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STUDIES OF BONE METABOLISM WITH THE AID OF RADIOACTIVE STRONTIUM

D. C. Jones and D. H. Copp, M.D.

January 16, 1948

Berkeley, California

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Berkeley, California

ABSTRACT

STUDIES OF BONE METABOLISM WITH THE AID OF RADIOACTIVE STRONTIUM

by
D. C. Jones and D. H. Copp, M.D.

January 16, 1948

The kinetics of skeletal uptake and urinary excretion of radio-strontium were studied during the critical first hour following intra-peritoneal injection of a carrier-free dose. These experiments not only provided valuable data concerning the metabolism and fixation of this important fission product, but, because of the close similarity of strontium and calcium, also gave basic information on the process of calcification. Three groups of rats were compared: normal mature adults, young growing normal animals, and young rachitic rats. In all groups, the blood radio-active strontium rose to a maximum in 10-15 minutes, and then declined as the strontium continued to deposit in the skeleton or to be excreted in the urine. Muscle and skin strontium curves followed those of blood quite closely, suggesting a rapid equilibrium between their extracellular fluid and blood plasma.

In all groups there was a continous uptake of strontium by the skeleton. In the adults, this was almost constant, suggesting uptake by absorption and exchange with the calcium of the bone mineral. In the young rats, both normal and rachitic, the very rapid initial rate of uptake of radio-strontium tapered off sharply with time, indicating that some of this radio-element was coming back from the bone into the blood stream. This suggested a rapid labile combination of strontium in these animals, which, since it also occured in the rachitic group in which normal calcification

is inhibited, probably associated with the protein osteoid matrix present in both. A hypothetical calcification mechanism was suggested by these findings.

Urinary excretion and renal clearance of strontium was constant in all three groups, but the clearance was almost ten times as great in the rachitic as in the normal young and adult rats. This would seem to indicate a direct effect of rickets on the renal mechanism of radio-strontium (and calcium) excretion.

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STUDIES IN BONE METABOLISM USING RADIOACTIVE STRONTIUM

D. C. Jones and D. H. Copp, M.D.

January 16, 1948

The application of radioactive tracers to the study of bone metabolism has been carried out with success during the last few years. Since bone is composed largely of calcium phosphate, the use of radio-calcium as a tool in the study of calcium metabolism in bone appears as the ideal choice. However, the radioactive isotopes of calcium available at present are of weak activity and are obtainable only in very small amounts.

Pecher (1-2) predicted and demonstrated that strontium, which is in the same group in the periodic system as calcium, is metabolized in a similar manner. In a series of experiments on mice, rats, and humans, he demonstrated that the uptake and distribution of radio-calcium and radio-strontium were similar qualitatively, although there were quantitative differences. Both concentrated in the skeleton, with very little in the soft tissues. In the long bones, the epiphysis showed greater activity than the diaphysis, and the vertebrae showed more activity than the other bones. Calcium and strontium previously fixed in the skeleton migrated to the fetus during the last days of pregnancy, and appeared in the milk. Other similarities in the metabolism of the two elements were demonstrated by Posin (3), and by Erf and Pecher (4). Because of this close similarity, Sr* [1] has been commonly used as a tracer for the study of calcium metabolism.

A later and more complete study of the metabolism of Sr* by Pecher (5) showed that the soft tissue activity twenty four hours after

1. Sr* indicates strontium "labelled" by the presence of radioactive strontium.

injection of Sr* was only about one percent that of the bone. Highest concentration of Sr* appeared in the regions of new bone formation, including some osteogenic sarcomas, as was verified by Treadwell, et al. (6). This suggested the possible use of Sr* as an agent in the treatment of bone cnacer, since it can be obtained with a half-life of fiftyfive days and an energetic beta radiation. Results have been disappointing, but this phase of the problem is still under investigation.

Species differences in the excretion of Sr were shown by McCance (7), working with the stable isotope, as well as by Pecher. Rats excreted strontium about equally in urine and feces, while mice excreted it primarily in the feces, and humans primarily in the urine.

Marx and Reinhardt (8) were unable to show any effect of growth hormone on the skeletal deposition of Sr*. Tweedy (9) demonstrated that the effect of parathyroid extract administered previous to and in conjunction with Sr* was to decrease retention in the bone, decrease fecal excretion, and increase urinary excretion. Hodge, Gavett, and Thomas (10) showed that adsorption of Sr* by bone occurs in vitro. Greenberg (11) demonstrated that vitamin D increased skeletal deposition of Sr* in rachitic rats, and Weissberger and Harris (12) suggested a method of Vitamin D assay using radio-strontium.

All of the previous work with Sr* has been done with assay at varying time intervals from one hour after administration upwards. However a large part of the Sr* is already taken up by bone at the end of one hour. Therefore it was thought that a careful investigation of the kinetics of Sr* metabolism during the first hour following injection would be of significance in studying certain basic problems of Ca metabolism.

Accordingly, a preliminary experiment was carried out to establish

technical procedures. It was found that most of the injected Sr* was distributed among the blood, skin, muscle, urine, and bone during the first hour after administration. For this reason analysis was limited to those tissues and fluids, and the following experiments were carried out.

METHODS

Animals

Group I-Adult. Twenty normal adult female rats, with body weights ranging from 235 to 320 grams, made up the first group. These were mature rats in which skeletal growth had practically ceased. They were maintained on our stock diet (Table A).

Group II-- Young Normal. Group II was made up of twenty young growing female rats. They were placed in standard cages and fed ad lib on our stock diet. After thirty days these animals weighted from 79 to 109 grams.

