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THE METABOLISM OF THE LANTHANONS IN THE RAT

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THE METABOLISM OF THE LANTHANONS IN THE RAT

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THE METABOLISM OF THE LANTHANONS IN THE RAT

For many years the behavior of the lanthanons in biological systems was regarded as a scientific curiosity. The name "lanthanon" has been suggested by Marsh[1] for the group of elements of atomic numbers 57 to 71, lanthanum through lutetium. Until recently the commercial use of these elements was limited and their chemistry relatively obscure. With the development of the chain-reacting pile, and the discovery that certain light members of this group were produced in relatively large quantities in the fission process, knowledge of their metabolism* and radiotoxicity assumed greater importance.

Rare earth history began in 1794 when Gadolin found a new earth which had been discovered at Ytterby, Sweden, six years before.[2] Ekeberg confirmed this discovery and suggested for the oxide the name "yttria" from the name of the village, and "gadolinite" for the name of the mineral.[3] Both Gadolin and Ekeberg considered that the new oxide contained but a single metal. The chemical similarity of this group is strikingly shown by the fact that yttria was not the oxide of a single metal but a mixture of the oxides of at least 15 different metals. It was not until 1842 that Mosander[4] demonstrated that these oxides were in reality complex. During the remainder of the 19th century other oxides were isolated one by one from the original mixtures. The detailed history is long, confusing, and laden with controversy because of the complex nature of these materials and the difficulty in obtaining pure compounds.

With the rapid advances in physical and inorganic chemistry between 1910 and 1920, great progress was made in techniques of lanthanon separation. The

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* There has been much dissension concerning the use of the word "metabolism" for elements not intimately involved in biological processes; this terminology, however, is in general use in tracer work of the type presented here.

improbability of the existence of further unidentified lanthanons was demonstrated by the work of Moseley.[5]

In recent years the development of ion-exchange techniques has reduced the time necessary for separation of the lanthanons to days rather than the months or years formerly involved. This technique, applicable to microscale work, provided the data necessary to establish the identity of the missing member of the group — promethium. Because the longest-lived isotope of this radioactive element is but 2.6 years,[6] it is doubtful that it exists naturally. Contrary to the opinions of the original discoverers of the lanthanons, this group of elements is widely distributed in nature. Distinctive minerals are numerous, although they are restricted to a few localities.

When Mendeleef first presented his Periodic Table he placed the lanthanons then known in order as individuals and not as the group which we today consider them. It is now realized that the simplest way of constructing the Periodic System is on the basis of electronic structure, and on this basis the lanthanons fall between barium (Atomic number 56, group II) and hafnium (Atomic number 72, group IV). The characteristic chemical similarity of the lanthanons is mainly attributable to the filling of an inner electron shell, 4f, rather than the addition of these electrons to the outermost or valence shell.

Certain members of this group can be reduced to the divalent state and others oxidized to the quadrivalent state; the principal valence state of the group as a whole, however, is plus three. Although the actual radius of an ion of a particular element depends principally upon its valency, the radii of the tervalent ions of the lanthanons show an interesting decrease with increasing atomic number. Goldschmidt[7] called this phenomenon the "lanthanide contraction". This decrease of ionic radius with increasing atomic number is due to the inability of the 4f shell of electrons to compensate completely for the growing nuclear

charge. As the ionic radius decreases the basicity of the lanthanons decreases and their compounds become more soluble, which may, to some extent, account for the differences in distribution of the light and heavy lanthanons described here.

A surprisingly large number of rare earth compounds have been prepared to date. Among the most important are the halides, oxides, and oxalates. Commercial uses and applications of the lanthanons are, so far, relatively limited. They were first used in the gas mantle industry, and are now employed in the manufacture of automatic lighter flints, in ceramics, as phosphors, and most recently -- as an important component of high-temperature and high-pressure resistant aluminum and magnesium alloys. A complete review of the history, occurrence, applications, and chemistry of the lanthanons has been published by Vickery.[8]

The relationship of the lanthanons to biological systems was studied almost as soon as the first members of the group were isolated. (A complete bibliography to 1935 on the biological occurrence, metabolism, and toxicity of the lanthanons has been prepared by Steidle.[9]) In such biological specimens as the ash of the tobacco plant, barley, grapevines, beechwood, and bone meal, traces of cerium and lanthanum were found. Living systems ranging in complexity from bacteria to mammals have received experimental exposures to lanthanons. A survey of such work indicates that in vertebrates the toxic effects following parenteral injection were probably due to the formation of insoluble phosphates and carbonates, which disturb the hydrogen ion concentration of the organism. The observation was frequently made that the lanthanons were nontoxic (even in large amounts) when given orally. This was probably because they are poorly absorbed from the gastro-intestinal tract.

Under the auspices of the Manhattan Project, tracer studies were performed in this laboratory[10,11] with some of the lighter members of the lanthanon series that are produced in nuclear fission. Some of these were carrier-free,* and others were administered with considerable amounts of stable isotope carrier, making direct comparisons difficult. Other sources of error in this work were present: (a) little attention was paid to the age, strain, or sex of the rats employed or to uniformity of dietary regimen; (b) experimental groups were not large enough to permit comparison of neighboring elements on a statistical basis; (c) the radioisotopes were administered as chlorides or nitrates, and it was frequently found, even in studies extending over many months, that a large proportion of the material was still unabsorbed.

The studies reported here were designed to correct some of the earlier defects and to expand the data to include all the lanthanons on a uniform and systematic basis. The recent availability of extremely pure specimens of the rarer lanthanons, and the construction of the high-neutron-flux Materials Testing Reactor, made possible the production of the necessary quantities of previously unobtainable radioisotopes of high specific activity. The age, sex, and the strain of the rats, and the care given them, were uniform throughout. The size of the groups was increased. The radioisotopes were administered as citrate complexes, which increased the speed of absorption from the site of injection. Further refinements were also included in counting apparatus and techniques, and in excretion separation.

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* A carrier-free preparation is one in which all the atoms present of a particular element are radioactive. The specific activity of such a preparation is, by definition, $\frac{\text{N active}}{\text{N total}} = 1$

EXPERIMENTAL

Preparation of Radioisotopes

The radioisotopes of cerium, europium, and promethium were obtained from Oak Ridge National Laboratory, Oak Ridge, Tennessee. The praseodymium data are reprinted with the kind permission of Josephine Crowley Ellis.[12] Radioactive thulium and terbium were provided by Drs. Glenn T. Seaborg and Stanley Thompson of the University of California Radiation Laboratory. Dr. Frank Spedding of the University of Iowa, Ames, Iowa, very kindly supplied 99.9% to 99.95% spectroscopically pure oxides of the remaining lanthanons from which radioisotopes were prepared by the (n,γ)* reaction.

