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THE METABOLISM OF THE LANTHANONS IN THE RAT. II. TIME STUDIES OF THE TISSUE DEPOSITION OF INTRAVENOUSLY ADMINISTERED RADIOISOTOPES

Patricia W. Durbin, C. Willet Asling, Muriel E. Johnston, Joseph G. Hamilton, and Marilyn H. Williams

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METABOLISM OF RADIOLANTHANONS

Contents

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ABSTRACT

Tracer studies have been performed to study the fate of citrate-complexed high-specific-activity Ce^{144}, Eu^{154}, Tb^{160}, and Tm^{170} following intravenous administration. Preliminary investigations of the mode of transport of microgram amounts of these lanthanons complexed with sodium citrate are also described. At a mole ratio of 1000:1 citrate to lanthanon, the distribution is similar to that previously found following intramuscular administration. It is postulated that following the introduction of microgram amounts of lanthanon-citrate into the blood stream, the citrate complex is destroyed and the lanthanon recomplexed by one of the plasma proteins.

The distribution studies at postinjection intervals from one minute to 24 hours showed that the rate of disappearance of intravenously administered lanthanons is dependent on the rate of circulation in the target organ; the greater liver deposition of the light lanthanons, and the greater skeletal deposition of the heavy lanthanons are apparent as early as 1 min after intravenous injection; both the liver and the skeleton are capable of accumulating lanthanons against a rather large concentration gradient. The urinary excretion rate of the lanthanons is dependent on the plasma level, i.e., the kidney does not seem to be able to excrete lanthanons against a concentration gradient.

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INTRODUCTION

The deposition of intramuscularly administered high-specific-activity citrate complexes of lanthanon radioisotopes has been investigated by Durbin et al.[1] It was shown that, on the basis of their metabolic behavior, the lanthanons could be separated roughly into three groups: the light group, lanthanum through samarium, which are deposited primarily in the liver and excreted in the feces; the transition group, europium and gadolinium, which are deposited approximately equally in liver and skeleton; and the heavy lanthanons, terbium through lutetium, which are deposited almost entirely in the skeleton and excreted largely in the urine.

Short-term studies (one and four days) were presented for radioisotopes of all 15 lanthanons. In all cases, extraskeletal lanthanon is quite rapidly excreted, with a half time of about 15 days. Regardless of the amount of any individual lanthanon initially deposited in the skeleton, elimination from this site occurs very slowly, with a half time of 2.5 years or more. Long-term data were presented for Ce^{144}, Pm^{147}, Eu^{154}, Tb^{160}, and Tm^{170}, because their radioactive half lives are sufficiently long to permit investigations of several months' duration.

Current interest in the chemistry of the lanthanons and the possible therapeutic applications of their radioisotopes provided the impetus for further study of the interactions of the lanthanons with biological systems. It is hoped that the experiments discussed here will provide some background for investigation of the interesting differences in the metabolic behavior of the light and heavy lanthanons.

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[1] P. W. Durbin, M. H. Williams, M. Gee, R. H. Newman, and J. G. Hamilton "The Metabolism of the Lanthanons in the Rat," University of California Radiation Laboratory Report No. UCRL-3066, July, 1955.

DISTRIBUTION OF INTRAVENOUSLY ADMINISTERED CERIUM-144, EUROPIUM-154, TERBIUM-160, AND THULIUM-170 PRELIMINARY INVESTIGATION

In the past, serious questions have been raised regarding the advisability of intravenous administration of trivalent cations (the lanthanons, gallium, and yttrium), because these elements tend to form insoluble nucleic acid complexes and insoluble phosphates, carbonates, and hydroxides at the pH of the animal body.[2, 3, 4] Gofman[5] has shown that the size of colloidal particles can be controlled by varying the mole ratio of complexing agent to trivalent metal ion. At ratios greater than 3:1, solutions are clear and show no Tyndall effect. In the pilot study described in the next paragraph, the isotopes were prepared with sufficient sodium citrate to obtain a mole ratio of 1000 to 1 (1 mg sodium citrate per microgram of lanthanon). It was expected that at pH = 7 the use of such a large mole ratio of complexing agent to lanthanon carrier would prevent the formation of aggregates of larger than crystalloidal dimensions.

In order to insure that the results of the experiments described here would be entirely comparable to the intramuscular studies previously reported, one-day tracer studies were conducted with intravenously administered long-lived radioisotopes of the four lanthanons: cerium, europium, terbium, and thulium. These four lanthanons were considered representative of the series, and all the studies in this paper are restricted to them.

Methods

Groups of five female Sprague-Dawley rats, approximately three months old, each received one of the following intravenous injections in a volume of

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[2] T. Cassperson, E. Hammarsten, and H. Hammarsten, "Interactions of Proteins and Nucleic Acid," Trans. Farady Soc. 31, 367 (1935).

[3] R. C. Vickery, "Chemistry of the Lanthanons," Butterworth's Scien. Publ., London (1953).

[4] H. D. Bruner, B. M. Cooper, and D. J. Rehbock, "A Study of Gallium. IV. Toxicity of Gallium Citrate in Dogs and Rats," Radiology 61, 550 (1953).

[5] J. W. Gofman, "Studies with Colloids Containing Radioisotopes of Yttrium, Zirconium, Columbium, and Lanthanum. I. The Chemical Principles and Methods Involved in Preparation of Colloids of Yttrium, Zirconium, Columbium, and Lanthanum," J. Lab. Clin. Med. 34, 297 (1949).

0.2 ml into the external jugular vein: 10.5 μc of carrier-free Ce^{144} plus 1 mg of sodium citrate; 1.25 μc of Eu^{154} plus 4.5 μg of carrier europium and 4.5 mg of sodium citrate; 5 μc of Tb^{160} plus 0.43 μg of terbium carrier and 0.43 mg of sodium citrate; 10 μc of Tm^{170} plus 0.12 μg of thulium carrier and 0.19 mg of sodium citrate. The biological techniques and the counting procedures employed have previously been described.[1]

Results and Discussion

The excretion pattern and tissue distribution 24 hours after intravenous administration of citrate complexes of these four radiolanthanons, as shown in Table I, were nearly identical with those found in the earlier intramuscular studies. Dobson et al.[6] have shown that intravenously administered colloids of moderate to small size remain in the blood stream for relatively long periods (half times from 30 to 80 min) but that the colloid is retained quantitatively in the plasma until cleared by the liver or bone marrow. Laszlo and his co-workers[7] compared the distribution of La^{140} in mice after intravenous injection as $LaCl_3$ with its distribution after administration as the stable ethylenediamine tetraacetic acid complex, La-EDTA. The 24-hour distribution in the mouse closely resembles that reported by Dobson's group for "intermediate size" colloidal yttrium-hydroxycitrate. La^{140} as the stable La-EDTA was more evenly distributed; in contrast to the apparently immobilized $LaCl_3$, the preparation was fairly rapidly excreted--primarily in the urine.

