THE METABOLISM OF STRONTIUM IN CHILDREN

BY

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The continued rise in the accumulated fall-out of strontium-90 (Libby, 1956; Stewart *et al.*, 1957; Eisenbud, 1959) has prompted several estimates of its rate of transfer from the food-chain to the skeleton of man (Comar *et al.*, 1957a; Bryant *et al.*, 1958; Eckelmann *et al.*, 1958; Kulp *et al.*, 1959). The retention of radioactive strontium in man has also been studied, and the results obtained have been compared with those for calcium, to which it is closely related chemically (Langham and Anderson, 1957; Comar *et al.*, 1957b; Laszlo and Spencer, 1958).

The rate of increase in skeletal calcium has been shown to be most rapid in early infancy and between the ages of 8 and 18 years (Mitchell *et al.*, 1945). Experimental work on the absorption of dietary calcium in children has also shown that it is highest in these age-groups (Duckworth and Warnock, 1942; Widdowson, 1947; Beal, 1954). Since strontium, like calcium, is absorbed from the gastro-intestinal tract and deposited in the skeleton, it is to be inferred that the increase in body strontium would be greatest for these age-groups. No direct information is available, however, on the dietary turnover of strontium in children or the excretion of strontium that follows known oral doses.

In the present experiments the daily urinary and faecal excretion of strontium and calcium has been measured in four children between the ages of 4½ and 14½ years, over an initial period of seven or eight consecutive days immediately before receiving an oral dose of about 100 mg. of strontium (as strontium chloride). After the dose the daily urine and faecal excretion of strontium and calcium was estimated for 12 to 18 days and the net retention of the dose deduced. The results obtained have been compared with the excretion of an oral dose of strontium by adults from this unit (Harrison *et al.*, 1955).

Method

The children (three sons and a daughter of members of this unit and all unrelated) were on normal diets. Urine was collected over 24-hour periods, and after the volume had been recorded a known aliquot (about 10 ml.) was made up to 50 ml. with distilled water and set aside for the estimation of calcium. The remainder was treated with ammonium oxalate at about neutral pH, and after warming and standing for about one hour the solids were separated by centrifuging and the supernatant was discarded. The residue was dissolved in a minimum volume of strong nitric acid and the strontium precipitated as strontium nitrate by the addition of fuming nitric acid (Harrison and Raymond, 1955). After separating the insoluble nitrate precipitate by centrifuging, it was dissolved and made up to a volume of 25 ml.

Faeces were air-dried and subsequently ashed at about 600° C. for about 14 hours. The resultant ash was dissolved in warm 4N hydrochloric acid and any insoluble material (silica and carbon) removed by centrifuging. A known aliquot (about 1% of the total) was removed for calcium estimation. The subsequent treatment of the remainder was exactly similar to that described for urine.

Calcium estimations were made on a Unicam SP900 flame-spectrophotometer by an additive standard method. Strontium was determined on the same instrument by a similar method (Harrison, 1958).

The single dose of strontium chloride (containing 100 mg. of strontium in 25 ml. of distilled water) was taken at breakfast-time on the seventh or eighth day of the experimental period.

Results

The results of the separate experiments are shown in Tables I to IV. The days preceding that on which

TABLE I.—*Urinary and Faecal Excretions of Strontium and Calcium in S.R.W. (Boy age 4 years 10 months). Dose, 99.5 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
-7	0.056	50	—	—
-6	0.048	36	1.19	1.21
-5	0.045	35	1.33	0.91
-4	0.032	30	—	—
-3	0.059	46	0.76	0.59
-2	0.033	27	—	—
-1	0.051	43	1.05	0.76
0	1.14	48	0.51	0.21
1	0.90	28	60.9	0.52
2	0.51	40	—	—
3	0.37	62	21.2	0.63
4	0.136	42	—	—
5	0.293	68	—	—
6	0.268	73	2.29	1.61
7	0.162	60	—	—
8	0.207	81	1.61	0.88
9	0.087	49	—	—
10	0.186	67	2.04	1.06
11	0.115	50	0.92	0.56
12	0.124	55	—	—
13	0.175	80	1.45	1.20
14	0.144	80	—	—
15	0.121	60	1.45	1.18
16	0.103	71	—	—
Total 0-16	5.04	1,014	92.4	7.85

