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DISTRIBUTION OF THE TRANSURANIC ELEMENTS IN MAMMALS

Patricia W. Durbin

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DISTRIBUTION OF THE TRANSURANIC ELEMENTS IN MAMMALS*

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The earliest investigations of the metabolism of the actinide elements and the light weight lanthanides produced in nuclear fission revealed some general similarities in their biologic behavior:(1-7) first, their tendency to accumulate in and remain fixed in the skeleton, and second, their tendency to deposit in the liver with subsequent rapid elimination from that organ via the gastrointestinal tract.**

In recognition of their common properties, particularly their prolonged residence in the skeleton, these elements have been classed in a general way as "bone seekers". Autoradiographic investigations reveal that the lanthanide and actinide elements deposit in essentially the same anatomical locations in bone--on endosteal, periosteal and trabecular surfaces, and in the vicinity of blood vessels -- with minor quantitative variations. (See appendix)

Modern biochemistry has brought forth thoroughly convincing evidence of the orderly and fundamentally chemical nature of living systems. It therefore seems reasonable to suggest that the biological behavior of these nonessential elements is the net result of orderly and chemically identifiable processes within the animal. If the tissue deposition of these elements is, in fact, the result of bona fide biochemical processes, such deposition should be predictable on the basis of chemical properties.

It is helpful to review some of the general chemistry of these elements.(8) Soon after the establishment of the concept of atomic number, the rare earth elements (cerium through lutetium) were properly fitted into the classification,

* This work was performed under the auspices of the U. S. Atomic Energy Commission.

** The rate of removal of these elements from the liver appears to be species dependent. It is most rapid in rodents and much less so in larger species.

and the periodic table assumed its present form. In the placement of the lanthanide elements their predominant tripositive character in aqueous solution was the major consideration. This was not the situation with the heaviest elements. Before the discovery of the transuranic elements, the heaviest natural elements--thorium, protoactinium and uranium--were placed in corresponding positions just below the VIth-period transition elements--hafnium, tantalum and tungsten, in which the 5d electron shell is being filled. The evidence now available leads to the definite view that the 5f shell is undergoing filling in this neighborhood, and that the heavy rare earth series begins at actinium in the same sense that the light rare earth series begins at lanthanum.

All the 4f elements, the lanthanides, exhibit trivalency, and most of them show only this valence state. The important consequences of the filling of the 4f shell are two-fold. First, the 4f electrons do not participate in bond formation, and as a result, atoms or ions whose electronic configuration differ only in the number of 4f electrons will show similar chemical behavior. Secondly, the filling of the 4f shell is accompanied by a slow contraction in atomic dimensions for a given valence state. The ionic radii of the lanthanides are shown in Table I.[8,9] Since the degree of chemical similarity between any two atoms with analogous electronic configurations depends on relative size, the effect of this 4f contraction occurs regardless of whether the bonding is of ionic, covalent or metallic character, and whether the valence is (II), (III), or (IV). This gradual decrease in atomic dimensions is accompanied by a decrease in basicity, an increase in solubility of the oxide, and an increase in the stability of chelates.[10,11]

Bohr suggested nearly 35 years ago that electrons might begin to enter the 5f shell near the end of the periodic system as it was then known (analogously to the 4f filling in the lanthanide series). Pioneer tracer experiments with neptunium revealed no similarity with its supposed homologue, rhenium. Likewise,

later work with plutonium failed to reveal any similarities with osmium. However, the existence of higher valence states for the elements thorium through plutonium, and the absence of a stable (III) state for these elements continued to confuse the issue. Discovery and identification of americium, curium, berkelium, and californium, for which the (III) state is dominant and nearly exclusive demonstrated conclusively the existence of a 5f transition series in which thorium was the first member.

Analogous compounds of the elements actinium to californium are almost invariably isostructural. Quite analogous to the lanthanide contraction, there is for isostructural compounds of the actinides a decrease in lattice dimensions with increasing atomic number, and in addition, the ionic radius of a given element is smaller for its higher valence states. The magnitude of the 5f contraction and the ionic radii of the different valence states of the actinides is shown in Table II.[8]

It is essential to consider the differences as well as the similarities between the 4f and 5f elements. Among the most conspicuous differences are (1) the greater multiplicity of valence states for the heavier series; and (2) the generally higher principal valence states of this group. Whereas no 4f element ever exhibits more than two valence states, namely (III) and (II) or (III) and (IV), there are two higher states for protoactinium: (IV) and (V), and four bona fide states for the elements uranium through americium, (III), (IV), (V), and (VI). The trivalent state is, for all practical purposes, nonexistent for thorium and protoactinium. These notable differences between the 4f and 5f elements arise primarily because of the lower binding and shielding of the 5f electrons.