Carrier-free Ce^{144} and high-specific-activity Eu^{154}, Tb^{160}, and Tm^{170} administered to rats in the form of citrate complexes in the presence of a large excess of citrate do not resemble either the colloidlike $LaCl_3$ or the "tight" La-EDTA complex. Direct comparison of Ce^{144} with La^{140} seems permissible because of the distributional similarity of these two neighboring lanthanons when administered intramuscularly. Admittedly, the mass of lanthanons administered in the experiments described here is a great deal smaller than was used in the studies by Laszlo et al.[7]

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[6] E. L. Dobson, J. W. Gofman, H. B. Jones, L. S. Kelly, and L. A. Walker, "Studies with Colloids Containing Radioisotopes of Yttrium, Zirconium, Columbium, and Lanthanum. II. The Controlled Selective Localization of Radioisotopes of Yttrium, Zirconium, and Columbium in the Bone Marrow, Liver, and Spleen," J. Lab. Clin. Med. 34, 305 (1949)

[7] D. Laszlo, D. M. Ekstein, R. Lewin, and K. G. Stern, "Biological Studies on Stable and Radioactive Rare Earth Compounds. I. On the Distribution of Lanthanum in the Mammalian Organism," J. Natl. Cancer Inst. 13, 559, (1952).

Table I

The deposition of citrate complexes of Ce^{144}, Eu^{154}, Tb^{160}, and Tm^{170} in the rat 24 hours after intravenous or intramuscular administration. Values are expressed in percent of administered intravenous dose or percent of absorbed intramuscular dose in whole organs and are corrected for deviation of recovery from 100%. (Sizes of groups and dosages of radioactivity, carrier, and sodium citrate are given in the text.)

Tissue	Ce^{144}		Eu^{154}		Tb^{160}		Tm^{170}	
	IM	IV	IM	IV	IM	IV	IM	IV
Spleen	0.08	0.17	0.15	0.15	0.12	0.09	0.12	0.11
Liver	53.7	63.2	33.3	41.7	15.8	11.0	3.40	4.37
Skeleton	28.5	20.3	35.3	24.8	53.3	58.3	64.8	66.5
Muscle	1.56	1.76	3.09	3.76	2.91	1.33	1.96	1.45
Balance	8.73	8.81	14.5	15.3	11.4	12.2	7.54	9.42
Urine	5.77	3.09	11.0	10.6	11.5	13.8	16.9	13.0
Feces	1.66	2.67	2.70	3.67	4.95	3.32	5.28	5.15

THE TRANSPORT OF MICROGRAM AMOUNTS OF THE LANTHANONS IN THE BLOOD STREAM

It is of interest to investigate how microgram amounts of lanthanons are transported in the blood.

Methods

Small volumes (0.1 ml) of the citrated lanthanon preparations described above were mixed with 2-ml portions of heparinized rat plasma. After thorough mixing, the solutions were placed in cellophane bags (sausage casing) and dialyzed for two hours against 250 ml of isotonic saline. The external saline was assayed. The proteins were separated by "salting out" the globulin-fibrinogen and albumin fractions with half-saturated and saturated $(NH_4)_2SO_4$, respectively. The proteins in a second set of plasma-lanthanon mixtures were separated, without preliminary dialysis, by salting out the globulin-fibrinogen with saturated NaCl and then precipitating the albumin with dilute acid and heat. A third set of plasma-lanthanon mixtures were dialyzed against several changes of deionized water (2 liters in all) for five days to precipitate the water-insoluble fibrinogen and euglobulin. Because of the large volume, the radioactivity in the dialyzates was estimated by difference. The lighter water-soluble globulins and albumin were coagulated with acid and heat as above.

Because of the high mass content of the samples obtained in the salting-out procedures, all samples and the standard aliquots were placed in tin bottle caps, diluted to a standard 10 ml with water, and assayed* with a NaI-Tl scintillating crystal gamma counter connected to a Tracerlab Autoscaler as described by Jenkins.[8]

Results and Discussion

The percentages of the three radiolanthanons in the dialyzates, protein fractions, and protein-free fractions are shown in Table II. The total recoverable activity for each fractionation procedure was 90% or better; the results of individual determinations, however, should be viewed with caution.

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* The weakest gamma-ray activity was that of Tm^{170}, a total of 250 gamma counts per sec per μc. The method of assay is capable of detecting 1.0 c/s,[9] or 0.4% of the Tm^{170} used. This is a measure of the accuracy of the method.

[8] K. D. Jenkins, "Scintillating Crystal Gamma Counter," University of California Radiation Laboratory Report No. UCRL-1766, May, 1952.

[9] R. P. Ghelardi and C. H. Brown, "Electronic Instruments for Use with Geiger-Muller Tubes," Nucleonics 1, 50 (1947).

Table II

Distribution of Ce^{144}, Eu^{154}, and Tm^{170} in the various fractions of rat plasma following in vitro incubation of plasma with lanthanon citrate. The results of three different methods of protein fractionation are shown. (See Text).

	Percent Lanthanon in Sample		
Ce^{144} ($<10^{-10}$)*	Dialysis against 0.9% saline; "salting out" with $(NH_4)_2SO_4$	"Salting out" with NaCl	Dialysis against deionized water
Dialyzate	8	-	1
Globulin	18	75	97
Albumin	5	17.5	2
Protein-free filtrate	67	7.5	1
Eu^{154} (7.1×10^{-9})*			
Dialyzate	15	-	44
Globulin	18.5	68	42
Albumin	8	12	8
Protein-free filtrate	58.5	20	6
Tm^{170} (2.1×10^{-10})*			
Dialyzate	4	-	1
Globulin	39	83	94
Albumin	5	15	5
Protein-free filtrate	52	2	1

* Moles of carrier per milliliter of plasma.

