RADIOELEMENT TOXICITY STUDIES

Included in this section are a miscellaneous group of radioelement toxicity studies which are not associated with the major programs covered in the previous sections. The first report describes recent observations in our 17 year old radioiodine toxicity program. Aside from a few sheep that remain on long-term observation, the only activity left in this program is a study in miniature swine, which will allow comparison of long-term radioiodine effects in sheep and swine.

Four reports are concerned with metabolic studies in rats, involving radioisotopes of plutonium, iodine, and cesium. Three of these reports deal with effects of age. Particularly in the case of plutonium, we are accumulating a body of data which attests to the extreme complexity of the dose-effect relationships as influenced by such factors as age, route of administration, and physicochemical form of the administered radionuclide. Some rather puzzling differences in the acute toxicity of ^{238}Pu and ^{239}Pu now seem to be reasonably explained in terms of physicochemical state as influenced by the greatly different specific activity of the two isotopes.

The past year saw the initiation of radionuclide distribution studies in human volunteers. A study employing the photon-emitting ^{143}Pm was jointly undertaken by Battelle-Northwest and the Hanford Environmental Health Foundation. Data from this experiment were not in shape for publication at year end, but the techniques of whole-body counting which can be employed with such radionuclides would seem to offer great promise for the future. Two reports in this section are concerned with this effort. One describes preliminary tests of the ^{143}Pm injectant in a miniature swine; the other describes preliminary investigations of the potentialities of the isotope ^{237}Pu for human studies.

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EFFECTS OF RADIOIODINE IN SHEEP AND SWINE

Thyroid glands of eight miniature swine fed 2000 μCi ^{131}I , a year previously, retained less of an ingested tracer dose of ^{131}I than did four control swine. Two thyroid adenomas and a chromophobe adenoma of the pituitary were observed in sheep previously exposed to ^{131}I .

Investigators:

M. T. Karagianes
J. L. Beamer
M. F. Gillis
J. L. Palotay

A study to determine the long-term effects of ^{131}I in miniature swine, for comparison with past studies in sheep, was initiated in 1966 (Annual Report, 1966). Eight 5-month-old females were given an oral dose of 2000 μCi . A year subsequent to this treatment a tracer dose of 10 μCi ^{131}I was administered to determine if partial ablation of the thyroid had occurred.

Observations

A year after oral administration of the 2000- μCi dose of ^{131}I , all swine appeared physically healthy with no external signs of hypothyroidism. Results of the oral administration of a 10- μCi tracer dose are shown in Figure 1. Thyroid deposition of the initial 2000- μCi

FIGURE 1. Thyroid Uptake of ^{131}I Following Ingestion of a 10 μCi Tracer Dose by Four Control Swine and eight Swine Fed 2000 μCi ^{131}I One Year Previously (Mean values $\pm$ std. dev.)

dose reached a peak at 45 hr with retention of approximately 25% of the fed ^{131}I . The tracer dose fed a year later to the same animals, which were 30-45 kg heavier, exhibited a maximum uptake time averaging 26 hr for controls and 31 hr for the previously treated swine. The maximum uptake averaged 13.8% for controls and 10.8% for the previously treated swine. Damage to the thyroids was evident not only in terms of reduced maximum uptake, but more impressively in terms of retention beyond the second day.

Loss of thyroid function in these animals will be determined annually. At 4 years following the initial insult, effects of hypothyroidism on reproductive ability will be evaluated and compared with similar data available on sheep.

A few animals remain on long-term observation from the extensive studies on ^{131}I effects in sheep which have been conducted at this laboratory over the past 17 years. Four of these animals died during the past year. All had received ^{131}I exposure during gestation and

from the dam's milk until weaning. Their dams were receiving 5 μCi orally per day. Histologic examination of the thyroids revealed one to be normal (8 years old) and two (7 and 11 years old) to have small localized proliferation of acinar epithelial cells constituting small adenomas. Most of these cells were nonfunctional, although some tended to form small acini with colloid formation. One of these sheep had a concurrent large chromophobe adenoma of the pituitary gland. Data are not yet available on the fourth animal.

Conclusions

Comparative studies of long-term effects of ^{131}I in miniature swine are still in the early stages. Any attempt at comparison with the extensive data available on sheep would be premature at this time. It is clear, however, that the 2000- μCi ^{131}I dose did partially ablate the thyroid glands of the treated swine, and further evidence of damage may be anticipated with continued observation.