TABLE II.—*Urinary and Faecal Excretions of Strontium and Calcium in M.A.L. (Girl aged 9 years 9 months). Dose 99.5 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
-8	0.062	82	2.91	1.96
-7	0.077	95	—	—
-6	0.122	96	2.68	1.35
-5	0.175	79	—	—
-4	0.065	90	—	—
-3	0.073	65	2.34	1.61
-2	0.132	128	—	—
-1	0.128	103	2.11	1.23
0	1.33	90	1.54	0.78
1	0.485	60	54.65	0.93
2	0.750	129	—	—
3	0.326	106	17.75	1.25
4	0.520	133	2.94	0.57
5	0.208	89	2.13	1.08
6	0.309	134	1.30	0.57
7	0.116	90	—	—
8	0.191	86	3.14	1.21
9	0.147	73	—	—
10	0.038	41	1.77	1.42
11	0.112	100	—	—
12	0.169	120	2.47	0.88
13	0.076	85	1.73	0.74
14	0.067	61	1.94	1.16
15	0.109	93	—	—
16	0.042	62	1.71	0.91
17	0.088	87	2.04	0.88
Total 0-17	5.08	1,639	95.11	12.38

TABLE III.—*Urinary and Faecal Excretions of Strontium and Calcium in A. S. H. (Boy) At Age 13 years 1 month. Dose 93 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
At age 13 years 1 month. Dose 93 mg. of Sr on day 0				
-7	0.097	81	5.24	2.43
-6	0.188	121	5.35	1.81
-5	0.063	97	1.4	0.56
-4	0.075	50	4.40	1.61
-3	0.166	123	4.83	2.10
-2	0.107	82	2.97	1.41
-1	0.066	53	—	—
0	0.405	54	—	—
1	0.684	120	—	—
2	0.364	91	29.1	1.26
3	0.529	126	42.2	1.87
4	0.408	151	—	—
5	0.236	107	9.7	1.73
6	0.228	86	—	—
7	0.348	139	—	—
8	0.183	78	6.65	3.09
9	0.142	63	—	—
10	0.234	134	—	—
11	0.131	82	7.13	2.04
12	0.175	101	—	—
13	0.192	104	—	—
14	0.172	96	4.90	2.45
Total 0-14	4.43	1,532	99.7	12.44
At age 14 years 4 months. Dose 100 mg. of Sr on day 0				
-8	0.053	113	—	—
-7	0.071	100	3.80	1.82
-6	0.115	178	—	—
-5	0.084	43	9.55	3.89
-4	0.126	45	—	—
-3	0.152	102	5.48	2.04
-2	0.140	82	—	—
-1	0.520	93	—	—
0	0.689	96	40.1	2.68
1	0.288	64	—	—
2	0.206	70	54.6	2.44
3	0.196	42	—	—
4	0.226	92	7.3	2.38
5	0.154	71	—	—
6	0.104	46	—	—
7	0.198	81	5.91	3.14
8	0.156	55	—	—
9	0.151	88	2.72	1.38
10	0.089	41	2.44	1.51
11	0.088	43	3.81	2.63
12	0.137	42	—	—
13	—	—	—	—
Total 0-13	3.20	924	116.9	16.16

the dose of strontium was taken (day 0) are denoted by a negative sign. Denoting the mean values of the ratio of strontium to calcium in the faeces and urine in the pre-dose period by $F \frac{Sr}{Ca}$ and $U \frac{Sr}{Ca}$, the respective excretions of dietary strontium during the experimental period may be taken as

$$F \frac{Sr}{Ca} \Sigma F_1 Ca \text{ and } U \frac{Sr}{Ca} \Sigma U_1 Ca$$

where $\Sigma F_1 Ca$ and $\Sigma U_1 Ca$ represent the total calcium excreted by the respective routes after taking the dose. The strontium excreted over the experimental period will then be given by

$$\Sigma F_1 Sr - F \frac{Sr}{Ca} \Sigma F_1 Ca + \Sigma U_1 Sr - U \frac{Sr}{Ca} \Sigma U_1 Ca \quad (1)$$

where $\Sigma F_1 Sr$, $\Sigma U_1 Sr$ represent the total strontium excreted in the faeces and urine respectively in the post-dose period.

