unusual side effects of this halogenated corticosteroid in the monkey is in marked contrast with effects noted in the rabbit.

*Discussion.* Byrnes and Shipley(2) reported a lack of progestational activity for 11 beta-hydroxyprogesterone at a dose of 5 mg in the Corner-Allen assay. It is evident that the introduction of either a chlorine or a fluorine atom in the 9 alpha position imparts progestational activity in hydrocortisone and 11-beta hydroxyprogesterone both of which were progestationally inactive at comparable doses.† Junckmann(3) has reported that 17 alpha-hydroxyprogesterone, slightly active as a progestational compound, becomes active upon esterification. Huggins and Jensen(4) have recently described the potent depressant activity of 9 alpha-fluorohydrocortisone and 9 alpha-11-beta-hydroxyprogesterone on estrone-induced uterine growth in the hypophysectomized rat. Hydrocortisone and cortisone were considered to be weak inhibitors in the same test.

*Summary.* Progestational activity of 9 alpha-chlorohydrocortisone acetate, 9 alpha-fluorohydrocortisone acetate and 9 alpha-fluoro-11-beta-hydroxyprogesterone has been demonstrated using progestational proliferation of the rabbit endometrium (Clauberg test) as index of activity. Hydrocortisone acetate and cortisone acetate show a lack of activity in the same test. Progestational activity of 9 alpha-fluorohydrocortisone is further demonstrated by prevention of estrogen withdrawal bleeding and characteristic histological changes in the endometrium of the ovariectomized rhesus monkey pre-treated with estrogen.

† However, 11-beta-hydroxy progesterone has one-eighth the activity of 9 alpha-fluoro-11-beta-hydroxy progesterone in the Clauberg Test.

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## Metabolism of the Lanthanons in the Rat.* (22175)

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For many years the behavior of the lanthanons in biological systems was regarded as a scientific curiosity. The name "lanthanon" has been suggested(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. 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. This phenomenon

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

† 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.

has been called the "lanthanide contraction." (2) 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 complete review of the history, occurrence, applications, and chemistry of the lanthanons has been published by Vickery(3). 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 (4). In many biological specimens traces of cerium and lanthanum were found. A survey of the experimental exposure of living systems to lanthanons 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 gastrointestinal tract. Under the auspices of the Manhattan Project, tracer studies were performed in this laboratory(5,6) 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.

The studies reported here were designed to correct some of the defects of the earlier work and to expand the data to include all the lanthanons on an 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.

*Methods. 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(7). 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 $(n,\gamma)$§ reaction. Weighed portions of the oxides were diluted in 6 *N* HCl. Aliquots were transferred to clean quartz ampules. 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. After bombardment, the materials were flown back to this laboratory. The ampules were placed in heavy plastic envelopes and crushed. The crushed ampule was transferred to a beaker and washed several times with 6 *N* HCl or 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 was 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

‡ 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, $\frac{\text{N active}}{\text{N total}} = 1$.

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

TABLE I. Summary of Time Intervals Investigated and the Amounts of Rare Earth, and Complexing Agent Administered per Rat.

| Isotope | Time interval (days) | Dose ($\mu$c) | Carrier ($\mu$g) | Sodium citrate (mg) |
|---|---|---|---|---|
| $La^{140}$ | 1, 4 | 29, 58* | 1.2, 2.4 | 6, 12 |
| $Ce^{144}$ | 1, 4, 64, 256 | 20–40† | c.f.‡ | 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 |

* One- and four-day dosages respectively.
† Dosages graded for time intervals involved.
‡ c.f. = carrier-free.

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 Hollander *et al.*(8).

*Biological Procedures.* The animals used in these tracer studies were female Sprague-Dawley rats that were from four to six 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 anesthesia, 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 I. Moderate amounts of high-specific activity preparations were used in order to avoid uncertainties introduced by either radiotoxicity or chemical toxicity. The largest amount of radioactivity administered, 0.5 $\mu$c/g of body weight, was felt to be well below radiotoxic level(9). 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 at least 5 rats were injected for each time interval.‖ 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 *N* $HNO_3$. Following administration of isotope, groups of 2 or 3 animals were placed in metabolism cages which were designed to provide adequate separation of urine and feces with a minimum of handling. Excretions were collected daily for the first 4 days after injection and twice weekly thereafter. In the intramuscular studies animals were sacrificed at intervals of one and 4 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 anesthesia, 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

‖ 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.

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 *N* $HNO_3$ and redrying. The soft-tissue ash in the carcass was removed from the skeleton by rinsing 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. 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 previously described(10). 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. A self-quenching Geiger-Muller counter was employed for the beta particle assays, and all samples were counted for a sufficiently long time to reduce the error of measurement to ± 5%(11).