Weighed portions of the oxides were diluted in a minimal amount of 6 N HCl. Aliquots of these solutions were transferred to quartz ampules which had been washed with concentrated HNO_3 and rinsed with conductivity water. The ampules containing the lanthanon solutions were dried overnight in an oven at 105°C and heated at 200°C for a few minutes to expel all traces of water. They were then sealed and sent to Arco, Idaho, where they were placed in the Materials Testing Reactor in the region of maximum neutron flux. The length of the bombardment was calculated from the half-life of the desired isotope, the neutron-capture cross section of the target isotope, and the weight of stable lanthanon in the sample. After bombardment, the materials were flown back to this laboratory. The ampules were placed in heavy plastic envelopes and crushed with a hammer. The crushed ampule was carefully transferred to a beaker and washed several times with 6 N HCl until a survey meter showed that no more activity could be removed from the quartz. Ten milligrams of NaCl were added to the solution, which

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* Dy^{166} was prepared by a second-order reaction, $Dy^{164}(n,\gamma)$, $Dy^{165}(n,\gamma)$ Dy^{166}.

was then evaporated to incipient dryness. Sodium citrate solution, 30 mg/ml, was added, the amount varying with the quantity of activity present, and the pH was adjusted to neutral with 9 N NaOH. The latter procedure -- evaporating with salt and redissolving -- was also followed with the isotopes obtained from other sources.

The radioactive purity of all the preparations and the identity of the isotopes were determined by the measurement of the half-life, the beta-ray absorption in aluminum, and the gamma-ray absorption in lead.

The specific activities were estimated from the weight of the bombarded sample and the total volume of the final citrate solution. The half-lives, beta energies, and the presence or absence of gamma rays of the isotopes employed are listed in Table I.

Biological Procedures

The animals used in these tracer studies were female Sprague-Dawley rats that were from 4 to 6 months of age (200-250 g) when injected. The animals were maintained on tap water and a pelleted stock diet developed by the University of California Institute of Experimental Biology, "Diet 14", for at least two weeks prior to isotope administration and until sacrifice.

While the animals were under light ether anaesthesia, isotopes of all the lanthanons were administered intramuscularly in the left hind leg and Ce^{144}, $Eu^{152,154}$, Tb^{160} and Tm^{170} were also given orally by stomach tube. In no case did the volume of solution administered exceed 1 ml. The time intervals investigated, the dosage of each radioisotope in microcuries per rat, the amount of stable lanthanon per rat, and the amount of sodium citrate administered per rat are shown in Table II.

Moderate amounts of high-specific-activity preparations were used in order to avoid uncertainties introduced by either radiotoxicity or chemical toxicity.

Table I

NUCLEAR PROPERTIES[6] OF THE RADIOISOTOPES OF THE LANTHANONS EMPLOYED IN METABOLIC STUDIES

Element	Atomic Number	Isotope	Half-life	β-Energy Mev.	γ-Rays
Lanthanum	57	La^{140}	40 hour	1.32-2.26[a]	++[b]
Cerium	58	Ce^{144}	282 day	0.17,0.30[c]	++
Praseodymium	59	Pr^{143}	13.7 day	0.93	-[d]
Neodymium	60	Nd^{147}	11.3 day	0.38-0.83	+[e]
Promethium	61	Pm^{147}	2.6 year	0.22	-
Samarium	62	Sm^{153}	47 hour	0.70,0.80	++
Europium	63	$Eu^{152,154}$	13-16 year	0.3-1.88	-
Gadolinium	64	Gd^{159}	18 hour	0.90	+
Terbium	65	Tb^{160}	73 day	0.40-0.86	+
Dysprosium	66	Dy^{166}	82 hour	0.20	-
Holmium	67	Ho^{166}	27 hour	0.55,1.84	+
Erbium	68	Er^{169}	9.4 day	0.33	-
Thulium	69	Tm^{170}	129 day	0.88,0.97	+
Ytterbium	70	Yb^{175}	102 hour	0.50	++
Lutetium	71	Lu^{177}	6.8 day	0.17-0.50	+

(a) E_1-E_n Several β^- energies within range shown.

(b) ++ Gamma-rays sufficiently intense for direct assay of samples.

(c) E_1,E_2 Only two β^- energies.

(d) - Gamma-rays absent.

(e) + Gamma-rays present at low intensity.

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Table II

SUMMARY OF TIME INTERVALS INVESTIGATED AND THE AMOUNTS OF RARE EARTH, AND COMPLEXING AGENT ADMINISTERED PER RAT.

Isotope	Time Intervals (Day)	Dose (μc)	Carrier (μgm)	Sodium Citrate (mgm)
La^{140}	1,4	29,58[a]	1.2,2.4	6,12
Ce^{144}	1,4,64,256	20-40[b]	c.f.[c]	3-6
Pr^{143}	1,4,15,32	180	c.f.	2
Nd^{147}	1,4,16	2.3-4.6	1.1-3.7	2.7-5.6
Pm^{147}	1,4,64,238	10-70	c.f.	3-6
Sm^{153}	1,4	30,75	0.3,0.6	3,7.5
$Eu^{152,154}$	1,4,64,256	1.8-2.6	5.2-7.8	5.7-8.6
Gd^{159}	1,4	3.8,20	2.0-10.8	2.3,12
Tb^{160}	1,4,64,256	3.0-12.0	3.0-12.0	2.8-11.2
Dy^{166}	1,4	4.3,11.0	0.1,0.3	3.0-7.5
Ho^{166}	1,4	14,84	0.02,0.12	1.3,7.8
Er^{169}	1,4,16	2.4-4.8	1.0-3.8	2.8-5.6
Tm^{170}	1,4,64,256	3-12	0.08-0.3	3-12
Yb^{175}	1,4,8	14-57	0.4-1.1	2.5-7.4
Lu^{177}	1,4,16	7.3-29	0.5-1.9	4.8-7.2

(a) One and four day dosages respectively.

(b) Dosages graded for time intervals involved.

(c) c.f. - Carrier-free.

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Except in the Pr^{143} stu dies, the la gest amount of radioactivity administered was 0.5 $\mu c/g$ of body weight, which was well below radiotoxic levels.[13] The amount of complexing agent used was roughly adjusted to the quantity of carrier present. The actual dosage for any given experiment both in microcuries and micrograms depended on the best balance obtainable among the following factors: specific activity, half-life, counting accuracy desired, and in most cases, beta particle energy.

In the intramuscular studies five rats were injected for each time interval except for the Ce^{144} and Nd^{143}, when it was found necessary to repeat the experiments with larger numbers of animals. An outbreak of pneumonia in the colony reduced the number of rats to four in the 256 day $Eu^{152,154}$ and Tb^{160} experiments. In the oral studies, groups of three animals were used. A standard was prepared for each experiment; at the time of injection an amount of the radioactive solution equal to that administered to each animal was diluted to 100 ml in 2 $\underline{N}$ HNO_3.

Following the administration of the isotope, groups of two or three animals were placed in metabolism cages which were designed to provide adequate separation of urine and feces with a minimum of handling. The cages were fabricated from No. 2 mesh galvanized screen, and rested on corks three-quarters inch above large porcelain pans over which was taped a circle of No. 8 mesh screen. Both the fine collecting screen and the cages were sprayed with acid-resistant paint1 Excretions were collected daily for the first four days after injection and twice weekly thereafter.

In the intramuscular studies animals were sacrificed at intervals of one and four days after injection in all the experiments, and when the half-life permitted, at longer time intervals ranging from 8 to 256 days. In the oral studies the animals were sacrificed at four days. Under chloroform anaesthesia, a blood sample

was withdrawn by heart puncture, after which the animals were returned to the chloroform for sacrifice. The left hind leg (the site of injection) was removed at the pelvic girdle, and the foot was cut off for assay with the carcass. The remaining carcass was then skinned and the following tissues and organs were dissected and weighed: pelt, spleen, liver, kidneys, gastrointestinal tract, gastrointestinal contents, the muscle from the right hind leg, and the femur, fibula, and tibia from the right hind leg.