There was no unusual turbidity of the plasma on the addition of the lanthanon-citrate solutions. From inspection of the data for the deionization procedure, it appears that the lanthanon-citrate complex is unstable with respect to the formation of a lanthanon-protein complex even in the presence of a large excess of citrate. The complexing protein is presumably one of the larger globulins, or possibly fibrinogen. The association of more than 90% of the Ce^{144} and Tm^{170} with the water-insoluble protein after five days of dialysis provides a measure of the stability of this complex. In contrast, nearly half of the initial Eu^{154} activity was removed by dialysis. The mass of carrier europium, 2.75 μg, was 40 times as great as that of the thulium carrier, 0.06 μg, and more than 450 times as great as that of the carrier-free Ce^{144}. It seems that the proteins in 1 ml of rat plasma can complex 1.5 μg of europium (0.01 μmole of lanthanon). The passage of Eu^{154} through the cellophane membrane provides evidence for the small size of the lanthanon-citrate entity.

Very little of either the Ce^{144} or Tm^{170} was transported away from the plasma via the membrane after two hours of dialysis against isotonic saline. The presence of more than 50% of all three radiolanthanons in the protein-free fraction after fractionation of the proteins with ammonium sulfate is most disturbing, unless it is assumed that the salting-out procedure alters the lanthanon-binding capacity in some manner.

If the total blood volume is 7% of the body weight, and the hematocrit is 0.43, the total plasma volume of a 250-g rat is 10 ml--a volume capable of complexing approximately 15 μg (0.10 μmole) of lanthanon.

The following mechanism is postulated for the fate of very small amounts of lanthanon-citrate in the blood stream of the intact animal:

$$\text{Lanthanon-citrate} + \text{plasma protein} \longrightarrow \text{lanthanon-plasma protein} + \text{citrate}.$$

Bruner et al.[4] investigated the acute toxicity of intravenously administered gallium citrate, $Ga(citrate)_3$, in rats. They found that its toxicity could be greatly reduced by the simultaneous injection of stoichiometric quantities of calcium gluconate. They concluded that the gallium-citrate complex was destroyed immediately upon entry into the blood stream and that the toxic entity was the free citrate. By analogy, administration of large amounts of trivalent lanthanon in the form of a citrate complex (in excess of the lanthanon-complexing capacity of the plasma protein) introduces the possibility of the formation of colloidal aggregates of an uncertain nature.

TIME STUDIES OF THE DISAPPEARANCE OF MICROGRAM AMOUNTS OF THE LANTHANONS FROM THE PLASMA AND OF DEPOSITION IN THE TARGET ORGANS

In these time studies, experimental conditions, radioisotope dosages, and the amounts of carrier and sodium citrate were the same as in the pilot intravenous study.

Methods

Lots of 45 to 50 rats (mean body weight 235 g) received intravenous injections of one of the four isotopes tested. The volume of solution injected was 0.2 ml and was given in no more than 2 sec. For the shorter time intervals, the injections were timed with a stopwatch. The 4-hour Ce^{144} and Tm^{170} rats were housed individually in metabolism cages, and excretions were collected 30, 60, 90, 120, and 240 min after injection. The animals were sacrificed in groups of five or six at intervals of 1, 3, 5, 15, 30, 60, 90, 120, and 240 min postinjection, with the one-day pilot study serving as a 1440-min interval. Under ether anesthesia, a blood sample was drawn from the inferior vena cava in a 20-sec time period into a heparinized syringe. Immediately after the blood sample was taken, the animals were sacrificed by decapitation, and the liver, bone, and (in certain cases) muscle of the right hind leg were taken for assay. The blood samples were transferred to heavy-walled 12-ml centrifuge cones and centrifuged for 30 min in an International clinical centrifuge. Plasma samples of measured volume were withdrawn and assayed. Samples of whole blood were occasionally taken prior to centrifugation to determine the lanthanon concentration of the red blood cells.

The percent of administered isotope in the total plasma was calculated for each time interval as follows:

$$\text{isotope in total plasma} = \frac{\%/\text{ml isotope} \times \text{g body wt} \times \text{ml plasma/g body wt}}{\text{hematocrit}}$$

The hematocrit was determined on 41 rats with a mean of 0.43 ± 0.004. The blood volume of 6.7% body weight was used in these calculations.

The total skeletal isotope was calculated as follows:

$$\text{total skeletal isotope} = \%/\text{g leg bones} \times \text{g body wt} \times \text{g bone/g body wt.}$$

The body weight and the percent lanthanon per gram of wet bone were determined by direct measurement. The weight of bone per gram of body weight

was based on 36.6 ± 0.7%, a previous determination of the ash content of adult rat bone[10] and the ash weights of the entire skeletons of 30 adult rats. On this basis, the skeleton of the adult female Sprague-Dawley rat constitutes 9.0 ± 0.08% of the total body weight. The total weight of muscle was taken as 45% of the body weight.[8]

Results and Discussion

Figures 1, 2, 3 and 4 are the semilog plots of the total plasma lanthanon (with standard deviations) as a function of time. The small size of the standard deviations is a good indication of the over-all reliability of the data.

Because of the number and complexity of the processes involved, curves of this nature are at best difficult to interpret. Graphic analysis of the components of curves of continually changing slope is also subject to some uncertainty. Some interpretation is possible, and some general comments may be made without absolute dependence on the numerical half-time values.

These curves appear to consist of three and possibly four components for Eu^{154} and Tb^{160}. The half times of these components are shown in the figures. The slopes of all the components are steepest for Ce^{144}, the lightest lanthanon studied, and flattest for Tm^{170}, the heaviest. The half time of the initial component, varying from 1 min for Ce^{144} to 3 min for Tm^{170}, probably represents the period of diffusion of the isotopes from the blood stream into the extracellular fluid and highly vascularized tissues. The second component (half-time Ce^{144}, 17 min; Tm^{170}, 66 min) probably represents the period of deposition in the target organs, urinary excretion, and re-entry into the blood stream from the other tissues. The third component (half-time Ce^{144}, 130 min; Tm^{170}, 220 min) accounts for the disappearance of less than 10% of the total Tm^{170} and less than 1% of the totals of the other three lanthanons. This phase probably represents a combination of the re-entry into the circulation from poorly vascularized tissues, and the other above-cited processes, proceeding at slower rates. A discussion of this material is developed further in the subsequent section.

Figures 5, 6, 7, and 8 show the lanthanon content of the three compartments--plasma, skeleton, and liver--and the total isotope that can be accounted for in them at the time intervals tested.

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[10] P. W. Durbin "The Metabolism of Fluorine in the Rat Using F^{18} as a Tracer," J. Dental Research 33, 789 (1954).

