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PHYSICO-CHEMICAL AND BIOLOGICAL INTERACTIONS IN RARE EARTH METABOLISM¹

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The complexity of rare earth chemistry results in many intriguing problems with regard to the biological disposition of these materials. Durbin(1,2) has shown that the distribution of the rare earths in various tissues is related to their ionic radii and chemical family. She has drawn attention to the dependence on such factors as oxidation state, solubility, the incorporation into organic compounds, and the tendency to form chelates with biological material as determinants of the behavior of the element in the mammal. In particular, Lindenbaum and coworkers(3,4) have drawn attention to the importance of the physico-chemical state of plutonium to both its metabolism and effect. In the first part of this report, we will consider a number of the physico-chemical and biological factors influencing the disposition of the rare earths in the living organism. Studies with cerium, neptunium, and plutonium will serve as examples. In the second part we will concern ourselves primarily with a number of factors which influence the biological effect of these elements.

Partition of Rare Earths Among Rat Tissues

Although elements within the same chemical family exhibit many similarities in biological behavior, many differences are also apparent. The partition of the lanthanides and actinides between skeleton and liver are obviously different (Table 1), although there is some overlap. Differences also exist between elements of the same series, e.g. the distribution of plutonium and neptunium.

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TABLE 1

Partition of Selected Rare Earths Between Skeleton
and Liver 4-7 Days after Intravenous Injection in Soluble Form

<u>Element</u>	<u>% of Administered Dose</u>	
	<u>Skeleton</u>	<u>Liver</u>
Pu	60	30
Np	30	15
Ce	30	60
Pm ¹	38	39

¹Data obtained from studies of Dr. V. H. Smith.

Some of the common variables encountered in biological studies of heavy metals involve differences in amount, chemical form, and route by which the material is administered. The compiled data in Table 2 provide a basis for analyzing the effect of these variables on the biological disposition of ²³⁷Np. In this study several doses of the element were administered in either of two different chemical forms by intravenous (IV) or intraperitoneal (IP) injection. The IV administration of approximately 5 mg/kg of body weight of either the nitrate or citrate results in a similar partition of material between liver and bone. The kidney and the spleen, however, were markedly different. Intraperitoneal injection of a tracer dose of the nitrate results in a smaller fraction of the dose being deposited in the liver. As the amount injected was increased, the amount deposited in the liver decreased further, as did that deposited in bone. The amount excreted in the urine and feces was much higher when small amounts were administered than when the larger dose was given. When tracer levels of the citrate were injected IP, the liver again took up relatively small amounts of the dose, but the deposition in bone was high as was the urinary excretion. As the dose was increased to 30 mg/kg of body weight, the amount taken up by the liver was not changed greatly, but the fraction deposited in the femur was markedly decreased. On the other hand, there was a further increase in the excretion of the material in the urine which probably resulted from damage induced in the kidney by the nuclide.

The importance of the state of oxidation of an element is illustrated in the data obtained from a study of Ballou et al.(5), which examined the effect of valence state on ²³⁷Np absorption from the GI tract (Table 3). Hexavalent neptunium was absorbed twice as well as pentavalent and approximately 7 to 8 times as well as tetravalent. However, the partition of ²³⁷Np between the liver and the femur was not vastly different for the three valence states.

TABLE 2

Metabolism of Neptunium by the Rat as Affected
by Dose, Chemical Form, and Route of Injection

Dose mg/kg	Form	Route	% Administered Dose				
			Liver	Kidney	Spleen	Femur	Feces + Urine
5	nitrate	I.V.	14.6	0.24	3.45	1.46	14.0
4	citrate ¹	I.V.	12.0	1.30	0.60	1.10	9.1
Tracer	nitrate	I.P.	3.9	1.22	0.05	1.93	28.5
10	nitrate	I.P.	0.44	0.15	0.01	0.31	4.8
Tracer	citrate	I.P.	4.1	0.92	0.03	1.97	26.0
10	citrate	I.P.	10.5	0.91	1.00	0.82	18.9
30	citrate	I.P.	5.5	0.70	0.65	0.67	36.2

¹Data obtained from studies of Dr. J. E. Ballou.