Preparation of Samples for Beta Assay

The blood, spleen, kidneys, muscle, and gastrointestinal tract (small samples) were placed in individual porcelain ashing capsules, and the liver, bone, skin, gastrointestinal contents, left leg, carcass and excreta (large samples) were placed individually into beakers. All tissues were dried for 24 hours at 100°C and ashed for 24 hours at 500°C. The ash from the small samples was spread evenly by dissolving in 2 ml of 2 N HNO_3 and redrying. The soft-tissue ash in the carcass was removed from the skeleton by rinsing several times with distilled water and filtering through gauze. The skeletal ash was dried and weighed. The large samples, including skeleton, were dissolved in 2 N HNO_3, and aliquots were transferred to weighed porcelain capsules and dried.

In order to correct for self-absorption of the beta particles in the mass of the sample, dilution curves were prepared for each isotope according to the methods of Yankwich et al.[14] The weights of the large samples were determined by difference. The weights of the small samples were estimated on the basis of 1.25% ash in soft tissues. An aliquot of the standard was assayed whenever samples were counted to eliminate corrections for decay and fluctuations in counter efficiency. The beta counter, used with a Tracerlab Autoscaler, consisted of a large, 6-cm diameter, Geiger-Muller tube (1.2 mg/cm^2 mica window) filled with 1 atmosphere of helium saturated with ethyl alcohol. All samples were counted for a sufficiently long time to reduce the error of measurement to ± 5%.[15]

Preparation of Samples for Gamma Counting

In La^{140}, Ce^{144}, Sm^{153}, and Yb^{175}, gamma rays were present in sufficient intensity for accurate measurement. The procedures employed for preparation of the skeleton and excreta samples were the same as described in the previous section. Other tissues and organs were placed in tin bottle caps, the larger ones often into two or more. The samples were assayed wet with a TlI-NaI scintillating crystal counter of the type described by Jenkins.[16]

Calculations

The total amounts of radioisotopes present in blood and muscle were calculated on the basis that these two tissues represent 7% and 45% of the body weight respectively. The lanthanon concentration in bone, percent of administered dose per gram of wet tissue, was calculated from the previously determined ash content of mature rat bone, 36.6 ± 0.7%. The amount of each isotope remaining at the site of injection was calculated by subtracting the activity present in the muscle and bone samples from that found in the whole left leg.

The percent of administered radioisotope in the muscle and blood samples was added to the percent of dose obtained for the soft-tissue ash washed from the skeleton. From this "total balance" were subtracted the calculated values for the blood and muscle. The residual percent of dose, which has been designated "balance" consisted of the thoracic organs; reproductive organs; cartilage; glandular, lymphoid, connective and nervous tissue; fat; and blood vessels.

All data are expressed as concentration and as the percent of the absorbed dose found in the whole specimens, and are corrected for deviation of recovery from 100%. The average values for liver and skeleton are presented as the mean for the group, ± the standard error, $S.E._{\bar{x}} = \frac{\Sigma dev^2}{n(n-1)}$.

RESULTS

The trend of the results of the tracer studies with the 15 lanthanons

are shown in Tables III, La^{140}, through XVII, Lu^{177}. The percent of the administered isotope remaining at the injection site and the mean recovery for each group are shown at the bottom of each table. The trend of the initial deposition in liver and skeleton is shown in Fig. 1.

The experimental recoveries of the injected material ranged from 86% for the 256 day Tm^{170} to 121% for the 4 day Lu^{177}. Some of the sources of error in this type of experiment are as follows; determination of self-absorption curve, weighing of samples, loss of material in sample preparation, and preparation and measurement of standards. Recoveries below 95% or greater than 105% were exceptional, however, indicating that on the whole the data are reliable.

Absorption: Absorption from the intramuscular injection site was, for the most part, fairly complete. In 11 of 15 experiments, the amount of isotope unabsorbed four days after injection was less than 6.5%. Three of the four exceptions, $Eu^{152,154}$ Gd^{159}, and Tb^{160} (15% unabsorbed at four days), were administered with 8 to 10 μg of carrier, the largest quantities employed. The ratio of micrograms carrier to milligrams sodium citrate was 0.9, also considerably higher than in most of the experiments. In La^{140} (22.5% unabsorbed at four days) only 2.4 μg of carrier was administered, with a ratio of carrier to complexing agent of 0.2 μg/ml. The insolubility of the compounds of lanthanum at physiological pH's is probably a major factor in its difficult absorption. The rate of absorption of the lanthanons from the intramuscular injection site seems to depend upon the solubility of their compounds, the amount of stable carrier administered and, to some extent, upon the ratio of the quantity of carrier to the quantity of sodium citrate administered.

Absorption of Ce^{144}, $Eu^{152,154}$, Tb^{160}, and Tm^{170} from the gastrointestinal tract was less than 0.1% of the administered dose.

Because of the great mass of the data, only significant trends will be discussed.

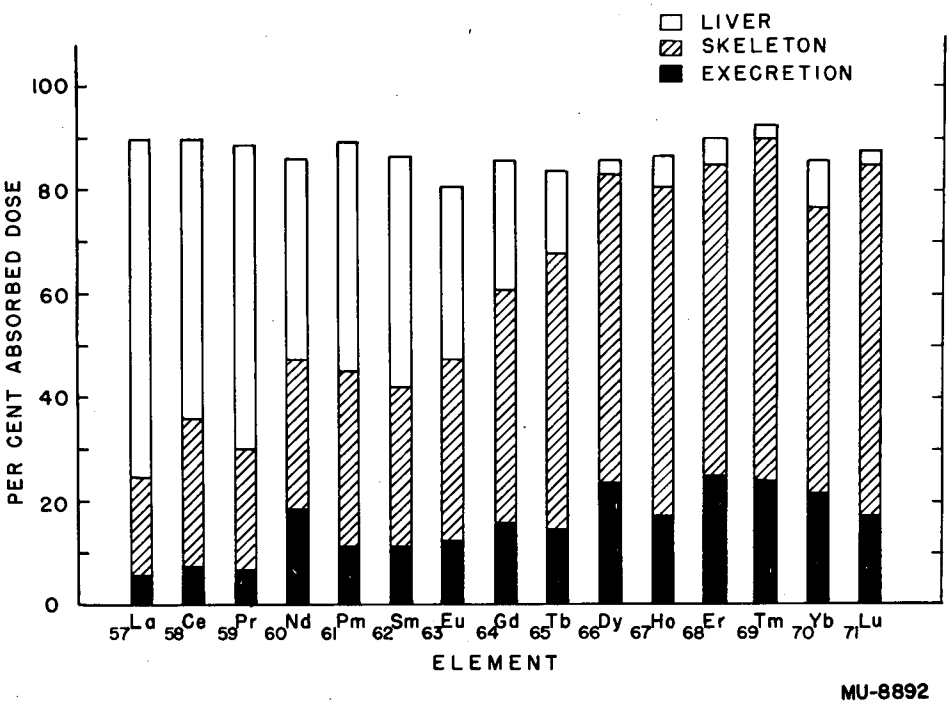

Fig. 1. Summary of the excretion, skeletal deposition, and liver deposition of the lanthanons 1 day after intramuscular administration. The difference between the end of each bar and 100% represents the percent of each isotope in the remainder of the animal.