PHYSICOCHEMICAL FORM AS A DETERMINANT OF THE TOXICITY OF ^{238}Pu IN THE RAT

The acute toxicity of ^{238}Pu is related to the physicochemical form injected, with the polymeric form being nearly twice as toxic as the monomer. The polymeric form produced earlier deaths, and was preferentially deposited in soft tissues, while the monomer was preferentially deposited in the skeleton.

Investigators:

D. D. Mahlum

M. R. Sikov

Technical Assistance:

Joan O. Hess

Nancy L. Lukens

Although ^{238}Pu and ^{239}Pu are both alpha emitters of similar energies, the $\text{LD}_{50/30}$ value for ^{238}Pu is about twice that for ^{239}Pu . Ballou et al. (1) suggested, on the basis of tissue distribution data, that this difference in toxicity is due to differences in the physicochemical state of the isotopes resulting from the 270-fold difference in specific activity. This led us to study directly the influence of physicochemical state on the acute toxic properties of ^{238}Pu .

Observations

Monomeric ^{238}Pu was prepared by mixing sodium citrate (>1000-fold molar excess) with an acid solution of the nuclide and adjusting the pH to 4.5 with anhydrous Na_2CO_3 . The polymeric form was prepared by adjusting an acid solution of ^{238}Pu to pH 4.5 in the absence of citrate.

Female rats of the Charles River CD strain, 3-4 months old, were injected intravenously with 54, 108, or 162 $\mu\text{Ci/kg}$ of the monomer, or 50, 100, or 150 $\mu\text{Ci/kg}$ of the polymer. These animals were kept for determination of survival times with

results as summarized in Table I.

In a second experiment rats were injected with 54 or 161 $\mu\text{Ci/kg}$ of the monomer, or 50 or 100 $\mu\text{Ci/kg}$ of the polymer, and groups killed at 1, 7, and 33 days postinjection for tissue radioanalysis. Results from this experiment are summarized in Table II.

Polymeric ^{238}Pu was significantly more toxic than the monomer. This was true whether 30- or 60-day survival figures or the median survival times were considered. Weight gain was inhibited in all of the plutonium-injected animals, but the greater toxicity of the polymer was again evident. Figure 1 shows growth curves for the groups with a substantial number of survivors beyond 60 days.

As shown in Table II, there was a substantial difference in the distribution of the monomer and the polymer. Nearly twice as much monomer, as polymer, was deposited in bone; while a substantially greater proportion of polymer was deposited in liver. The fraction in the liver decreased very little between 1 and 7 days, but was markedly reduced in the monomer-injected animals after 33 days. Femur

TABLE I. Mortality Following Intravenous Injection of Monomeric or Polymeric ^{238}Pu

Physicochemical Form	Dose Administered, $\mu\text{Ci/kg}$	Mortality ^(a)		Median Survival Time, days
		At 30 Days	At 60 Days	
Monomer	0	0/12	0/12	>224
[LD ₅₀ /30 >162 $\mu\text{Ci/kg}$]	54	0/12	0/12	>224
[LD ₅₀ /60 124 $\mu\text{Ci/kg}$]	108	0/12	6/12	62
[(91-156) ^(b)]	162	1/12	9/12	38
Polymer	50	0/12	2/12	77
[LD ₅₀ /30 98 $\mu\text{Ci/kg}$]	100	7/12	10/12	24
[(67-144) ^(b)]	150	10/12	12/12	20
[LD ₅₀ /60 75 $\mu\text{Ci/kg}$]				
[(56-156) ^(b)]				

(a) Number dead/number injected

(b) 95% Confidence interval

TABLE II. Distribution Among Tissues of Intravenously Injected Monomeric or Polymeric ^{238}Pu ^(a)

Days After Injection	Physico-chemical Form	Dose, $\mu\text{Ci/kg}$	Organ Content, % of administered dose				
			Liver	Spleen	Kidney	Adrenal	Femur
1	Monomer	54	21	0.2	0.47	0.007	1.5
		161	24	0.2	0.77	0.011	3.0
	Polymer	50	35	0.8	0.32	0.003	1.0
7	Monomer	54	14	0.2	0.40	0.006	2.8
		161	21	0.2	0.36	0.006	3.9
	Polymer	50	30	4.2	0.24	0.005	1.5
		100	28	2.1	0.32	0.004	1.5
33	Monomer	54	2	0.2	0.23	0.004	2.5
		161	2	0.2	0.16	0.005	3.1

(a) Average values from two to three rats

FIGURE 1. Effect of ^{238}Pu on the Weight of Female Rats from Groups with a Substantial Number of Survivors Beyond 60 Days

and spleen values increased beyond the first day postinjection, with particularly high spleen values attained in the polymer-injected animals.