TABLE 3

Effect of Valence State on ²³⁷Np Absorption¹

Tissue	Percent of Administered Dose		
	Np(IV)	Np(V)	Np(VI)
Liver	0.03	0.18	0.35
Femur	0.01	0.04	0.07
Total	0.30	1.1	2.3

¹Administered in citrate buffer at pH of 4. Data from reference (5).

Effect of Age on Nuclide Disposition

The enhanced sensitivity of the immature animal to various insults such as radiation and chemical poisoning is well known. It is also well known that many physiological systems are incompletely developed in the perinatal animal. This suggested that the age of the animal might influence rare earth metabolism. We, therefore, compared the metabolism of ²³⁹Pu and ¹⁴⁴Ce in the newborn and weanling animal with that in the adult. In the Pu studies, we varied both the dose and the physico-chemical state. In the case of ¹⁴⁴Ce, only differences in dose levels were superimposed on the age factor.

Plutonium was prepared as predominately monomer or polymer by bringing the pH of a nitric acid solution to 4.5 in the presence

or absence of sodium citrate. Newborn rats were injected intracardially and weanling and adult rats intravenously with the respective preparations. Twenty-four hours later, the animals were killed, tissues removed, and radioactivity determined. In the adult, the monomeric form was almost equally partitioned between bone¹ and liver with minimal deposition in the spleen (Table 4). In contrast, the weanlings incorporated relatively less in the liver and more into the femur. The deposition in the liver of the newborn more closely resembled that in the adult, but the amount deposited in the femur was much less. When the polymer was injected, the liver of the adult and newborn took up the major fraction of the material with substantial amounts in the spleen and much smaller quantities in the femur. The liver in the weanling, also, was a major site of deposition, but the amount deposited was considerably less than for either the adult or newborn. This nonlinearity of partition of polymeric plutonium with increasing age may result from differing relative activities of the reticuloendothelial system and mineral accretion by the skeleton in the animals at these three ages.

TABLE 4

Distribution of ^{239}Pu among the Liver, Spleen and Femur One Day after the Intravenous Injection of Monomer or Polymer into Newborn, Weanling or Adult Rats

Age at Injection	Percent of Administered Dose							
	Monomer				Polymer			
	Liver	Spleen	Femur	Carc.	Liver	Spleen	Femur	Carc.
Adult	35.5	0.26	1.48	60.3	61.6	6.62	0.46	28.8
Weanling	9.6	0.17	3.57	81.4	29.0	4.28	0.30	50.9
Newborn	43.0	-	0.30	36.1	59.3	1.54	0.32	17.1

In another experiment, ^{144}Ce was administered either in tracer amounts or at a level of $1\ \mu\text{Ci/g}$ of body weight to rats of these same ages. The distribution of cerium was also affected by the age of the animal (Table 5), with the adult showing greater deposition in the liver at 7 days after injection of a tracer dose than either the newborn or weanling animals. The deposition in the liver of the weanling was lower than even for the newborn, but the uptake by the femur was extremely high, exceeding the value for either the newborn or the adult. The administration of $1.0\ \mu\text{Ci/g}$ of ^{144}Ce changed the relative pattern of deposition observed for all three age groups. This is particularly noticeable

¹In the adult the skeletal content is assumed to be 25X the femur value. This assumption is probably not valid for the immature rat.

for the weanling in which the hepatic deposition increased markedly with a concomitant decrease in femoral concentration.

