The Metabolic Properties of the Fission Products and Actinide Elements

JOSEPH G. HAMILTON

Division of Medical Physics, Experimental Medicine and Radiology, University of California at Berkeley and San Francisco, California

AN extensive survey has been made of the metabolism of twenty-two different radio-elements in the rat.* A large share of the material included in this article has been the result of a program initiated October 15, 1942 at the Crocker Laboratory and continued since then by Dorothy Axelrod, M.A.; Assistant Professor D. H. Copp, M.D.; Josephine Crowley, A.B.; Henry Lanz, Jr., Ph.D.; Assistant Professor Kenneth G. Scott, Ph.D.; eight technicians, and the author. During the early phases of this project we were fortunate in having the advice and aid of Professors I. L. Chaikoff and D. M. Greenberg, who assisted the program materially, particularly in the studies with strontium, barium, and cesium. Also with the group during the war were Associate Professor Roy Overstreet and Assistant Professor Louis Jacobson, whose work included a large share of the radio-chemical isolation as well as a series of studies with soils and plants.[1] We acknowledge with gratitude the facilities that were extended to us to do this work in the Radiation Laboratory by Professor Ernest O. Lawrence, the constant advice and encouragement given to us by Doctor Robert S. Stone and Dean Stafford L. Warren, the operating crew of the 60-inch cyclotron for the preparation of most of the radio-elements used in these studies, and to Professor G. T. Seaborg, Dean W. M. Latimer, and their associates for providing us with certain key radio-elements for these studies, notably neptunium, plutonium, americium, and curium.

TABLE I. Part 1. Fission products and isotopically related radio-elements.

Isotope	Half-life	Type of radiation	Method of production
Sr^{85}*	65-d	K, γ, e^-	Rb-d-$2n$
Y^{88}*	87-d	K, γ	Sr-d-$2n$
Zr^{89}*	78-hr.	Positron	Y-d-$2n$
Zr^{95}	65-d	β^-, γ	U-n
Cb^{95}	37-d	β^-, γ	Zr^{95}-β^--decay
Ru^{103}	42-d	β^-, γ	U-n
Ru^{106}	1.0-yr.	β^-	U-n
Te^{127}	90-d	I.T., e^-, x-ray	U-n
Te^{129}	32-d	I.T., e^-	U-n
I^{131}	8.0-d	β^-, γ	Te^{130}-d-p, Te^{131}-β^--decay
Xe^{127}*	34-d	K, γ, e^-	I-d-$2n$
Cs^{137}	33-yr.	β^-, γ	U-n
Ba^{133}*	38.8-hr.	I.T., γ, e^-	Cs-d-$2n$
Ba^{140}	12.8-d	β^-, γ, e^-	U-n
La^{140}	40.0-hr.	β^-, γ	Ba^{140}-β^- decay
Ce^{141}	28-d	β^-, γ	U-n
Ce^{144}	275-d	β^-	U-n
Pr^{143}	13.8-d	β^-	U-n
61^{147}	3.7-yr.	β^-	U-n

Part 2. Actinide elements.

Ac^{227}	13.5-yr.	β^- (99%), α (1%)	Ra^{226}-n-γ · Ra^{227} β^--decay
Th^{234}	24.5-d	β^-, γ	U^{238} α decay
Pa^{233}	27.4-d	β^-, γ, e^-	Th^{232}-n-γ · Th^{233} β^--decay
U^{233}	10^5-yr.	α	Pa^{233} β^- decay
Np^{239}	2.2-d	β^-, γ	U^{238}-n-γ · U^{239} β^--decay
Pu^{239}	2.2×10^4-yr.	α	Np^{239} β^- decay
Am^{241}	500-yr.	α	Pu-α-p, n
Cm^{242}	150-d	α	Pu-α-n

* Radio-isotopes which are not formed by the fission of uranium in the chain reacting pile.

INTRODUCTION

The discovery and development of the chain-reacting pile brought with it a series of medical problems of considerable magnitude. The production of plutonium on the kilogram scale is associated with the formation of a comparable mass of fission products whose radioactivity is at the level of hundreds of megacuries.

Radioactive substances can produce injury either by external or internal radiation of the body. Of the two, the potentialities for injury are greater if the radioactive substance is within the body. The history of the radium industry is illustrative of this point. Up to the time of World War II about one kilogram of radium had been isolated. A large number of cases of radium poisoning have been reported, notably in the luminous dial industry, a considerable proportion of which terminated fatally.

* This research work was carried out under the direction of the Manhattan Project, Contract No. W-7405-eng-48-A and the Atomic Energy Commission.

[1] L. Jacobson and R. Overstreet, Soil Science 65, 129 (1948).

The medical program of the plutonium project, under the direction of Dr. R. S. Stone, was faced with the responsibility of protecting the personnel against quantities of radioactivity which were of the order of a millionfold greater than had been encountered by the radium industry over a period of nearly half a century. Here the problems had to be met quickly in the haste of wartime urgency for the thousands of scientists and technicians working on the Atomic Energy Project. One of the many research programs that arose from these needs was a survey of the metabolism of the various radio-elements created by the release of nuclear energy. A review of part of this work has been presented recently.[2]

It is appropriate to mention a few of the salient factors involved in the problem of radioactive poisoning, because it was these considerations that shaped the pattern of the research to be described in this article. In order to evaluate the potential hazard of a given radio-element or compound it is necessary to consider the half-life, radiation characteristics, route of entry into the body, assimilation, distribution, retention, excretion, and the relative susceptibility of the different organs and tissues to the radiations emitted by the deposited material.

Radiation injury, both acute and chronic, is a function of the intensity of the radiation and the duration of exposure to the radiation. A radioactive substance, either as an element or a compound, may enter the body by one or more of four routes, namely, the lungs, the digestive tract, the intact skin, and cuts or abrasions. Once the material has been absorbed, regardless of the portal of entry, it will be distributed to the many tissues of the body and will be taken up in widely varying concentrations and be retained for different intervals of time in these tissues. The degree of injury will vary with the character of the radiation and the radio-sensitivity of the irradiated organ or tissue. For example, alpha-particles are relatively more destructive to most living organisms than beta- or gamma-rays, when the biological effects are compared on the basis of equivalent amounts of total ionization in the tissue. With regard to variations of vulnerability to radiation, the bone marrow which is the center of hemopoeisis is very sensitive, while structures such as liver, brain, and muscle are relatively radio-resistant.

If the assimilation, distribution, retention, and excretion of a given radio-element is determined, it is possible to make an estimate of the amount of exposure to such a substance which might be expected to produce either acute or chronic injury. If the tracer or metabolic studies are done with laboratory animals, as they were in these experiments, there is a variable error introduced in extrapolating from the experimental animals to man. However, in many instances this error is probably not much greater than the individual variations between different humans in their response to a novel biological experience

[2] J. G. Hamilton, Radiology **43**, 425 (1947).