Such treatment of the results corrects for day-to-day variations in the amount of food eaten by the children provided that the strontium:calcium ratio of the diet remains unchanged before and after the dose is taken.

Table V gives the results for the mean daily urinary and faecal excretion of strontium and calcium before the oral dose as well as the mean ratio of strontium

to calcium excreted by the separate routes. Table VI summarizes the results obtained for the excretion and retention of the oral dose together with the means and their standard errors. For comparison the corresponding results for adults are shown in each of these tables. The latter were derived from previous observations by Harrison *et al.* (1955). To make the two sets of results comparable, those for the adults are given for a period of 16 days after the dose. The calculation of the net excretion, as in the case of the children, was made by the use of formula 1.

The results for R.M. (Table VI), a boy 14½ years old whose growth rate was less and whose physical development was more mature than that of the other children, are exceptional in that his urinary excretion of the dose was intermediate between that of the other children and the adults, while his faecal excretion was very nearly the mean of that obtained for the adults. Presumably R.M. was in the transitional stage between child and adult, when it is known that the excretion of calcium shows a pronounced change (Widdowson, 1947). The results for R.M. are therefore excluded from the means for the other children.

It will be seen from Table VI that the general pattern of excretion of an oral dose of strontium differed markedly in children and adults. Thus there is a pronounced decrease in the percentage of the dose which is excreted in the urine and a smaller but clearly significant increase in the percentage excreted in the

TABLE IV.—*Urinary and Faecal Excretions of Strontium and Calcium in R.M. (Boy Aged 14 years 6 months). Dose 100 mg. of Strontium on Day 0*

Day	Urine		Faeces	
	Sr (mg.)	Ca (mg.)	Sr (mg.)	Ca (g.)
-8	—	—	3.90	1.49
-7	0.317	267	0.33	0.17
-6	0.215	175	5.40	1.88
-5	0.265	129	2.28	1.04
-4	0.347	177	4.87	2.60
-3	0.292	191	—	—
-2	0.292	189	—	—
-1	0.334	266	7.15	2.82
0	4.43	249	—	—
1	1.79	152	2.65	0.90
2	1.59	211	19.96	1.88
3	0.85	198	12.25	0.34
4	0.60	156	40.40	2.86
5	0.67	43	4.0	1.55
6	0.64	212	—	—
7	0.39	171	—	—
8	0.66	342	—	—
9	0.45	240	5.41	2.37
10	0.31	170	2.80	1.04
11	0.37	230	3.85	1.22
Total 0-11	12.75	2,374	91.3	12.16

TABLE V.—*Comparison of the Excretion of Calcium and Strontium by Children and Adults on a Normal Diet*

	Sex	Age yr. mths	Urinary Excretion			Faecal Excretion		
			Sr (mg.)	Ca (g.)	Sr/Ca × 10 ³	Sr (mg.)	Ca (g.)	Sr/Ca × 10 ³
Children:								
S.R.W.	M	4 10	0.049	0.039	1.25	0.62	0.50	1.24
M.A.L.	F	9 9	0.104	0.093	1.12	1.26	0.77	1.63
A.S.H. (1)	M	13 1	0.109	0.087	1.25	3.46	1.42	2.44
" (2)	M	14 4	0.093	0.083	1.12	2.35	0.97	2.42
R.M.	M	14 6	0.293	0.199	1.46	2.99	1.25	2.39
Adults:								
H.C.C.	F	29	0.271	0.246	1.10	2.97	1.49	1.99
A.H.	F	31	0.152	0.153	1.00	1.61	0.90	1.79
R.H.M.	M	40	0.333	0.386	0.86	2.32	1.13	2.05
J.F.L.	M	45	0.435	0.500	0.87	1.58	0.56	2.82

