THE DEPOSITION OF URANIUM IN BONE*

I. ANIMAL STUDIES

BY W. F. NEUMAN, M. W. NEUMAN, AND B. J. MULRYAN

(From the Division of Pharmacology and Toxicology, Department of Radiation Biology, School of Medicine and Dentistry, The University of Rochester, Rochester, New York)

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Studies of the distribution of uranium in animal tissues (1, 2) have shown that a large proportion of the injected dose accumulates initially in the bone and kidney. 40 days after injection, however, bone is the only tissue which has retained significant quantities of the metal (2). Because of the importance of bone as a storage site for uranium, more specific information has been obtained concerning the factors which influence the deposition of uranium in bone in the animal.

One of the problems presented by the previous work concerned the differences in the skeletal distribution of uranium which occurred between the sexes. The bones of male rats consistently accumulated greater quantities of uranium than those of females. All of these rats weighed 200 gm. At this weight, the male rats averaged 9 weeks in age, the females 16 weeks. Were these differences related to age or sex?

Recent studies with radioactive phosphorus (3) have emphasized the importance of the relative vascularity of bone in determining the rate and, as a result, the amount of deposition of minerals in bone. This suggested that the differences observed in young male and adult female rats resulted from variation in the relative vascularity of the skeleton with age. To test this hypothesis, normal male and female rats of various ages and rats in a state of severe rickets were injected with uranium and their bones analyzed. An analysis of the content of uranium in different types of bone structures as represented by skull, vertebra, and long bone was also made. Epiphysis, metaphysis, and diaphysis from rabbits, and periosteum from a dog were examined for purposes of comparison. A study of the uptake of radiophosphate in different parts of the skeleton supplemented the experiments with uranium.

EXPERIMENTAL

Methods

Rats from a colony of Wistar strain animals were maintained on a fox chow diet unless otherwise indicated. After a 3 to 5 day observation

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period, they were injected intraperitoneally with 2.5 mg. of uranium per kilo as a 0.1 per cent aqueous solution of either uranyl nitrate or acetate. This is a toxic and sometimes lethal dose. The rats were sacrificed by decapitation 48 hours after injection. By this time, the distribution of uranium throughout the animal has reached a fairly steady state (2). The bones to be analyzed were removed, freed of flesh, ashed in a muffle furnace, and analyzed by the fluorophotometric method (4).

Analyses of the skull included the jaw and teeth. All femora and humeri of each animal were combined for analysis. Three vertebrae were taken from the lumbar region. In one case, the epiphyses, metaphyses, and shafts of the long bones of two 6 week-old chinchilla rabbits were separated and analyzed.

A similar routine was followed in the investigation of the distribution of radioactive phosphorus. Rats 2 and 15 weeks old were injected intraperitoneally with a saline solution of P32 as Na2HPO4, 0.1 mg., 1 microcurie per kilo. After an equilibrating period of 24 hours, the rats were killed, the bones removed, ashed in a muffle furnace, dissolved in HCl, and the radioactivity measurements made in the conventional manner (5).

Results

Concentration of Uranium in Bones at Various Ages—The effect of the age of the rat on the deposition of uranium in bone is clearly demonstrated in Fig. 1. On the basis of ash weight, the young rat (2.5 weeks of age) evidenced a deposition of uranium in the femora and humeri nearly 6 times that which occurred in the adult rat (15 weeks of age). No sex differences were observed over the range of ages studied, including animals before, during, and after sexual maturation.
The results obtained from two 11 week-old rats, which had been maintained for 2 months on a rachitogenic diet, are also recorded in Fig. 1. These animals were in a state of severe rickets. The ash content of their bones was 11 and 15 per cent, respectively, as compared to a value of 40 per cent normally found at this age. The concentration of uranium observed was excessively high if compared with that of normal animals of the same age.

Concentration of Uranium in Bones of Different Structural Types—The relative activity of the skull, vertebra, and combined femur and humerus in accumulating injected uranium and radiophosphate is shown in Table I. In all cases, vertebra fixed greater quantities of uranium than did skull. Long bone was intermediate, but, in general, gave results comparable to vertebra in young rats and to skull in adult rats. The differences between the bones were smaller in the adult rats.

The uptake of $P^{32}$ by the three skeletal components followed a pattern strikingly similar to that seen with uranium.

Material for a comparison of the deposition of uranium in the epiphysis, metaphysis, and shaft of rapidly growing femur was obtained from two young rabbits also given 2.5 mg. of uranium per kilo intraperitoneally.

Analyses of the pooled samples gave the following content of uranium, in micrograms per gm. of ash: metaphysis 2.3, epiphysis 1.8, shaft 1.6.

In this case, the metaphysis accumulated greater quantities per gm. of ash than did the rest of the bone. It is also interesting that smaller quantities of uranium were found in the bones of rabbits than of rats of a corresponding age.

1 A modified Steenbock diet, Diet 2, obtained from General Biochemicals, Inc., Chagrin Falls, Ohio.
Periosteum was obtained from the ribs and long bones of a dog which had received thirteen injections of 0.3 mg. of uranium per kilo (as \( \text{UO}_2(\text{NO}_3)_2 \)) over a period of 6 weeks and a final dose of 5 mg. of uranium per kilo. The dog was sacrificed 9 days after the final injection. For comparison, samples of bone and muscle were taken from each of the areas from which periosteum was obtained. Bone and muscle specimens were pooled separately; periosteum from tibia and femur was kept separate from the periosteum taken from rib. The analytical results are presented in Table II.

The amount of uranium found in muscle is comparable to values reported for such tissues from normal untreated rats (2). The values for periosteum, while significantly higher than for muscle, were low in comparison to those of the adjacent bone. Calcified bone is apparently the principal site of deposition, not periosteum.

**Table II**

*Comparison of Uranium Content of Bone, Periosteum, and Muscle from Dog after Repeated Uranium Injections*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Uranium content (( \gamma ) per gm. wet weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td></td>
</tr>
<tr>
<td>Periosteum (rib)</td>
<td>2.1</td>
</tr>
<tr>
<td>&quot; (tibia and femur)</td>
<td>0.42</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The age of the rat proved to be an important factor in determining the extent of uranium deposition in bone. The young, more rapidly growing animals, irrespective of sex, showed a greater fixation of injected uranium. A comparison of different parts of the femur also showed a direct correlation between growth activity and uranium fixation.

There seems reason to doubt, however, that the deposition of uranium is directly related to the calcification process *per se*. Rather, it appears more likely that some factor closely associated with bone growth, vascularity perhaps, is responsible. For example, in the rachitic animals, large amounts of uranium were found in bones where no net accretion of mineral was taking place. Radiophosphate, the fixation of which has been established to be principally an exchange process not directly associated with growth (3, 6), showed the same relative distribution as did uranium. Finally, it has been shown (2) that uranium is cleared from the blood within 45 minutes after injection. During this time, the amount of new calcifi-
cation is so small that, to account for uranium deposition as part of the calcification process, nearly every mole of hydroxylapatite laid down must bind a uranyl ion. At the concentrations of uranium in the plasma during this period, such a phenomenon seems improbable.

It has been reported (7) that uranium is deposited principally in the periosteum and endosteum. Direct analyses of periosteum did not confirm this view.

SUMMARY

The deposition of injected uranium in bone was found to be directly related to growth activity. Young rats, irrespective of sex, showed a greater concentration of uranium in bone than did older animals.

BIBLIOGRAPHY

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W. F. Neuman, M. W. Neuman and B. J. Mulryan


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