UCRL 35
cy 76/A
c2

UNIVERSITY OF CALIFORNIA

Radiation Laboratory

BERKELEY, CALIFORNIA

UCRL-35
c.2

Lawrence Radiation Laboratory Library
University of California, Berkeley

Special Review of
Declassified Reports

Authorized by USDOE JK Bratton

Unclassified TWX P182206Z May 79

REPORT PROPERLY DECLASSIFIED

[redacted]
...ized Derivative Classifier

AUG 15 1979
Date

Standard Distribution	No. Copies
Argonne National Laboratory	10
Atomic Energy Commission, Washington	3
Battelle Memorial Institute	1
Brookhaven National Laboratories	8
Carbide & Carbon Chemical Corp.(K-25 Area)	2
Carbide & Carbon Chemical Corp.(Y-12 Area)	2
Clinton National Laboratories	8
General Electric Company	4
Hanford Engineer Works	2
Iowa State College	1
Los Alamos	3
Madison Square Area	1
Massachusetts Institute of Technology	1
Monsanto Chemical Company, Dayton	1
National Bureau of Standards	1
Patent Advisor	1
Research Division (for NEPA), Oak Ridge	1
Research Division, Oak Ridge	15
University of Rochester	2

Declassification Procedure	
Declassification Officer	4
Publications Officer	1
Patent Department	2
Dr. E. O. Lawrence	1
Atomic Energy Commission, Berkeley	1
Information Division	2
Total	78

THE METABOLISM OF CURIUM IN THE RAT

by

K. G. Scott, D. Axelrod, and
J. G. Hamilton

January 15, 1948

Special Review of Declassified Reports
Authorized by USDOE JK Bratton
Unclassified TWX P182206Z May 79

REPORT PROPERLY DECLASSIFIED

8-15-79
Date

8-20-79
Date

This document is based on work performed under Contract No. W-7405-eng-48-A-1 for the Atomic Energy Commission.

THE METABOLISM OF CURIUM IN THE RAT

The heaviest of the known elements is curium, which was recently discovered by Seaborg and his associates (1). This new element can be produced by the alpha particle transmutation of plutonium by the following reaction:

$$_{94}Pu^{239} + {}_{2}He^{4} \longrightarrow {}_{96}Cm^{242} + {}_{0}N^{1}$$

This isotope of curium is radioactive and decays by the emission of an alpha particle to form plutonium 238 which, in turn, is also radioactive. Curium 242 has a half-life of 150 days, and its radioactive daughter, plutonium 238, has a half-life of 50 years. This isotope of plutonium decays by the emission of an alpha particle to form uranium 234 which has a half-life of 233,000 years.

Shortly after the organization of the Atomic Energy Project, it became apparent that formidable problems would be presented as the result of the release of nuclear energy. One of the most urgent of these was the hazard presented by the production of large quantities of the radio-elements created by the fission of uranium and the coincidental formation of neptunium and plutonium. In an attempt to evaluate the potential danger presented by these radio-elements from the chain reacting pile, a large series of metabolic studies with experimental animals were undertaken in a number of laboratories working upon the Atomic Energy program. These studies, which have been briefly summarized elsewhere(2), included a series of investigations on the metabolism in the rat of the more important members of the fission products in the carrier-free state, as well as most of the heaviest elements at the end of the periodic table. These studies made it possible to predict on a semi-quantitative basis the potential hazards that this large number of radioactive elements might present should they gain entry into the body.

Recently a description of the metabolism of americium has been reported in considerable detail (3). This element immediately precedes curium in the periodic table and is also radioactive. Americium and curium are not available in sufficient amounts to make them extensive hazards to those working in the field of nuclear energy as compared to the potential dangers presented by the relatively enormous quantities of plutonium and fission products that are produced. Americium and curium resemble plutonium and certain members of the fission products in their chemical and physical properties. An investigation into their metabolic properties was desirable for two reasons, first, to assay their potential health hazard and, second, to compare their metabolic characteristics with those of plutonium and its chemical analogues.

The tracer studies of americium have shown that this element is accumulated principally in the liver and the skeleton following parenteral administration. The concentration in the liver initially accounts for approximately 55% of the americium which is absorbed from the site of injection. The skeleton accumulates about 25% and the remaining 20%

is distributed throughout the other tissues and excreta.