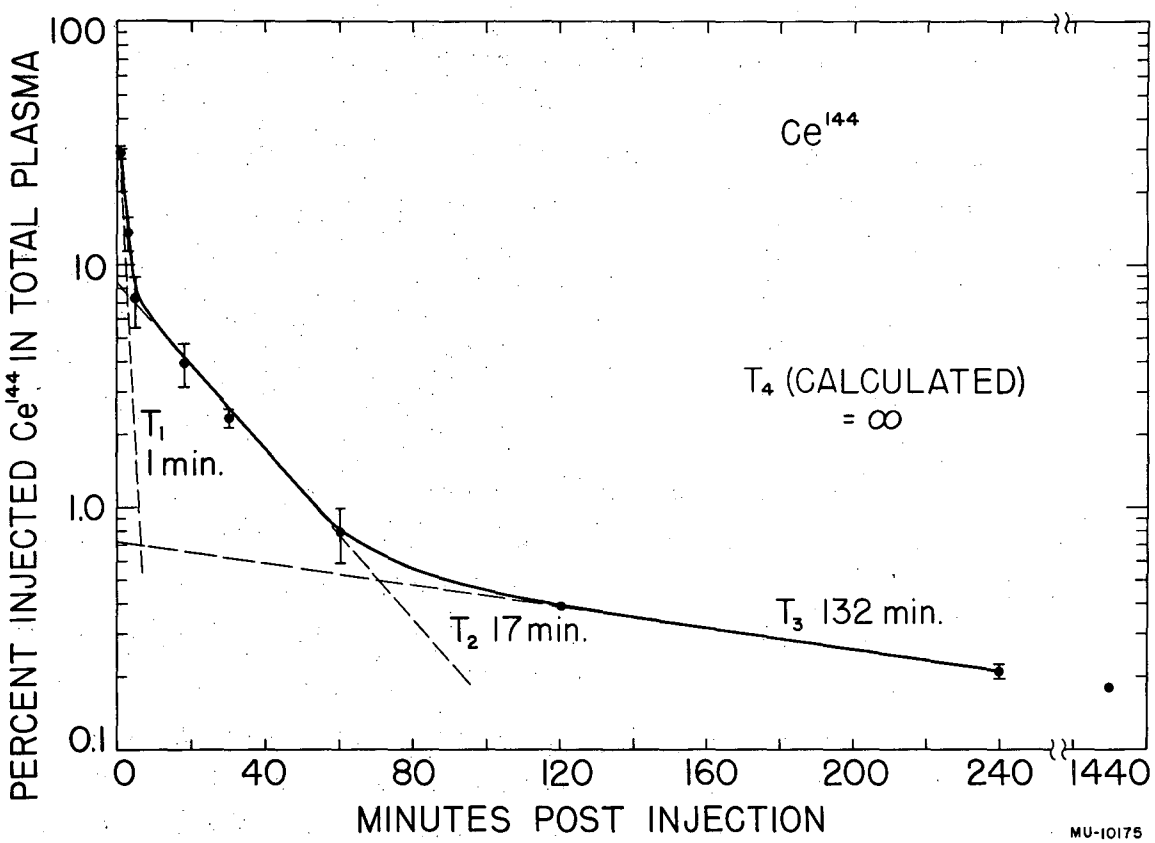

Fig. 1. The disappearance of carrier-free Ce^{144}, complexed with sodium citrate, from the plasma of the rat following intravenous injection. Each point is the mean for five rats, with the standard deviation. Calculation of total plasma volume is shown in the text.

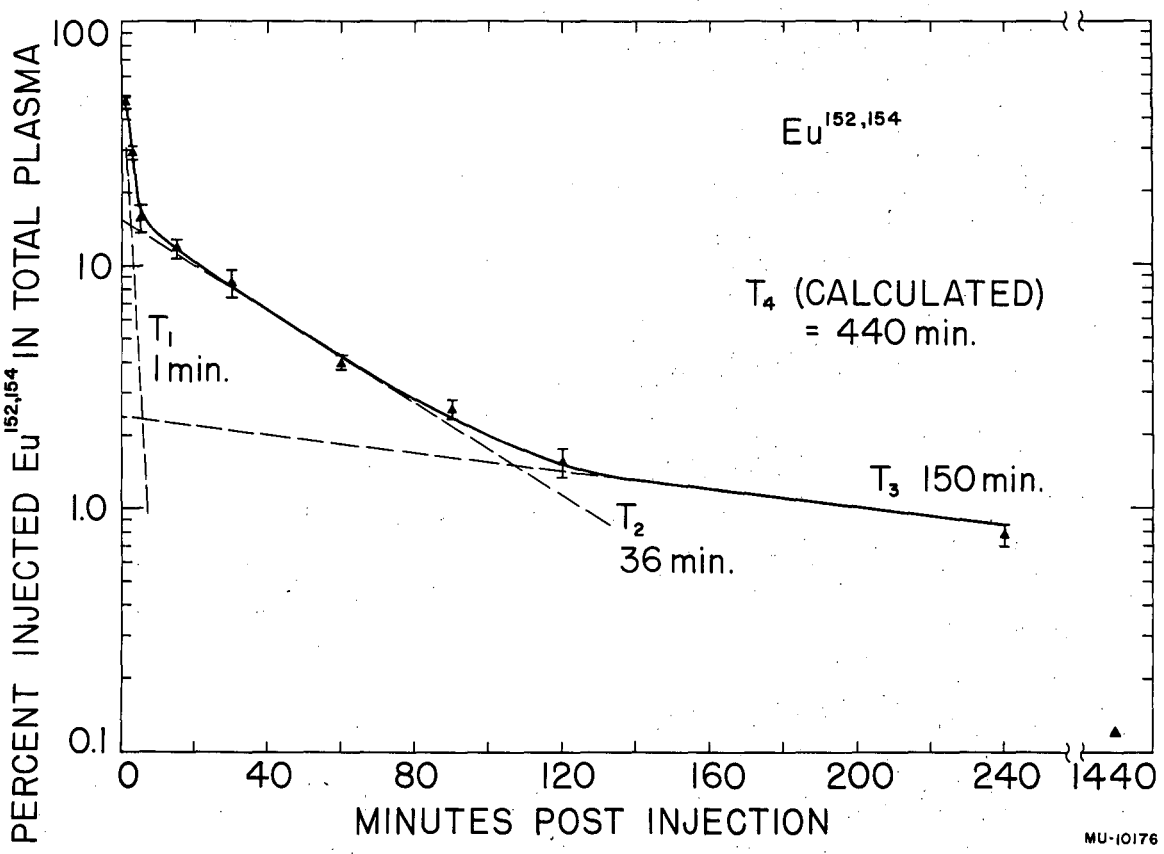

Fig. 2. The disappearance of 4.5 μg of europium tagged with Eu^{154} and complexed with sodium citrate from the plasma of the rat following intravenous injection. Each point is the mean for five rats, with the standard deviation. Calculation of total plasma volume is shown in the text.