TABLE VI.—Percentage Excretion and Retention of an Oral Dose of Strontium

	Period, Days	Excretion			Retention
		Urinary	Faecal	Total	
Children:					
S.R.W.	17	3.8	83.0	86.8	13.2
M.A.L.	18	3.3	75.3	78.6	21.4
A.S.H. (1)	15	2.7	74.3	77.0	23.0
" (2)	14	2.2	78.0	80.2	19.8
Mean ..	16	3.0±0.4	77.7±1.9	80.7±2.2	19.3±2.2
R.M. ..	12	9.1	62.9	72.0	28.0
Adults:					
R.H.M.	16	20.5	64.8	85.3	14.7
G.E.H.	16	15.8	63.5	79.3	20.7
H.C.C.	16	19.1	66.2	85.3	14.7
Mean ..	16	18.5±1.4	64.8±0.8	83.3±2.0	16.7±2.0

faeces for the children as compared with the adults. However, the percentage of the dose retained after about 16 days (equal to the dose minus the total excretion) is not significantly different for the children and the adults. If the faecal excretion were to be taken to represent the unabsorbed fraction of the dose, the absorption of strontium from the gastro-intestinal tract in the adults would be about 1.6 times greater than in the children.

Table VII shows values which have been derived for the mean daily dietary intake and the mean daily increment in strontium and calcium deposited in the skeleton. The daily increments in skeletal calcium (column 5) were obtained from results given by Mitchell *et al.* (1945). Obviously these are approximate means which apply to standard children on an adequate calcium diet. Bryant *et al.* (1959) have determined the ratio of strontium to calcium in selected bones from children of various ages. This ratio is approximately constant (280 $\mu\text{g.Sr/g.Ca}$) over the age-group 5 to 16 years. The daily increment in skeletal calcium multiplied by the ratio 280 $\mu\text{g.Sr/g.Ca}$ was used to give an estimate of the mean daily increment in skeletal strontium for the various children (column 4). The mean daily intake of strontium and calcium (columns 6 and 7) was derived as the sum of the mean daily excretion and the daily increment in skeletal strontium or calcium.

Columns 8 and 9 give the ratio of the skeletal increment to the dietary intake for strontium and calcium, while column 10 shows the relative increment of strontium to calcium in the skeleton divided by the ratio of strontium to calcium in the diet. This ratio is a measure of the overall discrimination for strontium relative to calcium. The derived values are surprisingly close considering the approximations involved in their derivation. That the ratio is less than unity implies an

overall discrimination, bone $\rightarrow$ diet, against strontium. The mean value, 0.17, is less than the value for adults (0.25) derived by Bryant *et al.* (1958). It could be inferred that the overall discrimination between strontium and calcium is rather greater in children than in adults.

Discussion

It is specially noteworthy that 16 days after an oral dose of strontium the mean percentage retained in the skeleton in the case of the children (19.3 ± 2.2) was not significantly different from that for the adults (16.7 ± 2.0)— $0.4 < P < 0.5$. It might be expected that the growth rate in the youthful skeleton would result in a higher uptake of an oral dose of strontium in children compared with adults. For example, in rats it has been shown that the percentage of a single dose of radioactive strontium deposited in the skeleton is about five times greater in young animals than in adults (Copp *et al.*, 1947). It is important to note, however, that the rate of skeletal growth in children of age-group 5–15 years is about 20 times less than in rats about 4 to 5 weeks old.

It is perhaps significant that the mean urinary excretion of calcium for the children was one-third of that for the adults (Table V). This must indicate a relatively lower renal clearance of calcium in the children. That the total urinary excretion of a single dose of strontium was so much less in the case of the children than in the adults (Table VI) suggests that the renal clearance for strontium may also be less in children. However, the present data provide no information on whether there is any difference between children and adults in the renal discrimination between strontium and calcium.

The radiation dose to the skeleton resulting from an ingestion of radioactive strontium cannot be assessed from the present data. Limited experimental evidence obtained in this laboratory (Bishop *et al.*, 1960) on the decrease in the retention of a radioactive dose of strontium in adults shows that it is very rapid during the first 15 days and thereafter becomes progressively slower over the next 200 days. From the form of this retention-time relationship it is shown that this initial period of rapid change in the retention contributes only a small fraction to the total radiation dose to the skeleton from strontium-90 in, say, 200 days. In other words, the integral radiation dose depends principally upon the long-term retention of strontium-90. There is no experimental evidence on the long-term retention following a single dose of strontium to children, and obviously extrapolation beyond the 15-day period covered in the present investigation would be unreliable. However, if the retention-time relationship were to be independent of age, the

TABLE VII.—Values of the Overall Discrimination* in Children Between Strontium and Calcium Deduced from the Mean Daily Excretion