It is perhaps useful to consider the actinides as consisting of two subgroups--those for which the stable state is (III), and those for which the stable state is (IV) or greater. The most stable state of uranium is (VI),

and its most stable form in aqueous solutions is UO_2^{++}. In biological systems the uranyl ion behaves so differently from the other actinides that it will be neglected in the subsequent discussion.[12]

Comparison of Tables I and II reveals that the size of the 5f atoms is not much greater than that of the 4f atoms in corresponding valence states. Consequently, the 4f elements are extremely good chemical standins for the 5f elements insofar as the tripositive and tetrapositive states are concerned. It would seem, therefore, that in biological systems the tripositive actinides should closely resemble their lanthanide homologues of similar atomic dimensions.

As soon as very pure specimens of the heavy lanthanides became available, and an intense neutron source (the MTR) was built, the metabolism of the entire lanthanide group was investigated systematically in our laboratory. The results of these investigations have been reported, but bear repetition here.[12-14]

In Table III are shown the experimentally determined constants of the exponential equations that describe the disappearance from the plasma and deposition in the skeleton of four representative lanthanides.[15] It is apparent that the heavier lanthanides leave the plasma more slowly. Following an initial rapid accumulation phase, the heavier lanthanides continue to deposit in the skeleton. Deposition of cerium in the skeleton is very nearly complete 20 minutes after an intravenous injection; thulium, on the other hand, is still being laid down in bone 24 hours after injection. Unpublished work indicates that actinium is laid down in bone at essentially the same rate as is cerium, and it is a common finding that a significant proportion of protoactinium, neptunium, and plutonium remains in the circulation many hours after either intramuscular or intravenous injection.

Preliminary data suggest that a significant fraction of these highly charged cations are combined with the serum proteins shortly after their introduction intravenously as citrate complexes.

Urinary excretion in the first 24 hours after intravenous or intramuscular injection as a citrate complex varies from 3% to 5% for actinium and lanthanum, and from 20% to 30% for thulium and neptunium. The known increase in chelate stability with decreasing atomic dimensions suggests that some of the metal ions remain in the circulation combined with citrate or some other small species which can be filtered by the kidney. A systematic investigation of the extent and nature of serum protein binding is an essential first step in our understanding of the biological behavior of these elements.

The available data for the deposition of the lanthanide series, the actinide series and yttrium in skeleton and liver are collected in Table IV.*** The animals were female albino rats 3 to 6 months old which were sacrificed from 1 to 8 days after isotope administration. Carrier-free or high specific activity radioisotopes were used wherever possible. The mass of a particular element administered was occasionally more than 1 μg, but never exceeded 5 μg ($Eu^{152,154}$). Radioisotopes were injected intramuscularly (in a few cases, intravenously) in isotonic sodium citrate. The liver deposition shown in the Table IV is the sum of the percent of dose in liver, gastrointestinal tract and feces up to the day of sacrifice. It has been shown that for the rat the liver deposit is eliminated almost exclusively via the gastrointestinal tract, so that this sum should represent the total liver burden a few hours after injection.

It can be seen from Table IV that for the lanthanide series the skeletal burden increases, and the liver burden diminishes with increasing atomic number (and decreasing ionic size). On the basis of the skeletal deposition, yttrium has been placed in the tabulation just below its nearest lanthanide neighbor, erbium. The fit of yttrium in this sequence with respect to liver burden would be between europium and gadolinium. In any case, the appropriate parameter appears to be ionic size rather than atomic number (yttrium is number 39).

It was suggested earlier that in biological systems, the tripositive actinides should closely resemble their lanthanide homologues. It can be seen from Table IV that the actinides for which the most stable state is (III) are deposited in the skeleton and liver of the rat to about the same extent as their nearest lanthanide neighbors. The agreement between the groups is good for americium, curium, and californium; the abberant behavior of actinium is somewhat puzzling. The agreement between the biological behavior of these two groups of elements is not surprising, if it is assumed that their metabolism has a fundamental chemical basis.