Adrenal weights were increased at both the 50 and 100 $\mu\text{Ci/kg}$ levels of polymer, whether considered on an absolute basis or as a percent of body weight. Spleen weights, on the other hand, were decreased in both monomer- and polymer-injected animals. No remarkable changes were noted in weights of other organs.

Conclusions

The acute toxicity of ^{238}Pu , like that of ^{239}Pu , is related to the degree of polymerization of the injected material. This effect seems most reasonably attributable to differences in distribution of monomeric and polymeric forms, with the enhanced soft-tissue deposition of the polymer favoring acute lethality.

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EFFECT OF AGE AND PHYSICOCHEMICAL FORM ON PLUTONIUM TOXICITY
AND METABOLISM IN THE RAT

The distribution and toxic effects of monomeric and polymeric plutonium in neonatal, weanling, and adult rats were compared. The polymer was more acutely toxic than the monomer to weanlings and adults, but there was little difference between the two forms in newborn rats. These differences in acute lethality relate to marked age-dependent differences in distribution of the two forms, which also leads to age-dependent alterations in organs such as liver, spleen, and skeleton.

Investigators:

M. R. Sikov
D. D. Mahlum

Technical Assistance:

D. L. Catt
Joan O. Hess
Nancy L. Lukens

Liver and bone are the principal sites of deposition of injected plutonium. In the adult, the partition between these two tissues, as well as the resulting late effects, has been shown to be dependent on the state of the plutonium administered.(1) These tissues undergo profound alterations between birth and adulthood, but it is not known how these changes affect the metabolism of plutonium. The present studies represent the beginnings of an effort to fill this void.

Observations

Monomeric plutonium was prepared by adding a solution of $^{239}\text{Pu}(\text{NO}_3)_4$ to sufficient sodium citrate to provide a 100-fold molar excess of citrate. The pH was then adjusted to 4.5. The polymeric form was prepared by adjusting the pH of the nitrate to 4.5 in the absence of citrate. These solutions were injected intravenously into rats of the Charles River CD strain at birth,

weaning (21 days), or as young adults, at levels ranging from 6-90 $\mu\text{Ci/kg}$ body weight. Animals from selected age and dose groups were sacrificed at 1, 3, 7, 30, and 90 days for radioanalysis and determination of pathology. Other previously selected animals were observed over a 60-day period for gross mortality. Still other animals were kept for sacrifice and observation of late effects at 9 months.

Acute lethality data are summarized in Table I. The polymer was more toxic to weanlings and adults than was the monomer, but no such difference was evident in the newborn animals.

Weight gains were suppressed in animals of all age groups by ^{239}Pu administration. Figure 1 illustrates the results with a 60 $\mu\text{Ci/kg}$ dose in female rats of the three ages studied. At each dose level the weight gains of the newborns were less severely affected than those of the weanlings or adults.

TABLE I. Acute Lethal Effect of ^{239}Pu Administered as Monomer or Polymer to Rats of Different Ages (Average values from 12 animals)

Age at Administration	Form Administered	Median Survival Times. days for various injected doses ^(a)			LD ₅₀ $\mu\text{Ci/kg}$ ^(b)	
		30 μCi	60 μCi	90 μCi	30 Days	60 Days
Newborn	Monomer	>60	28	20	74 (61-90)	53 (40-66)
	Polymer	>60	>60	14	66 (48-107)	63 (45-96)
Weanling	Monomer	>60	>60	>60	>90 ^(c)	104 ^(c)
	Polymer	>60	20	13	47 (32-60)	43 (31-54)
Adult	Monomer	>60	>60	48	97 ^(c)	76 (66-87)
	Polymer	>60	21	13	47 (36-58)	38 (29-47)

(a) Administered dose levels below 30 $\mu\text{Ci/kg}$ showed no acute mortality

(b) 95% Confidence interval shown in parentheses

(c) Estimated by extrapolation

Monomeric plutonium was deposited in the skeleton to a greater extent than in the liver, while, with the polymer, liver deposition predominated. From the detailed data on tissue deposition and retention, average tissue radiation dose rates were calculated as a function of age, form administered, and time since administration. Figures 2 and 3 illustrate these findings for liver and femur, and serve to explain many of the observed pathologic effects.

