the route of administration of the isotope and the urinary Sr^{85} excretion differs in various subjects depending on the state of the metabolism of the skeleton.

3. Another pathway of excretion of strontium is the intestinal tract: approximately 10 per cent of the absorbed strontium is eliminated via this route, *i.e.*, endogenous fecal strontium.

4. The absorption of ingested radiostrontium was determined by subtracting the endogenous fecal strontium from the stool radioactivity. Strontium is poorly absorbed from the gastrointestinal tract, an average of 80 per cent of the dose passes unabsorbed.

5. The metabolism of the absorbed fraction of the oral dose of Sr^{85} agreed well with that of the intravenous dose. The body load of strontium is approximately four to six times higher after the intravenous than after the oral dose.

6. Comparison of the metabolism of oral Sr^{85} and Ca^{45} revealed that calcium is better absorbed than strontium while the latter is preferentially excreted. For these reasons—poorer absorption and preferential excretion—significantly less strontium than calcium remains in the human body.

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