TABLE 5

Distribution of ^{144}Ce among Liver, Spleen and Femur
7 Days after Injection into Newborn, Weanling or Adult Rats

Age of Injection	Percent of Administered Dose					
	Trace			1.0 $\mu\text{Ci/g}$		
	Liver	Femur	Spleen	Liver	Femur	Spleen
Newborn	26.8	0.82	0.50	37.2	0.78	0.30
Weanling	17.0	3.23	0.69	40.2	1.86	0.45
Adult	51.6	1.32	1.95	57.8	0.67	1.58

Age-related differences have also been seen in our studies with the prenatal rat. In one representative study, pregnant rats were injected at 15 or 19 days of gestation with either monomeric or polymeric ^{239}Pu and killed 24 hours later (at 16 and 20 days). The concentration of monomer in the total fetus and fetal liver was similar at both times (Table 6). However, the concentrations in the placenta and membranes at 20 days were twice those at 16. When the polymer was administered, the concentration in all tissues was lower than after injection of the monomer. Moreover, the concentration in all tissues at 20 days was higher than at 16. This difference was particularly striking in the liver, in which there was a 20-fold increase.

Subcellular Distribution

In addition to gross measures of metabolism, such as partition between organs, localization within the tissue and the cells of the tissue are of interest. This becomes particularly important since factors which may not change the total amount of an element incorporated into a tissue may change the intracellular localization and, thereby, the resulting biological effect. Toward this end, we have examined the influence of the magnitude of the dose of neptunium and cerium on their subcellular distribution in the liver. Adult rats were injected with radioactive isotopes of these elements. They were killed 24 hours later and homogenates of the liver centrifuged to obtain the subcellular fractions. Tracer levels of neptunium and cerium localized primarily in the mitochondria and cytoplasm with lesser amounts associated with the nuclear and microsomal fractions (Table 7). When the dose of neptunium was increased to 6 mg/kg, the nuclear fraction incorporated greater than 50 percent of the activity with decreases in the other fractions. Increasing the dose of cerium likewise increased the cerium content of the nuclear fraction, in this case from 9 to 30% of the injected dose. However, there was also a slight

increase in the mitochondrial content with a concomitant decrease in the supernatant fraction.

Table 6

Distribution of ^{239}Pu 24 hr after
Injection into Tail Veins of Pregnant Rats¹
(% of injected dose/g wet wt.)

	<u>Tissue</u>	<u>Dam</u>	<u>15-16 Day Fetus</u>	<u>19-20 Day Fetus</u>
Monomer	Liver	2.5	0.04	0.04
	Femur	0.73	--	2.07
	Fetus	--	1.01	0.01
	Membranes	--	1.93	3.20
	Placenta	--	0.40	0.91
Polymer	Liver	3.18	0.001	0.02
	Femur	0.16	--	0.06
	Fetus	--	0.0002	0.0004
	Membranes	--	0.03	0.07
	Placenta	--	0.01	0.02

¹Data taken from reference (7).

Carcinogen Feeding and Nuclide Distribution

The environment contains many substances which might be postulated to change the metabolic state of an animal. Among the carcinogenic or tumor-inducing chemicals, we have had particular interest in those which induce liver tumors, the hepatocarcinogens. Since they act on the liver it was speculated that they might particularly affect the metabolism of elements, such as cerium, which localize in the liver.

TABLE 7

Subcellular Distribution of Neptunium and Cerium in Rat Liver at
24 Hours after Injection as Influenced by Administered Dose¹

<u>Nuclide</u>	<u>Dose</u>	<u>Percent of total cellular content/fraction</u>			
		<u>Nuclear</u>	<u>Mitochondrial</u>	<u>Microsomal</u>	<u>Super- natant</u>
Np	Tracer	14.0	31.2	14.5	40.2
Np	6 mg/kg	52.5	24.2	12.5	10.7
Ce	Tracer	8.9	33.7	23.2	34.9
Ce	4 mg/kg	30.4	40.0	22.8	7.1

¹Data taken from reference (8).

Our first question was: does feeding of a hepatocarcinogen affect the retention of Ce by the liver? Preliminary investigation showed that cerium retention by the liver was enhanced by the presence of dimethylaminoazoabenzene (DAB), a moderately active carcinogen. To obtain further information rats were injected intravenously with ^{144}Ce and fed a control diet or one which contained either of the two potent hepatocarcinogens, diacetylaminofluorene (DAF, 0.03%) or ethionine (0.3%). The animals were then killed after 20 days and selected tissues removed for determination of ^{144}Ce content. Only 14% of the ^{144}Ce was retained in those animals fed the control diet while those receiving DAF or ethionine retained 28% and 40%, respectively (Table 8). On the other hand, the amount retained in the other tissues was not greatly influenced by diet.