A large fraction of the americium deposited in the liver is lost from that organ rather rapidly and at an approximately exponential rate with a half-period of 10 days. The elimination of this element from the liver presumably takes place by way of the bile since the amount of americium lost from the liver can be accounted for by the quantity that appears in the feces. It seems probably that very little, if any, of the americium deposited in the liver is reabsorbed since the amount of this element in the skeleton does not change during the period that the liver content is decreasing. The fraction of americium taken up by the skeleton is held in that organ without perceptible loss for time intervals extending to nearly one year. The distribution of americium in the bone has been investigated by the radioautographic technique. Apparently americium is deposited primarily in the region of the osteoid matrix and about the small blood vessels of the cortical bone. Very little appears to be laid down in the mineralized structure of the skeleton. Other tissues of the body do not show any striking degree of localization or retention of this element. Another point of interest is that americium is not absorbed from the digestive tract to any significant degree.

Another group of elements have been observed to possess almost identical metabolic properties to those of americium. This group of elements, which arise from the fission of uranium and plutonium, includes the rare earths, lanthanum, cerium, praseodymium, and element 61 (2). It is presumed likely that other members of the lanthanide series of the rare earth elements, such as neodymium, samarium, europium, gadolinium, etc., have similar metabolic characteristics. This presumption is based upon the fact that all of these elements are very much alike with respect to most of their chemical properties. The similarity in the metabolic properties of americium to the lanthanide rare earths is duplicated to a considerable degree by its chemical properties. The principal valence state of americium is plus 3, which is also the principal valence state for the rare earths, and it forms insoluble hydroxides, phosphates, carbonates, and fluorides, as do the rare earths.

The very close similarity in chemical properties of the lanthanum group of rare earths to one another is due to the fact that this series of 15 elements, starting with an atomic number of 57 and ending with 71, have the outer valence electrons arranged essentially the same. The additional electron for each successive element goes into the inner 4f electron shell, which is incomplete. The very minor differences of most chemical and physical properties of the lanthanide series is the result of this phenomenon. Seaborg and his associates have pointed out that a somewhat analogous situation presumably exists in the elements at the far end of the periodic table, starting with element 89 which is actinium (1). The picture is less clear cut for the first few elements of the actinide series since thorium and protoactinium show considerable similarity in chemical properties to their corresponding lighter homologues, hafnium and tantalum respectively, in the classical form of the periodic table. The resemblance in chemical properties of uranium to its lighter homologue, tungsten, is slight in most respect. The next two members of the actinide series, neptunium and plutonium, are totally unlike their respective lighter homologues, rhenium and osmium, in the conventional periodic table. With uranium, there appears a plus 3 valence state.

While not normally very stable, it does exist, and plus 3 uranium possesses chemical properties akin to those of the rare earths. The stability of the plus 3 state increases, going on to neptunium and plutonium. At the same time, the higher oxidation states of uranium, neptunium, and plutonium become increasingly difficult to attain. The theory proposed by Seaborg predicted that americium and curium should demonstrate very stable plus 3 valence states. This concept has been amply borne out by the study of the chemical properties of these two elements, for the only valence observed to date with americium and curium has been the plus 3 state. It is predicted that elements beyond curium will continue to exhibit chemical properties very similar to one another and to the lanthanide series of rare earths until element 103 is reached. At this point a sudden transition is predicted with the result that element 104 would be expected to resemble hafnium. This concept of the actinide group is based on the premise that this series of elements continues until all of the vacancies of the 5f electron shell have been filled. An analogous situation with the lanthanide group exists since this series continues until the incomplete 4f electron shell becomes filled, at which point the last rare earth, lutecium, is followed by hafnium.

In view of this interesting theory, which certainly has many observed facts to substantiate its validity, a series of animal tracer studies have been undertaken with curium, which is element 96, in order to compare its metabolic properties with those of americium, which it so closely resembles in almost all of its chemical and physical properties. We are indebted to Professor Seaborg and his colleagues for making available to us the curium employed in the tracer studies which are described below.