It is worth recalling that the lanthanide elements are eluted from a cation exchange column with buffered citrate in order of their decreasing atomic radii -- lutetium is removed first and lanthanum last.[11] Not only the order of removal, but the spacing between the elution peaks appears to depend on the size of the ions, so that the spacing between lanthanum and cerium is greater than that between holmium and erbium.[11] Yttrium elutes in the holmium position, and americium and curium peak between neodymium and promethium.[8] Californium, and berkelium, and elements 99, 100, and 101 were similarly identified by analogy to their lanthanide homologues of theoretically similar ionic radius.

The biological data for the actinides whose stable state is (IV) or (V) (Th, Pa, Np, and Pu), are included in Table IV alongside the lanthanides of similar ionic size. Insofar as the skeletal data are concerned, the relationship between ionic radius and bone uptake is reasonably good except for thorium.

In Fig. 1 the liver and bone depositions for all of these elements are shown on a linear scale as functions of ionic radius. Although the fit is not perfect, it appears to be a good first approximation for the lanthanide elements, the tripositive actinides, plutonium, and yttrium. If this apparent relationship is real, it is obviously not invariant, nor can it be considered the sole factor governing the metabolism of any or all of these elements. The demon-

stration of a regular trend in biological behavior as a function of a fundamental chemical property is, however, highly suggestive.

Recalling that with decreasing atomic size there is a regular increase in solubility and chelate stability and a decrease in basicity, it would appear that the initial deposition patterns of these elements in liver and skeleton are the net result of fundamental chemical processes. In the absence of systematic data on the adsorption of colloidal metal hydroxides or oxides onto bone crystals, the existence of such a process cannot be summarily dismissed. However, the available evidence points more strongly to formation of a chelate or a series of competing chelates as the initial biochemical process in the skeleton. The eventual fate of these elements undoubtedly depends as much or more on the subsequent biological processes in the tissues as on the chemical nature of the elements in question.

We are obviously a long way from a satisfactory explanation of why these highly charged cations behave as they do in mammalian systems. Their chemical state in the circulation, the identity of the chelating molecules at the sites of deposition, and perhaps most important, the mechanisms involved in their transport across the cells lining the capillaries remain to be elucidated. I should like to suggest that our attention turn to these problems, for in the course of their solution, we will learn much about the tissues themselves, and much about the practical problem of removing them from the human skeleton.

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Table I

IONIC RADII OF LANTHANIDE ELEMENTS IN VARIOUS VALENCE STATES

Element	Ionic radius, A, in indicated valence state			
	+1	+2	+3	+4
Cesium[a]	1.67			
Barium[a]		1.29		
Lanthanum			1.06	
Cerium			1.03	0.92
Praseodymium			1.01	0.90
Neodymium			1.00	
Promethium			(0.98)	
Samarium		1.11	0.96	
Europium		1.09	0.95	
Gadolinium			0.94	
Terbium			0.92	0.84
Dysprosium			0.91	
Holmium			0.89	
Erbium			0.88	
Thulium			0.87	
Ytterbium		0.93	0.86	
Lutetium			0.85	
Hafnium				0.77

[a] The ionic radii of cesium and barium and hafnium are shown here for comparison.

Table II

IONIC RADII OF 5f ELEMENTS IN VARIOUS VALENCE STATES

Element	Ionic radius, A, in indicated valence state			
	+3	+4	+5	+6
Actinium	1.11			
Thorium	(1.08)	0.99		
Protactinium	(1.05)	0.96	0.90	
Uranium	1.03	0.93	0.87	0.83
Neptunium	1.01	0.92	0.88	0.82
Plutonium	1.00	0.90	0.87	0.81
Americium	0.99	0.89	0.86	0.80
Curium	0.98			
Berkelium	-			
Californium	0.94			

Table III

CONSTANTS OF EXPONENTIAL EQUATIONS DESCRIBING DISAPPEARANCE FROM THE SERUM AND UPTAKE IN THE SKELETON OF FOUR RADIOACTIVE LANTHANIDE ELEMENTS INJECTED INTRAVENOUSLY IN THE FORM OF THEIR CITRATE COMPLEXES. COEFFICIENTS (N) ARE IN PERCENT OF INJECTED DOSE AND RATE CONSTANTS (k) ARE EXPRESSED IN MIN^{-1}