The most obvious changes in the femurs consisted of a decreased osteoblastic activity and extreme disorganization of the epiphyseal

plate. In the weanling, this resulted in fracture of the shaft with abnormal callous formation. Breaking strength (fracture force per unit cross-sectional area) of the femur was determined at 9 months postexposure; the results are summarized in Table II. Administration of the monomer produced a dose-dependent decrease in strength in the weanling and adult groups, but had little effect in the newborn group; the polymer was less effective.

Gross and histological damage was noted in the livers, particularly in the animals receiving the polymer, but also evident in those receiving

FIGURE 1. Weight Changes of Rats After Treatment as Newborns, Weanlings, or Adults with 60 $\mu\text{Ci/kg}$ of Monomeric or Polymeric ^{239}Pu

the monomer. The changes were most severe in those exposed as weanlings, less in those treated at birth, and least in the adults.

The rate of clearance of rose-bengal by the liver was determined in the animals sacrificed at 9 months after exposure to the three lowest dose levels (6, 12, 18 $\mu\text{Ci/kg}$). The major effect was noted in the adult group treated with 18 $\mu\text{Ci/kg}$ of the polymer. A limited number of animals

receiving the other levels of plutonium showed a decreased clearance rate.

Neurologic function was measured at 9 months after plutonium administration to determine if the developing central nervous system, which is highly radiosensitive, had been damaged by plutonium incorporated into the skeletal elements surrounding it. The ability to learn a water maze was found to be unaltered. The data

FIGURE 2. Calculated Average Radiation Dose to the Liver Normalized to Administration of 60 $\mu\text{Ci/kg}$ of Monomeric or Polymeric ^{239}Pu to Newborn, Weanling, or Adult Rats

shown in Figure 4 indicate a general tendency toward a dose-dependent increase in the susceptibility to audiogenic seizures after exposure of the weanlings to the monomer. The rats exposed at birth were the only group to show increased seizure incidence after exposure to the polymer. Similar studies were made after Metrazol administration which should lower the threshold for audiogenic seizures. Results were less consistent, with some indication

that ^{239}Pu may inhibit the usual threshold-depressing action of Metrazol.

The weights of several organs, in relation to total body weight, were altered by exposure to plutonium. The direction and magnitude of these changes related differently to the three variables, age, physicochemical form, and dose, as well as to time postexposure. This created a highly complex matrix which has not yet been completely analyzed. As an

FIGURE 3. *Calculated Average Radiation Dose to the Femur Normalized to Administration of 60 $\mu\text{Ci/kg}$ of Monomeric or Polymeric ^{239}Pu to Newborn, Weanling, or Adult Rats*

example of the results obtained, the relative weights of the spleens at 3 months after exposure are shown in Table III. The splenic weight of the rats injected at birth with the highest doses of the monomer tended to be increased while those from animals which received the polymer were largely unchanged. The spleens of animals exposed as weanlings or adults, on the other hand, were less responsive to the monomer, but were greatly decreased in size at 3 months after injection of the polymer.

Conclusions

Most of the parameters studied in these investigations were differently affected by the two physicochemical forms of plutonium and the effects varied as a function of the age of the animal studied. These parameters included radionuclide distribution and retention, growth, acute and chronic toxicity, and damaging effects on a number of specific organ systems. Although it is not yet

FIGURE 4. Percent Incidence of Audiogenic Seizures 9 Months After Exposure to ^{239}Pu (Shaded bars indicate severe seizures; open bars, total seizures. Statistically significant differences from controls are indicated by an asterisk. Numbers of animals tested are given in parentheses.)