Group III--Young Rachitic. Twenty young female rats were placed in darkened cages and maintained on a standard rachitic test diet (Table B). After thirty days on this diet, the animals ranging in weight from 37 to 75 grams were used. for the experiment.

Table A

Composition of Stock Diet

Whole wheat, ground	68.5%
Fish oil	5.0%
Casein	5.0%
Alfalfa leaf meal	10.0%
Fish meal	10.0%
Sodium chloride	1.5%

Table B

Rachitogenic Diet No. 2 (USP XII)

Corn meal	76%
Gluten	20%
Calcium cabonate	3%
Sodium chloride	1%
Supplemental: 1 gm. Vit. B-1	
1 gm. Vit. B-2	

Experimental Procedure. No anaesthetic was used. Each animal was injected intraperitoneally with carrier-free radioactive strontium, which was a mixture of Sr^{89} and Sr^{90}, chiefly the latter. The Sr* was obtained by fission of uranium in the pile. The Sr^{90} decays by beta emission to Y^{90}, which is itself radioactive and decays with a sixty hour half-life and an energetic beta radiation to a stable isotope of zirconium, Zr^{90}. Because of the Y daughter, samples were left for twenty four days in order to reach equilibrium with this yttrium daughter.

The five microcurie dose was administered in 0.25 milliliters of isotonic saline solution. After injection, the animal was placed on a screen in a covered beaker, to permit urine collection. At the end of the appropriate time interval the animal was chloroformed inside the beaker, and tissue and fluid samples were obtained. The time intervals used were five, ten, fifteen, thirty, and sixty minutes after injection. As soon as the chloroform had taken sufficient effect, a blood sample was withdrawn from the inferior vena cava. The entire femur, a skin sample, and a muscle sample were taken from the right hind leg, and weighed immediately. The bladder contents were washed into the original beaker to make up the total urine. In addition the remaining carcass was taken to determine recovery.

Analytical Procedure. Blood samples were collected in syringes rinsed with heparin. After centrifuging, plasma was drawn off and diluted to an appropriate volume with distilled water. The total urine was diluted to volume with distilled water. Femur, muscle sample, skin sample and carcass were ashed at 650 degrees C. for ten hours. The ash was then dissolved in 2 normal hydrochloric adid and diluted to volume. An aliquot of from one to four milliliters was withdrawn from each of the solutions, placed in a capsule, and dried. After waiting for the Y* to reach equilibrium,

the radioactivity of each sample was determined with a G-M counter using a mica window counter tube. A standard aliquot of the administered dose was counted at the same time, and the radioactivity was expressed as percent of the administered dose.

RESULTS

General Considerations. In an experiment with time intervals up to an hour, and with such great variation in body weight in the three groups, the values for total tissues and fluids are probably of more significance than the values per gram or per milliliter. Therefore, for purposes of comparison between the three groups of animals in this experiment, values for total tissues and fluids were used.

The figures of Donaldson (13) were used to calculate the total skeleton, skin, and muscle on a basis of body weight, while the amount of Sr* in a given tissue was calculated by multiplying the measured activity per gram by the total weight of the tissue. In the case of blood, different investigators give varying values for the total volume versus body weight. For example, Donaldson gives the total volume as $0.099\ (\text{Body Weight})^{0.9}$ for animals less than 150 grams in weight, and $0.10494\ (\text{Body Weight})^{0.9}$ for females with body weights between 150 and 350 grams.

Griffith and Campbell (14), using a vital red dye technique, give the blood volume as 4.3 milliliters per 100 grams of body weight. Still another value, 6.7 milliliters per 100 grams of body weight is given by Cartland and Koch (15). Any selection of a numerical value is more or less arbitrary in nature, and therefore the factor of 6 percent of body weight was used to calculate the blood volume, and 3 percent to determine the approximate plasma volume.

In some cases, the animal showed little or no activity in any sample but the carcass. This was probably due to injection of the dose directly into the lumen of the intestine, since the amount absorbed from the intestine in an hour is very small. Such animals were rejected. The number of animals at each time interval is as indicated.

The percent Sr* in each organ was plotted against time, and smoothed curves were drawn. The tangents to these curves at different points gave a measure of the rate of increase or decrease of Sr* in the tissues at these times. The figures given in the tables are expressed as the arithmetic mean plus or minus the standard deviation, where the standard diviation is $\sqrt{\frac{D^2}{N}}$

Adult Group. The results from the mature adult group are given in Tables I and II, and in Figure 1.

Table I

Uptake and Distribution of Sr* in Adult Female Rats

Time (Min.)	No. Rats	Blood % Dose/cc.	Blood % Dose	Muscle % Dose	Skin % Dose	Skeleton % Dose	Urine % Dose
5	4	0.645±0.10	5.55±0.75	9.0±2.6	6.7±1.2	2.15±0.3	0.04±0.02
10	3	0.964±0.20	7.50±0.87	14.9±1.6	10.4±0.6	3.53±0.7	0.27±0.12
15	3	0.849±0.02	8.17±0.27	17.7±0.5	20.1±1.6	6.44±0.4	0.82±0.16
30	3	0.586±0.05	5.46±0.33	15.0±1.1	21.1±0.6	10.30±0.3	0.63±0.44
60	4	0.469±0.05	4.23±0.90	14.0±3.4	17.7±3.5	17.20±4.8	2.77±1.67

The adult blood Sr* increased at a moderate rate during the first fifteen minutes after injection, reaching its maximum at the end of the third period. It then decreased slowly during the remaining forty five minutes. The skin content increased rapidly during the first fifteen minutes, increased slowly during the next fifteen minutes and then decreased slowly during the last half hour. The muscle Sr* curve was similar to that