METHOD

Adult white rats weighing from 200 to 250 grams were employed as the experimental animals. Fifteen rats were each given, by intramuscular injection, 1 microcurie of $CmCl_3$ in a solution of normal saline at pH 5. Three animals were given the same quantity of curium by stomach tube. Two rats received, by intramuscular injection, 10 microcuries each. These two animals were given a larger dose in order to have a sufficient quantity of curium deposited in the skeleton to make it possible to secure satisfactory radioautographs. The 15 rats which received 1 microcurie by intramuscular injection and the three which were given the curium by stomach tube were divided into groups of three and each group was placed in a metabolism cage which permitted the separate recovery of the urine and the feces at daily intervals. The 15 animals in the intramuscular series were sacrificed in groups of three at 1, 4, 16, 64, and 256 day intervals. The three animals given curium by stomach tube were sacrificed at 4 days and the two animals for the radioautographic studies were sacrificed at 8 days. The animals were sacrificed by the use of chloroform. The tissues and organs removed for separate assay of their curium content included heart, lungs, liver, kidneys, spleen, digestive tract, muscle, skin, testes, brain, blood, and bone from the uninjected hind leg. The injected leg was removed and assayed separately so as to determine

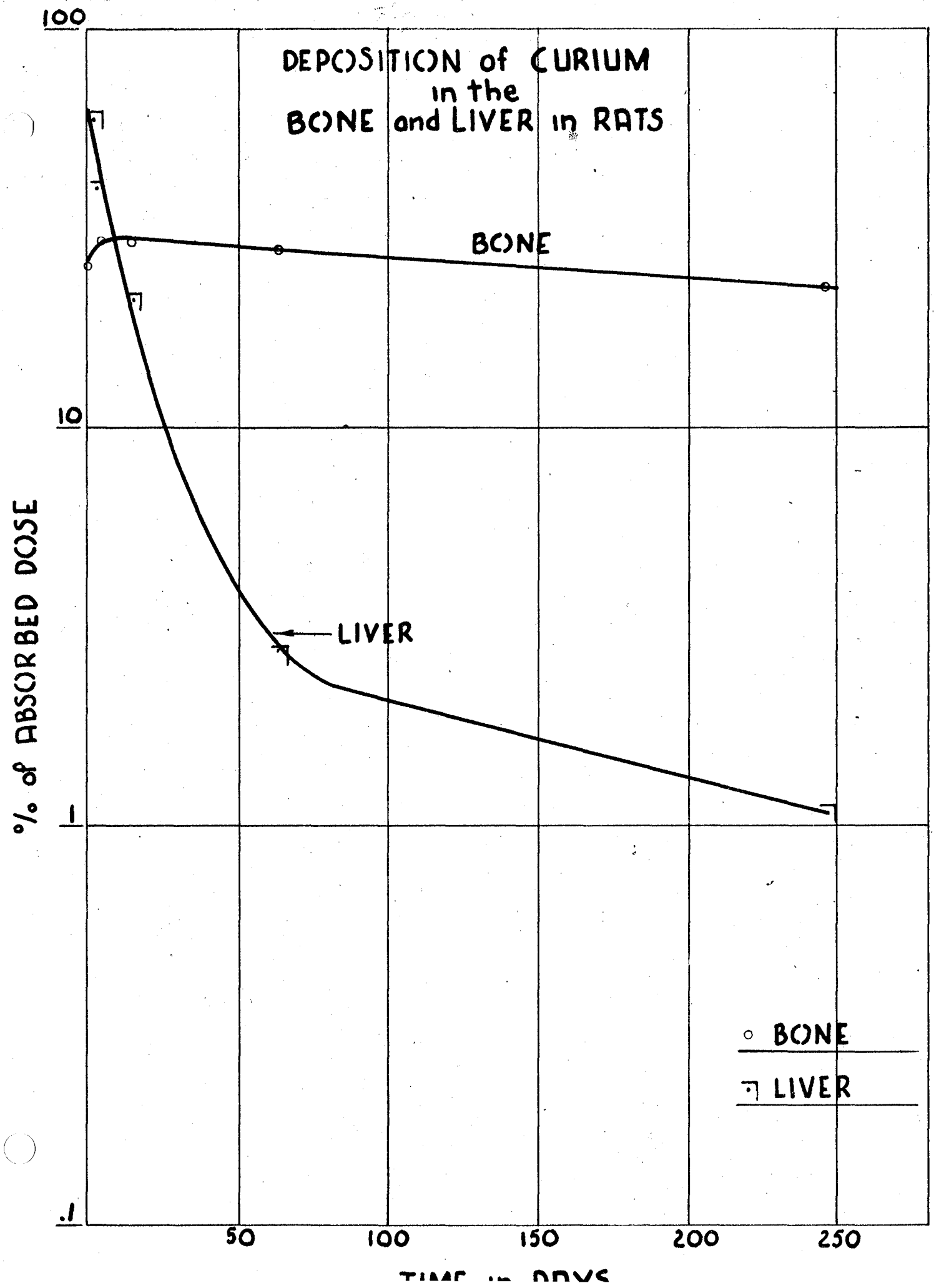
the fraction of administered curium which had not been absorbed from the site of administration. The individual tissues, injected leg, urine, and feces were dried at 100° C. for 24 hours and ashed at 500° C. for 48 hours. The skinned carcass, which consisted primarily of the skeleton, muscle, fat, and blood, was dried and ashed as a unit. The skeleton of the carcass was separated from the soft tissue and ashed by sifting the material through a fine screen. The curium was separated from the tissue and excreta ash by coprecipitation with lanthanum fluroide and its radioactivity determined. The procedures employed were identical to the methods of assay used for the experiments with americium (3).