TABLE II. Femoral Breaking Strength 9 Months After Administration of Monomeric or Polymeric ^{239}Pu to Newborn, Weanling, or Adult Rats

Age at Administration	Dose, $\mu\text{Ci/kg}$	Breaking Strength, g/mm ² (a)	
		Monomer	Polymer
Newborn	0	286 $\pm$ 22 ^(b) (16) ^(c)	
	6	237 $\pm$ 20 (4)	283 $\pm$ 48 (4)
	12	261 $\pm$ 20 (3)	283 $\pm$ 50 (4)
	18	254 (2)	306 $\pm$ 95 (4)
Weanling	0	269 $\pm$ 26 (8)	
	6	226 $\pm$ 36 (6)	205 $\pm$ 9 (5)
	12	227 $\pm$ 22 (8)	315 $\pm$ 13 (7)
	18	184 $\pm$ 21 (5)	257 $\pm$ 20 (6)
Adult	0	296 $\pm$ 20 (8)	
	6	240 $\pm$ 80 (8)	250 $\pm$ 34 (8)
	12	232 $\pm$ 73 (5)	275 $\pm$ 19 (6)
	18	195 $\pm$ 81 (4)	181 $\pm$ 22 (7)

(a) Uncorrected for mechanical advantage of system

(b) Standard error

(c) Number of animals

TABLE III. Relative Spleen Weight ($\frac{\text{Spleen Weight}}{\text{Body Weight}}$) at 3 Months After Intravenous Injection of ^{239}Pu (Average values from three or more animals)

Form Injected	Dose, μCi	Age at Injection		
		Newborn	Weanling	Adult
Control		0.16	0.17	0.15
Monomer	6	0.15	0.22	0.23
	12	0.14	0.14	0.26
	18	0.21	0.17	0.15
	30	0.14	0.13	0.084
	60	0.27	0.25	0.21
	90	0.39	0.25	0.18
Polymer	6	0.14	0.12	0.06
	12	0.12	0.17	0.06
	18	0.14	0.06	0.02
	30	0.14	0.018	0.051
	60	0.14	0.024	0.039
	90	0.26	0.017	0.073

possible to synthesize these observations into a unified cause-effect picture, the damaging effects seem generally to correlate with radiation dose as estimated from distribution data, and the variations in distribution seem reasonably explainable in chemical and physiological terms.

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RADIOELEMENT TOXICITY STUDIES

AGE DEPENDENCE OF RADIOIODINE METABOLISM AND EFFECT IN RATS

A Low-iodine diet increased the uptake of ^{131}I and altered its retention. Quantitative and qualitative differences were seen between prenatal, newborn, weanling, and adult rats. Incorporation and retention were altered when greater than minimal tracer levels of ^{131}I were administered.

Investigators:

*M. R. Sikov
D. D. Mahlum*

Technical Assistance:

*Joan O. Hess
Barbara J. Schulz
Nancy L. Lukens*

This is a continuation of studies described last year on the age-related metabolism and radiosensitivity of the thyroid gland (Annual Report, 1966). No systematic data are available on the changes in iodine metabolism which must occur between the early stages of thyroid development and the adult state. Though it is well recognized that an iodine deficient diet will increase the percentage of a tracer dose incorporated in the thyroid, there are no data relating this effect to age. These factors and their interrelations were investigated in these studies.

Observations

Gravid female rats, after 19 or 20 days of gestation, and normal females of the same age, were injected intraperitoneally with 1, 10, or 25 μCi of carrier-free ^{131}I as sodium iodine. Half of the animals were placed on a low-iodine diet 1 week prior to radioiodine injection and maintained on the diet until sacrifice. This resulted in six dose-diet groups with four or five normal females and eight gravid females

(combined 19- and 20-day gestation) within each group. All rats were sacrificed 24 hr after exposure for determination of thyroidal ^{131}I .

Results are presented in Table I. As expected, both pregnant and non-pregnant females on the low-iodine diet showed a greater incorporation than did the comparable animals on a stock diet. The incorporation of ^{131}I in the thyroid gland of the pregnant rats was significantly less than in the nongravid females. This effect of pregnancy was more marked on a normal diet than on the low-iodine diet. Raising the administered dose above 1 μCi produced a statistically significant decrease in uptake only in the gravid females receiving the low-iodine diet.