Uptake and Distribution of Sr* in Adult Female Rats

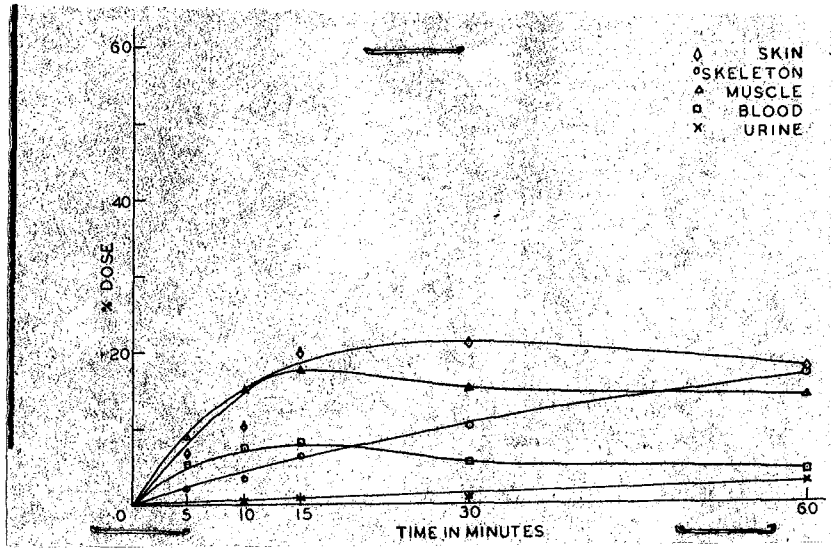


Figure 1

Table II

Adult Rate of Change of Sr* Content in % Dose Per Minute

Time Interval	Blood	Muscle	Skin	Skeleton	Urine
0---5 minutes	+1.11	+1.8	+1.3	+0.4	+0.05
5--10 minutes	+0.39	+1.2	+1.2	+0.4	+0.05
10-15 minutes	+0.13	+0.6	+0.8	+0.4	+0.05
15-30 minutes	-0.18	-0.2	+0.2	+0.4	+0.05
30-60 minutes	-0.04	-0.02	-0.1	+0.3	+0.05

of skin, but at a somewhat lower level. The general shape of the muscle and skin curves is similar to that of the blood.

The Sr* in the adult skeleton continued to increase throughout the experiment at a slow steady rate. The excretion in the urine of the adults was slow and fairly constant. The curves for the skeleton and urine Sr* did not resemble the blood curve.

Young Normal Group. The results from the group of normal young growing rats are shown in Table II, Table IV, and Figure 2.

Table III

Uptake and Distribution of Sr* in Young Normal Female Rats

Time (Min.)	No. Rats	Blood % Dose/cc.	Blood % Dose	Muscle % Dose	Skin % Dose	Skeleton % Dose	Urine % Dose
5	3	1.58±0.12	4.53±0.26	12.3±2.0	10.7±3.6	12.1±1.7	0.15±0.06
10	2	1.22±0.15	3.42±0.38	13.2±2.0	17.6±1.3	22.8±2.9	0.52±0.02
15	3	1.58±0.29	4.02±0.88	11.2±2.0	15.6±1.3	28.8±5.7	1.41±1.60
30	4	0.720±0.18	2.07±0.61	8.7±1.3	10.6±1.9	50.4±8.5	3.01±1.80
60	4	0.437±0.02	1.10±0.05	4.9±0.5	5.2±1.2	61.7±10.1	1.19±0.41

The blood of the young normal rats showed a moderate initial rise in Sr*, reaching a maximum at the end of ten minutes. This was followed by a moderate decrease during the next thirty five minutes, tapering off finally to a slow rate of fall.

Both the skin and the muscle Sr* curves resembled that of blood, although at a much higher level. The skeletal Sr* increased continuously throughout the experiment. The rate was rapid for the first half hour after injection, but tapered off rapidly to a moderate rate during the rest of the