The femurs from the two animals given curium by intramuscular injection for the radioautographic studies were removed, fixed, and embedded by a histological technique which has been described elsewhere (4). The technique employed made it possible to cut undecalcified sections from 4 to 8 microns in thickness. These sections were then placed in contact with photographic film in order to obtain the radioautographic pattern of distribution of curium in the tissue.

RESULTS

The average values for the distribution of curium in the various tissues and excreta at the 1, 4, 16, 64, and 256 day intervals are shown in Table I. These data give the actual measured values, including the fractions remaining unabsorbed in the hind leg, which was the site of injection. The recovery value for each group indicates the fraction of the administered curium which could be accounted for by the assay procedures employed. Table II presents the same data which has been corrected for the fraction of curium remaining unabsorbed in the injected leg and the deviation of the recovery value from 100%. In this second table there has been added to the values for the skeleton twice the amount of curium present in the bone of the uninjected leg. This additional correction was made necessary because the injected leg contained a considerable amount of unabsorbed curium and was therefore assayed separately. The opposite hind leg was removed from the carcass for a separate assay which could be compared with the activity found in the skeleton.

The high degree of deposition in the liver and skeleton are the two most striking findings to be noted in this series of studies. An examination of Figure I shows that most of the curium accumulated by the liver disappears from that organ quite rapidly. However, the fraction of curium deposited in the skeleton appears to be fixed to a remarkable degree. The bone retention curve shown in Figure I suggests that about 500 days would be required for the rat to eliminate one-half of the curium deposited in the skeleton from the fourth day after injection. The variations in curium content of the skeleton from the 1 day to 256 day intervals, after the appropriate corrections were made, is felt to be within the range of the experimental error. The kidney and spleen were the only other tissues observed that appeared to possess any significant tendency for the preferential accumulation of curium. The excretion of curium takes place primarily by way of the digestive tract and after most of this element stored in the liver


DEPOSITION of CURIUM
in the
BONE and LIVER in RATS
BONE
LIVER
100
10
1
.1
% of ABSORBED DOSE
50
100
150
200
250
TIME in DAYS
BONE
LIVER

has been released by that organ, the rate of elimination falls to a very small value, as can be seen in Figure II. This chart presents the change in the daily rate of excretion of curium in the urine and the feces with time. The values employed to prepare these curves were obtained from the corrected data. This, of course, produces some error due to the fact that an appreciable amount of curium is presumably absorbed from the site of injection for quite some interval of time. The effect of this situation will, of course, make the values of the daily rates of elimination slightly higher at earlier time intervals than appears from the data. The degree of error introduced by this manipulation of data is felt to be trivial after the first 4 days; since it is apparent the amount of curium remaining unabsorbed after the 4 day interval neither changes very significantly at the later time intervals nor does it represent more than a small proportion of the total dose given. The correlation between content of curium in the liver and the fecal excretion if shown graphically in Figure III. It is apparent that the removal of curium from the liver at the various time intervals is closely paralleled by the quantity of this element appearing in the feces.

