UCRL-873

UNIVERSITY OF CALIFORNIA — BERKELEY

TWO-WEEK LOAN COPY

This is a Library Circulating Copy which may be borrowed for two weeks. For a personal retention copy, call Tech. Info. Division, Ext. 5545

RADIATION LABORATORY

DISCLAIMER

This document was prepared as an account of work sponsored by the United States Government. While this document is believed to contain correct information, neither the United States Government nor any agency thereof, nor the Regents of the University of California, nor any of their employees, makes any warranty, express or implied, or assumes any legal responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by its trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof, or the Regents of the University of California. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof or the Regents of the University of California.

Copy 2

UCRL-873

Unclassified Distribution

UNIVERSITY OF CALIFORNIA

Radiation Laboratory

Contract No. W-7405-eng-48

UNCLASSIFIED

A STUDY OF THE METABOLISM OF RADIOACTIVE STRONTIUM IN ADULT, YOUNG AND RACHITIC RATS

D. C. Jones and D. H. Copp

August 28, 1950

Berkeley, California

INSTALLATION:	No. of Copies
Argonne National Laboratory	8
Armed Forces Special Weapons Project	1
Atomic Energy Commission, Washington	2
Battelle Memorial Institute	1
Brush Beryllium Company	1
Brookhaven National Laboratory	4
Bureau of Medicine and Surgery	1
Bureau of Ships	1
Carbide and Carbon Chemicals Division (K-25 Plant)	4
Carbide and Carbon Chemicals Division (Y-12 Plant)	4
Chicago Operations Office	1
Columbia University (J. R. Dunning)	1
Columbia University (G. Failla)	1
Dow Chemical Company	1
H. K. Ferguson Company	1
General Electric, Richland	3
Harshaw Chemical Corporation	1
Idaho Operations Office	1
Iowa State College	2
Kansas City Operations Branch	1
Kellex Corporation	2
Knolls Atomic Power Laboratory	4
Los Alamos Scientific Laboratory	3
Mallinckrodt Chemical Works	1
Massachusetts Institute of Technology (A. Gaudin)	1
Massachusetts Institute of Technology (A. R. Kaufmann)	1
Mound Laboratory	3
National Advisory Committee for Aeronautics	1
National Bureau of Standards	3
Naval Radiological Defense Laboratory	2
New Brunswick Laboratory	1
New York Operations Office	3
North American Aviation, Inc.	1
Oak Ridge National Laboratory	8
Patent Branch, Washington	1
Rand Corporation	1
Sandia Corporation	1
Santa Fe Operations Office	2
Sylvania Electric Products, Inc.	1
Technical Information Division (Oak Ridge)	15
USAF, Air Surgeon (Lt. Col. R. H. Blount)	1
USAF, Director of Armament (Captain C. I. Browne)	1
USAF, Director of Research and Development (Col. R. J. Mason, and Fred W. Bruner)	2
USAF, Eglin Air Force Base (Major A. C. Field)	1
USAF, Kirtland Air Force Base (Col. Marcus F. Cooper)	1
USAF, Maxwell Air Force Base (Col. F. N. Moyers)	1
USAF, NEPA Office	2
USAF, Office of Atomic Energy (Col. H. C. Donelly, A.A.Fickel)	2
USAF, Offutt Air Force Base (Col. H. R. Sullivan, Jr)	1
USAF, Wright-Patterson Air Force Base (Rodney Nudenberg)	1