The ability of the fetal thyroid to incorporate radioiodine was significantly greater in the 23 hr period between 20 and 21 days of gestation than it was in the preceding 24 hr period. The effect of diet was also more evident in the older fetuses. Doses larger than 1 μCi had a substantial effect on iodine uptake by the fetal thyroid, particularly when the mothers were on a low-iodine diet.

TABLE I. Effect of Pregnancy, Size of Dose, Iodine Content of Diet, and Stage of Gestation on Incorporation of Intraperitoneally Administered ^{131}I

Diet	^{131}I Dose. μCi	Percent of Administered ^{131}I in Thyroid			
		Normal Females	Gravid Females	19-20 Day Fetus	20-21 Day Fetus
Stock	1	34.6 $\pm$ 3.8 ^(a)	17.7 $\pm$ 5.1	0.25 $\pm$ 0.03	0.62 $\pm$ 0.10
	10	26.3 $\pm$ 7.5	15.9 $\pm$ 1.4	0.17 $\pm$ 0.02	0.55 $\pm$ 0.18
	25	33.1 $\pm$ 11.9	15.5 $\pm$ 1.3	0.15 $\pm$ 0.02	0.45 $\pm$ 0.05
Low-Iodine	1	56.1 $\pm$ 11.5	49.6 $\pm$ 6.0	0.41 $\pm$ 0.07	1.09 $\pm$ 0.18
	10	53.9 $\pm$ 6.1	31.7 $\pm$ 4.8	0.18 $\pm$ 0.04	0.86 $\pm$ 0.06
	25	43.1 $\pm$ 3.6	34.4 $\pm$ 5.8	0.17 $\pm$ 0.02	0.77 $\pm$ 0.11

(a) Standard error

To further define these various relations of age and dietary iodine content, radioiodine was administered intraperitoneally at levels of 0.01 $\mu\text{Ci/g}$ body weight to 19-day fetuses (via the mother), newborns, weanlings (21 days), young adults (3 months), and older adults (9-11 months). Half of the animals were placed on a low-iodine diet 1 week prior to radioiodine injection and maintained on this diet until sacrifice. Three to five animals of each age-diet group were killed at intervals to 20 days for tissue radioanalysis. Thyroid incorporation data are shown in Figure 1. The percentage uptake by animals exposed prenatally is calculated on the assumption of uniform partition of radioiodine between dam and fetus at the time of administration. The retention curves for the prenatal animals are distorted by continuing intake of ^{131}I supplied in

the mother's milk. The low-iodine diet increased the iodine content of the thyroid most markedly in the animals exposed prenatally and in the young adults. The weanling animals showed a substantially lower uptake of radioiodine than adults and were relatively unaffected by a low-iodine diet.

Comparable studies were performed at substantially higher dose levels (0.5, 1, and 3 $\mu\text{Ci/g}$) in animals on a low-iodine diet. Thyroid uptake and retention curves for these animals are shown in Figure 2. In this case, the uptake by the animals exposed prenatally is presented in terms of percent of the total dose administered to the dam. Age-related differences in level of incorporation were similar to those observed at the lower dose level (Figure 1). However, the shape of the retention curves are clearly altered by the radiation

FIGURE 1. Interrelations of Age and Dietary Iodine on the Incorporation and Retention of Intra-peritoneally Injected ^{131}I

FIGURE 2. Influence of Dose on Uptake and Retention of Injected ^{131}I by Rats of Various Ages

effect produced at higher levels of ^{131}I incorporation.

Conclusions

A low-iodine diet alters the metabolism of administered radioiodine at all ages, and to a degree which

varies markedly with age. Pregnancy tends to decrease the incorporation of radioiodine in the thyroid gland. Administration of thyroid-damaging levels of radioiodine alters incorporation and retention in a manner which is complexly related to age and radiation dose.

AGE-RELATED DIFFERENCES IN THE METABOLISM OF ^{137}Cs BY THE RAT

The whole-body retention and tissue distribution of ^{137}Cs was measured over a 30-day period in newborn and adult rats. The rate of loss was initially slower in the newborn but accelerated after the second week. Other age-dependent dissimilarities were noted in distribution among various tissues.

Investigators:
D. D. Mahlum
M. R. Sikov

Technical Assistance:
Joan O. Hess

We previously reported that ^{137}Cs does not pass freely from the maternal circulation to the fetus and that the distribution of ^{137}Cs differs in the fetus, newborn and adult (Annual Report, 1966). In a continuation of these studies we have compared the retention and subsequent redistribution of ^{137}Cs in the neonatal and adult rat hoping to clarify the changes in cesium metabolism which must occur during the neonatal period.