Table III

DEPOSITION OF LANTHANUM IN THE RAT 1 AND 4 DAYS AFTER INTRAMUSCULAR INJECTION USING La^{140} AS A TRACER

	1 D		4 D	
	%/org.	%/g	%/org.	%/g
Spleen	.11	.21	.10	.19
Blood	.08	.01	.02	<.01
Liver*	65.4	8.45	64.2	7.94
Kidney	2.50	1.59	1.35	.83
G.I. Tract	.78	.12	.45	.08
G.I. Contents	.75	-	2.63	-
Muscle	1.62	.02	1.21	.01
Skeleton**	18.5	.84	18.4	.83
Balance	2.92	-	2.55	-
Skin	1.60	.04	.99	.03
Urine	4.56	-	5.62	-
Feces	1.20	-	2.60	-
Injection Site	33.0	-	22.5	-
Avg. Recovery	102.	-	101	-
Std. Error of Mean	* ±.90 ** ±.15	±.27 ±.05	±1.6 ± .7	±.60 ±.02

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Table IV

DEPOSITION OF CARRIER-FREE CERIUM^{144} IN THE RAT 1, 4, 64 AND 256 DAYS AFTER INTRAMUSCULAR INJECTION

	1 D		4 D		64 D (10 rats)		256 D	
	%/org	%/g	%/org	%/g	%/org	%/g	%/org	%/g
Spleen	.08	.17	.10	.11	.06	.11	.04	.10
Blood	.06	<.01	<.01	<.01	<.01	<.01	<.01	<.01
Liver*	53.7	7.42	51.0	6.57	6.55	.68	3.31	.33
Kidney	1.60	.99	1.45	.76	.70	.34	.43	.22
G.I. Tract	.76	.15	1.01	.11	.23	.02	.08	.01
G.I. Contents	.63	-	1.77	-	.09	-	.02	-
Muscle	1.56	.02	1.78	.02	.81	.01	.37	<.01
Skeleton**	28.5	1.52	27.7	1.40	19.9	.89	21.7	.87
Balance	4.99	-	2.01	-	.98	-	1.16	-
Skin	1.26	.04	1.01	.04	.34	.01	.22	<.01
Urine	5.77	-	5.95	-	11.2	-	10.3	-
Feces	1.03	-	6.21	-	59.2	-	62.4	-
Injection Site	10.2	-	6.15	-	2.75	-	6.04	-
Avg. Recovery	98.2	-	89.6	-	97.3	-	100.	-
Std. Error of Mean *	±3.1	±.50	±.67	±.18	±2.29	±.26	±1.30	±.14
**	±1.90	±.08	±.95	±.07	± .74	±.04	± .25	±.03

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Table V

DEPOSITION OF CARRIER-FREE PRASEODYMIUM^{143} IN THE RAT 1, 4, 15 AND 32 DAYS AFTER INTRAMUSCULAR INJECTION

	1 D		4 D		15 D		32 D	
	%/org.	%/g	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.14	.12	.11	.10	.13	.11	.10	.10
Blood	.14	<.01	.17	.01	.01	<.01	<.01	<.01
Liver*	58.9	4.76	48.4	4.71	18.6	1.54	6.33	.45
Kidney	4.62	1.54	3.18	1.13	1.07	.44	.59	.20
G.I. Tract and Contents	1.45	-	1.01	-	1.28	-	.43	-
Muscle	2.45	.01	1.66	.01	1.49	.01	1.87	.01
Skeleton**	20.6	.73	26.6	.98	33.0	1.53	23.1	.94
Balance	2.81	-	2.36	-	2.75	-	1.30	-
Skin	2.66	.05	2.37	.04	1.23	.03	.93	.01
Urine	5.9	-	6.56	-	7.19	-	6.55	-
Feces	.33	-	7.59	-	33.3	-	58.8	-
Injection Site	8.31	-	5.46	-	5.52	-	2.51	-
Avg. Recovery	94.7	-	96.2	-	107.	-	90.3	-
Std. Error of Mean *	±1.6	±.48	±3.6	±.62	±.4	±.15	±1.7	±.14
**	±1.8	±.08	±3.0	±.02	±1.2	±.22	±1.0	±.03

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Table VI

DEPOSITION OF NEODYMIUM IN THE RAT 1, 4, and 16 DAYS AFTER INTRAMUSCULAR INJECTION USING ND^{147} AS A TRACER

	1 D, 13 rats		4 D, 13 rats		16 D, 8 rats	
	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.10	.16	.08	..11	.06	.08
Blood	.21	.02	.03	<.01	<.01	<.01
Liver *	38.8	4.67	27.1	3.07	14.8	1.60
Kidney	2.30	1.26	1.59	.79	.68	.42
G.I. Tract	.80	.12	.52	.08	.22	.04
G.I. Contents	2.84	-	1.39	-	.65	-
Muscle	2.45	.02	2.02	.02	1.01	.01
Skeleton**	29.3	1.49	31.2	1.52	21.0	1.07
Balance	3.26	-	3.27	-	1.17	-
Skin	2.18	.07	1.67	.05	.77	.03
Urine	15.9	-	22.1	-	28.6	-
Feces	1.94	-	8.68	-	30.2	-
Injection Site	8.75	-	6.07	-	3.16	-
Avg. Recovery	97.3	-	98.0	-	96.8	-
Std. Error of Mean *	±1.20	±.24	±1.40	±.15	±3.20	±.27
Std. Error of Mean **	±1.50	±.14	±2.10	±.12	±1.50	±.13

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Table VII

DEPOSITION OF CARRIER-FREE PROMETHIUM^{147} IN THE RAT 1, 4, 64 AND 238 DAYS AFTER INTRAMUSCULAR INJECTION

	1 D		4 D		64 D		238 D	
	%/org.	%/g	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.09	.19	.07	.15	.04	.07	.03	.05
Blood	.05	<.01	<.01	<.01	<.01	<.01	<.01	<.01
Liver*	43.8	6.37	41.4	6.12	1.70	.19	.97	.11
Kidney	1.76	1.17	1.44	1.04	.46	.26	.37	.19
G.I. Tract	1.36	.20	.63	.09	.25	.04	.12	.01
G.I. Contents	1.75	-	1.45	-	.09	-	.02	-
Muscle	1.98	.02	.73	.01	.86	.01	.28	<.01
Skeleton**	34.3	1.82	36.4	2.13	28.6	1.28	26.7	1.02
Balance	2.55	-	2.32	-	1.01	-	.50	-
Skin	1.63	.05	.73	.03	.45	.01	.21	<.01
Urine	9.79	-	9.61	-	14.5	-	17.3	-
Feces	.86	-	5.07	-	49.8	-	53.5	-
Injection Site	4.24	-	4.75	-	3.21	-	1.75	-
Avg. Recovery	97.6	-	94.0	-	91.2	-	91.3	-
Std. Error *	±1.95	±.35	±2.4	±.35	.32	±.03	±.40	±.04
of Mean **	±1.6	±.12	±2.3	±.28	1.19	±.08	±.65	±.05

MU-10073

Table VIII

DEPOSITION OF SAMARIUM IN THE RAT 1 AND 4 DAYS AFTER INTRAMUSCULAR INJECTION USING SM^{153} AS A TRACER

	1 D		4 D	
	%/org.	%/g	%/org.	%/g
Spleen	.09	.18	.08	.12
Blood	.08	<.01	.02	<.01
Liver*	44.5	5.81	34.8	4.34
Kidney	2.18	1.38	1.30	.84
G;I. Tract	.78	.12	.54	-
G.I. Contents	2.00	-	1.50	-
Muscle	1.77	.02	1.24	.01
Skeleton**	30.7	1.37	33.2	1.65
Balance	5.40	-	1.74	-
Skin	1.58	.04	1.25	.03
Urine	8.94	-	12.7	-
Feces	1.94	-	11.6	-
Injection Site	5.58	-	2.38	-
Avg. Recovery	96.1	-	99.2	-
Std. Error of Mean *	±1.9	±.36	±1.5	±.27
**	±1.5	±.06	± .5	±.06