*Preparation of Samples for Gamma Counting.* Gamma rays were present in sufficient intensity for accurate measurement of $La^{140}$, $Ce^{144}$, $Sm^{153}$, and $Yb^{175}$. 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 samples were assayed wet with a Tl-NaI scintillating crystal counter of the type described by Jenkins(12).

*Calculations.* The total amounts of radioisotopes present in blood and muscle were calculated on the basis that these two tissues

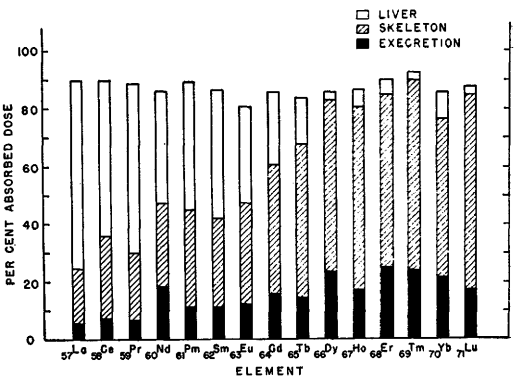


FIG. 1. Summary of the excretion, skeletal deposition, and liver deposition of the lanthanons one day after intramuscular administration. The difference between the end of each bar and 100% represents the % of each isotope in the remainder of the animal.

represent 7 and 45% of the body weight respectively. The lanthanon concentration in bone was calculated from the ash content of mature rat bone, 36.6 ± 0.7%. The amount

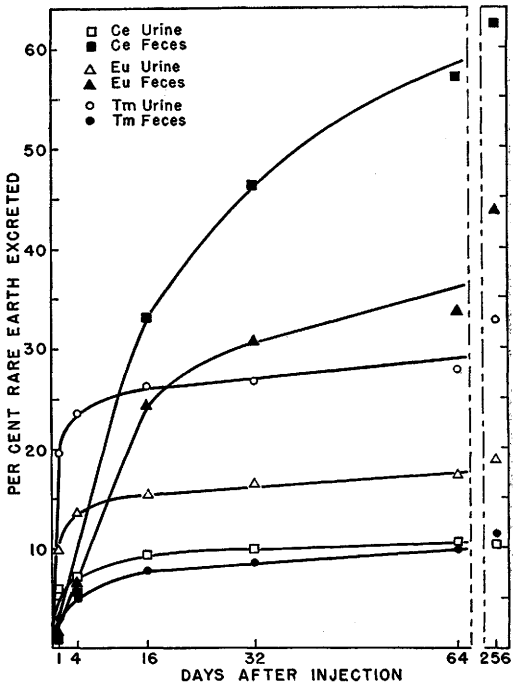


FIG. 2. The cumulative excretion of $Ce^{144}$, $Eu^{152,154}$, and $Tm^{170}$ in urine and feces. Values are corrected for deviation of recovery from 100% and are expressed as % of absorbed dose. The one-day points represent eight determinations, the four-day points six determinations, the 16-, 32- and 64-day points four determinations, and the 256-day points two determinations.

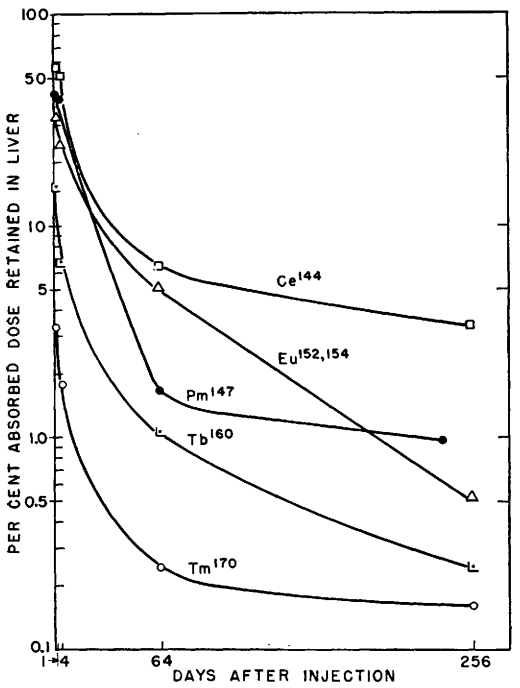


FIG. 3. The liver retention of $Ce^{144}$, $Pm^{147}$, $Eu^{152,154}$, $Tb^{160}$, and $Tm^{170}$. Each point represents five animals.

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 residual per cent 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 per cent of the absorbed dose found in the whole specimens, and are corrected for deviation of recovery from 100%.

*Results.* The trend of the results of the tracer studies with the fifteen lanthanons is represented in Fig. 1, which shows the per cent of administered dose in liver, skeleton and excreta one day after lanthanon administration. Fig. 2 shows the cumulative excretion of three representative lanthanons. The retention of five representative lanthanons in the liver and skeleton are shown in Figs. 3 and 4.