TABLE 8

Effect of DAF and Ethionine on the Distribution of ^{144}Ce among Selected Tissues of Rats Given 20 μCi of ^{144}Ce Intravenously¹

Tissue	Control (10) ²	Percent of Administered Dose	
		DAF (7)	Ethionine (3)
Liver	14±2.21 ³	28±4.3	40±7.4
Kidney	0.49±0.07	0.54±0.02	0.76±0.10
Spleen	0.72±0.08	0.84±0.09	0.45±0.09
Femur	0.83±0.05	0.79±0.03	0.94±0.11
Carcass	18±1.65	17±0.67	--

¹Data taken from reference (9).

²Number of animals.

³Standard Error.

The fact that the bile has been implicated as the major route of elimination of Ce(6) raised a second question: do the hepatocarcinogens affect ^{144}Ce retention by decreasing biliary excretion? To answer this question, we injected animals with ^{144}Ce as before and fed them a diet containing ethionine, DAF, DAB, or no added carcinogen. After 20-23 days the animals were anesthetized and a cannula inserted into the common bile duct. Bile was collected for 4 to 6 hours and the radioactivity determined. Animals which received carcinogen in the diet excreted markedly less ^{144}Ce in the bile, although the flow rate for bile was not changed (See Ref. 9). These data suggest that the carcinogens, somehow, prevented the ^{144}Ce from being incorporated into or linked with substances destined for the bile.

Our third question was: does feeding of carcinogens prior to injection of the nuclide affect its disposition? Ethionine or DAF was fed to rats for a period of 21 days. Cerium-144 was then injected intravenously, the animals killed 24 hours later

and the liver, kidney, spleen and femur analyzed for ^{144}Ce . Both DAF and ethionine decreased the hepatic deposition of ^{144}Ce (Table 9). At the same time, it increased the deposition in the femur, spleen, and kidney. If the data are expressed as percent of administered dose per gram of tissue, there seems to be little difference in the liver, although other tissues show an increase similar to that seen when the data are expressed as percent of administered dose per tissue.

Similar experiments were performed in which animals were fed ethionine for 21 days and a test dose of ^{239}Pu administered intravenously. Again the animals were killed after 24 hours and the liver, kidneys, spleen and femur removed and analyzed for plutonium content. There was little effect on the hepatic deposition of plutonium but renal and splenic deposition was increased approximately 4 to 5 fold with a concomitant decrease in the plutonium content of the femur.

The effect of the hepatocarcinogen administered prior to the nuclide injection would appear to be related to an effect of the chemical on the organ of major concern in the metabolism of a specific element. For example, it could be postulated that DAF and ethionine functioned by reducing the ability of the liver to remove ^{144}Ce from the blood. The resultant increase in retention time in the blood permitted other organs to extract a larger fraction of the nuclide from the blood. This postulate was examined in two ways. In the first experiment, approximately 2/3 of the liver was removed surgically. At 2 or 24 hours after the operation, ^{144}Ce was injected intravenously and the animals killed 24 hours postinjection. Physical removal of hepatic tissue decreased the fraction of administered dose deposited in the liver with a concomitant increase in other tissues (Table 10). This result seems to be analogous to those obtained in animals fed DAF or ethionine.

Further confirmatory evidence was obtained for our hypothesis by results from a study on the rate of removal of ^{144}Ce from the blood of animals partially hepatectomized or those fed DAF or ethionine. ^{144}Ce was removed from the blood of the controls at a fairly rapid rate, the half-time being approximately 40 minutes. Removal in all the treated groups could be described by a single curve, with a half-time in the range of 90-100 minutes. We believe that these two experiments provide reasonable evidence that these materials act by decreasing the rate of accretion by the tissue normally responsible for removal and consequently increasing the retention time in blood.