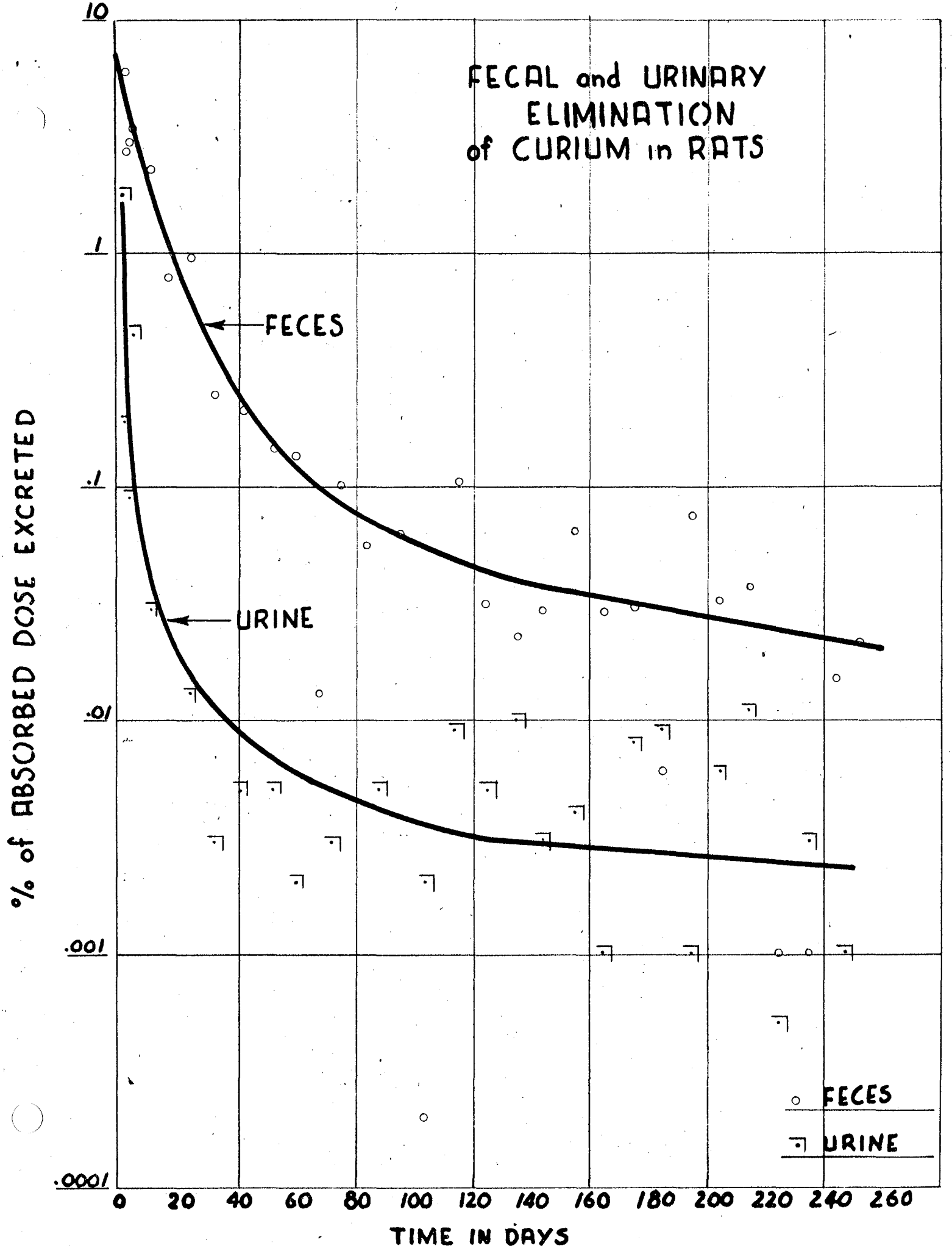
The degree of absorbtion of curium from the digestive tract, following administration by stomach tube, was observed to be less than 0.05% of the dose given to the animals.