TABLE II. Summary of the metabolism of the principal members of the long-lived fission products and certain of the fissionable elements in the rat following parenteral and oral administration.

Radio-element	Half-life	Fission yield (%)	% Oral absorb-tion	% Accumulation in principal organ of retention	Rate of elimination from principal organs of retention	
Sr^{89} Sr^{90}	53-d 25-yr.	4.6	5–60	70% bone	bone	>200-d
Ba^{140}	12.8-d	6.1	5–60	60% bone	bone	>50-d
I^{131}	8.0-d	2.8	100	20% thyroid*	thyroid	> 30-d*
Cs^{135}	33-yr.		100	45% muscle	muscle	15-d
Y^{91}	57-d	5.9	<0.05	65% bone	bone	>500-d
La^{140}	40-hr.	6.1	<0.05	70% liver 30% bone	liver bone	10-d > 25-d
Ce^{141} Ce^{144}	28-d 275-d	5.7 5.3	<0.05 <0.05	50% liver 25% bone	liver bone	10-d >100-d
Pr^{143}	13.8-d	5.4	<0.5	35% liver 50% bone	liver bone	10-d >100-d
61^{147}	3.7-yr.	2.6	<0.05	55% liver 35% bone	liver bone	10-d >100-d
Zr^{95}	65-d	6.4	<0.05	35% bone	bone	>100-d
Cb^{95}	37-d	6.4	<0.5	30% bone 25% blood	bone blood	30-d 1-d
Ru^{103} Ru^{106}	42-d 1-yr.	3.7 0.5	<0.05	3.5% kidney	kidney	20-d
Te^{127} Te^{129}	90-d 32-d	0.033 0.19	25 25	15% blood 6% kidney	blood kidney	15-d 15-d
Xe^{133}	5.3-d	4.5		Distribution proportional to fat content of body; half-time in the body two hours		
Ac^{227}	13.5-yr.		<0.05	50% liver 30% bone	liver bone	> 4-d > 4-d
Th^{234}	24.5-d		<0.05	50% bone	bone	>200-d
Pa^{231}	3×10^4 yr.		<0.05	40% bone	bone	>100-d
U^{233}	1.6×10^5-yr.		<0.05	45% kidney 20% bone	kidney bone	5-d 60-d
Np^{239}	2.2-d		<0.05	65% bone	bone	> 50-d
Pu^{239}	2.2×10^4-yr.		0.007	75% bone	bone	> 2-yr.
Am^{241}	500-yr.		<0.05	60% liver 25% bone	liver bone	10-d > 1-yr.
Cm^{242}	150-d		<0.05	60% liver 25% bone	liver bone	10-d > 1-yr.

* Human studies (10).

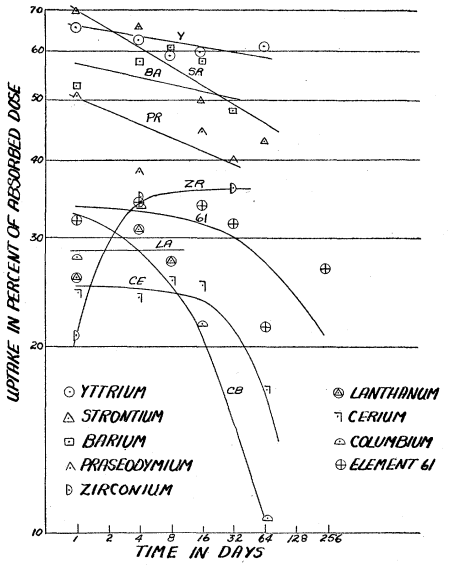

FIG. 1. Deposition of carrier-free fission products in the skeleton of the rat, following their parenteral administration.

such as is offered to the body by most of the radio-elements discussed in this article.

The metabolism of the 22 different elements listed in Table I has been investigated in considerable detail. With the exception of strontium, iodine, and uranium, little or nothing was known prior to 1944 about the metabolic properties of these substances, most of which are not presumed to be normal constituents of living organisms.

EXPERIMENTAL PROCEDURES

Radioactive isotopes of each of the 22 elements were prepared in the carrier-free state and individually administered to rats.[3–8] Three of the four possible routes of entry into the body were simulated by administering the radio-isotopes orally and by injection, and introducing them directly into the lungs. The fourth possible route of entry, namely, through the intact skin, was not investigated. Each radio-element was prepared and used in the carrier-free state for two reasons. First, all of the fission products and several of the heaviest elements would be encountered only in this situation. Second, it is possible that the quantitative metabolic pattern might be altered if appreciable amounts of the inert material isotopic with the radio-element were present. An excellent example of this second consideration may be found in comparing the metabolism of carrier-free radio-iodine with radio-iodine diluted with stable iodine.[9] Here, there are large quantitative variations in the distribution of the labeled iodine when different amounts of inert iodine are added to the radio-iodine. In addition to the quantitative variations encountered under these conditions, there is a very striking qualitative difference observed in the behavior of carrier-containing and carrier-free radio-iodine in the thyroids of patients suffering from hyperthyroidism. A similar phenomenon has been recently demonstrated with carrier-free and carrier-containing radio-silver.[10]

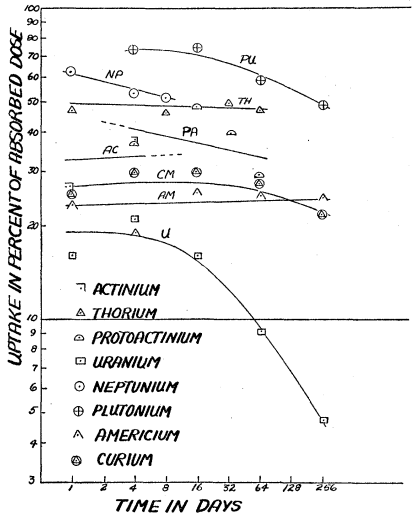

FIG. 2. Deposition of actinium, thorium, protoactinium, uranium, neptunium, plutonium, americium, and curium in the skeleton of the rat, following their parenteral administration.

[3] Scott, Overstreet, Jacobson, Hamilton, Fisher, Crowley, Chaikoff, Entemann, Fisher, Barber, and Loomis, Plutonium Project Record of the National Nuclear Energy Series, MDDC-1275.

[4] Scott, Axelrod, Fisher, Crowley, Barber, and Hamilton, Plutonium Project Record of the National Nuclear Energy Series, Div. IV, **22G** (Part 5).

[5] Lanz, Scott, Crowley, and Hamilton, Plutonium Project Record of the National Nuclear Energy Series, Div. IV, **22H** (Part 5.28).

[6] Scott, Copp, Axelrod, and Hamilton, J. Biol. Chem. (in press).