INSTALLATION	No. of Copies
U. S. Army, Atomic Energy Branch (Lt. Col. A. W. Betts)	1
U. S. Army, Army Field Forces (Captain James Kerr)	1
U. S. Army, Commanding General, Chemical Corps Technical Command (Col. John A. MacLaughlin thru Mrs. Georgia S. Benjamin)	1
U. S. Army, Chief of Ordnance (Lt. Col. A. R. Del Campo)	1
U. S. Army, Commanding Officer, Watertown Arsenal (Col. Carroll H. Deitrick)	1
U. S. Army, Director of Operations Research (Dr. Ellis Johnson)	1
U. S. Army, Office of Engineers (Allen O'Leary)	1
U. S. Army, Office of the Chief Signal Officer (Curtis T. Clayton thru Maj. George C. Hunt)	1
U. S. Army, Office of the Surgeon General (Col. W. S. Stone)	1
U. S. Geological Survey (T. B. Nolan)	2
USAF, Director of Plans and Operations (Col. R.L.Applegate)	1
U. S. Public Health Service	1
University of California at Los Angeles	1
University of California Radiation Laboratory	5
University of Rochester	2
University of Washington	1
Western Reserve University	2
Westinghouse Electric Company	4
Naval Medical Research Institute	1
~~University of Rochester~~	1
California Institute of Technology (R. F. Bacher)	1
University of Rochester (Marshak)	1

Information Division
Radiation Laboratory
University of California
Berkeley, California

A STUDY OF THE METABOLISM OF RADIOACTIVE STRONTIUM IN ADULT, YOUNG AND RACHITIC RATS*

By D. C. Jones** and D. H. Copp***

(From the Division of Physiology, School of Medicine, and Crocker Laboratory, University of California, Berkeley and San Francisco)

August 28, 1950

The radioactive isotopes of strontium make up an important fraction of the products of nuclear fission (1). Because of their long half-lives and specific localization in bone, they present a serious health hazard, and even relatively small amounts of Sr^{90} have been found to induce bone tumors in experimental animals (2). The ease with which strontium is absorbed from the intestinal tract increases the danger from contaminated food or water.

In addition, radioactive strontium has been extensively used as a tracer for the study of calcium metabolism. Pecher (3) was the first to demonstrate the close similarity in the biological behavior of radioactive isotopes of these two alkaline earths. Radio-strontium has been used as an indicator for calcium in investigating the effects of growth hormone (4), parathormone (5) and rickets (6).

In the following experiments, a study has been made of the deposition of radio-strontium in the skeleton and its elimination by the kidney, particularly during the critical first 24 hours following parenteral administration. Jones and Copp have reported earlier a preliminary study covering the first hour (7). Three types of animals were used: mature adult rats in which

---

*This document is based on work performed under contract No. W-7405-eng-48-A-I of the University of California under the U. S. Atomic Energy Commission. The authors are indebted to Freeke van N. Kohl, J. G. Hamilton and Ruth Lerner for valuable assistance in conducting these experiments.

**Present address: Radiological Defense Laboratory, San Francisco Naval Shipyard, San Francisco.

***Present address: Department of Physiology, University of British Columbia, Vancouver, Canada.

skeletal growth had ceased; young rapidly growing rats in which there was active new bone formation; and young animals with low phosphorus rickets in which, despite formation of osteoid tissue, actual calcification does not occur.

EXPERIMENTAL

The radio-strontium used was carrier-free and consisted of a mixture of Sr^{89} and Sr^{90} formed by nuclear fission. Since Sr^{90} decays to a radioactive daughter, Y^{90}, with a 60-hour half-life, all samples were held for 24 days before counting so that equilibrium might be attained, and any Y^{90} present at the time of the experiment would have decayed. A dose of approximately 5 microcuries of radio-strontium in 0.25 ml. neutral isotonic saline was injected intraperitoneally into each animal. A total of 112 animals were used. They were all female rats of the Long-Evans strain. The adult animals were 5 - 6 months old, and ranged in weight from 235 to 320 grams. They were raised and maintained on the regular stock diet. The young animals were 51 days old at the time of the experiment, and ranged in weight from 79 to 109 grams. They were also maintained on the stock diet.