Uptake and Distribution of Sr* in Young Normal Female Rats

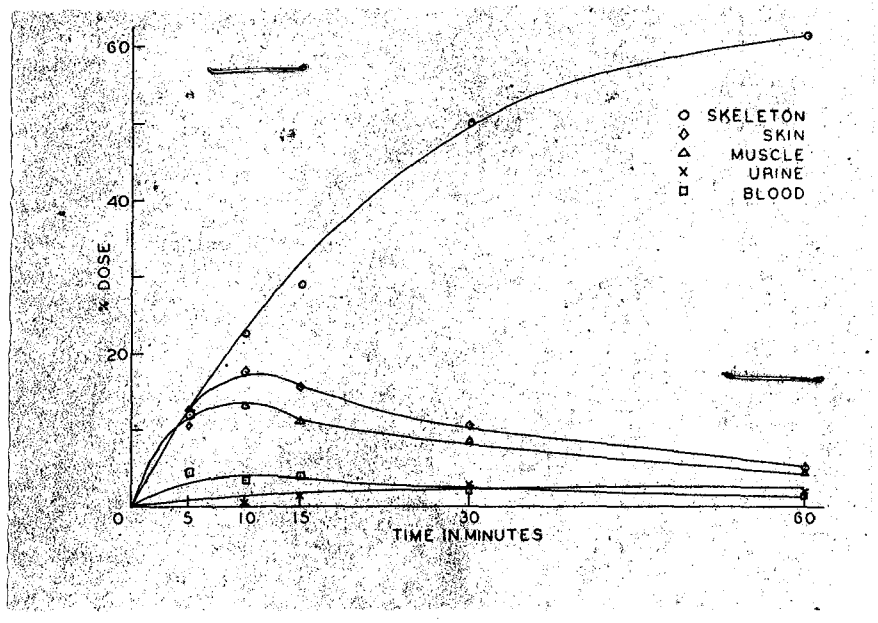


Figure 2

Table IV

Rate of Change of Sr* Content in % Dose Per Minute In Young Normal Rats

Time Interval	Blood	Muscle	Skin	Skeleton	Urine
0---5 minutes	+0.60	+2.5	+2.1	+2.3	+0.03
5--10 minutes	+0.20	+0.2	+1.4	+2.1	+0.03
10-15 minutes	-0.10	-0.4	-0.4	+1.8	+0.03
15-30 minutes	-0.10	-0.2	-0.3	+1.3	+0.03
30-60 minutes	-0.03	-0.1	-0.2	+0.4	+0.03

of the hour. The urinary Sr* also rose continuously throughout the experiment, but at a constant and very slow rate.

Young Rachitic Group. The results from the group of young rachitic rats are shown in Tables V and VI, and in Figure 3.

Table V

Uptake and Distribution of Sr* in Young Rachitic Female Rats

Time (Min.)	No. Rats	Blood % Dose/cc.	Blood % Dose	Muscle % Dose	Skin % Dose	Skeleton % Dose	Urine % Dose
3	3	3.45±0.77	4.99±2.07	7.10±3.4	11.0±5.5	11.0±2.3	1.55±0.76
10	4	2.48±0.21	4.83±1.74	8.40±2.0	15.1±2.0	23.2±3.8	3.98±0.46
15	4	3.25±0.31	5.46±1.31	8.50±1.8	12.6±2.9	27.8±5.0	4.97±1.11
30	4	1.86±0.12	3.15±0.24	5.43±0.8	7.9±1.2	36.8±2.7	10.3 ±3.88
60	4	1.35±0.33	2.28±0.66	3.70±1.4	4.0±0.4	41.0±4.4	14.5 ±4.35

Table VI

Rate of Change of Sr* Content in % Dose Per Minute In Young Rachitic Female Rats

Time Interval	Blood	Muscle	Skin	Skeleton	Urine
0---5 minutes	+0.80	+1.4	+2.2	+2.7	+0.4
5--10 minutes	+0.30	+0.3	+0.8	+1.7	+0.4
10-15 minutes	-0.06	-0.02	-0.5	+1.6	+0.4
15-30 minutes	-0.17	-0.2	-0.3	+0.6	+0.3
30-60 minutes	-0.03	-0.06	-0.1	+0.1	+0.2

Uptake and Distribution of Sr* in Young Rachitic Female Rats

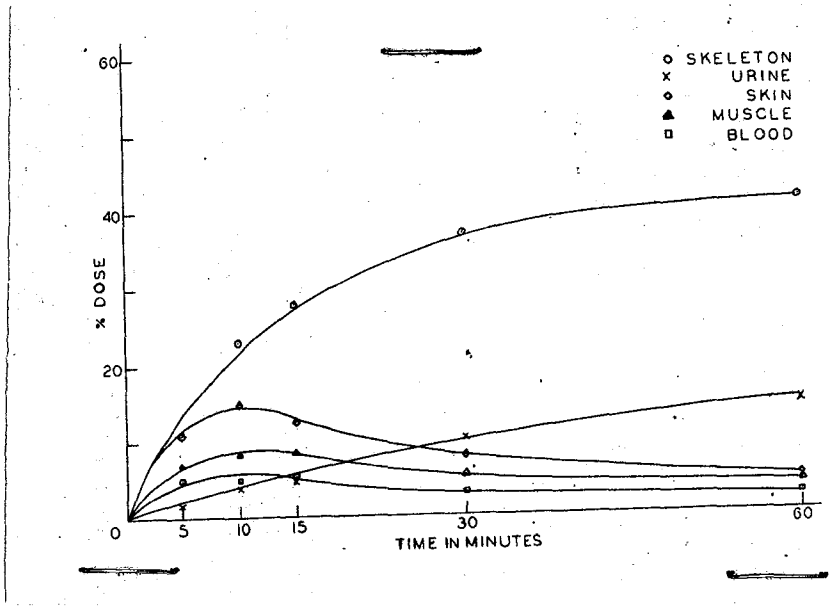


Figure 3

The Sr* level in the blood of the young rachitic group rose at a moderate rate during the first ten minutes after injection. After the ten minute maximum had been passed, the blood content decreased at a moderate rate during the next fifteen minutes, finally decreasing at a slow rate during the last half hour.

Skeletal uptake of Sr* in the young rachitic group resembled that in the young normals. The Sr* rose rapidly for the first fifteen minutes, and then tapered off to a rather slow rate of increase during the last half hour.

Urinary excretion in the rachitic group was relatively high compared to the other groups. The rate was five to ten times as great as in the other animals, but declined slowly during the experimental period, corresponding to the fall in blood Sr*.

DISCUSSION OF RESULTS

Blood. Since the metabolism of strontium is similar to that of calcium, the blood Sr* (Figure 4) presumably is present almost entirely in the plasma.