[7] K. G. Scott, D. J. Axelrod, and J. G. Hamilton, AECD-1805 (submitted for publication).

[8] K. G. Scott, D. J. Axelrod, and J. G. Hamilton (unpublished data).

[9] J. G. Hamilton, Radiology **35**, 541 (1942).

[10] K. G. Scott and J. G. Hamilton (submitted for publication).

The fission products selected for the studies reviewed in this report were chosen on the basis of two major considerations: First, that they are produced in relatively high yields from fission and, second, that they have half-lives in the range of days to months. Such a selection includes most of the fission products that might be considered as the major hazards insofar as internal radioactive poisoning is concerned. All eight of the heaviest elements, recently classified as the actinide rare earths by Seaborg,[11] were also subjected to metabolic study. In a number of instances the radio-isotopes were prepared by cyclotron bombardment. This was done for a number of different reasons, notably greater ease of radio-chemical isolation, unavailability

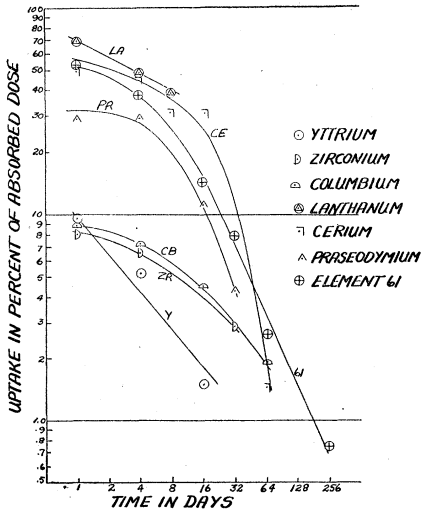

FIG. 3. Deposition of carrier-free fission products in the liver of the rat, following their parenteral administration.

of pile-produced radioactivities at the time the experiments were undertaken, and more desirable radioactive properties of the cyclotron-produced radio-isotopes for the type of tracer studies to be done. The radio-isotopes employed, together with their radioactive properties and methods of production, are listed in Table I.

Each radio-element, whether produced by fission, cyclotron bombardment, pile irradiation, or from the decay of a radioactive parent, was isolated in the carrier-free state and free from measurable amounts of radioactive contaminants. With the exception of xenon, each radio-element was prepared and administered to rats in an isotonic solution of sodium chloride at a *p*H range from 2.7 to 5. The solution was given by intraperitoneal injection, intramuscular injection, or by stomach tube. The rats were sacrificed at various time intervals extending from 1 to 64 days. In several of the experiments the time intervals extended to 256 days, and in a number of instances the studies had to be concluded before 64 days because of the limiting half-life of the radio-element being investigated. The excreta and from 12 to 18 organs were removed and individually assayed for their content of radioactivity. Frequently the assays were very laborious and time consuming. This was particularly true for plutonium, americium, and curium, which emit alpha-particles, as well as for element 61 whose beta-rays are very soft, having a maximum energy of 0.2 Mev. In such instances, for each individual radioactive assay it was necessary to free the radio-element from the ashed tissue and excreta by chemical means. A discussion of the more detailed aspects of the techniques employed in handling the biological materials and their assay is reported elsewhere.[6] Likewise, the behavior of the fission products

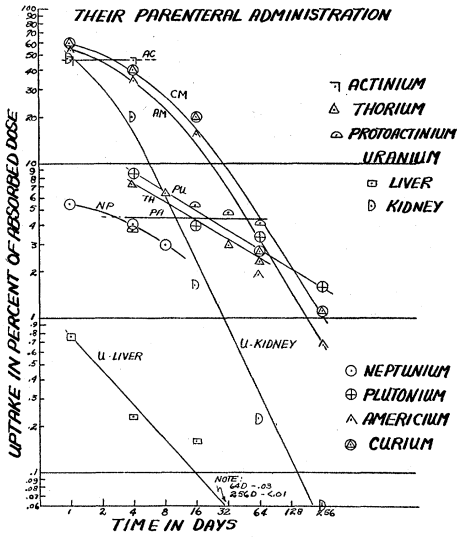

FIG. 4. Deposition of actinium, thorium, protoactinium, uranium, neptunium, plutonium, americium, and curium in the liver, and of uranium in the kidney of the rat, following their parenteral administration.

[11] G. T. Seaborg, Science **104**, 379 (1946).

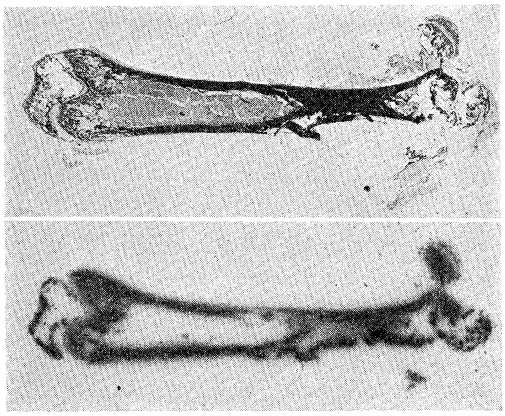

FIG. 5. Femur from young rat injected with radiostrontium and sacrificed at 1 week. Note strontium deposition in shaft and calcified areas below epiphysis (×6½).

and of plutonium, following their entry into the lungs, has been described in another report.[12]

In addition to the tracer experiments described above, a considerable amount of effort was directed to a study of the sites of localization of a number of the fission products and the actinide elements in bone by means of the radioautographic technique.[13] This is an issue of importance because nine of the fourteen fission products studied and all eight of the actinide elements are accumulated and tenaciously retained by the skeleton. Longitudinal sections of the femur were prepared from the undecalcified bone. These sections were of uniform thickness in the range of from 4 to 6 microns. The technique of cutting thin sections of undecalcified bone was developed by Axelrod[14] and McLean and Bloom.[15] The necessity for using this difficult procedure instead of using decalcified specimens arises from the fact that the agents employed to remove the mineral elements from bone are very likely to either leach out or translocate the radio-element deposited in the bone.

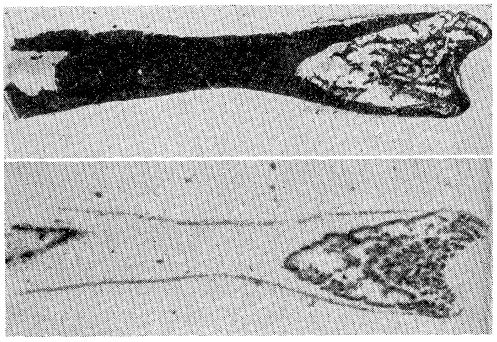

FIG. 6. Femur from adult rat injected with plutonium and sacrificed at 8 weeks. Note superficial plutonium deposition in area of trabecular bone, periosteum, and endosteum. A comparable pattern is found after 7 days and 256 days (×10).