The rachitic rats were prepared according to the method described by Coleman et al. (8). They were weaned at 21 days and restricted to a diet which was very low in phosphorus (0.015 percent P). At the end of 30 days, the animals were x-rayed, and those showing +3 or +4 rickets were selected for the experiment. These animals ranged in weight from 50 - 80 grams.

Following injection of the radio-strontium, the animals were placed in large beakers with screens at the bottom which permitted separate collection of urine and feces. They were sacrificed with chloroform at time intervals from 5 minutes to 72 hours following administration of the isotope. A terminal blood sample was withdrawn from the inferior vena cava in a heparin rinsed syringe. This was centrifuged, and an aliquot of plasma was taken for determination of radio-strontium. The total amount of radio-strontium in plasma was

estimated using the value of 2.4 percent of body weight reported by Berlin (9). The bladder was opened, and its contents were rinsed into the urine collected in the beaker, so that the total amount of radio-strontium excreted by the kidney could be determined. The femur and the residual carcass were dried and ashed in a muffle furnace at 650°C for 10 hours. The ash was dissolved in 2 N HCl, diluted to volume, and a suitable aliquot was taken for determination of radio-strontium.

The amount of radio-strontium present in the skeleton at 24 hours was determined as follows. The animals were skinned and eviscerated, leaving only muscle and skeleton. The small amount of radio-strontium in a sample of muscle was measured, and from this the quantity in the total musculature was computed from the ratio of muscle to body weight reported by Donaldson (10). This was subtracted from the value for the eviscerated carcass to give the amount of radio-strontium in the skeleton alone. The correction was quite small in all cases. The ratio of radio-strontium in femur to radio-strontium in the total skeleton was found to be quite similar in all animals, and amounted to 0.040 in the adult animals, 0.044 in the young normals, and 0.042 in the rachitic rats. These ratios were used to estimate the radio-strontium present in the total skeleton from the values obtained for the femur.

RESULTS AND DISCUSSION

The results, given in Table I, show the percent of the administered dose of radio-strontium in plasma (calculated), femur, skeleton (calculated) and urine at various time intervals after its administration. The plasma clearance of radio-strontium by the kidney is also given. The data for the three groups of animals are shown graphically in Figures 1 - 3. Each point represents the average of 3 - 10 animals.

The plasma level rises during the first 15 minutes, as the radio-strontium is absorbed from the peritoneal cavity. It then falls rather rapidly in the young and rachitic animals; more slowly in the adults. Indeed, the plasma

radio-strontium in the latter remains 5 - 10 times higher than in the younger animals. This may be explained by slower removal by skeleton and kidney.

As was observed by Norris and Kisielski (11), radio-strontium rapidly concentrates in the skeleton. The uptake was continuous in the adult animals up to 2 hours, and reached a maximum value at 2 - 4 hours. This may be accounted for by ion exchange with bone salt (12). In young animals, the initial rate of uptake was five times as great, and the maximum was reached within 30 minutes. The radio-strontium remained fixed in the skeleton, and very little loss was observed even 4 - 8 days after injection (13). It is probable that this rapid uptake and fixation is associated with incorporation of the strontium in the newly formed bone salt.

The same initial rapid uptake was observed in the rachitic animals, and the maximum reached was similar. However, this was followed by active removal from the skeleton, so that at the end of 24 hours, less than 1/3 of the radio-strontium present at 1 hour remained in the bones. This was associated with a tremendous excretion of radio-strontium in the urine. New bone salt is not formed in these rachitic animals, so that radio-strontium cannot be incorporated in this form, although ion exchange with existing bone salt may take place as it does in the adult. The evidence suggests that the initial rapid uptake is due to a labile combination with bone, from which the radio-strontium is readily released in the rachitic animal. This may be a step in the calcification process, to be followed in the normal animal by incorporation in new bone salt.