	N_1	$k_1 \times 10^{-1}$	N_2	$k_2 \times 10^{-2}$	N_3	$k_3 \times 10^{-3}$
			Disappearance from serum			
Ce^{144}	90	7	8.2	5	0.7	5
$Eu^{152,154}$	70	7	16.5	3.5	2.4	4.4
Tb^{160}	66	3.5	29	3.5	3.8	4.2
Tm^{170}	58	3.5	25	3.3	17.5	3.3
			Bone uptake			
Ce^{144}	16.8	4.6	9.3	2.8		
$Eu^{152,154}$	20.5	4.6	20.3	2.8		
Tb^{160}	13.2	3.5	50.5	1.6		
Tm^{170}	17.5	3.5			48.1	6.7

Table IV

SKELETAL AND LIVER DEPOSITION OF HIGH SPECIFIC ACTIVITY RADIOISOTOPES OF THE LANTHANIDE AND ACTINIDE RARE EARTHS 1 TO 8 DAYS AFTER PARENTERAL ADMINISTRATION CORRELATED WITH THE IONIC RADIUS OF THE VARIOUS ELEMENTS[a]

	Valence	Ionic Radius	% dose Skeleton	% dose Liver & Feces[b]		Valence	Ionic Radius	% dose Skeleton	% dose Liver & Feces[b]
					Ac^{227}	III	1.11	26.8	62.2
La^{140}	III	1.06	18.4	67.4					
Ce^{144}		1.03	27.7	59.0					
Pr^{143}		1.01	26.6	57.0					
Nd^{147}		1.00	31.2	37.2	Th^{227}	IV	.99	66.3	9.6
Pm^{147}		.98	36.4	47.9	Am^{241}	III	.99	32.8	57.4
Sm^{153}		.96	33.2	47.9	Cm^{242}	III	.98	29.4	58.9
$Eu^{152,154}$		.95	35.6	36.1					
Gd^{159}		.94	41.4	20.3	$Cf^{249,252}$	III	.94	53.0	21.6
Tb^{160}		.92	60.5	13.7					
Dy^{166}		.91	59.9	9.0	Pa^{230}	V	.90	44.6	23.3
Ho^{166}		.89	55.6	15.6	Pu^{238}	IV	.90	55.4	29.7
Er^{169}		.88	56.4	8.6	Np^{237}	V	.88	44.4	17.8
(Y^{91})		.88	55.6	22.8					
Tm^{170}		.87	64.1	6.4					
Yb^{175}		.86	57.8	9.8					
Lu^{177}		.85	67.6	10.0					

[a] Original references containing the metabolic data for these elements are as follows: Y^{91}(16), La^{140} through Lu^{177}(13), Ac^{227}(17), Th^{227}(18), Pa^{230}(19), Np^{237}(20), Pu^{238}(21), Am^{241}(22), Cm^{242}(23), and $Cf^{249,252}$(24).