[12] Scott, Axelrod, Crowley, Lanz, and Hamilton, Plutonium Project Record of the National Nuclear Energy Series, MDDC-1276.

[13] D. J. Axelrod and J. G. Hamilton, Supp. to U. S. Naval Med. Bull. 122 (March-April 1948).

RESULTS

The most important metabolic characteristics of the fission products and the actinide elements studied are listed in Table II. It will be noted that most of the fission products and all of the actinide series are not absorbed to any significant degree by way of the digestive tract. Following intramuscular administration these substances are accumulated by the skeleton and eliminated from this organ very slowly. Only five of the listed fission products are absorbed from the digestive tract to a significant degree, notably strontium, barium, tellurium, iodine, and cesium. Xenon is readily and rapidly absorbed through the lungs following inhalation and is as readily eliminated from the lungs. Strontium and barium are deposited and retained to a high degree by the skeleton. Iodine is accumulated and retained by the thyroid. Tellurium shows some accumula-

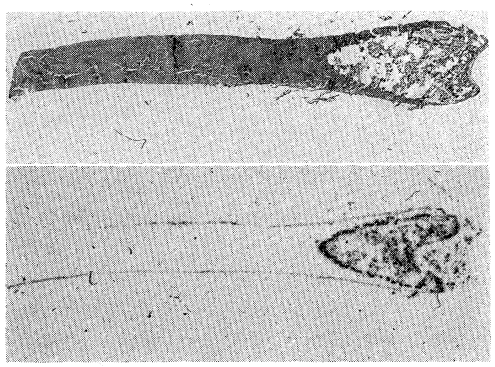

FIG. 7. Femur from adult rat injected with zirconium and sacrificed at 2 weeks. Note similarity to plutonium deposition in Fig. 6 (×7½).

[14] D. J. Axelrod, Anat. Rec. **98**, 19 (1947).

[15] F. C. McLean and W. Bloom, Anat. Rec. **78**, 333 (1940).

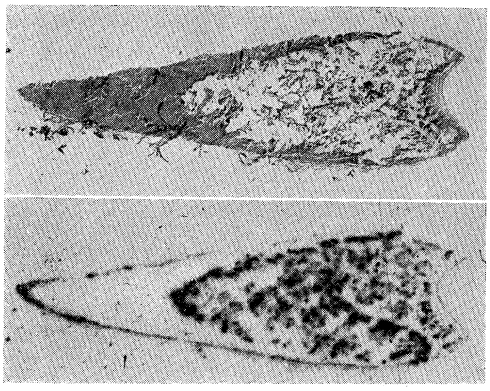

FIG. 8. Femur from adult rat injected with columbium and sacrificed at 8 days. Superficial deposition appears to be similar to that of plutonium and zirconium (×14).

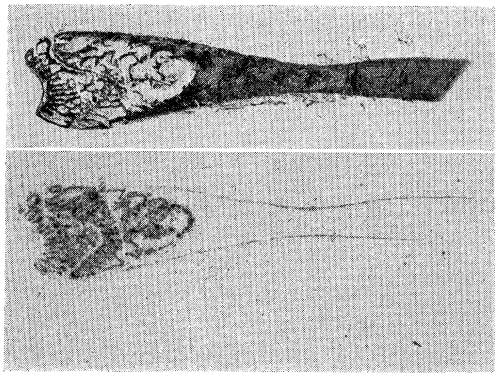

FIG. 9. Femur from adult rat injected with thorium and sacrificed at 8 days. Superficial deposition resembles zirconium, columbium, and plutonium bone deposition (×8).

tion in the kidneys and blood, with a rather rapid rate of release from these tissues. Cesium is distributed quite uniformly throughout all of the tissues, the greatest accumulation occurring is the muscle, and it is quite promptly excreted. The pattern of distribution of strontium, barium, tellurium, iodine, and cesium following oral absorption is indistinguishable from their metabolism after intramuscular administration. With the exception of ruthenium, the remainder of the fission product series and all of the actinide elements listed in Table II show a considerable accumulation and varying degrees of retention by the skeleton as shown in Figs. 1 and 2. In the case of lanthanum, cerium, praseodymium, element 61, actinium, americium, and curium, there is an initially high degree of accumulation by the liver, but they are quite rapidly excreted from this organ, presumably by way of the bile (Figs. 3 and 4). Uranium is unique among the actinide group in that there is a very high initial accumulation in the kidney, and excretion from the skeleton is more rapid than with the remaining seven elements of this group. The data on uranium presented in this report confirms earlier studies done elsewhere.[16–18] With the exception of the liver and kidney, the content in the other soft tissues is relatively small following the parenteral administration of the fission products and actinide elements. After two months the spleen and kidney usually had the highest concentration per gram wet weight of the soft tissues and ranged from one-tenth to one-quarter that of bone.

It will be noted in Table II that with the exception of Cb^{95} and possibly Sr^{90}, Ce^{144}, and 61^{147}, the rates of elimination of the different fission products that are accumulated in the skeleton are less than their rates of radioactive decay. The long-lived fission products that fall into this category include Sr^{89}, Y^{91}, Zr^{95}, Ba^{140}, La^{140}, Ce^{141}, and Pr^{143}. With the exception of iodine in the thyroid, the remainder of the fission products listed in Table II, namely, Ru^{103},

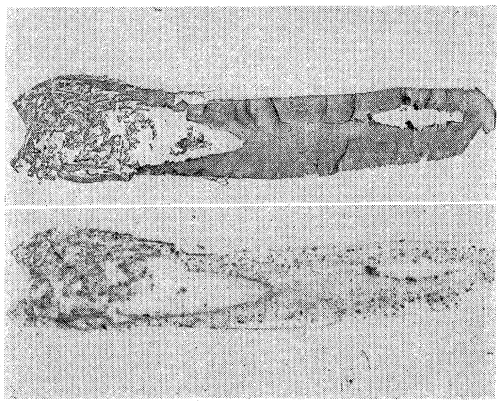

FIG. 10. Femur from adult rat injected with cerium and sacrificed at 64 days. Note cerium deposition on surface of bone and the spotty distribution in the shaft (×8).

[16] Neuman, Neuman, Main, and Mulryan, National Nuclear Energy Series.
[17] W. F. Neuman and M. W. Neuman, National Nuclear Energy Series.
[18] A. Tannenbaum, H. Silverstone, and J. Kozoil, Plutonium Project Record of the National Nuclear Energy Series.

Ru^{106}, Te^{127}, Te^{129}, Xe^{133}, and Cs^{135}, are rapidly excreted and at rates greater than their half-lives.