Child (1)	Mean Daily Excretion		Mean Skeletal Increment		Calculated Daily Intake		Ratio Skeleton/Diet		Overall Discrimination
	Sr (mg.) (2)	Ca (g.) (3)	Sr (mg.) (4)	Ca (g.) (5)	Sr (mg.) (6)	Ca (g.) (7)	Sr (8)	Ca (9)	Sr Ca (10)
S.R.W. ..	0.67	0.54	0.015	0.055	0.69	0.59	0.022	0.093	0.24
M.A.L. ..	1.36	0.86	0.045	0.16	1.41	1.02	0.032	0.16	0.20
A.S.H. (1) ..	3.57	1.51	0.064	0.23	3.62	1.74	0.018	0.13	0.14
" (2) ..	2.44	1.05	0.064	0.23	2.50	1.28	0.025	0.18	0.14
R.M. ..	3.28	1.45	0.064	0.23	3.34	1.68	0.019	0.14	0.14

* The overall discrimination between strontium and calcium is taken as the ratio of the daily increase of strontium to calcium in the skeleton divided by the ratio of strontium to calcium in the diet.

integral dose to bone would be from two to four times greater in children than in adults purely as a result of the higher concentration of the radioactive dose in the smaller juvenile skeleton. It is possible that the higher rate of remodelling in the youthful skeleton as compared with the adult would contribute to a higher rate of removal of the radioactive dose in children.

Summary

The daily urinary and faecal excretion of strontium and calcium for four children between the ages of 4½ and 14½ years has been measured over an initial period of seven or eight consecutive days immediately before an oral dose of about 100 mg. of strontium (as strontium chloride) taken at breakfast-time. Subsequently, the daily urine and faecal excretion of strontium and calcium was estimated over a period of from 12 to 18 days and the net retention of the dose deduced. The results are compared with the excretion of an oral dose of strontium by adults from this unit.

The mean, cumulative, urinary excretion of a single oral dose of strontium was about 3% for the children up to 16 days after the dose, with the exception of a boy 14½ years old. The corresponding faecal excretion was about 78% of the dose. The respective excretions, over a similar period, for adults were 19% and 64% of the dose. Thus the retention (dose-excretion) up to 16 days after the dose was not significantly different in the two age-groups.

An attempt made to compare values derived for the overall discrimination of strontium relative to calcium in children and adults tends to show that it is rather higher in children.

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HAEMOPTYSIS

BY

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For most patients and not a few doctors, the expectoration of blood signals either pulmonary tuberculosis or carcinoma. We have been impressed by the number of patients with haemoptysis in whom neither of these conditions was present. A reassessment of this symptom is necessary, particularly since the pattern of respiratory disease has been changing during the past ten years.

Our purposes therefore were: (1) to examine the causes of haemoptysis in chest-clinic practice; (2) to consider whether there are features of the haemoptysis peculiar to different diseases; and (3) to determine the need for follow-up of patients presenting with haemoptysis without apparent cause.

Material and Methods

Haemoptysis is defined here as the expectoration of blood or blood-stained mucus not due to bleeding in the upper respiratory tract or associated with gastrointestinal bleeding. We recognized that often there was no immediate confirmation of the bleeding, and it was unusual for the patient to be able to produce blood-stained sputum on request. We depended on the patient's account of this bleeding episode, on the observations made by his own general practitioner, and on such further details as we could elicit on close questioning. To facilitate the last, the accompanying form was designed, since we could not hope to find the details required from all patients in any analysis of previous records. A little experience shows that there is

Date of first attendance:

INVESTIGATION OF CASES OF HAEMOPTYSIS

Patient's Name Ref. No.

Details concerning the haemoptysis

1. (a) Doubtful:
- (b) Probable:
- (c) Certain:
2. Any associated upper respiratory bleeding:
3. Any history of acute upper respiratory infection:
4. Estimate of the amount of blood expectorated:
5. A frank haemoptysis or merely staining:
6. Single or repeated haemoptysis:
7. Can the patient locate the site of the haemoptysis?
8. Duration of the haemoptysis:
9. Any other bleeding tendency:
10. Smoking history:

Clinical findings

1. U.R.T.
2. B.P.
3. Heart:
4. ? Added sounds in the chest:
5. X ray of chest:
6. Predominant pathogens in the sputum:
7. Cultures for *M. tuberculosis*:

Diagnosis