In the young animal, very little radio-strontium was lost in the urine in contrast to the rachitics, in which a large part of the dose was eliminated by this route within 24 hours. Plasma clearances were calculated by dividing the excretion rate (determined graphically) by the radio-strontium level in the plasma. Since there was great divergence in the weights of the animals in the different groups, consistency was obtained by expressing the clearance as the

percent of the total blood plasma "cleared" of radio-strontium by urinary excretion per minute, rather than the more usual cc of plasma "cleared" per minute.

Plasma clearance was similar in both young and adult normal animals, with approximately 1 percent of the blood plasma "cleared" per minute. In the rachitic rats, the plasma clearance was 10 - 15 times greater than in the normals, indicating a direct effect of this condition on the excretion of radio-strontium by the kidney. This may be associated with the low level of inorganic phosphate in the blood of these animals (8).

SUMMARY

1. The metabolism of carrier-free radio-strontium was studied in adult, young and rachitic rats during the critical first 24 hours following intraperitoneal injection.
2. Radio-strontium is removed from the plasma much more slowly in the adult animals than in the other two groups.
3. The uptake of radio-strontium by adult bone is continuous for the first 2 hours, and reaches a maximum within 4 hours.
4. Skeletal uptake of radio-strontium is much more rapid in the young animals, reaching a maximum within 30 minutes. The deposited isotope appears to remain fixed in the bone.
5. In rachitic rats, the rapid initial uptake was similar to that in the normal young animals, but was followed by active loss from the skeleton, so that only 1/3 was left at 24 hours. This suggests a labile combination with bone.
6. A large part of the dose of radio-strontium was excreted by the rachitic rats within the first 24 hours, and the plasma clearance was 10 - 15 times as great as in the normal animals. This may be due to a direct effect of rickets on excretion by the kidney.

TABLE I

DISTRIBUTION AND EXCRETION OF RADIOSTRONTIUM IN ADULT, YOUNG AND RACHITIC RATS DURING THE FIRST 24 HOURS*

(Percent of the administered dose of $Sr^{89,90}$)

	Time After Injection of Radiostrontium									
	5 min.	15 min.	30 min.	1 hour	2 hours	4 hours	8 hours	12 hours	24 hours	72 hours
A. No. of Animals										
Adult	4	3	3	4	4	4	4	4	4	5
Young	3	3	4	4	8	7	9	8	4	5
Rachitic			5	10		5	5	3	5	5
B. Plasma (calculated)										
Adult	4.6±0.3	6.6±0.2	4.7±0.2	3.4±0.4	2.9±0.1	2.3±0.2	1.1±0.1	0.7±0.2	1.0±0.2	
Young	3.7±0.2	3.2±0.4	1.7±0.2	0.9±0.1	0.24±0.01	0.22±0.02	0.3±0.07	0.1±0.02	0.05±0.01	
Rachitic		2.2±0.2	1.6±0.2	0.8±0.1		0.24±0.04	0.16±0.04	0.16±0.08	0.05±0.01	
C. Femur										
Adult	0.13±0.01	0.42±0.02	0.67±0.02	1.06±0.18	2.35±0.02	2.68±0.02	2.56±0.09	2.64±0.14	2.47±0.11	1.63±0.06
Young	0.73±0.08	1.94±0.09	2.92±0.08	2.84±0.06	3.04±0.32	3.07±0.29	3.08±0.31	2.74±0.26	3.42±0.39	3.01±0.09
Rachitic			2.85±0.22	3.04±0.13		2.54±0.32	1.64±0.06	1.40±0.24	0.92±0.21	0.69±0.17
D. Skeleton (calculated)										
Adult	3.2±0.3	10.5±0.5	16.8±0.4	26.5±4.4	56.2±0.4	68.0±0.6	64.0±2.3	66.1±3.4	61.8±2.7	40.6±1.4
Young	16.6±1.9	44.0±2.0	66.3±1.8	64.4±1.3	68.9±7.2	69.7±6.5	70.0±7.0	62.0±6.0	77.5±8.8	68.5±2.1
Rachitic			67.9±5.2	72.3±3.1		60.6±7.5	39.0±1.4	33.2±5.8	21.8±4.9	16.3±4.1
E. Urine										
Adult		0.8±0.2	0.6±0.2	2.8±0.9	8.4±2.7	4.2±0.8	13.1±2.6	13.9±1.2	24.3±3.4	26.4±1.3
Young		1.4±1.0	3.0±0.9	1.2±0.2	1.9±0.3	2.0±0.7	3.0±0.0	2.0±0.5	5.0±0.7	13.5±2.1
Rachitic			9.9±1.9	13.6±1.6		28.1±5.8	42.7±3.6	39.9±8.7	58.6±2.8	81.3±7.4
F. Plasma Clearance % total plasma cleared/min.										
Adult			1.2	1.1	1.2	0.8	0.8	1.1		
Young			0.8	1.2	2.7	1.1	0.8	2.5		
Rachitic			12.3	20.3		10.6	11.4	14.7		