The rates of elimination from the skeleton of the actinide elements, with the exception of uranium, listed in Table II, are very slow. In the case of plutonium, the excretion in the rat falls to 0.01 percent per day of the amount remaining in the body a year following the intramuscular administration of this radioactive element. The excretion of uranium differs both qualitatively and quantitatively from the other members of the actinide series in that the urine is the principal channel of elimination and the loss from the skeleton, while quite slow, is relatively much more rapid than in the case of the other seven members of the group of elements. The metabolism of plutonium following intramuscular injection is essentially the same after the administration of this element as Pu^{3+}, Pu^{4+}, and Pu^{6+}. This suggests that plutonium is converted by the body to one valence state regardless of the valence of this element when administered. This observation has been confirmed in subsequent studies made with plutonium by Langham and his co-workers.[19]

Radioautographic studies were made of the distribution of Sr^{89}, Zr^{95}, Cb^{95}, Ce^{144}, 61^{147}, Ac^{227}, Th^{228}, Pu^{239}, Am^{241}, and Cm^{242} in 5-micron sections of undecalcified rat femurs. The metabolism of strontium in the skeleton is very similar to that of calcium and, as might be expected, the radioautographs revealed that the accumulated radio-strontium in the femur was quite evenly distributed throughout the mineral structure of the bone in young rats (Fig. 5). The other radio-elements studied by this technique showed a startling deviation from the pattern of distribution of the radio-strontium. Plutonium exhibits this phenomenon to a marked degree, and in Fig. 6 it can be seen that most of this element is deposited in the periosteum and endosteum, and in the region of the trabecular bone. These results suggest that the plutonium in the trabecular structure is not incorporated in the bone, but rather is deposited in the covering of the trabeculae.

Radioautographs of zirconium, columbium, and thorium are shown in Figs. 7–9. It will be noted that these three radio-elements are apparently distributed in bone in a pattern very similar to that noted with plutonium. The radioautographs of cerium, element 61, actinium, americium, and curium, shown in Figs. 10–14, indicate concentration of radioactive material about the surfaces of the bone and trabeculae as has been indicated with the previous group. In addition, there is an appreciable amount of activity laid down in a spotty manner throughout the calcified shaft of the bone. The deposited radio-elements are apparently accumulated in

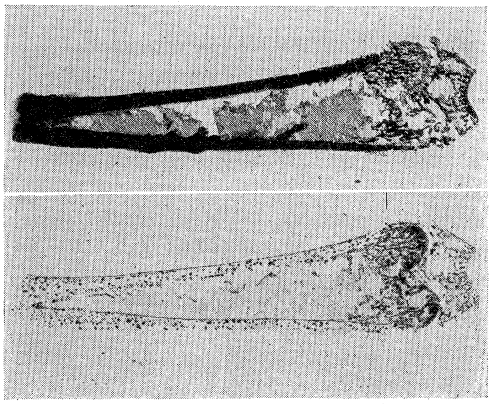

FIG. 11. Femur from adult rat injected with element 61 and sacrificed at 4 days. Note resemblance to cerium (Fig. 10), i.e., superficial deposition and spotty distribution throughout calcified shaft. Note surface deposition on trabecular bone (×7).

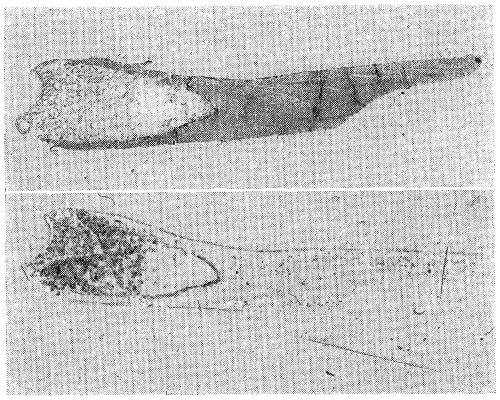

FIG. 12. Femur from adult rat injected with actinium and sacrificed at 17 days. Note resemblance to cerium and element 61. The specimen was allowed to age for 100 days before making the autograph to permit equilibrium of the radioactive daughter to be attained (×7½).

[19] Carritt, Fryxell, Kleinschmidt, Kleinschmidt, Langham, San Pietro, Schaffer, and Schnap, J. Biol. Chem. **171**, 273 (1947).

the region of the small blood vessels present in the mineralized cortical bone. In order to establish this point, a number of bone sections containing cerium, actinium, element 61, americium, and curium and their corresponding radioautographs were studied at higher magnification, and the results indicated that the accumulation of radioactivity was in the region of the small blood vessels. However, the resolution was not sufficiently great to establish whether the material was actually in the walls of the blood vessels or had penetrated 20 to 50 microns beyond the vessels into the adjacent mineral structure of the bone. A representative example of this phenomenon is shown with americium in Fig. 15.

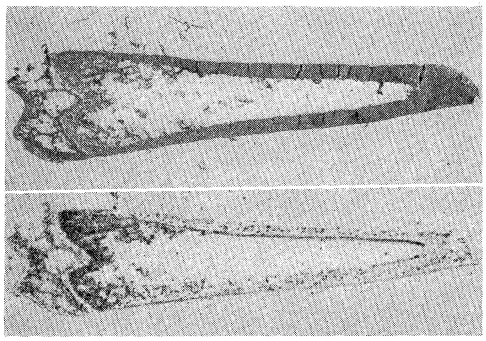

FIG. 13. Femur from adult rat injected with americium and sacrificed at 16 days. Note similarity to cerium, element 61, and actinium (×8).

The patterns of distribution observed with actinium, curium, cerium, and element 61 appear to be similar in character.

The results obtained by radioautographic experiments with zirconium, columbium, cerium, element 61, actinium, thorium, plutonium, americium, and curium suggest that accumulation of these radio-elements in the skeleton occurs to a considerable degree in the superficial layers of the bone structure and very possibly are bound to proteins rather than being directly incorporated into the inorganic bone salts. It is noteworthy that the distribution patterns for these elements in adult animals does not appear to change significantly with time. Radioautographs from adult female rats which have received plutonium nearly a year before they were sacrificed showed no fundamental differences in distribution in the bone compared to studies in

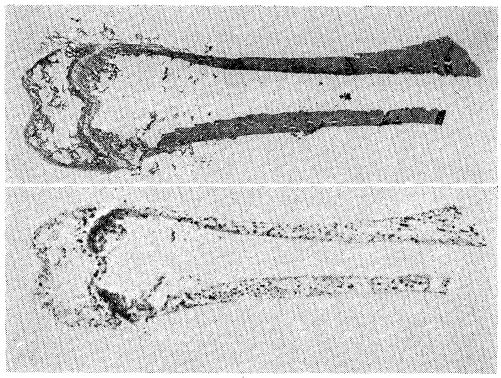

FIG. 14. Femur from adult rat injected with curium and sacrificed at 7 days. Note similarity to cerium, element 61, actinium, and americium (×7).

which the animals were sacrificed a few days after the administration of this radio-element.[4]

DISCUSSION

Two aspects of the metabolic characteristics of the fission products and actinide elements are of importance to consider. First, there is the evaluation of their relative hazards as radioactive poisons and, second, the apparent correlation of their chemical properties with their fate in the body in a number of instances.