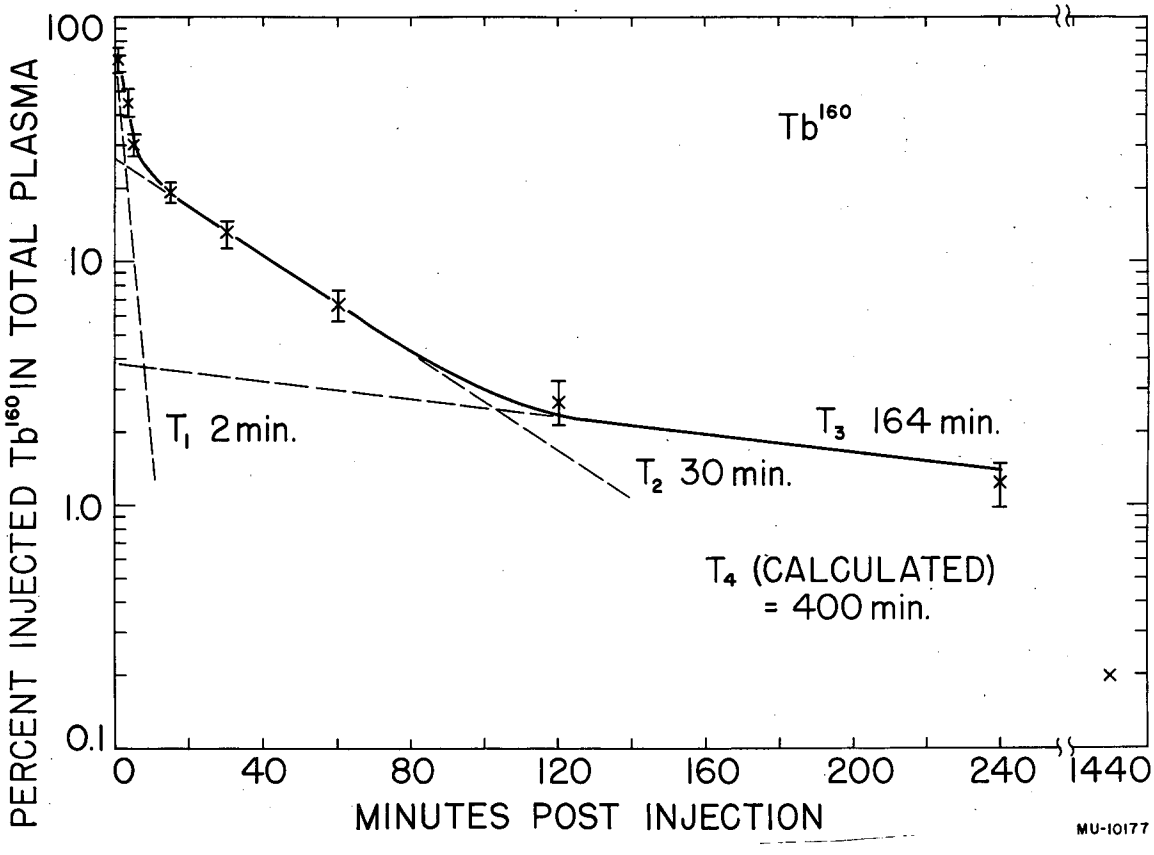

Fig. 3. The disappearance of 0.43 μg terbium tagged with Tb^{160} and complexed with sodium citrate from the plasma of the rat following intravenous injection. Each point is the mean for five rats, with the standard deviation. Calculation of total plasma volume is shown in the text.