MU-10074

Table IX

DEPOSITION OF EUROPIUM IN THE RAT 1,4, 64 AND 256 DAYS AFTER INTRAMUSCULAR INJECTION USING $Eu^{152,154}$ AS A TRACER

	1 D		4 D		64 D		256 D 4 rats	
	%/org.	%/g	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.15	.20	.13	.21	.09	.13	.04	.07
Blood	.10	.01	.06	<.01	<.01	<.01	<.01	<.01
Liver*	33.3	4.94	25.0	2.69	5.26	.54	.52	.05
Kidney	3.36	1.86	2.39	1.23	1.64	.94	2.52	1.05
G.I. Tract	1.17	.14	.92	.12	.25	.04	.16	.02
G.I. Contents	4.11	-	2.02	-	.02	-	.01	-
Muscle	3.09	.03	3.17	.03	1.10	.01	.82	.01
Skeleton**	35.3	1.40	35.6	1.4	37.25	1.53	32.0	1.02
Balance	4.71	-	2.65	-	1.70	-	1.17	-
Skin	3.03	.08	2.43	.06	.94	.03	.55	.01
Urine	11.0	-	16.6	-	19.55	-	18.5	-
Feces	.68	-	9.08	-	32.2	-	43.7	-
Injection Site	15.9	-	14.1	-	11.6	-	5.24	-
Avg. Recovery	106.	-	109.	-	116.	-	112.	-
Std. Error of Mean *	±1.6	±.35	±1.3	±.10	±2.1	±.19	±.10	<±.01
**	±1.9	±.09	±1.8	±.11	±1.5	±.11	±.60	±.08

MU-10075

Table X

DEPOSITION OF GADOLINIUM IN THE RAT 1 AND 4 DAYS AFTER INTRAMUSCULAR INJECTION USING GD^{159} AS A TRACER

	1 D		4 D	
	%/org.	%/g	%/org.	%/g
Spleen	.10	.18	.15	.27
Blood	.32	.03	.14	.01
Liver*	25.1	3.82	12.1	1.48
Kidney	1.63	1.06	1.87	1.16
G.I. Tract	1.06	.16	.71	.12
G.I. Contents	2.18	-	.95	-
Muscle	2.49	.02	2.89	.03
Skeleton**	45.0	2.07	41.4	1.82
Balance	4.37	-	3.81	.04
Skin	2.20	.06	1.76	-
Urine	14.8	-	26.9	-
Feces	.79	-	7.24	-
Injection Site	23.4	-	15.4	-
Avg. Recovery	120.	-	88.5	-
Std. Error of Mean	* ±1.0 ** ± .6	±.27 ±.05	± .3 ±1.2	±.10 ±.09

MU-10076

Table XI

DEPOSITION OF TERBIUM IN THE RAT 1, 4, 64 AND 256 DAYS AFTER INTRAMUSCULAR INJECTION USING TB^{160} AS TRACER

	1 D		4 D		64 D		256 D	
	%/org.	%/g	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.12	.24	.13	.24	.09	.17	.03	.06
Blood	.20	.02	.06	<.01	<.01	-	<.01	<.01
Liver*	15.8	2.23	6.83	.85	1.09	.12	.24	.03
Kidney	2.75	1.68	2.05	1.36	.78	.42	1.55	.80
G.I. Tract	1.43	.22	.84	.13	.34	.04	.17	.02
G.I. Contents	2.47	-	.73	-	.06	-	.02	-
Muscle	2.91	.03	2.31	.02	1.0	.01	1.00	<.01
Skeleton**	53.3	2.44	60.5	2.96	57.1	2.52	48.5	1.84
Balance	4.66	-	2.70	-	1.70	-	1.50	-
Skin	2.44	.08	2.10	.06	.76	.02	.66	.01
Urine	11.5	-	15.6	-	21.0	-	25.7	-
Feces	2.48	-	6.17	-	16.1	-	20.6	-
Injection Site	27.2	-	15.2	-	10.5	-	5.97	-
Avg. Recovery	113.	-	116.	-	109.	-	98.0	-
Std. Error of Mean	*± .6 **±1.0	±.11 ±.11	± .85 ±1.6	±.11 ±.08	±.26 ±.8	±.03 ±.05	± .03 ±1.6	<±.01 ±.08

MU-10077

Table XII

DEPOSITION OF DYSPROSIUM IN THE RAT 1 AND 4 DAYS AFTER INTRAMUSCULAR INJECTION USING Dy^{166} AS A TRACER

	1 D		4 D	
	%/org.	%/g	%/org.	%/g
Spleen	.11	.20	.09	.18
Blood	1.08	.01	.03	<.01
Liver*	6.55	.91	2.80	.37
Kidney	1.36	.97	1.01	.67
G.I. Tract	1.09	.14	.59	.10
G.I. Contents	.88	-	.39	-
Muscle	2.0	.02	1.75	.02
Skeleton**	62.4	3.39	59.9	3.17
Balance	3.02	-	2.54	-
Skin	1.54	.05	1.19	.04
Urine	17.4	-	24.1	-
Feces	2.63	-	5.77	-
Injection Site	3.45	-	2.32	-
Avg. Recovery	101.	-	99.5	-
Std. Error of Mean	* ± .32 ** ±3.8	±.08 ±.08	± .02 ±1.1	±.01 ±.07

MU-10078

Table XIII

DEPOSITION OF HOLMIUM IN THE RAT 1 AND 4 DAYS AFTER INTRAMUSCULAR INJECTION USING Ho^{166} AS A TRACER

	1 D		4 D	
	%/org.	%/g	%/org.	%/g
Spleen	.10	.19	.10	.17
Blood	.13	.01	.04	<.01
Liver*	5.80	.73	2.44	.28
Kidney	1.64	1.07	1.35	.81
G.I. Tract	1.35	.21	.65	.08
G.I. Contents	2.36	-	.29	-
Muscle	2.40	.02	1.78	.02
Skeleton**	63.7	3.26	55.6	2.74
Balance	3.96	-	2.41	-
Skin	1.97	.06	1.33	.04
Urine	11.9	-	21.2	-
Feces	4.62	-	12.9	-
Injection Site	3.61	-	2.72	-
Avg. Recovery	93.8	-	100.	-
Std. Error of Mean *	±.26	±.06	±.18	±.02
**	±.5	±.09	±.4	±.05