[b] Includes G.I. tract

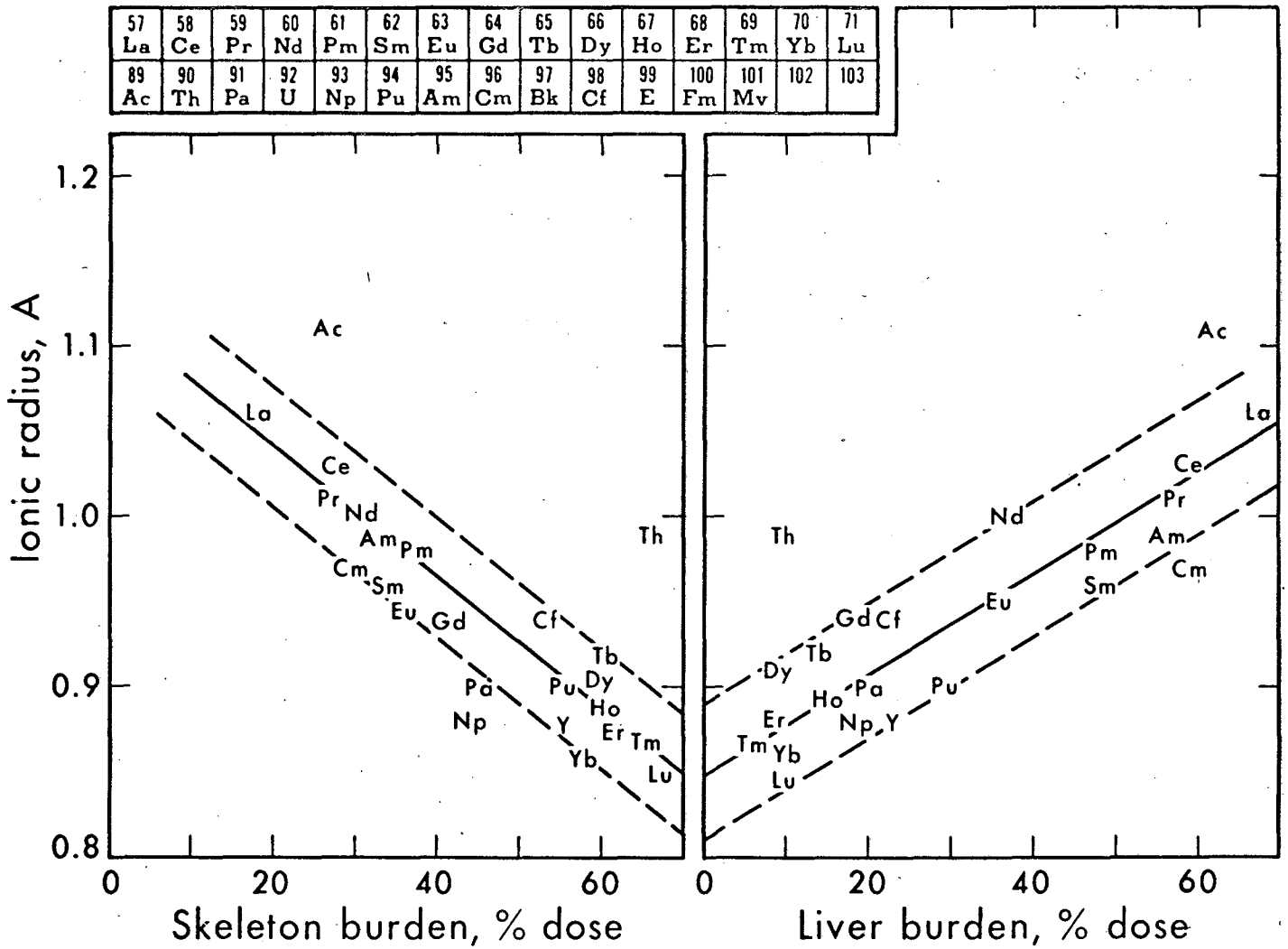

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Fig. 1. Skeletal and liver burdens (as shown in Table IV) of the actinide and lanthanide elements plotted as linear functions of the ionic radius of the most stable valence state.

APPENDIX

Autoradiographs of deposition in bone are shown in Figs. 2 through 15 for some representative lanthanide and actinide elements, radiocalcium, yttrium, niobium, and zirconium. Although many have already been published, it seems appropriate to collect them in this review. Figures 3 and 10 have been reproduced from ref. 6, and Figs. 4 and 9, and 11 through 14 appeared in ref. 6a.

Autoradiographs were prepared from histologic sections of undecalcified bone cut 4 to 6 microns thick from nitrocellulose blocks (except for the bone containing Ca^{45} which was embedded whole in plastic and milled to a flat surface). Two autoradiographs of the same radioelement, Ce^{144}, are shown in Figs. 2 and 3 to indicate the extent of variations that can be expected with the same element in the same animal but using different film, a slightly thicker section (in the case of Fig. 2), and a different method of maintaining close contact between section and film. The autoradiograph of Ca^{45} (Fig. 5) is included to show those regions of the long bone diaphysis and metaphysis in which there is still active bone growth in the 120-day old female rat.

Yttrium, the lanthanides, and the tripositive actinides (Ac^{227}, Am^{241}, and Cm^{242}) are deposited in essentially the same anatomical locations--on trabecular surfaces, below the periosteum and endosteum (to a lesser degree than on the periosteum), beneath the articular surface, and in the neighborhood of blood vessels in the compact bone of the diaphysis.