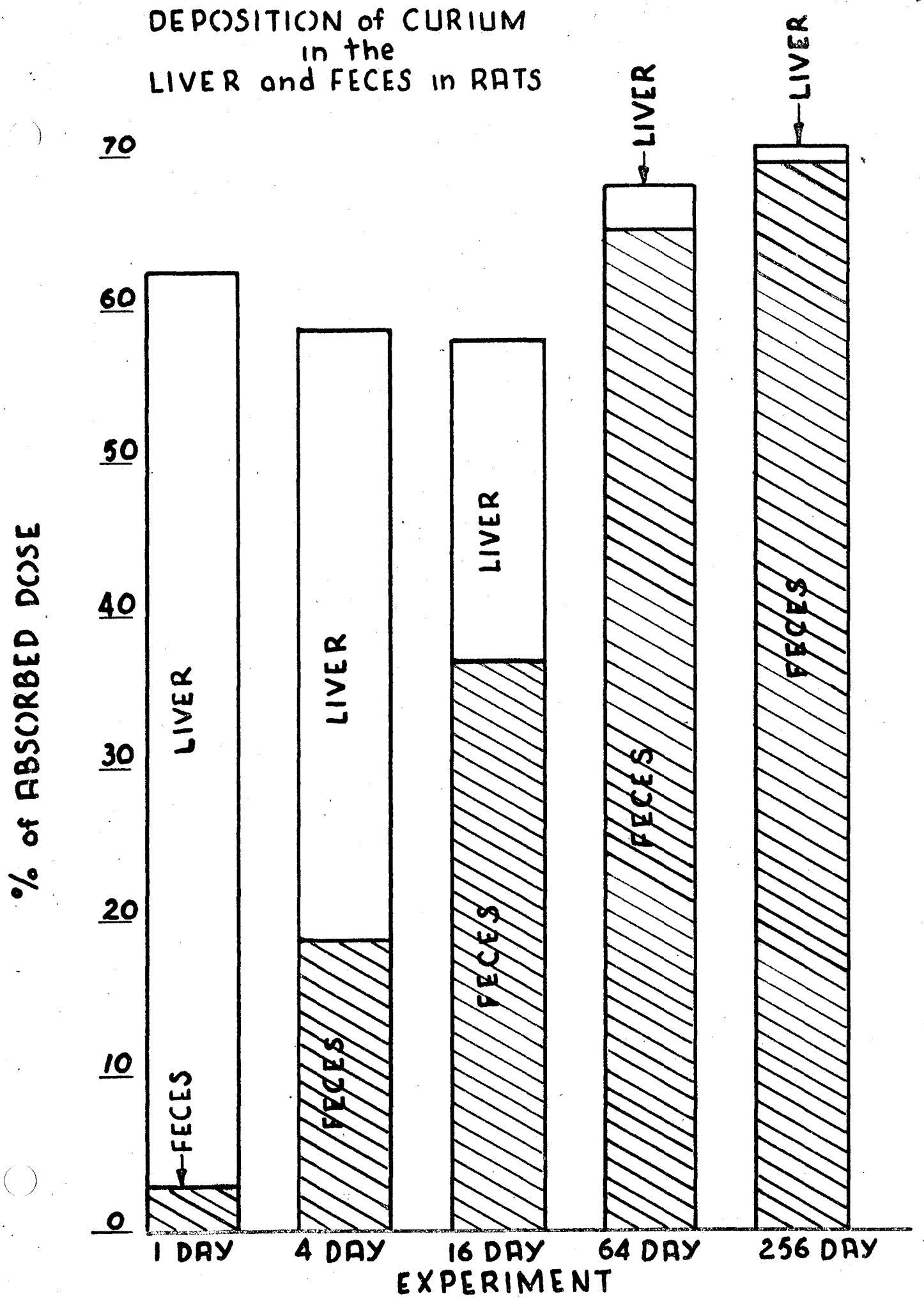
The section of femur and its corresponding radioautograph, shown in Plate I, indicate that curium is deposited in the region of the periosteum, endosteum, and the trabeculae. The mineralized portion of the bone shows little deposition of curium except for small spotty areas of localization. At the magnification shown in Plate I, it is difficult to correlate the regions where curium has been apparently laid down in the cortical bone with its histological structure. Plate II shows a small area of cortical bone and the corresponding region of the radioautograph at a higher magnification. Here the apparent deposition of curium in the region of the small blood vessels of cortical bone can be seen. These radioautographic studies suggest that the curium deposited in the femur was localized principally in the region of the osteoid matrix and about the small blood vessels of the cortex.

DISCUSSION

The close similarity of the metabolic characteristics of americium to those of the lanthanum group of rare earths has already been discussed briefly. It is of interest to compare the almost identical behavior of americium and curium in the animal body. The three most striking metabolic properties of these two heavy elements are their high uptake and comparatively rapid exretion by the liver, their deposition and prolonged retention by the skeleton, and the curious pattern of distribution in the region of the osteoid matrix and about the small blood vessels of cortical bone.