Blood Content of Radioactive Strontium

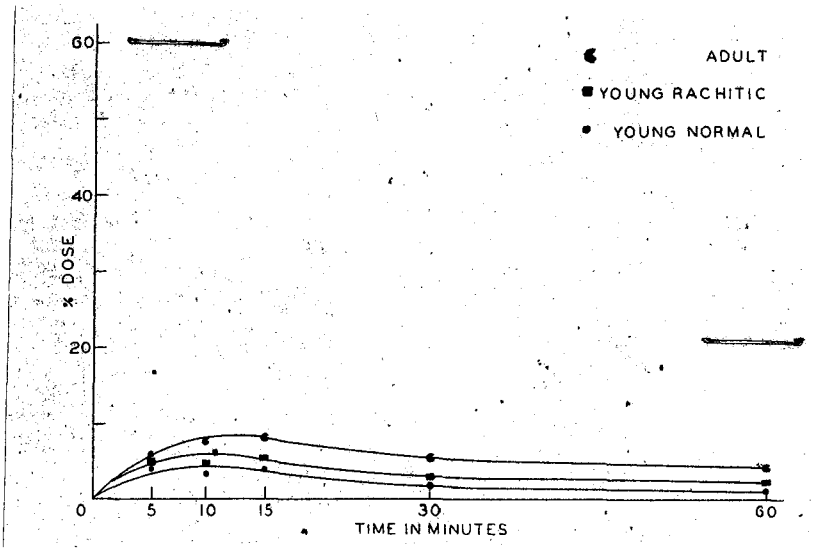


Figure 4

The general shapes of the blood curves represent the inter-action of several factors. The first of these is the rate and extent of absorption of the dose from the peritoneal cavity. Second, the diffusion of the Sr* throughout the plasma and into the interstitial spaces. Third, the uptake of the Sr* by the tissues themselves (especially the skeleton), and fourth, the excretion of Sr*. In the preliminary study, practically no Sr* was found in feces during the first hour after injection, so that during the times of this experiment only renal excretion is of consequence.

As may be seen from Figure 4, the absorption of Sr* from the peritoneal cavity during the first fifteen minutes exceeds loss to tissues and urine in all groups. After fifteen minutes the blood content drops at approximately the same rate in each of the three groups. Since, during this

same period, the Sr* in muscle and skin is also decreasing, this drop in blood level depends chiefly upon the uptake of the Sr* by the skeleton and its excretion by the kidney.

Muscle. The curves for muscle Sr* are shown in Figure 5.

Muscle Content of Radioactive Strontium

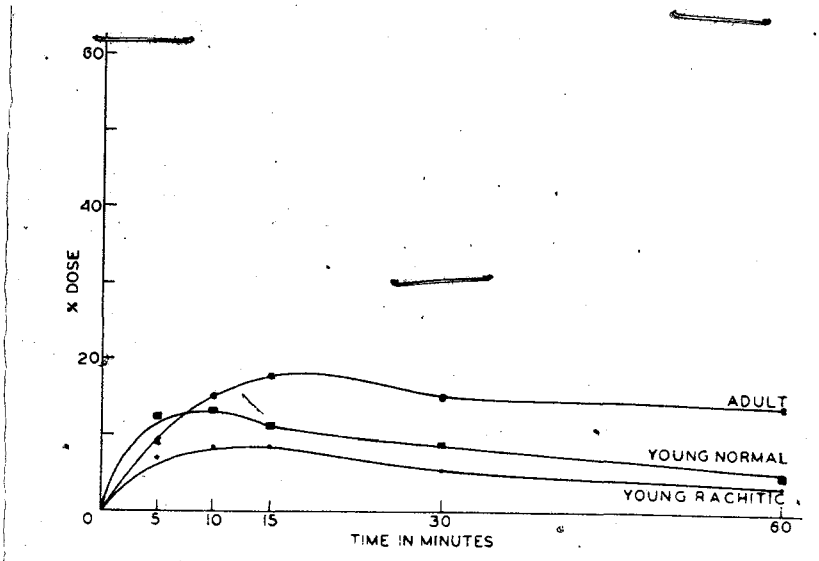


Figure 5

The adult muscle curve rises more slowly than the others and reaches its maximum at a slightly later time after injection. The young normal group has a consistently higher muscle value than the young rachitics, in addition to a more rapid initial rise. Since, during the initial period, the skeletal deposition in the two groups is similar, the inverse relationships of the muscle and blood curves may be explained by the more rapid excretion of the Sr* in the urine of the young rachitics.

The greatest difference in muscle content between the two groups of young animals if found during the first fifteen minutes, after which

time the curves approach each other as the rate of decrease of muscle Sr* is greater in the young normal than in the rachitic group. This convergence of the curves probably reflects the more rapid deposition of the Sr* in the young normal skeleton during the last forty five minutes.

Skin. As in the case of muscle, the skin curves follow those of the blood with respect to shape and time of maximum, indicating a rapid rate of diffusion. The higher value for skin is accounted for by its large volume of extracellular fluid.

The adult skin curve has the slowest initial rise of the three groups, reaching its maximum at fifteen minutes. This slowness may be due to the low blood concentration in the adults. The rate of decrease of skin Sr* in the adults is slightly less than in the two young groups, probably due to the slow uptake in the adult skeleton.