MU-10079

Table XIV

DEPOSITION OF ERBIUM IN THE RAT 1,4 AND 16 DAYS AFTER INTRAMUSCULAR INJECTION USING ER^{169} AS A TRACER

	1 D		4 D		16 D	
	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.09	.16	.06	.13	.07	.13
Blood	.19	.02	.05	<.01	<.01	<.01
Liver*	3.12	.40	1.15	.14	.60	.07
Kidney	1.31	.80	.76	.48	.35	.20
G.I. Tract	.90	.15	.57	.09	.31	.04
G.I. Contents	1.60	-	.31	-	.11	-
Muscle	2.39	.02	1.75	.02	1.44	.01
Skeleton**	60.0	2.70	56.4	2.49	56.6	2.51
Balance	3.96	-	2.66	-	1.07	-
Skin	2.08	.06	1.76	.06	.90	.02
Urine	19.6	-	27.4	-	30.8	-
Feces	4.79	-	7.09	-	7.69	-
Injection Site	3.76	-	3.92	-	1.56	-
Avg. Recovery	116.	-	113.	-	97.5	-
Std. Error of Mean	* ±.13 ** ±.42	±.04 ±.12	±.09 ±.80	±.02 ±.13	±.09 ±.90	±.01 ±.07

MU-10080

Table XV

DEPOSITION OF THULIUM IN THE RAT 1, 4, 64 AND 256 DAYS AFTER INTRAMUSCULAR INJECTION USING Tm^{170} AS A TRACER

	1 D		4 D		64 D		256 D	
	%/org.	%/g	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.12	.20	.13	.22	.09	.12	.04	.06
Blood	.16	.02	.02	<.01	<.01	<.01	<.01	<.01
Liver*	3.40	.46	1.86	.24	.25	.03	.16	.01
Kidney	1.43	.92	1.07	.64	.35	.17	.26	.12
G.I. Tract	.81	.12	.59	.10	.18	.02	.07	<.01
G.I. Contents	1.28	-	.50	-	.03	-	<.01	-
Muscle	1.96	.02	1.59	.01	1.08	.01	.57	<.01
Skeleton**	64.8	3.09	64.1	2.72	61.7	2.57	54.0	2.00
Balance	3.63	-	1.98	-	.78	-	.59	-
Skin	1.53	.03	1.33	.03	.39	.01	.16	<.01
Urine	16.9	-	22.1	-	25.3	-	32.7	-
Feces	4.00	-	4.66	-	9.88	-	11.4	-
Injection Site	5.31	-	5.15	-	1.63	-	2.45	-
Avg. Recovery	96.6	-	95.0	-	98.8	-	86.1	-
Std. Error of Mean	* ±.10 ** ±.1	±.01 ±.06	±.18 ±.3	±.04 ±.09	- ±.8	- ±.07	- ±1.6	- ±.07

MU-10081

Table XVI

DEPOSITION OF YTTERBIUM IN THE RAT 1, 4 AND 8 DAYS AFTER INTRAMUSCULAR INJECTION USING YB^{175} AS A TRACER

	1 D		4 D		8 D	
	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.52	.98	.48	.96	.30	.61
Blood	.61	.06	.09	.01	.03	<.01
Liver*	4.07	.50	2.59	.30	1.08	.13
Kidney	4.56	2.79	3.34	1.95	2.38	1.38
G.I. Tract	1.80	.23	.93	.12	.47	.06
G.I. Contents	2.70	-	.52	-	.21	-
Muscle	2.21	.02	2.21	.02	1.45	.01
Skeleton**	55.1	3.02	57.8	2.97	57.7	.84
Balance	6.37	-	4.45	-	3.71	-
Skin	2.06	.06	1.68	.04	.84	.03
Urine	17.4	-	19.3	-	25.6	-
Feces	2.75	-	6.67	-	6.18	-
Injection Site	3.18	-	1.54	-	1.83	-
Avg. Recovery	99.8	-	103.	-	95.6	-
Std. Error *	±.15	±.03	±.14	±.02	± .10	±.01
of Mean **	±.9	±.05	±.8	±.17	±1.0	±.10

MU-10082

Table XVII

DEPOSITION OF LUTECIUM IN THE RAT 1, 4 AND 16 DAYS AFTER INTRAMUSCULAR INJECTION USING LU^{177} AS A TRACER

	1 D		4 D		16 D	
	%/org.	%/g	%/org.	%/g	%/org.	%/g
Spleen	.14	.29	.13	.25	.13	.26
Blood	.11	.01	.05	<.01	<.01	<.01
Liver*	3.67	.59	2.74	.35	1.35	.18
Kidney	1.33	.96	.63	.39	.44	.28
G.I. Tract	1.92	-	.86	.13	.46	.06
G.I. Contents	4.52	-	.35	-	.12	-
Muscle	2.07	.02	2.36	.03	1.38	.01
Skeleton**	65.9	3.88	67.6	3.57	65.5	3.41
Balance	3.98	-	1.81	-	1.10	-
Skin	2.16	.07	1.04	.03	1.08	.04
Urine	13.0	-	15.6	-	16.4	-
Feces	1.23	-	6.91	-	12.1	-
Injection Site	7.35	-	6.50	-	4.69	-
Avg. Recovery	116.	-	121.	-	109.	-
Std. Error of Mean	*± .13 **± .9	±.04 ±.13	±.12 ±.4	±.03 ±.12	±.29 ±.6	±.04 ±.06

MU-10083

Spleen: The concentration of the lanthanons in the spleen one day after administration was less than 0.5% per gram of wet tissue. When these elements are administered by vein as halides or nitrates as in the work of Laszlo et al.,[17] high concentrations are found in the spleen as well as in other components of the reticulo-endothelial system. These workers concluded that they were dealing, to a large extent, with radiocolloids. Bruner and his coworkers[18] in studies with radiogallium (principal valence +3) reached similar conclusions.

The intramuscular route was chosen in the present experiments in order to minimize the formation of insoluble lanthanon colloids in the blood stream. The low spleen concentrations demonstrated that this aim was largely achieved. We are, therefore, confident that these data represent the metabolism of these elements in truly ionic form.

Blood: The level of these elements in the blood at one day never exceeded 0.02% per milliliter, and there was a steady decrease to unmeasurable levels thereafter.

Muscle: The initial muscle concentration of the lanthanons was the same as for blood, but decreased at a somewhat slower rate.

Skin: The skin concentrations throughout the series, at the early time intervals, were about three to four times as great as those found for muscle and blood, subsequently decreasing at about the same rate as did the concentrations in muscle. It is possible that at the early time intervals there may have been some contamination of the skin by the urine. This would apply particularly to the heavy members of the series, for which the urine is the main route of excretion.

Gastrointestinal Tract: The gastrointestinal tract generally showed a concentration about ten times that of blood and muscle at the earlier time intervals. At the later intervals, two to eight months after administration, the gastrointestinal concentrations had dropped to low but still measurable levels in the lighter half of the series, for which the gastrointestinal tract is the chief excretion route, and

to unmeasurable levels in the latter half of the series. Retained fecal matter, particularly in the cecum, may have contributed to the initial high concentrations in the gastrointestinal tract, since the tract was not washed but the contents merely squeezed from it.

Balance: The soft-tissue balance, consisting of the thoracic organs and other tissues previously enumerated, contained less than 6% of the administered dose throughout the series, indicating that the values employed for total blood and total muscle were satisfactory and that the separation of the soft-tissue ash from skeletal ash was relatively good.

Kidney: Initially the concentration of the light lanthanons in the kidney was about 1.6%/g , a much greater concentration than was found for any other soft tissue except liver. The kidney concentrated more of the heavy lanthanons than did any other soft tissue, about 0.9%/g. Eight months after administration the concentration in the kidney had in all cases decreased to low levels, about 0.25%/g. There was no apparent correlation between either the one-day or eight-month kidney concentrations and the quantity of the isotope excreted in the urine.