Figures are mean values for 3 - 10 animals, ± the standard error. (std. error $= \sqrt{\frac{d^2}{n(n-1)}}$)

UCRL-873

BIBLIOGRAPHY

1. Hamilton, J. G., Rev. Mod. Phys. 20, 718 (1948)

2. Lisco, H., Finkel, M. P. and Brues, A. M., Radiology, 49, 361 (1947)

3. Pocher, C., Proc. Soc. Exp. Biol. Med., 46, 86 (1941)

4. Marx, W., and Reinhardt, W. O., Proc. Soc. Exp. Biol. Med., 51, 112 (1942)

5. Tweedy, W. R., J. Biol. Chem., 161, 105 (1945)

6. Greenberg, D. M., J. Biol. Chem. 157, 99 (1945)

7. Jones, D. C. and Copp, D. H., AECD-1962, Technical Information Division, Oak Ridge Directed Operations, U. S. Atomic Energy Commission. (1948)

8. Coleman, R., Becks, H., Kohl, F. van Nouhuys, and Copp, D. H., Arch. Path. 50, 209 (1950)

9. Berlin, N. I., Huff, R. L., Van Dyke, D. C., and Hennessy, T. G., Proc. Soc. Exp. Biol. Med., 71, 176 (1949)

10. Donaldson, H. H., The Rat, Memoirs of the Wistar Institute of Anatomy and Biology, Philadelphia, 2nd Ed., 1924.

11. Norris, W. P., and Kisielski, W., Cold Spr. Harb. Symp. Quant. Biol., 13, 164 (1948)

12. Hodge, H. C., Gavett, E., and Thomas, I., J. Biol. Chem., 163, 1, (1946)

13. Copp, D. H., Greenberg, D. M., and Hamilton, J. G., AECD-2483, Technical Information Division, Oak Ridge Directed Operations, U. S. Atomic Energy Commission. (1946)

UNIVERSITY OF CALIFORNIA

Radiation Laboratory

November 21, 1950

To: Recipients of Unclassified Distribution for UCRL-873

From: Information Division

The attached copies of Figures 1, 2, and 3 should be inserted in your copies of the document UCRL-873, "A Study of the Metabolism of Radioactive Strontium in Adult, Young and Rachitic Rats" by D. C. Jones and D. H. Copp.