Skin Content of Radioactive Strontium

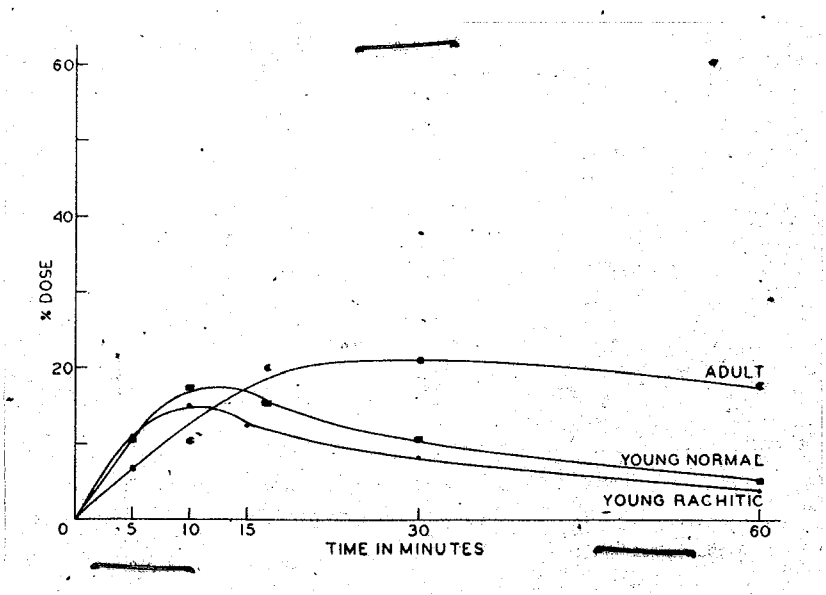


Figure 6

The two young groups show no appreciable difference in skin Sr* during the first five minutes after injection. During the next five minutes, the young normal curve continues to rise at a rate greater than that of the young rachitics. As in the case of muscle, skin Sr* is higher in the young normals, except during the first period, although the blood curves are both in inverse order to the skin curves. Again, as in muscle, this may depend upon the greater excretion of Sr* in the urine of the rachitics during the first ten minutes, as the two curves for skin tend to approach each other toward the end of the experiment.

Skeleton. The skeleton curves, as shown in Figure 7, illustrate the chief controlling factor in this experiment, namely, the active uptake of the radioactive strontium by the bone.

Skeleton Content of Radioactive Strontium

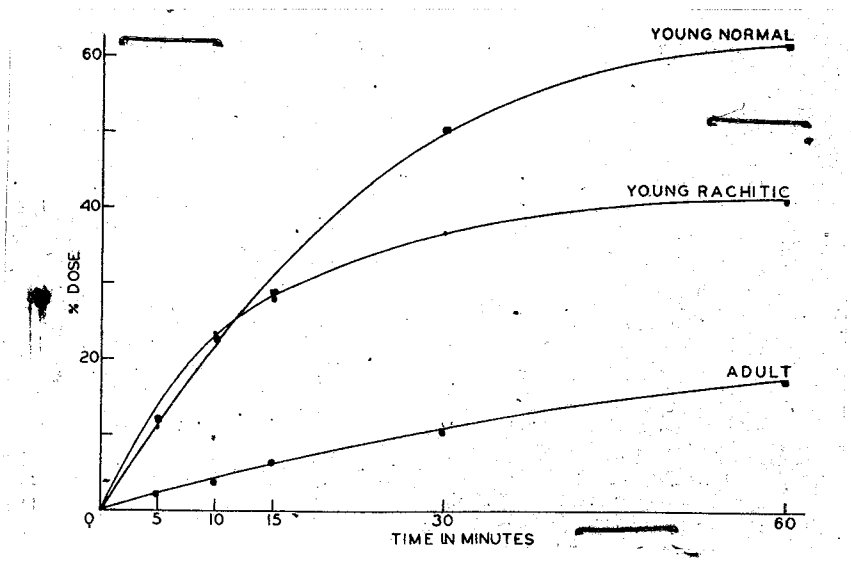


Figure 7

In each of the three groups, the uptake in the skeleton was continuous throughout the experiment. The adult group took up the least amount of Sr*, and at a fairly steady rate. The young rachitic animals showed a rapid initial uptake in the bone which decreased rapidly with time, while the young normals showed the most rapid and quantitatively greatest uptake by the skeleton.

The amount of Sr* being deposited in bone at any time is, presumably, dependent upon the concentration of plasma Sr*, since this is the immediate precursor. To allow for this factor, and to give comparable values, plasm clearances were calculated as follows:

The rate of uptake of Sr* by the skeleton was determined at each time interval by drawing tangents to the skeletal uptake curves (Figure 7). This value, divided by the total plasma Sr* at that time, gave the plasma clearance. Thus:

$$\text{Plasma clearance (\% Pl. cleared/min.)} \quad \frac{\text{Rate of uptake of Sr* by bone (\% Dose/min.)}}{\text{Plasma Sr* (\% Dose in Total plasma)}} \times 100$$

The calculated clearances are shown in Table VII. In the adult animal, the uptake of Sr* presumably takes place almost entirely by adsorption-exchange with calcium in the bone mineral, since little new bone is being formed in these animals. This may account for the practically constant clearance values obtained, as shown in Figure 8, where the clearances are plotted against time, since, during this short period, Sr* is passing continuously into bone at a rate dependent upon the blood concentration, while non-radioactive calcium is coming out of the skeleton.

Table VII

Skeletal Clearance of Plasma Sr*

Time (Min.)	Adult % Plasma Sr*/min.	Young Normal % Plasma Sr*/min.	Young Rachitic % Plasma Sr*/min.
5	9.0	80	44
10	5.7	58	23
15	4.4	46	17
30	5.1	33	10
60	4.5	13	3