Excretion: The lanthanons are excreted both by the kidney and by the liver via the gastrointestinal tract. The relative importance of either excretion route for any given element of the series is dependent upon its position in the series. More than 50% of the administered dose of the lighter lanthanons is accumulated by the liver, and it is thereafter rapidly excreted in the feces presumably by way of the bile. The heavier lanthanons are excreted primarily by the kidney. Those lanthanons in the middle of the series are excreted by both routes and to approximately the same extent. The cumulative excretion in both urine and feces is shown in Fig. 2 for Ce^{144}, a representative light lanthanon; $Eu^{152,154}$, a representative of the transition group; and Tm^{170}, a heavy lanthanon. Very little of any of the lanthanons

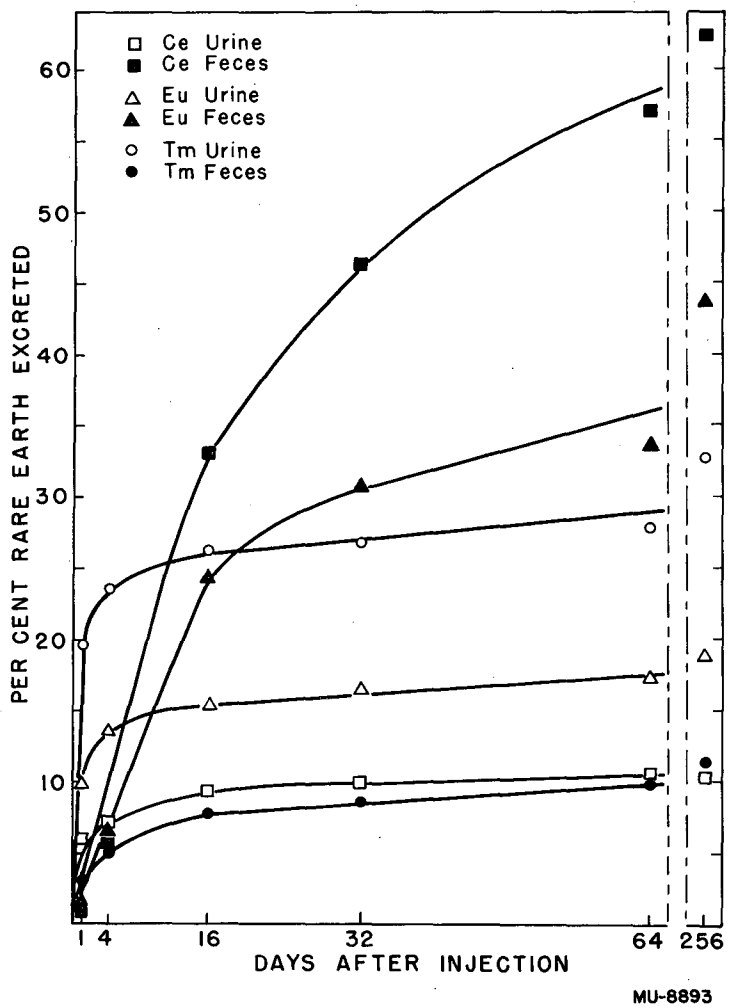

Fig. 2. The cumulative excretion of Ce^{144}, $Eu^{152,154}$ and Tm^{170} in urine and feces. Values are corrected for deviation of recovery from 100% and are expressed as percent of absorbed dose. The 1 day points represent 8 determinations, the 4 day points 6 determinations, the 16, 32 and 64 day points 4 determinations and the 256 day points 2 determinations.

was found in the urine after the first week postinjection, although there was a slight tendency towards continued urinary excretion of the heavier members of the series. Most of the fecal excretion of Tm^{170}, and presumably of the other heavy lanthanons, occurred in the first two weeks after administration. Fecal excretion of the light and medium weight lanthanons occurred throughout the entire eight-month investigation, but at a slower rate after the first two weeks.

Liver: The major deposition site of the lighter members of the series is the liver. At the heavy end of the series the liver is a secondary deposition site and contains less than 5% of the initially administered radioisotope. The retention of five representative members of the lanthanons in the liver is shown in Fig. 3. All the lanthanons are excreted from the liver, with half times ranging from 10 to 20 days, so that two months after injection less than 10% of that initially deposited remains.

Skeleton: The most important deposition site for all the members of this group is the skeleton. It is the primary target organ of the heavier lanthanons, and although initially it is apparently a secondary deposition site for the lighter members of the group, it becomes increasingly important because of their extended retention at this site. The skeletal retention of five representative lanthanons is shown in Fig. 4. The retention curves obtained for Ce^{144} and Pm^{147} (lighter lanthanons) show two components. One-third of these isotopes initially deposited in bone is somewhat labile with a half time of about 15 days, and the remaining two-thirds is apparently firmly fixed. The curve obtained for $Eu^{152,154}$ is unique in that it is convex. This presumably is due to deposition in the skeleton of $Eu^{152,154}$ only gradually absorbed from the site of injection. The skeletal half time for $Eu^{152,154}$, based on the best straight line through all the points, is about 2.5 years. The retention curves for Tb^{160} and Tm^{170} were straight lines for which the half time values are about 2.8 years.

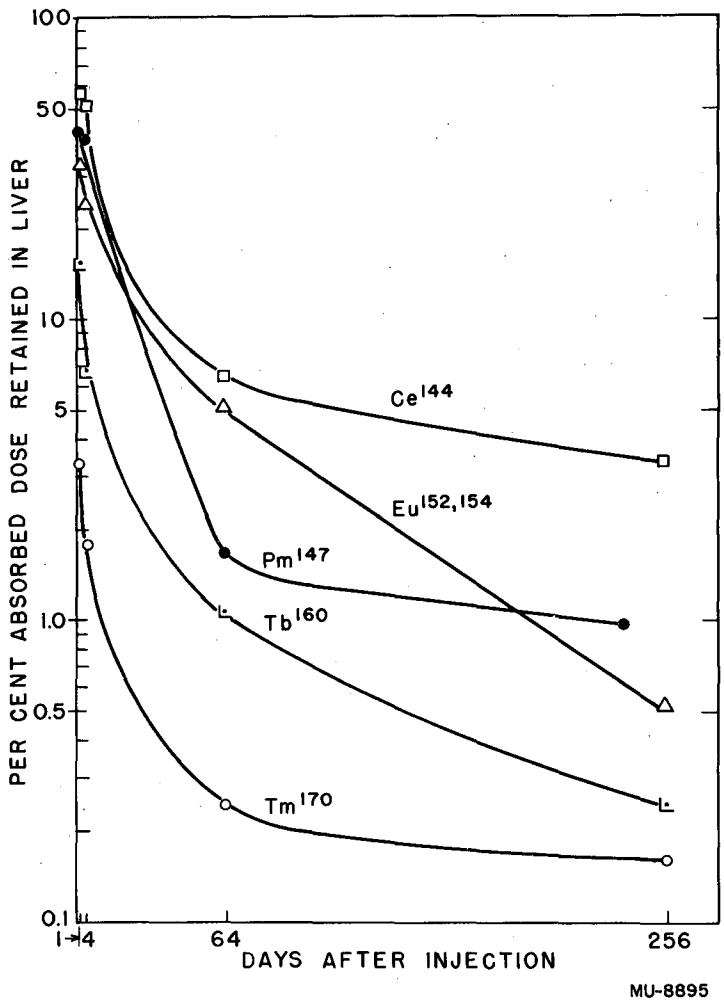

Fig. 3. The liver retention of Ce^{144}, Pm^{147}, $Eu^{152,154}$, Tb^{160}, and Tm^{170}. Each point represents 5 animals.