Enclosures

FIG. I

NORMAL ADULT RATS

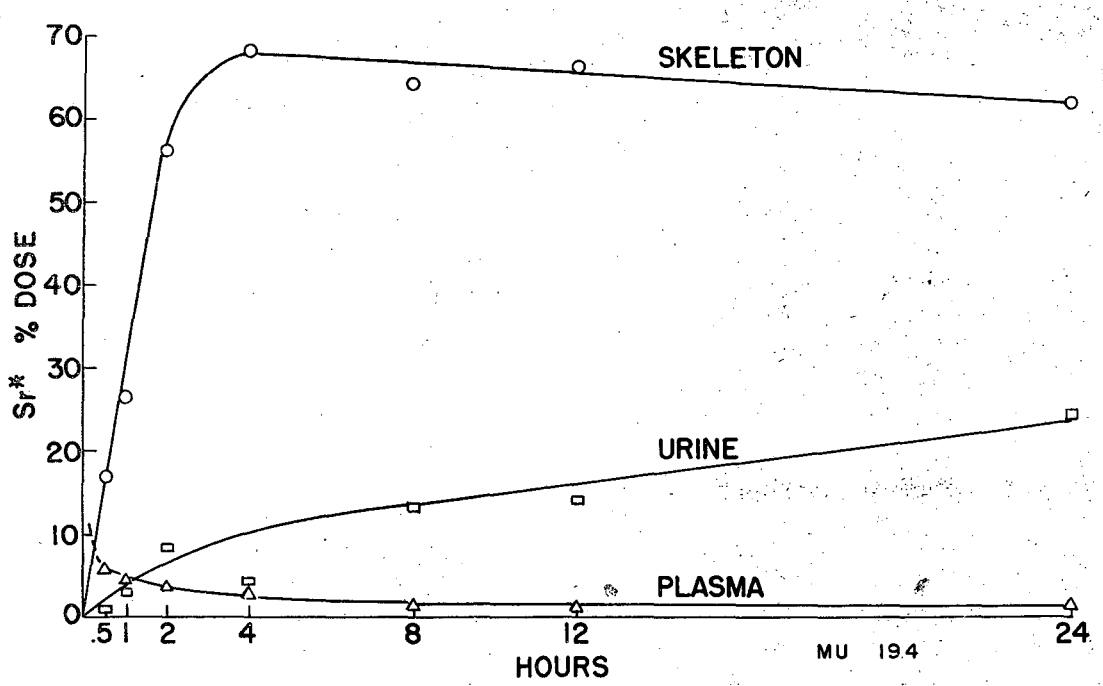


FIG. 2

NORMAL YOUNG RATS