Insofar as they also deposited to a large extent on the surfaces of trabeculae, and on the periosteal and endosteal surfaces, the cations whose most stable state is (IV) or (V) resemble the tripositive lanthanide and actinide elements. There are, however, some notable differences between the two groups. The more highly charged cations -- Th(IV), Pu(IV), Zr(IV), and Nb(V) -- are deposited in very high concentrations on the endosteal surface and to a lesser degree on the periosteal surface. They are not deposited on

the articular surface, and are very nearly absent from the areas around the blood vessels in the compact bone.

These differences in the skeletal deposition of the trivalent ions and those ions with a stable valence state of (IV) or (V) were originally noted by Hamilton[6a] who pointed out that the autoradiographs of the tripositive elements all resembled cerium, and that the distribution patterns of plutonium, zirconium, thorium, and niobium, while similar to one another, were not exactly the same as those of the "cerium" group.

APPENDIX FIGURES

2. Ce^{144} autoradiograph on industrial x-ray film, type A; distal femur, 4-month old female rat sacrificed 4 days after isotope injection.

3. Ce^{144} autoradiograph on no-screen x-ray film; distal femur, 10 to 12 month old female rat sacrificed 8 days after isotope injection.

4. Pm^{147} autoradiograph on no-screen x-ray film; distal femur, 6 to 8 month old female rat sacrificed 4 days after isotope injection.

5. Ca^{45} autoradiograph on industrial x-ray film, Type A; proximal tibia, 4 month old female rat sacrificed 4 days after isotope injection.

6. $Eu^{152,154}$ autoradiograph on industrial x-ray film, type A; distal femur, 4 month old female rat sacrificed 4 days after isotope injection.

7. Tm^{170} autoradiograph on industrial x-ray film, type A; distal femur, 4 month old female rat sacrificed 4 days after isotope injection.

8. Y^{91} autoradiograph on no-screen x-ray film; distal femur, 42 day old female rat sacrificed 4 days after isotope injection.

9. Ac^{227} autoradiograph on no-screen x-ray film; distal femur, 6 to 8 month old female rat sacrificed 17 days after isotope injection.

10. Am^{241} autoradiograph on no-screen x-ray film; distal femur, 6 to 8 month old female rat sacrificed 16 days after isotope injection.

11. Cm^{242} autoradiograph on no-screen x-ray film; distal femur, 6 to 8 month old female rat sacrificed 7 days after isotope injection.

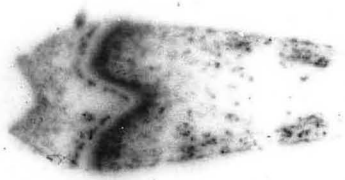
12. Nb^{95} autoradiograph on no-screen x-ray film; distal femur, 10 to 12 month old female rat sacrificed 8 days after isotope injection.

13. Zr^{95} autoradiograph on no-screen x-ray film; distal femur, 10 to 12 month old female rat sacrificed 14 days after isotope injection.

14. Th^{234} autoradiograph on no-screen x-ray film; distal femur, 6 to 8 month old female rat sacrificed 8 days after isotope injection.

15. Pu^{239} autoradiograph on no-screen x-ray film; distal femur, 10 to 12 month old female rat sacrificed 8 days after isotope injection.

Magnification varies from 4.5 x to 5.2 x.



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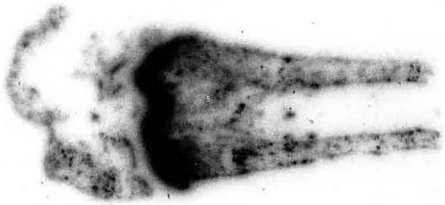

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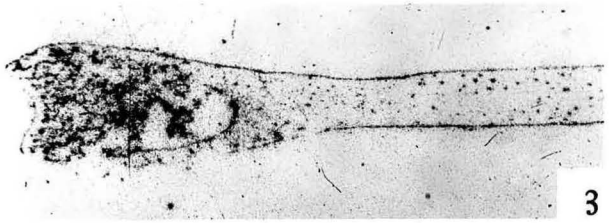

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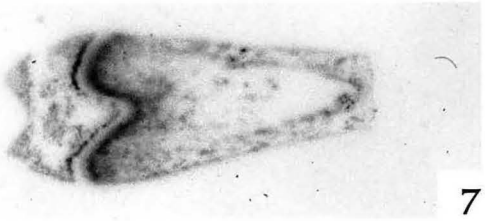