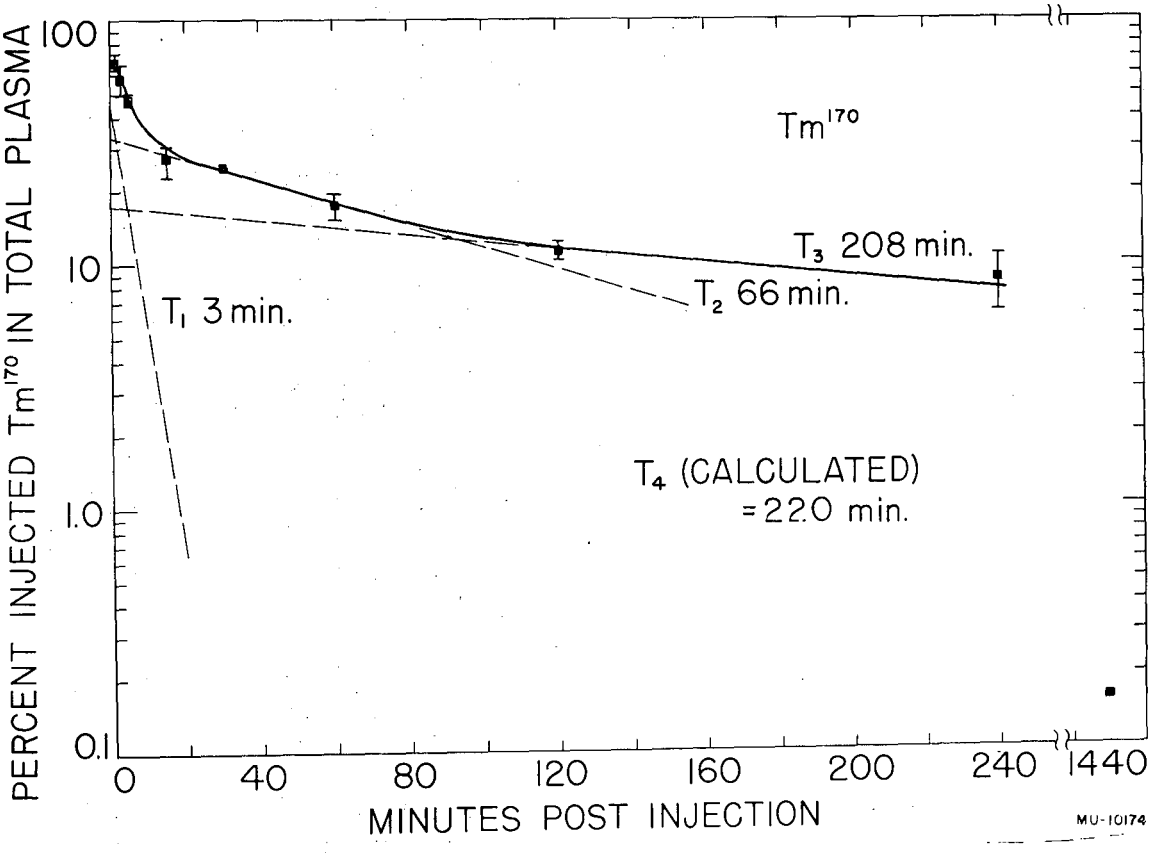

Fig. 4. The disappearance of 0.12 μg thulium tagged with Tm^{170} and complexed with sodium citrate from the plasma of the rat following intravenous injection. Each point is the mean for five rats, with the standard deviation. Calculation of total plasma volume is shown in the text.

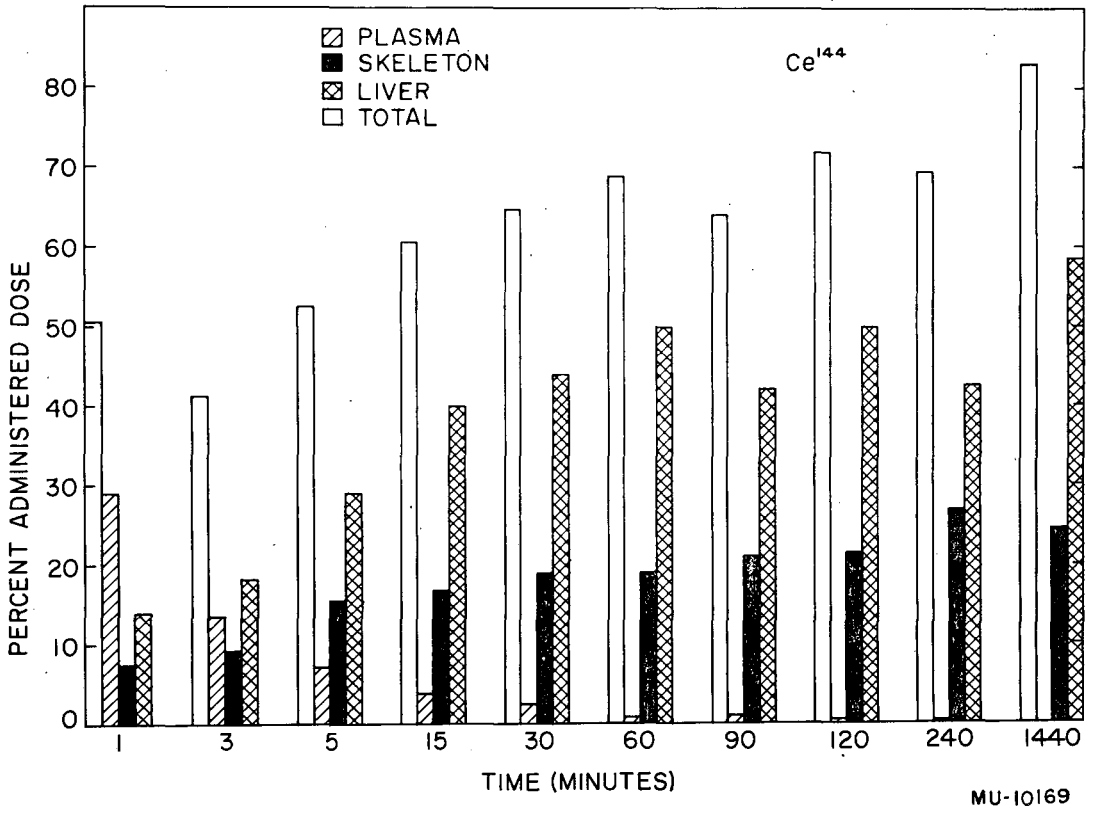

Fig. 5. The change with time in the distribution of Ce^{144} in skeleton, liver, and total plasma, and the total isotope in these three tissues. Each bar is the mean for five rats. Calculation of total plasma volume and skeletal weight is described in the text.

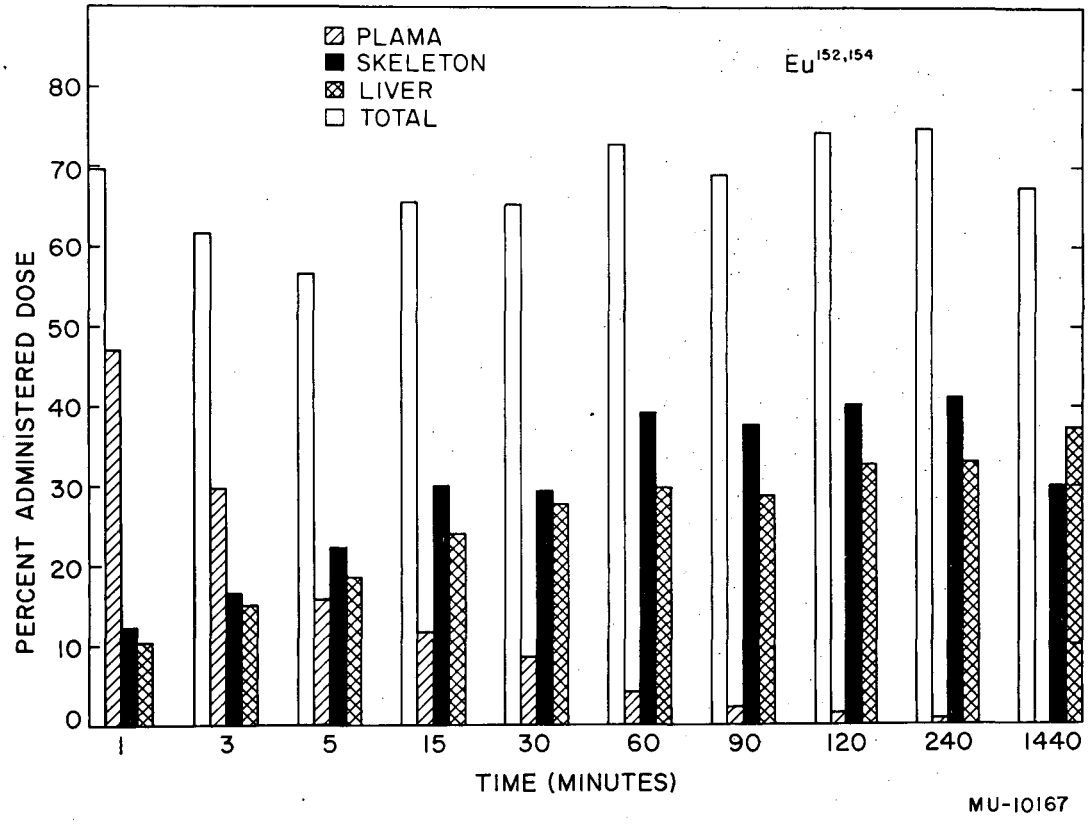

Fig. 6. The change with time in the distribution of Eu^{154} in skeleton, liver, and total plasma, and the total isotope in these three tissues. Each bar is the mean for five rats. Calculation of total plasma volume and skeletal weight is described in the text.