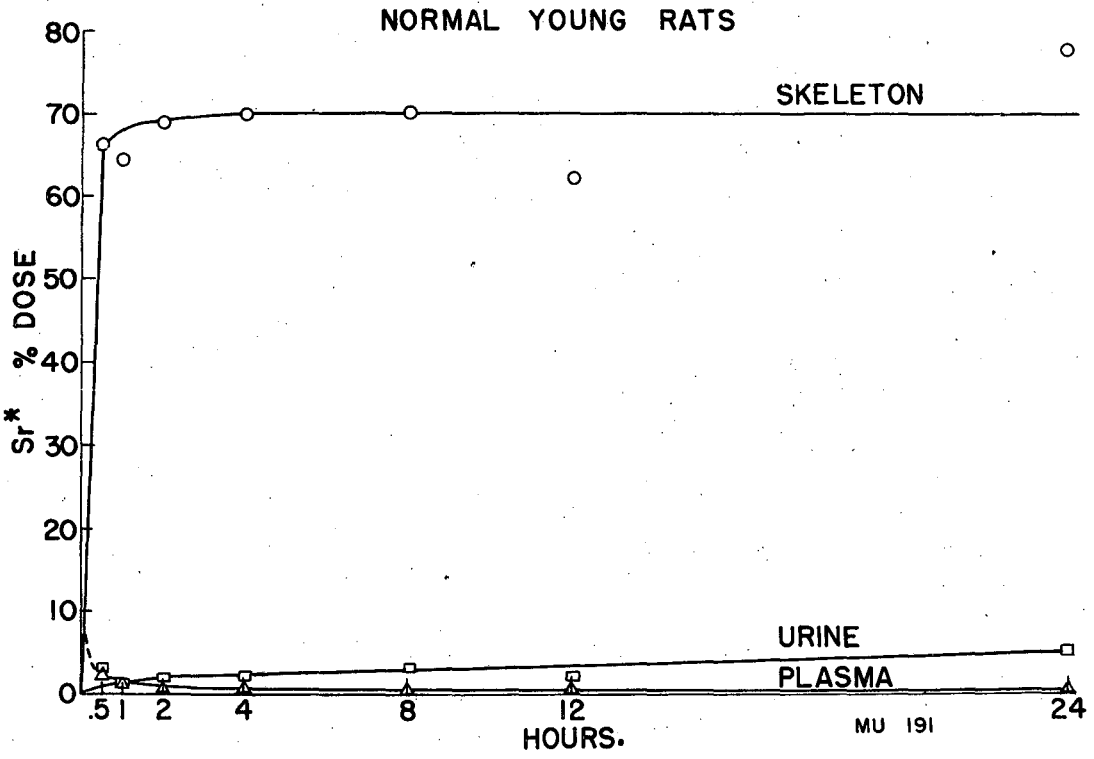
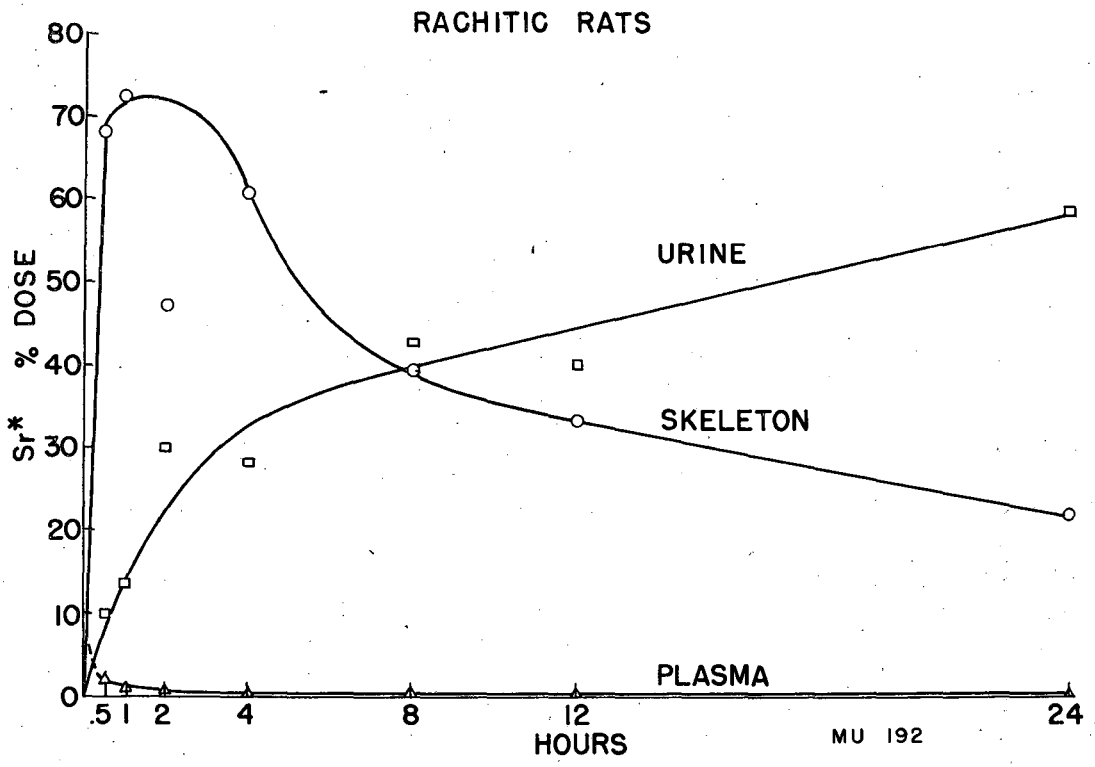


FIG. 3

RACHITIC RATS