The experimental recoveries of the injected material ranged from 86% for the 256-day $Tm^{170}$ to 121% for the 4-day $Lu^{177}$. 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 4 days), were administered with 8 to 10 $\mu$g 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 the $La^{140}$ studies (22.5% unabsorbed at 4 days), the ratio of carrier to complexing agent was 0.2 $\mu$g/mg. 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

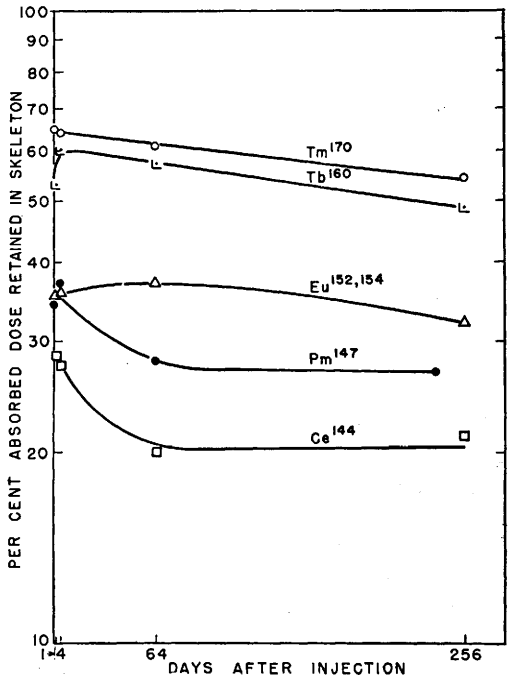


FIG. 4. The skeletal retention of $Ce^{144}$, $Pm^{147}$, $Eu^{152,154}$, $Tb^{160}$, and $Tm^{170}$. Each point represents five animals.

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.¶

*Spleen.* The concentration of the lanthanons in the spleen one day after administration was less than 0.5% per g of wet tissue. When these elements are administered by vein as halides or nitrates, high concentrations are found in the spleen as well as in other components of the reticulo-endothelial system. Laszlo *et al.*(13) concluded that they were dealing, to a large extent, with radiocolloids. Bruner *et al.*(14) in studies with radiogallium (principal valence plus three) 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; that these data represent the metabolism of these elements in non-colloidal form.

*Blood, Muscle, and Skin.* The level of these elements in the blood at one day never exceeded 0.02% per ml, and there was a steady decrease to unmeasurable levels thereafter. The initial muscle concentration of the lanthanons was the same as for blood, but declined at a somewhat slower rate. 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 diminishing 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. 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, because the contents were 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% per 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% per g. Eight months after administration the concentration in the kidney had, in all cases, decreased to low levels. There was no apparent correlation between either the 1-day or 8-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. 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 $Ce^{144}$, $Eu^{152,154}$, and $Tm^{170}$. Very little of any of the lanthanons

¶ The tabular data are available from the authors upon request.

was excreted 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 radioisotopes. 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 fifteen 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 the delayed deposition in the skeleton of $Eu^{152,154}$, which was 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.

*Discussion.* The data shown here establish definite differences in excretion patterns and deposition sites between the light and heavy lanthanons; however 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: (3) the light lanthanons —lanthanum through samarium; the transition group—europium, gadolinium and terbium; and the heavy lanthanons—dysprosium through lutetium.

Radioautographs of long bones(5) and of costochondral junction(15) 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.*(16) 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(16). $Y^{88}$ 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 phosphorous deficiency. Radioautographs of rachitic bone demonstrated that both $Ce^{144}$ and $Y^{88}$ were deposited almost entirely superficially in the shaft and in the uncalcified osteod 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 suggest that these two groups may be handled somewhat differently in the skeleton. It is likely that these differences are determined by the type or strength of the chemical combination of the lanthanons with the bone protein. Ketelle and Boyd(17) 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 sequence 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. This is in the same order as the 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.

*Summary.* 1. The metabolism of the lanthanons has been studied in the rat on a systematic basis using tracer technics. High-specific activity preparations were administered orally or intramuscularly as citrate complexes. 2. Data are presented for the fifteen lanthanons 1 and 4 days after administration and at intervals up to 8 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 4 lanthanons administered orally was insignificant. 3. 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 8 months. 4. 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. 5. The heavy lanthanons (terbium through lutetium). Deposition was mainly skeletal, 50 to 65% of the administered dose. Elimination from the skeleton was slow with a half-time of approximately 2.5 years. Excretion of extra-skeletal heavy lanthanon occurred within the first two weeks after injection and was almost entirely urinary.

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