The outstanding characteristic of nine of the fission products described in this report and seven of the eight actinide elements to be accumulated and tenaciously retained by the skeleton has a most ominous significance. Justification for this opinion is borne out by the tragic situation which has surrounded the radium industry. There is evidence to show that prolonged retention over a period of many years of about 1 microgram of radium may result in the appearance of bone tumors with a fatal outcome. Somewhat larger quantities of radium, in the range of 10 micrograms, deposited in the skeleton are frequently associated with a profound anemia and occasionally the victim develops leukemia, which is fatal. Both of these disorders are presumably the result of the bombardment of the very radio-sensitive bone marrow. The gloomy picture of radium poisoning is darkened further by the fact that to date no successful method has been developed for removing significant quantities of the radium from the body once it has been locked in the mineral structure of the bone.

The fission products which localize in the skeleton are similar to radium in that they also tend to be tenaciously held in that tissue, and to date no satisfactory procedure for removing these substances from the bone has been developed.[20] A number of considerations reduce the relative menace of these substances as radioactive poisons in comparison to radium. First, they give up much less energy per disintegration and the amount of ionization is relatively much less since they emit only beta- and gamma-rays. Added to this is the fact that on the basis of an equal amount of ionization per unit volume of tissue, alpha-particles are considerably more destructive than beta- and gamma-radiation. Second, with the exception of Sr^{90} and 61^{147}, the more abundant fission products that are accumulated in the skeleton have half-lives of less than one year, whereas the half-life of radium is approximately 1600 years. Most of these fission products have half-lives in the range of from two weeks to two months. Third, with the exception of strontium and barium, a negligible degree of absorption of these fission products takes place through the digestive tract.

Zirconium, columbium, and the lanthanide rare earths are deposited to a high degree in the immediate vicinity of the bone marrow as contrasted to the more diffuse distribution of strontium, and presumably barium, throughout the mineral structure of the bone. This behavior tends to enhance the radio-toxicity of this group of fission products both on the basis of geometrical considerations and a minimal amount of self-absorption of the beta-radiation, which is quite soft for several of the fission products under discussion.

The actinide series of elements in general share the dangerous characteristics of radium, namely, long half-lives, alpha-particle emission, and selective deposition with prolonged retention in the skeleton. Their tendency to deposit themselves adjacent to the bone marrow potentially gives them a relatively greater degree of radiotoxicity than radium. The only important metabolic property of the actinide elements that tends to reduce their hazardous quality is the fact that absorption from the digestive tract is negligible as compared to radium. Extensive studies have been made with regard to developing procedures that might effect the release of plutonium that has been deposited in the bone. As yet progress in this direction has been discouraging.[20, 21]

The second aspect of the studies described in this report is the apparent correlation of the chemical properties of a number of the different elements with their metabolic behavior. It can be seen from Table I that of the fission products described in this report there are two members of the alkaline earths, strontium and barium, four members of the lanthanide group of rare earths, lanthanum, cerium, praseodymium, and element 61, and yttrium, whose chemical properties are similar to those of the lanthanide series of elements. The behavior of strontium and barium is essentially indistinguishable insofar as their assimilation, distribution, retention, and excretion are concerned, as determined by following their fate in the body with carrier-free radioisotopes of these two elements. The outstanding metabolic characteristics shared by both are their ease of absorption from the digestive tract, selective deposition and prolonged retention in bone, relatively minute accumulation in all of the soft tissues, and slow rates of elimination. The radioautographic studies of bone indicate that strontium is deposited primarily in the mineral structure. It is presumed likely that a similar pattern of distribution in the bone would be observed with barium. A number of factors which are known to affect the calcium metabolism of bone, such as age, calcium-deficient diet, pregnancy, prolonged lactation, phosphorus-deficient diet, rickets, fracture, a number of drugs such as ammonium chloride, and the parathyroid hormone influence the metabolism of carrier-free radio-strontium in the same direction and to a comparable degree.[20, 21] Similar studies with barium are now in progress, and preliminary results indicate a close resemblance in the behavior of this element to strontium in all of the circumstances listed above that have been subjected to study at the present time.[22]

The four rare earths and yttrium share the common properties of negligible absorption from

[20] D. H. Copp, D. J. Axelrod, and J. G. Hamilton, Am. J. Roent. and Rad. Therap. **58**, 10 (1947).

[21] L. Van Middlesworth, Univ. of Calif. (Berkeley) Ph.D. thesis (1947).

[22] D. H. Copp (unpublished data).

the digestive tract, a high degree of deposition and prolonged retention by the skeleton, excretion primarily via the digestive tract, and an appreciable accumulation in several of the soft tissues, notably liver, kidney, and spleen. The metabolism of zirconium and columbium is similar in many respects to the five elements listed above, although columbium is apparently eliminated more rapidly from the skeleton than the others. The four lanthanide rare earths share in common the phenomenon of the very high transient uptake by the liver. It is noteworthy that this does not take place with yttrium, in view of the fact that this element is quite similar chemically to the lanthanide rare earths. The observed fact that the metabolic behavior of cerium is so much like that of lanthanum, praseodymium, and element 61 suggests that cerium exists in the body in the trivalent state. Tetravalent cerium is chemically quite similar to thorium, and it would appear probable that tetravalent cerium would demonstrate metabolic characteristics like those of thorium rather than those which are characteristic of the trivalent rare earths.

When the histological structure of bone is compared with the regions of deposition of these different fission products in this organ, a number of different and interesting points arise. The fact that strontium and barium are laid down in the calcium-containing mineral portion of the bone is reasonable in view of the similar chemical properties of the alkaline earths. That none of the other fission products behaved in this manner in bone was not predictable and as has been mentioned before, zirconium, columbium, and the lanthanide rare earths are apparently laid down primarily in the region of the non-mineralized areas. As yet it has not been definitely established that some of the material may combine with the superficial surfaces of the mineralized structure of the bone. An interesting variation occurs which is peculiar to the lanthanide rare earths, namely, the deposition of some activity in the regions of the small blood vessels within the heavy mineralized shaft of the bone. The radioautographic data that demonstrate this point are only available for cerium and element 61 because of the relatively short half-lives of La^{140} and Pr^{143}. However, it appears almost certain