Effects of Some Rare Earths

The biological effects of the rare earths are dependent on the same factors which alter their metabolism, as discussed above, as well as many factors unique to the biologic system itself. The

TABLE 9

Effect of DAF and Ethionine on the 24-hour
Retention of ^{144}Ce by Selected Tissues of the Rat

<u>Treatment</u>	<u>Tissue</u>	<u>% of Administered Dose¹</u>		<u>% of Administered Dose/g Tissue</u>	
		<u>Control</u>	<u>Treated</u>	<u>Control</u>	<u>Treated</u>
DAF	Liver	65.0(7;58) ²	52.1 ± 3.86	5.91(6.75;5.11)	5.69 ± 0.39
	Kidney	3.10(3.18;3.02)	3.89 ± 0.78	0.12(1.17;1.07)	1.87 ± 0.47
	Spleen	1.17(1.72;0.61)	1.78 ± 0.09	1.27(1.98;0.62)	2.34 ± 0.3
	Femur	0.99(1.07;0.91)	1.62 ± 0.09	0.95(1.0;0.89)	1.56 ± 0.05
Ethionine	Liver	61.7 ± 2.85	41.8 ± 2.19	3.77 ± 0.21	4.41 ± 0.23
	Kidney	4.29 ± 0.29	7.40 ± 0.58	1.40 ± 0.09	2.80 ± 0.22
	Spleen	4.42 ± 2.14	5.63 ± 1.94	5.03 ± 2.36	8.13 ± 2.47
	Femur	0.78 ± 0.05	1.24 ± 0.06	0.65 ± 0.04	1.15 ± 0.10

¹Mean ± standard error.

²Individual values.

importance of the chemical properties is illustrated by the toxicity of certain elements for specific tissues, such as uranium for the kidney. Since examples of this are relatively well-known, we will not pursue this aspect, but will use our experience with ^{237}Np toxicity to illustrate some of the other factors pertaining to the biological effects of heavy metals. It should be pointed out that not all of the factors which influence neptunium toxicity are of importance in the toxicity of other heavy metals but most have to be considered when evaluating biological effects.

TABLE 10

The Influence of Partial Hepatectomy (PH)
on the 24-hour Retention of ^{144}Ce
(Mean $\pm$ standard error)

Treatment	Time ¹ (hrs) post-hepat.	% Dose/Tissue			
		Liver	Kidney	Spleen	Femur
Control (6) ²	--	79.7 $\pm$ 2.40	1.30 $\pm$ 0.11	0.73 $\pm$ 0.70	0.70 $\pm$ 0.05
PH (6)	2	47.7 $\pm$ 2.36	3.57 $\pm$ 0.36	3.13 $\pm$ 0.34	1.64 $\pm$ 0.12
PH (6)	24	40.8 $\pm$ 2.86	3.69 $\pm$ 0.35	4.77 $\pm$ 0.41	1.75 $\pm$ 0.08

¹Radionuclide was injected intravenously at stated time following partial hepatectomy. The animals were killed 24 hours post-injection.

²Number of animals.

Preliminary experiments with ^{237}Np showed that a characteristic response of the animal involved development of a fatty liver. The difference in response of the female and male rat to neptunium administration and the temporal pattern of lipid accumulation are shown in Table 11. It is obvious that the male rat responded only slightly while there were large increases in fat content of the liver of the female. We reexamined these sex-related differences in response to ^{237}Np by measuring levels of the serum enzymes, isocitric dehydrogenase (ICD) and glutamic pyruvic transaminase (GPT), since elevated levels are often used as sensitive indicators of liver damage. The levels of both enzymes increased in both male and female rats at 24 hours after administration of neptunium, (Table 12), but the increases were much larger in the female.

Studies with other hepatotoxic materials have demonstrated that there are various dietary and hormonal factors which may influence the fatty liver development. We, therefore, examined some of the likely candidates for modification of the effect of ^{237}Np . We found, for example, (Table 13) that removing the adrenal (adrenalectomy) or the pituitary gland (hypophysectomy) prior to administration of ^{237}Np protected against the fatty liver development. A similar protective effect was obtained if the animal received large amounts of glucose or nicotinic acid prior to and

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following ^{237}Np injection (Table 14). On the other hand, some of the manipulations such as feeding adenine sulfate, adenosine triphosphate, choline and methionine or by removing the thyroid or gonads, which have been shown to alter fatty livers induced by a number of other agents, did not alter the fatty liver response to ^{237}Np .