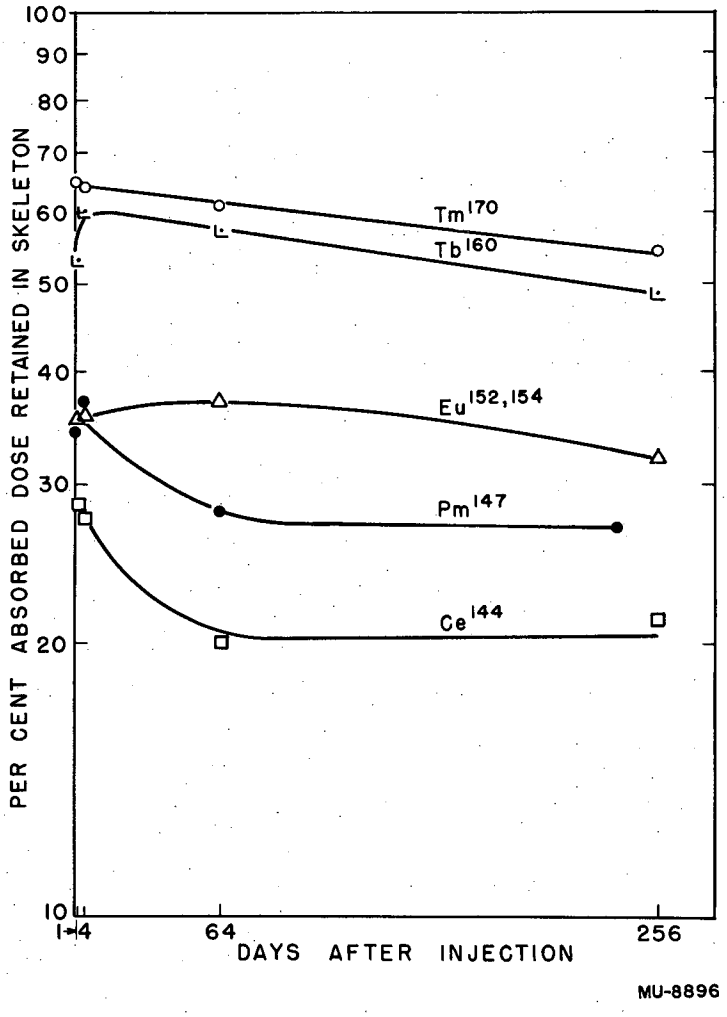

Fig. 4. The skeletal retention of Ce^{144}, Pm^{147}, $Eu^{152,154}$, Tb^{160}, and Tm^{170}. Each point represents 5 animals.

DISCUSSION

It has often occurred that an investigator has applied one of the lighter, more abundant lanthanons to a particular biological study and has stated that, the behavior of this element is typical of the entire series.[10,11] This is not altogether untrue, for although the data shown here establish definite differences in excretion patterns and deposition sites between the light and heavy lanthanons, these differences seem to be more a matter of degree than of kind. According to their behavior in the mammalian organism, the lanthanons can be divided into the same three groups familiar to modern lanthanon chemists:[8] the light lanthanons -- lanthanum through samarium; the transition group — europium, gadolinium and terbium; and the heavy lanthanons -- dysprosium through lutetium.

Radioautographs of long bones presented by Hamilton[10] and of costochondral junction shown by Asling et al.[20] demonstrated that in the normal rat Ce^{144} and Pm^{147} (light lanthanons) are deposited on the endosteal and periosteal surfaces and in the vicinity of the small blood vessels in the compact bone. Copp et al[21] compared the skeletal distribution in normal adult, normal young, and rachitic rats of the alkaline earths, Ce^{144} and Y^{88}. On the basis of chemical properties and metabolic behavior[20] Y^{88} can be grouped with the heavy lanthanons. They found that the skeletal deposition of Ce^{144} was moderately increased in normal young over normal adults, and strikingly increased in rachitic rats. The amount of Y^{88} deposited in the skeleton (about 70% of the administered dose) was unaffected by either rapid skeletal growth or rickets. Radioautographs of rachitic bone demonstrated that both Ce^{144} and Y^{88} were deposited almost entirely superficially in the shaft and in the uncalcified osteoid matrix below the epiphysis. All these findings strongly suggest that the lanthanons have a specific affinity for the bone protein even in the absence of bone salt.

The increased skeletal deposition of the heavier members of the lanthanon series and the difference in skeletal retention curves for the light and heavy

lanthanons indicate that these two groups may be deposited somewhat differently in the skeleton. It is likely that these differences are determined by the type of strength of the chemical combination of the lanthanons with the bone protein. Ketelle and Boyd[22] have made an interesting presentation of the effect of ionic radius on the absorbability of the lanthanon ions on cation-exchange columns. They found that the sequency of relative absorbability was the exact reverse of the positions of these elements in the Periodic Table, i.e., lanthanum was the most strongly absorbed and lutetium the least, with yttrium falling between dysprosium and holmium. This is in the same order as the decrease of ionic radius, decrease of basicity, and increase in the stability of combinations with various chelating agents. It is this greater stability of the heavy lanthanon chelates that may be the basis for their greater skeletal deposition.

Gallium, which has a valence of plus three is, in many respects, chemically similar to the lanthanons. Brucer et al.[19] in extensive laboratory and clinical studies with Ga^{72} (half life 14 hours) have found that it is concentrated in bone to about the same extent as are the lighter lanthanons (25% in 24 hours). They concluded that Ga^{72} was not suitable for the therapy of cancer of the bone because of its short half life, its rapid urinary excretion, the undesirable total-body irradiation from the associated gamma rays, and the high chemical toxicity of the low-specific-activity preparations available. The heavy lanthanons might well be studied with possible therapeutic applications in mind, since they are more favorably distributed in bone (50% to 65% in 24 hours), their excretion is relatively low, many of their isotopes are associated with little or no gamma radiation, they have longer half lives, and they are readily available in preparations of quite high specific activity.

SUMMARY

The metabolism of the lanthanons has been studied in the rat on a systematic basis using tracer techniques. High-specific-activity preparations were administered orally or intramuscularly as citrate complexes.

Data are presented for the 15 lanthanons one and four days after administration and at intervals up to eight months for those isotopes with sufficiently long half-lives. In general, absorption from the parenteral injection site was relatively complete at four days. Gastrointestinal absorption of the four lanthanons administered orally was insignificant.

1. The light lanthanons (lanthanum through samarium). Deposition was primarily in the liver and skeleton, 50% and 25% of the administered dose respectively. Elimination from the liver (presumably by way of the bile duct to the gastrointestinal tract) was quite rapid with a half time of about 15 days. Two months after injection the skeleton retained about two-thirds of its initial deposition; there was no further elimination from the skeleton during the subsequent eight months.

2. The transition lanthanons (europium and gadolinium). Deposition was more nearly equal in liver and skeleton, 30% and 40% of the administered dose respectively. Excretion was both fecal and urinary.

3. The heavy lanthanons (terbium through lutetium). Deposition was mainly skeletal, 55% to 65% of the administered dose. Elimination from the skeleton was slow with a half time of approximately 2.5 years. Excretion of extraskeletal heavy lanthanon occurred within the first two weeks after injection and was almost entirely urinary.

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