Figure IV presents the change in content of americium and curium in the liver and bone at the five time intervals, which extend from 1 to 256 days. It can be seen that the degree of differences


FECAL and URINARY
ELIMINATION
of CURIUM in RATS
FECES
URINE
% of ABSORBED DOSE EXCRETED
10
1
.1
.01
.001
.0001
0
20
40
60
80
100
120
140
160
180
200
220
240
260
TIME IN DAYS
FECES
URINE


DEPOSITION of CURIUM
in the
LIVER and FECES in RATS
% of ABSORBED DOSE
70
60
50
40
30
20
10
0
LIVER
FECES
LIVER
FECES
LIVER
FECES
LIVER
FECES
LIVER
FECES
1 DAY
4 DAY
16 DAY
64 DAY
256 DAY
EXPERIMENT

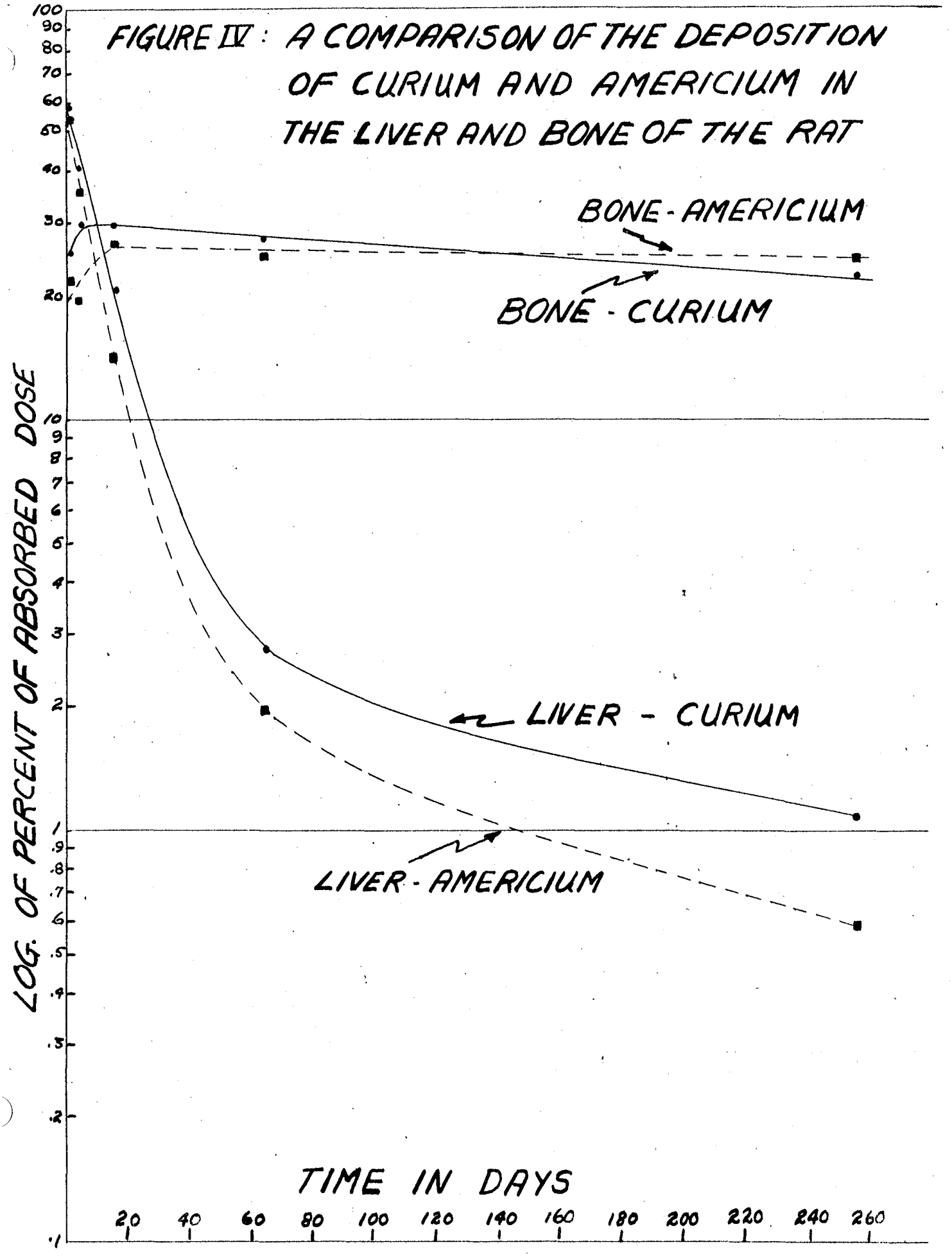


FIGURE IV: A COMPARISON OF THE DEPOSITION OF CURIUM AND AMERICIUM IN THE LIVER AND BONE OF THE RAT
BONE - AMERICIUM
BONE - CURIUM
LIVER - CURIUM
LIVER - AMERICIUM
LOG. OF PERCENT OF ABSORBED DOSE
TIME IN DAYS
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
.9
.8
.7
.6
.5
.4
.3
.2
.1
20
40
60
80
100
120
140
160
180
200
220
240
260

of their content in these two organs are small at the corresponding time intervals. In fact, it is felt that the variations noted are within the experimental errors common to both series of studies.