TABLE 11
Effect of ^{237}Np on Hepatic Lipid Levels¹
[Percent fat (dry wt. basis)]

	Time after Injection (hrs)				
	0	6	12	24	48
Females	12.9	15.0	19.3	23.4	44.9
Males	11.2	--	--	14.3	12.3

¹Data taken from reference (10).

TABLE 12
Effect of ^{237}Np (6 mg/kg) on Serum Activities
of Isocitric Dehydrogenase and Glutamic-pyruvic
Transaminase in Male and Female Rats¹

	ICD (Sigma units/ml)		SGPT (Sigma units/ml)	
	Control	^{237}Np	Control	^{237}Np
Female	561±145 ² (8)	3200±125 (7)	21±3.0 (8)	714±197 (7)
Male	430±44 (3)	1860±820 (3)	21±3.0 (3)	127±60 (3)

¹Data from reference (11).

²Mean ± standard error.

³Number of animals.

We have also found that subtle differences in the physico-chemical state of the neptunium solution can result in a difference in the response of the liver to the effects of the element. For example, injection of a citrated solution of Np results in significant elevation of liver fat at 48 hours after injection when administered at a pH of 4.5 but not pH 9. However, injection of the citrated neptunium at pH of 9.0 failed to elevate liver fat by 48 hours.

The potential hazard of many of the radioactive isotopes of the rare earths are of particular concern to the nuclear industry. The effects from radiation can be measured in many ways and are themselves influenced by many of the same parameters that have been discussed. The administration of plutonium to small laboratory animals can produce effects which vary according to the age

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of the animal at the time of administration and the physico-chemical state of the plutonium administered. We have shown, for instance, that the administration of monomeric ^{239}Pu can produce decreased skeletal strength in animals exposed as weanlings while those exposed as newborns or adults show only minor changes. On the other hand, the administration of polymeric ^{239}Pu fails to decrease the strength of the skeleton in even weanling animals.

Several other parameters such as tumor induction, embryocidal effects, hepatic function, and sensitivity to audiogenic seizures have all been shown to be affected by many of the factors described. The many possible permutations of these variables indicate the difficulties inherent in expressing an all-encompassing view of the biological fate or effect of any specific element.

TABLE 13

Effect of Endocrine Ablation on the Induction
of Fatty Livers by ^{237}Np (12 mg/kg)¹

<u>Treatment</u>	<u>No. of rats per treatment</u>	<u>Time after ^{237}Np (hr)</u>	<u>Sex</u>	<u>mg lipid g wet liver</u>
Np	6	24	F	55 ± 7.9 ²
Np + Hypophysectomy	5	24	F	41 ± 2.2
Np + Thyroidectomy	5	24	F	72 ± 14
Np	6	24	F	58 ± 5.6
Np + Ovariectomy	3	24	F	81 ± 8.0
Np	3	24	M	44 ± 1.9
Np + Castration	3	24	M	53 ± 5.2
Np	7	24	F	88 ± 8.9
Np + Adrenalectomy	7	24	F	49 ± 4.8

¹Data from reference (11).

²Mean ± standard error.

TABLE 14

Effect of Diet on Induction on Fatty
Livers by ^{237}Np (12 mg/kg)¹

<u>Treatment</u>	<u>No. of rats per treatment</u>	<u>mg lipid g wet liver</u>
None	6	41 ± 2.7 ²
Np	4	50 ± 1.0
Np + Glucose	4	33 ± 2.0
Np	4	72 ± 7.3
Np + BHT	4	54 ± 4.2
Np	16	75 ± 3.5
Np + Nicotinic acid	13	57 ± 5.4

¹Data from reference (11).

²Mean ± standard error.

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