Skeletal Clearance of Plasma Sr*

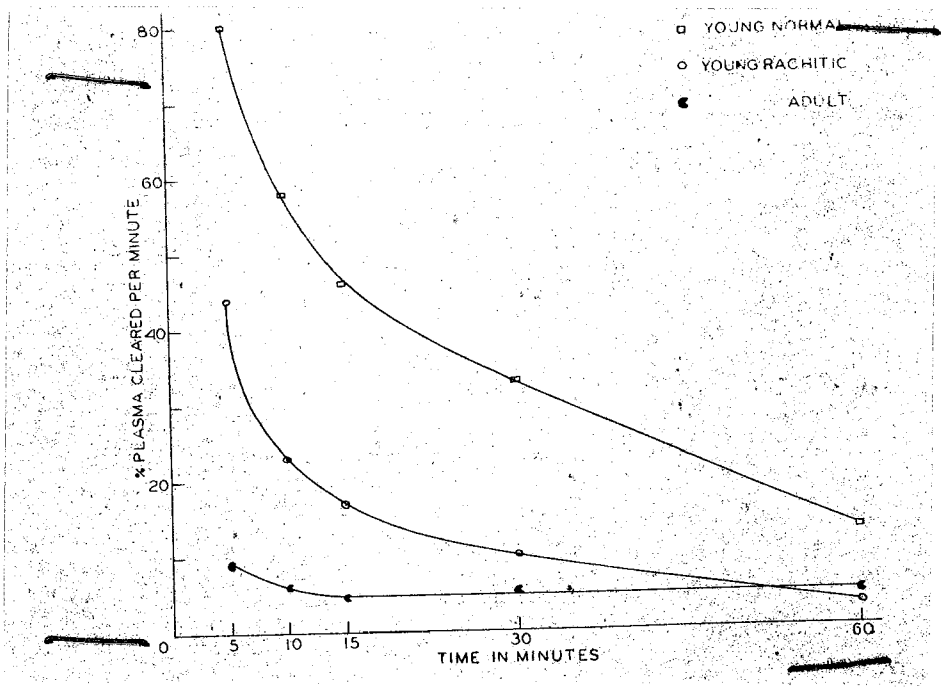


Figure 8

Clearances in the young normal animals differ sharply from those in the adult group, presumably due to the active formation of new bone in the former. The initial rate of uptake by bone and the clearance values are very high, but fall off rapidly throughout the experimental period. This suggests a second mechanism related to new bone formation, in addition to adsorption-exchange with the bone mineral.

Since carrier-free Sr* was used and the conditions throughout the experiment were constant, it would be expected that the rapid rate of deposition and high plasma clearance would persist. The rapid falling off in plasma clearance and Sr* deposition in the skeleton of the young normals actually observed may best be explained by assuming that Sr* passes from bone back to plasma as the experiment progresses. This would decrease the apparent net rate of skeletal uptake.

It suggests a labile and dissociable combination of Sr* in a restricted region of the bone. This reversibility may be associated with the process of new bone formation, since it is not evident in the adult group. However, the uptake and clearance by the rachitic rats is similar to that in the young normals, despite the fact that little bone mineral is being laid down in these animals. Clearance, although lower than in the young normals, exceeds that in the adults, and falls rapidly to a rather low value by the end of the hour. This indicates an active and reversible process of Sr* deposition in the bone of rachitic rats, similar to that in the young normal animals.

The common factor may be the osteoid matrix which is present in both groups. This material forms a matrix for new bone, but does not mineralize normally in the rachitic animals because of the low blood

phosphorus. It would appear probable that the active and reversible process of Sr* deposition in both groups may be associated with a labile combination of Sr* with the osteoid matrix.

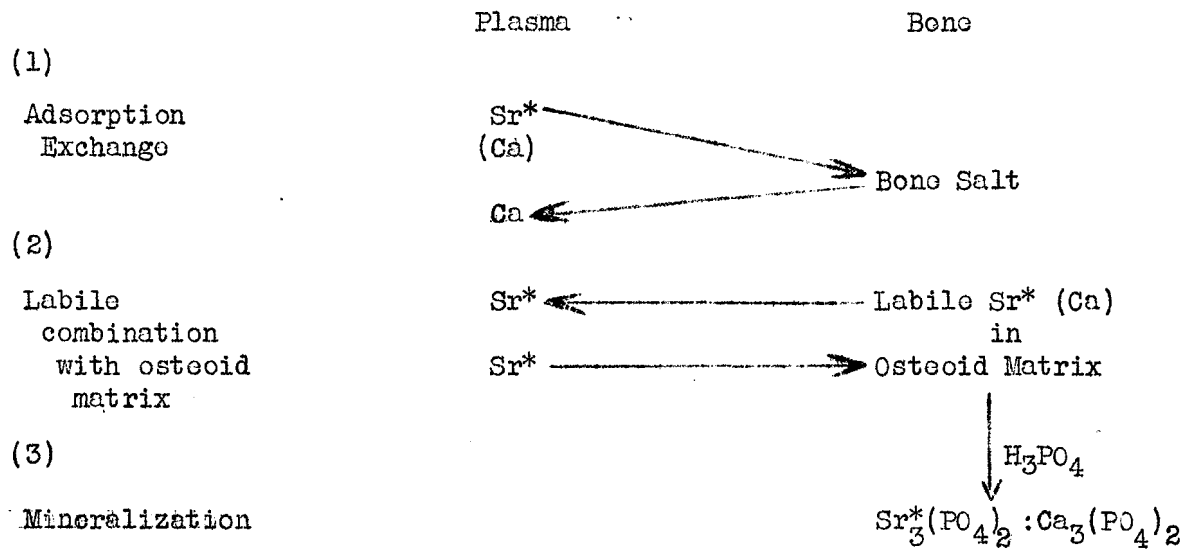
These observations suggest the following hypothetical mechanisms for Sr* uptake in the skeleton:

1. Simple adsorption-exchange with the calcium of bone mineral, which probably takes place in all groups, but is the predominant process in the adults.

2. Rapid uptake by the osteoid matrix of young normal and rachitic animals, in a labile combination from which the Sr* is released readily with very active turnover.