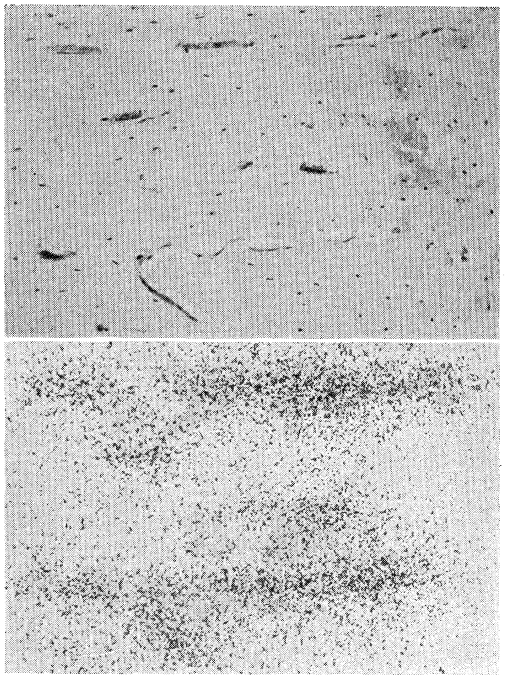

FIG. 15. Higher power magnification of a section of femur and americium radioautograph shown in Fig. 13. Note deposition of americium in the region adjacent to the blood vessels of the shaft (×270).

that lanthanum, praseodymium, and neodymium possess the same pattern of distribution in the bone. It will be noted that this effect is correlated with the high but transient uptake of the four rare earths by the liver. The uptake by the liver of yttrium, zirconium, and columbium is relatively small, as compared to the lanthanide series, and no appreciable activity appears in the region of the small blood vessels of cortical bone with zirconium and columbium.

If the effects of the various agents which alter calcium and strontium metabolism of the skeleton are tried with representative members of the fission product series, notably yttrium, zirconium, and cerium, the results indicate that their deposition, retention, and distribution in bone remain essentially unchanged.[20–22] Presumably the same indifference to these agents would apply to other members of the lanthanide rare earths. In the case of columbium it is not as completely predictable, but a similar lack of effect would not be unexpected.

The metabolic behavior of the actinide series of rare earths brings forth a number of interesting

apparent correlations. The most impressive is the fact that actinium, americium, and curium behave in an almost indistinguishable manner from the lanthanide rare earths. This quality of apparent metabolic identity includes the phenomena of high liver uptake and the accumulation of material about the small blood vessels of cortical bone. Presumably this situation arises from the fact that these three members of the actinide series and the four lanthanide rare earths studied are all trivalent with chemical properties of great similarity. These observations tie in closely with the prediction and subsequent demonstration by Seaborg and his colleagues[11] that the chemical properties of americium and curium should resemble closely those of the lanthanide rare earths and actinium. While uranium, neptunium, and plutonium all possess the trivalent state, they are treated in the animal body quite differently from these other two groups of trivalent elements. Neptunium and plutonium are much alike in their metabolic characteristics and in turn resemble those of thorium, which normally exists only in the plus-four valence state. Since plutonium follows the same metabolic pattern, whether administered as Pu^{+3}, Pu^{+4}, or Pu^{+6}, it appears that the body converts it to one valence state. The tracer studies and bone radioautographs show no significant differences between the metabolic characteristics of thorium and plutonium, which suggests that plutonium in the body is in the tetravalent state, regardless of the valency of the administered material. The same situation is likely with neptunium, but sufficient data are not yet available to firmly establish this point.

It is of interest to examine the metabolic behavior of uranium which is rather different from the other seven members of the actinide series in that the uptake and retention by the skeleton is less, excretion is primarily by way of the urine, and there is a very high and fairly prolonged accumulation in the kidney. It would appear probable that U^{+3} would behave in the animal body as do the lanthanide rare earths, actinium, americium, and curium. On the same basis, U^{+4} should resemble metabolically thorium and plutonium, which it doesn't. Since U^{+5} is very unstable under most conditions, it seems plausible, but not certain, that uranium in the body exists as U^{+6} in the form of compounds of UO_2^{+2}.

The effects of agents which alter calcium and strontium metabolism have been investigated with only one member of the actinide group, namely, plutonium.[20–22] As in the case of the comparable studies with yttrium, zirconium, and cerium, these agents did not disturb the normal metabolism of plutonium. It would appear likely that, with the possible exception of uranium, the same indifference would be observed for the remaining six members of this group of elements.

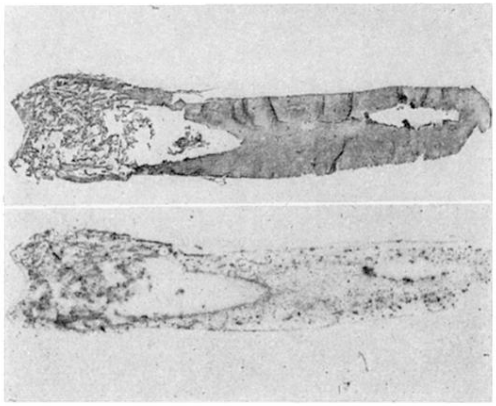

FIG. 10. Femur from adult rat injected with cerium and sacrificed at 64 days. Note cerium deposition on surface of bone and the spotty distribution in the shaft (×8).

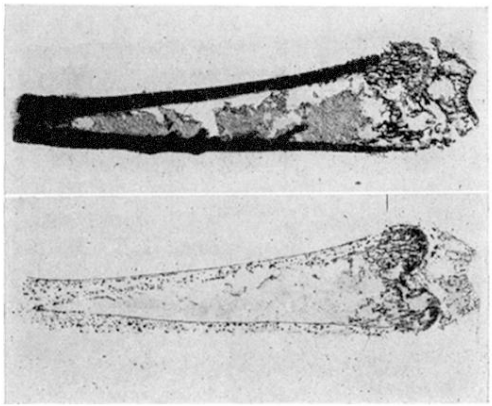

FIG. 11. Femur from adult rat injected with element 61 and sacrificed at 4 days. Note resemblance to cerium (Fig. 10), i.e., superficial deposition and spotty distribution throughout calcified shaft. Note surface deposition on trabecular bone (×7).

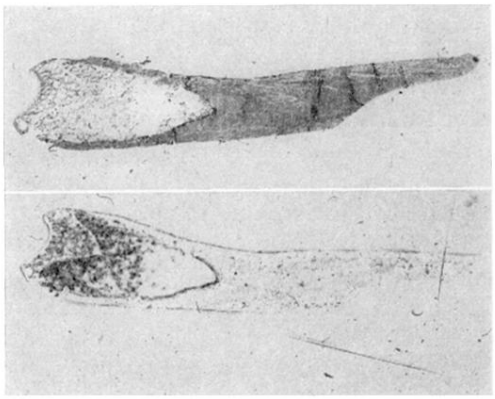

FIG. 12. Femur from adult rat injected with actinium and sacrificed at 17 days. Note resemblance to cerium and element 61. The specimen was allowed to age for 100 days before making the autograph to permit equilibrium of the radioactive daughter to be attained ($\times 7\frac{1}{2}$).