BIBLIOGRAPHY

Seaborg, G. T. "The Transuranium Elements", Science 104:379-386 (1946)

Hamilton, J. G., "The Metabolism of the Fission Products and the Heaviest Elements", Radiology 49:325-343 (1947)

Scott, K. G., Copp, D. H., Axelrod, D. J., Hamilton, J. G., "The Metabolism of Americium in the Rat", Jour. Clin. Investigation (To be submitted for publication).

Axelrod, D. J., "An Improved Method for Cutting Undecalcified Bone Sections and its Application to Radioautography", Anat. Record 98:19-24 (1947).

TABLE I

DEPOSITION OF CURIUM IN THE TISSUES OF THE RAT AFTER INTRAMUSCULAR ADMINISTRATION INTO THE LEFT LEG. VALUES GIVEN ARE IN PERCENT OF DOSE. AVERAGE VALUES FOR 3 RATS AT EACH TIME INTERVAL.

	Days after Injection									
	1		4		16		64		256	
Tissue	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.11	.13	.09	.01	.06	.09	.02	.03		
Lungs	.25	.19	.19	.13	.13	.11	.11	.07	.08	.02
Spleen	.08	.16	.10	.17	.10	.24	.09	.20	.09	.15
Blood	.16	.01	.00	--	.01	.001	.01	.001	.03	.001
Liver	51.4	6.70	38.1	5.70	18.0	2.83	2.14	.23	.95	.10
Kidney	2.44	1.51	1.47	.90	1.00	.69	.69	.36	.41	.19
G.I. Tract	2.77	.19	5.48	.35	1.39	.06	.20	.01	.07	.002
Bone	21.6	1.18	27.9	1.40	25.6	1.54	21.1	1.07	19.0	1.17
Muscle	1.86	.02	1.20	.02	1.63	.02	.90	.01	.41	.003
Lt Leg	16.0	.76	15.0	.72	10.8	.59	5.91	.19	4.80	--
Skin	1.63	.07	1.34	.06	.94	.03	.31	.01	.08	.003
Urine	1.47	--	1.22	--	5.10	--	1.34	--	5.23	--
Feces	2.46	--	17.7	--	32.1	--	50.6	--	60.2	--
% Recovery	102.2		109.8		96.8		83.4		91.4	

TABLE II

DEPOSITION OF CURIUM IN THE TISSUES OF THE RAT
CORRECTED FOR RECOVERY AND FOR THE UNABSORBED
BALANCE AT THE INJECTION SITE.
AVERAGE VALUES FOR 3 RATS AT EACH TIME INTERVAL.

	Days after Injection									
	1		4		16		64		256	
Tissue	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram	% per organ	% per gram
Heart	.13	.15	.09	.01	.07	.10	.03	.04		
Lungs	.29	.22	.20	.14	.15	.13	.14	.09	.09	.02
Spleen	.09	.19	.11	.18	.12	.28	.12	.26	.10	.17
Blood	.19	.01	.00	--	.01	.001	.01	.001	.03	.001
Liver	59.6	7.77	40.2	6.01	20.9	3.29	2.76	.30	1.10	.12
Kidney	2.83	1.75	1.55	.95	1.16	.80	.89	.46	.47	.22
G.I. Tract	3.21	.22	5.78	.37	1.61	.07	.26	.01	.08	.002
Bone	25.1	1.37	29.4	1.48	29.7	1.79	27.2	1.38	21.9	1.35
Muscle	2.16	.02	1.27	.02	1.89	.02	1.16	.01	.47	.003
Skin	1.89	.08	1.41	.06	1.09	.03	.40	.01	.09	.003
Urine	1.71	--	1.29	--	5.92	--	1.73	--	6.04	--
Feces	2.85	--	18.7	--	37.3	--	65.3	--	69.6	--
	100.0		100.0		99.9		100.0		100.0	