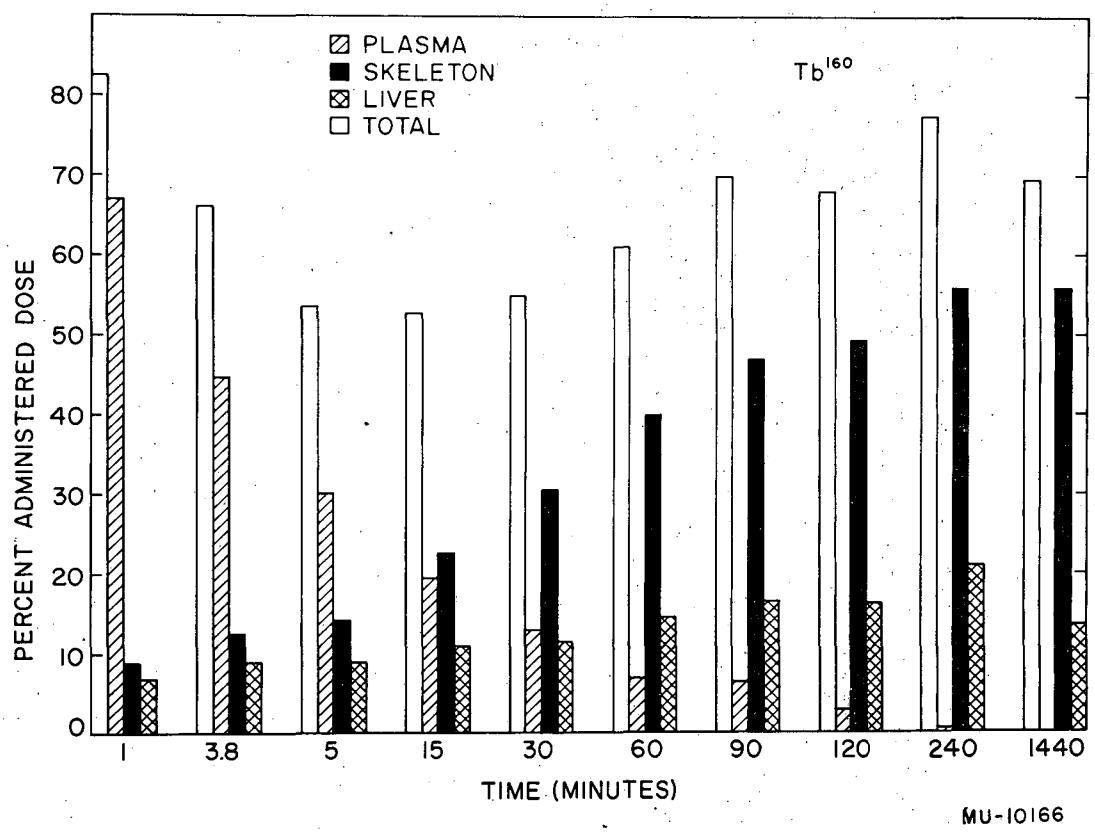

Fig. 7. The change with time in the distribution of Tb^{160} in skeleton, liver, and total plasma, and the total isotope in these three tissues. Each bar is the mean for five rats. Calculation of total plasma volume and skeletal weight is described in the text.

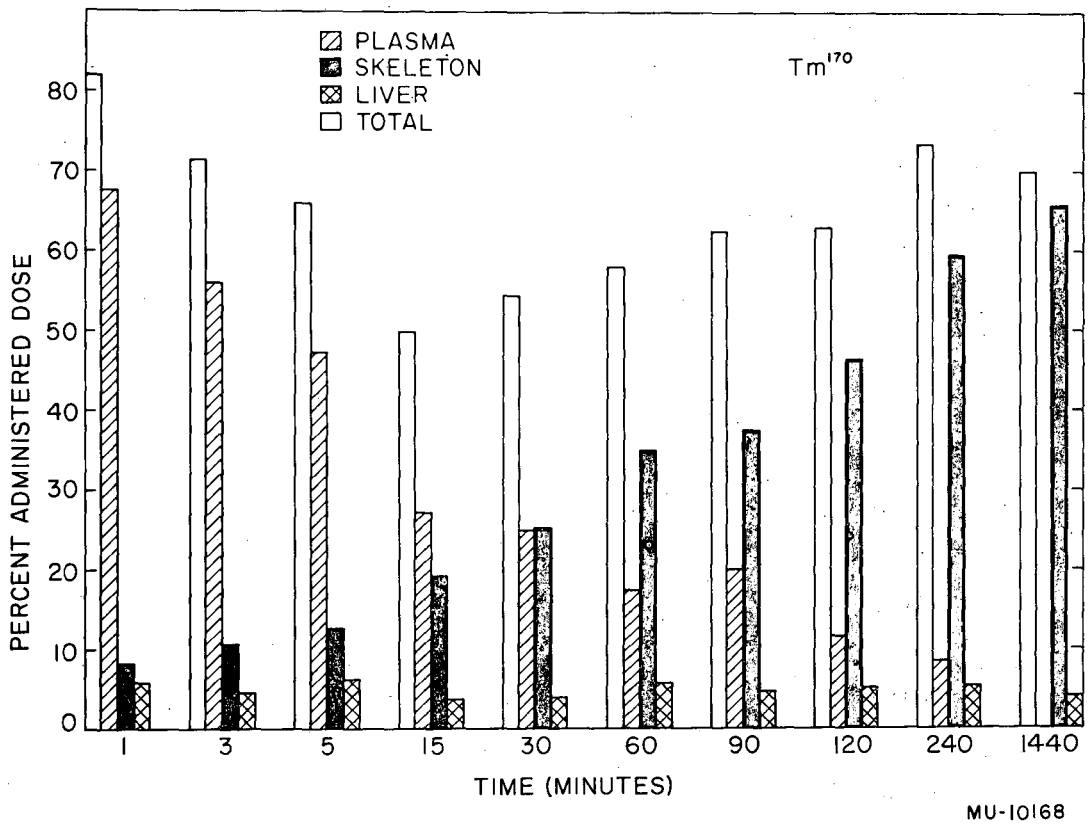

Fig. 8. The change with time in the distribution of Tm^{170} in skeleton, liver, and total plasma, and the total isotope in these three tissues. Each bar is the mean for five rats. Calculation of total plasma volume and skeletal weight is described in the text.