3. Presumably, in young growing animals this labile Sr* becomes fixed by mineralization, accounting for the higher over-all uptake and clearance compared to the rachitics.

Assuming a close parallel between calcium and strontium, these preliminary experiments point to a possible hypothetical calcification mechanism which may be represented schematically as follows:



Urine. The curves of urinary Sr* excretion are shown in Figure 9. Renal clearances of Sr* at the different times are given in Table VIII. They were calculated, as in the case of bone, by dividing the rate of renal excretion by the blood level of Sr*, and expressing clearance as either cc. plasma cleared per minute, or as the percent of the total plasma cleared per minute. In all groups, this renal clearance remained remarkably constant throughout the experiment.

Renal Excretion of Radioactive Strontium

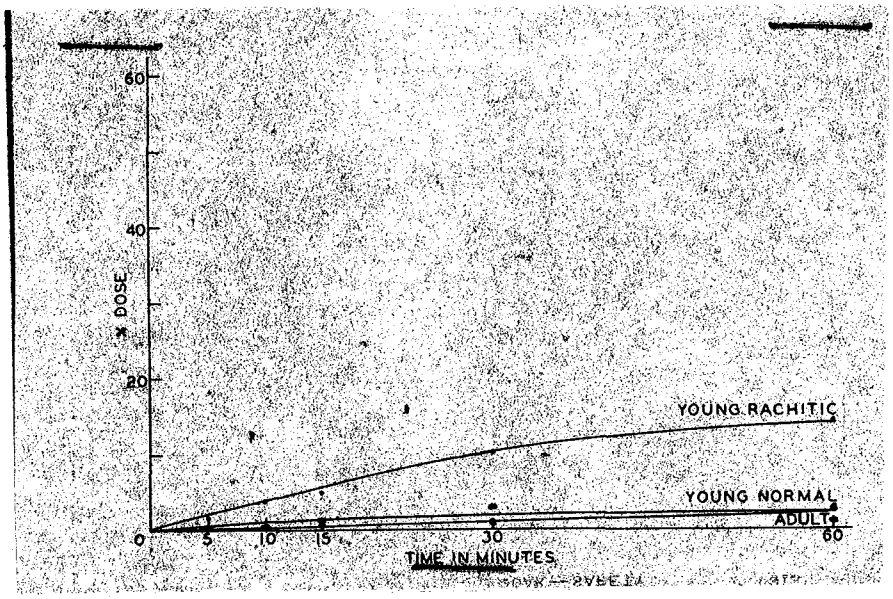


Figure 9

Table VIII

Renal Clearance of Radioactive Strontium

Time (Min.)	Adult Plasma Cleared cc./min.	Adult Plasma Cleared %/min	Young Normal Plasma Cleared cc./min	Young Normal Plasma Cleared %/min.	Young Rachitic Plasma Cleared cc./min.	Young Rachitic Plasma Cleared %/min.
5	0.108	1.25	0.043	1.50	0.116	8.02
10	0.060	0.77	0.013	0.46	0.161	8.28
15	0.060	0.63	0.012	0.46	0.123	7.32
30	0.072	0.77	0.029	1.00	0.161	9.52
60	0.090	1.00	0.038	1.50	0.148	8.77

In both the adult and young normal rats, very little Sr* is excreted during the one hour period, and the renal clearance is low. This indicates active tubular reabsroption of Sr* in these animals. The rachitic rats excreted Sr* at a much higher rate, and the clearance value is five to ten times as great as in the other groups. Since the calcium level in the blood of rachitic rats is within normal limits, this indicates a direct effect of rickets upon the tubular reabsorption of Sr*, assuming that the filtration rates are the same.

SUMMARY AND CONCLUSIONS

1. Carrier-free radioactive strontium was used as a tracer for calcium to study the kinetics of skeletal uptake and excretion during the first hour following intraperitoneal injection. Samples were taken at five, ten, fifteen, thirty, and sixty minutes.

2. Studies were carried out on three groups of female rats: (i) Adult; (ii) Young Normal; (iii) Rachitic.

3. In all groups, the blood curve rose rapidly to a maximum at ten to fifteen minutes, as the Sr* was absorbed from the peritoneal cavity, then fell off slowly. Skin and muscle curves followed those of blood, and these organs, with the other soft tissues, apparently provided a reservoir of Sr* in equilibrium with the blood. The highest blood curves were in the adult group and lowest in the young normals, while the rachitic rats were intermediate.

4. The uptake of Sr* by adult bone was less than in the other two groups, but progressed steadily throughout the hour, and the plasma clearance by adult bone remained almost constant. This indicates that deposition of Sr*

in those animals is chiefly by adsorption-exhange with the calcium of the bone mineral.

5. The most active uptake of Sr* by bone occured in the young normal animals. Plasma clearance by bone, initially very high, fell off rapidly throughout the hour. Similar uptake and clearances were obtained with the rachitic rats, although at a lower level. This suggests that in both groups there is a labile combination of Sr* with the bone osteoid by a reversible process such that, as time progresses, Sr* begins to come back out of the bone, cutting down the apparent clearance rate.

6. A hypothetical mechanism for calcification is suggested, involving labile combination of Sr* (or Ca) with osteoid, and subsequent mineralization. The role of adsorption-exchange is also mentioned.

7. In all groups, renal clearance was fairly constant throughout the experimental period. Low clearances and urinary excretion in the adult and young normal groups indicate active tubular reabsorption. Renal clearance was five to ten times as great in the rachitic as in the normal animals, suggesting a direct effect of rickets on tubular reabsorption of Sr*.

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