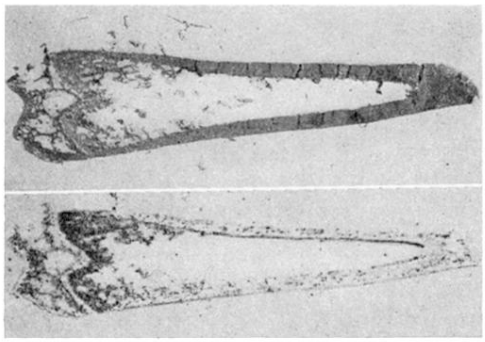

FIG. 13. Femur from adult rat injected with americium and sacrificed at 16 days. Note similarity to cerium, element 61, and actinium (×8).

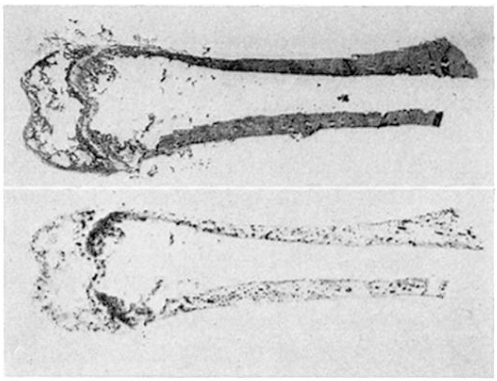

FIG. 14. Femur from adult rat injected with curium and sacrificed at 7 days. Note similarity to cerium, element 61, actinium, and americium (×7).

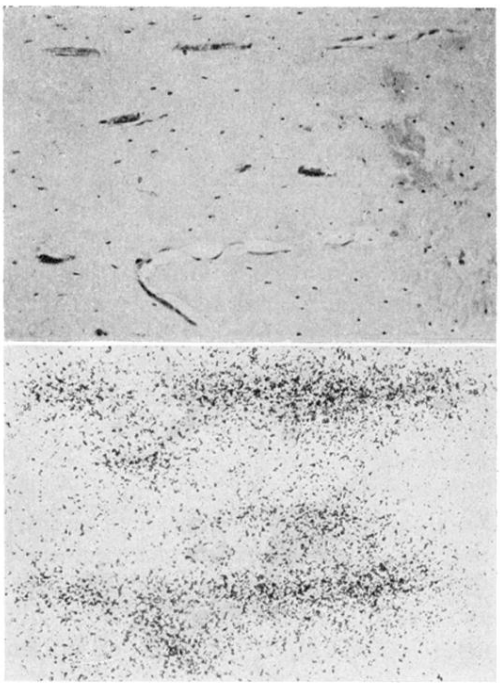

FIG. 15. Higher power magnification of a section of femur and americium radioautograph shown in Fig. 13. Note deposition of americium in the region adjacent to the blood vessels of the shaft (×270).

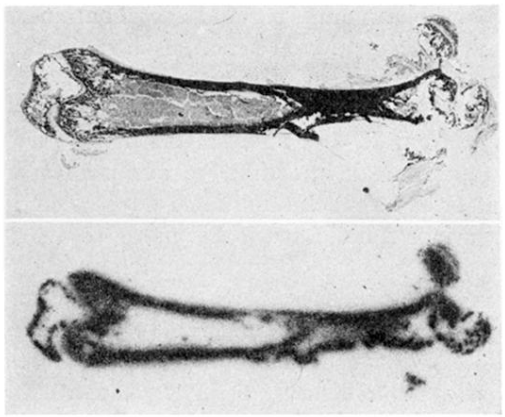

FIG. 5. Femur from young rat injected with radiostrontium and sacrificed at 1 week. Note strontium deposition in shaft and calcified areas below epiphysis ($\times 6\frac{1}{2}$).

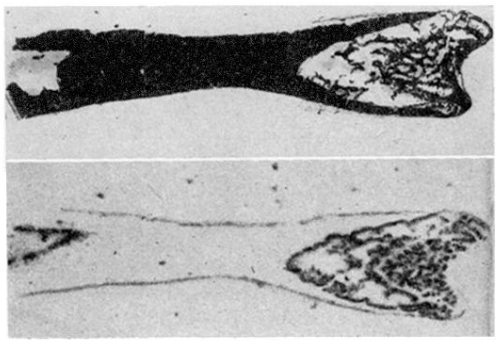

FIG. 6. Femur from adult rat injected with plutonium and sacrificed at 8 weeks. Note superficial plutonium deposition in area of trabecular bone, periosteum, and endosteum. A comparable pattern is found after 7 days and 256 days (×10).

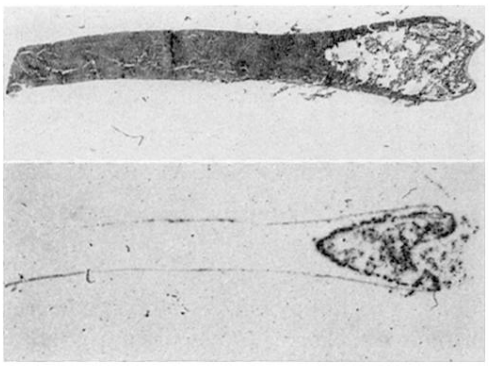

FIG. 7. Femur from adult rat injected with zirconium and sacrificed at 2 weeks. Note similarity to plutonium deposition in Fig. 6 ($\times 7\frac{1}{2}$).

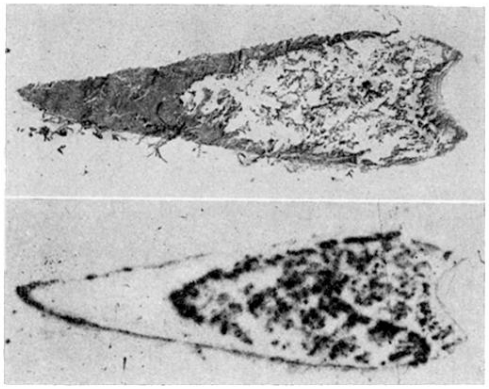

FIG. 8. Femur from adult rat injected with columbium and sacrificed at 8 days. Superficial deposition appears to be similar to that of plutonium and zirconium (×14).

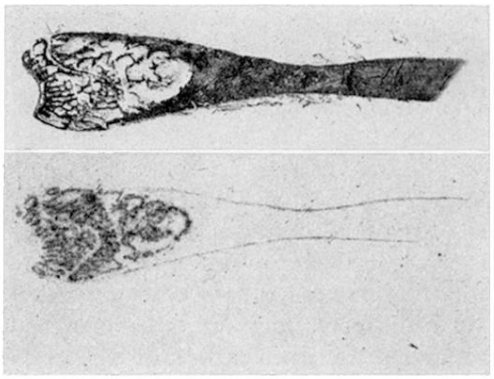

FIG. 9. Femur from adult rat injected with thorium and sacrificed at 8 days. Superficial deposition resembles zirconium, columbium, and plutonium bone deposition (×8).