Ce^{144}: One minute after injection, the plasma, liver, and skeleton account for 50% of the administered Ce^{144} and only 41% at 3 min. During the first 5 min the Ce^{144} disappears from the plasma almost completely, but fails to appear in the target organs. At 3 min skeletal muscle contains 16.6% of the injected Ce^{144} at a concentration of 0.14% per g.

The second component of the Ce^{144} plasma-time curve extends from the 5th to the 60th min after injection. By the end of this period the liver and skeleton have accumulated almost 90% of their 24-hour Ce^{144} contents. The drop in plasma concentration from 7% at 5 min to 0.1% at 60 min is not by itself sufficient to account for the marked rise in liver and skeletal Ce^{144}. The fivefold decrease in muscle concentration from 0.14%/g at 3 min to 0.03%/g at 90 min, and the simultaneous thirteenfold decrease in the plasma level, indicate that Ce^{144} is diffusing back into the plasma from the tissue. A parallel decrease would have been observed if the Ce^{144} muscle content were due merely to trapped blood.

The rate of urinary excretion dropped from 7.66% per hour during the first hour to 0.66% per hour during the 2nd to 4th hours. Thus, it appears that the urinary excretion rate is dependent on the plasma level, and that the kidney does not possess any special mechanism for excreting Ce^{144} against a concentration gradient.

It is most noteworthy that both the liver and the skeleton are capable of accumulating Ce^{144} against a rather large concentration gradient.

Eu^{154}: In general, most of the findings for Ce^{144} apply to Eu^{154}. The processes involved appear to be similar but occur at a slower rate. The second component of the plasma-disappearance curve (deposition phase) extends over 120 min, twice as long as that for Ce^{144}. One minute after injection, the plasma, liver, and skeleton account for 70% of the total Eu^{154}. At 5 min, only 56% of the Eu^{154} can be accounted for in these tissues.

The pattern of nearly equal deposition of Eu^{154} in liver and skeleton is apparent as early as 1 min after administration. The liver accumulation is 90% complete after 30 min; the skeletal deposition is complete at 60 min. During the succeeding 21 hours there seems to be some recirculation and transfer of Eu^{154} from the skeleton to the liver.

Tb^{160}: The half times of the components of the plasma-disappearance curves of Eu^{154} and Tb^{160} are almost identical. Comparing Figs. 6 and 7, we see, however, some differences in the distributional patterns of these two closely related lanthanons. One minute after injection 67% of the injected

Tb^{160} remains in the plasma, as compared to 47% of the Eu^{154}. The minimum Tb^{160} (53%), which can be accounted for in plasma, liver, and skeleton, appears 15 min after injection in contrast to 5 min for Eu^{154} and 3 min for Ce^{144}. The trend toward greater skeletal deposition is established at 1 min. Liver accumulation is nearly complete by 60 min, skeletal deposition, by 240 min. From the 4th to the 24th hour 8% of the liver Tb^{160} is released into the circulation but is apparently not accumulated by the skeleton or excreted.

Tm^{170}: The data obtained for Tm^{170}, the heaviest lanthanon studied, most closely resemble those for Tb^{160}. The 1-min plasma levels are similar, 70% of the administered dose. Initially the plasma, liver, and skeleton account for 82% of the administered Tm^{170}. As for Tb^{160}, this total declines to 50% at 15 min, and rises steadily to between 70 and 80% at 4 hours. The liver accumulation (6.5%) is complete, however, as early as 1 min after injection, and there seems to be very little movement of Tm^{170} into and out of this organ in the ensuing 24 hours. The very slow decline in the plasma level, slower than that of Tb^{160}, is very likely a reflection of the relatively slow circulation in bone.

The urinary excretion rate of Tm^{170} remains at a fairly high level during the first 4 hours (0 to 1 hour, 3.26%; 1 to 2 hours, 5.42%; and 2 to 4 hours, 2.31%). It should be noted that the plasma still contains 8.5% of the administered Tm^{170} after 4 hours.

Some information regarding the diffusibility of Ce^{144} and Tm^{170} is shown in Table III. The ratios R were calculated for muscle and red blood cells by using the relationship,

$$R = \frac{\%/\text{ml plasma}}{\%/\text{g tissue}}.$$

The change of the ratios with time, and the magnitude of these ratios, indicate that Ce^{144} is more readily diffusible than is Tm^{170}. It should be pointed out that the method employed in the determination of the red blood cell concentration--measurement of the difference in concentrations of plasma and whole blood--does not differentiate between radioactivity inside of or merely adsorbed onto the surface of the red cells. The blood trapped in the muscle introduces a small but constant error. The ratios of plasma to muscle would seem to be the more reliable.

Table III

The ratios of the concentration of Ce^{144} and Tm^{170} in plasma to their concentrations in muscle and red blood cells

	Ce^{144}			Tm^{170}		
Minutes after injection	%/ml plasma	R* Muscle	R* Red Cells	%/ml plasma	R* Muscle	R* Red Cells
3	1.44	10	3	5.83	30	10
90	0.11	4	3	2.00	20	4
240	0.02	1	-	0.88	10	-

* $R = \frac{\%/\text{ml plasma}}{\%/\text{g tissue}}$

The distribution studies at postinjection intervals from one minute to 24 hours showed the rate of disappearance of intravenously administered lanthanons is dependent on the rate of circulation in the target organ; the greater liver deposition of the light lanthanons, and the greater skeletal deposition of the heavy lanthanons, are apparent as early as 1 min after intravenous injection; both the liver and the skeleton are capable of accumulating lanthanons against a rather large concentration gradient. The urinary excretion rate of the lanthanons is dependent on the plasma level, i.e., the kidney does not seem to be able to excrete lanthanons against a concentration gradient.

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