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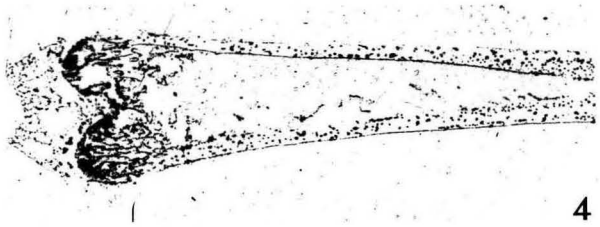

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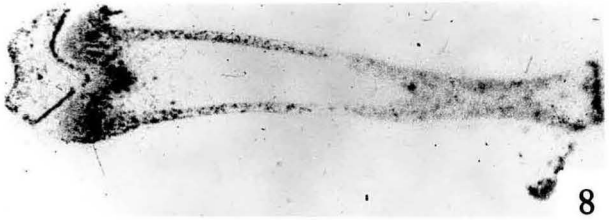

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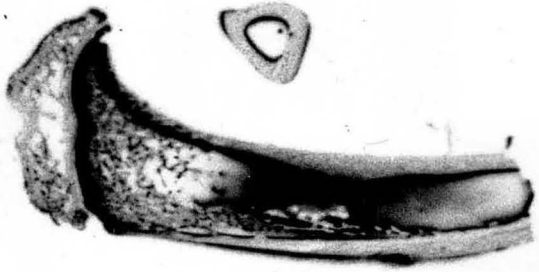

5

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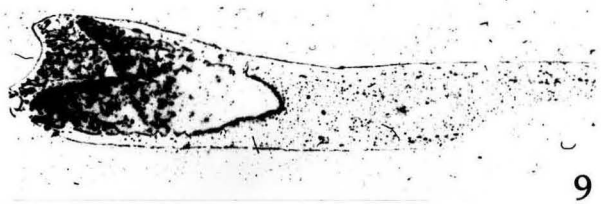

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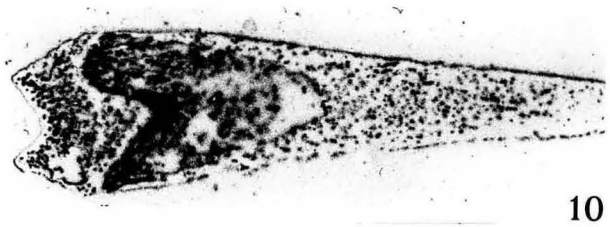

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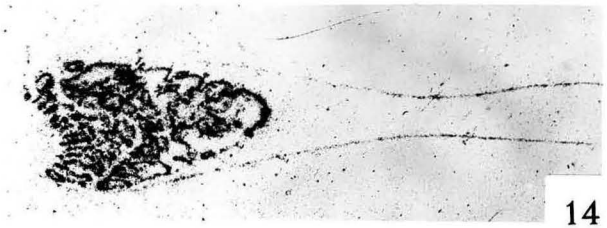

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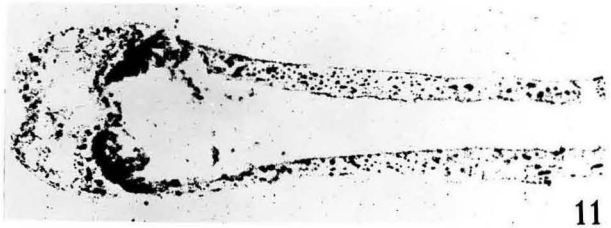

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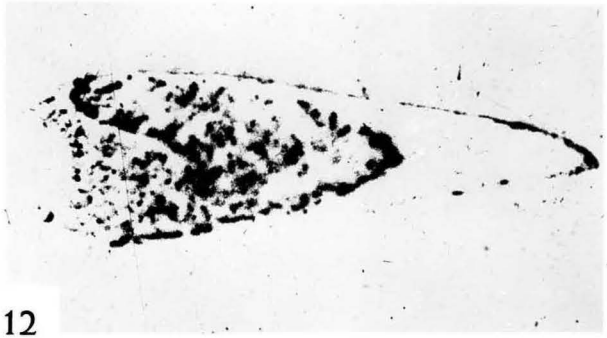

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