Observations

Newborn and adult rats were injected intraperitoneally with 7.5 μCi of ^{137}Cs . The whole-body radio-

activity was assayed immediately after injection and semi-weekly thereafter for a 30-day period. Other newborn and adult rats were injected with 10 μCi of ^{137}Cs and randomly selected animals killed at 1, 3, 9, or 23 days postinjection for analysis of radioactivity in selected tissues.

Newborn rats initially retained a somewhat larger fraction of the administered dose than did adults (Figure 1). However, at approximately 2 weeks postinjection the body burden of the neonates began to decrease more rapidly so that by the end of the 30-day experimental period the adults had twice the ^{137}Cs content of the neonates.

FIGURE 1. Retention of Intra-peritoneally Injected ^{137}Cs by Adult and Neonatal Rats

The concentrations of ^{137}Cs in several tissues of the neonate and adult at 1, 3, 9, and 23 days after injection are shown in Table I. To facilitate comparison, values have been normalized to the concentration in striated muscle for the given age and time of sacrifice. At 24 hr postinjection, the neonates show a generally more uniform distribution than do the adults. These differences are less apparent by 9 days postinjection, as a result of more rapid elimination from some adult tissues. By 23 days postinjection, the values were similar for most tissues in both age groups, with the notable exception of blood and most

TABLE I. Relative Concentrations of Tissue ^{137}Cs in Adult and Newborn Rats (Tissue Conc./Muscle Conc.) at Various Times After Injection

Tissues	Newborn ^(a)				Adult ^(b)		
	1 Day	3 Day	9 Day	23 Day	1 Day	9 Day	23 Day
Blood	0.16	0.21	0.19	0.13	0.27	0.095	0.076
Diaphragm	1.51	1.26	1.01	0.57	2.36	1.02	0.67
Kidney	1.65	1.53	1.41	0.79	2.76	0.75	0.57
Liver	1.26	1.36	1.23	0.50	3.00	0.62	0.50
Heart	1.08	0.95	0.83	0.45	2.25	0.54	0.44
Trachea	0.61	0.71	0.33	0.26	0.78	0.36	0.21
Larynx	0.90	0.86	0.56	0.33	1.82	0.53	0.42
Sternal Rib	1.01	1.09	0.78	0.64	1.30	0.83	0.57
Vertebral Rib	0.77	0.93	0.56	0.32	0.92	0.40	0.12
Skull	0.40	0.47	0.38	0.14	0.21	0.07	0.04
Xiphoid	1.61	0.98	0.41	0.29	0.81	0.10	0.13
Femur	0.61	0.63	0.49	0.30	0.46	0.20	0.15

(a) Average values from 3 animals

(b) Average values from 2 animals

skeletal tissues which remained relatively higher in the young animals than in the adults.

Conclusions

The rate of loss of ^{137}Cs from neonatal rats was slower than from adults during the first 2 weeks following administration of the nuclide

as indicated by both total body counting and tissue analyses. Thereafter, the rate of loss from the neonate increased, resulting at 30 days postinjection in a distribution pattern more similar to that of the adult and a total ^{137}Cs burden which was half that of the adult.

METABOLISM OF ^{143}Pm IN A MINATURE SWINE

At 100 times the projected dose in human studies, ^{143}Pm caused no toxic effects in a male pig. The isotope is an easy-to-use tracer for ^{147}Pm , simplifying whole-body counting and radioanalyses of blood, urine, and feces.

Investigators:
V. H. Smith
R. L. Amster
C. R. Watson

Technical Assistance:
Alison T. Clark

As a precaution before using ^{143}Pm in studies with human volunteers (to be jointly undertaken by Battelle-Northwest and the Hanford Environmental Health Foundation), a male 71.3 kg Hanford Miniature Swine was intravenously injected with 9.56 μCi of $^{143}\text{PmCl}_3$ in 8 ml of pH 3.5 solution. This was 100 times the projected human dose. The animal was observed for any signs of toxicity, blood and excreta were collected for radioanalysis, and periodic total-body counts were made. Results are available for the first 28 days postinjection.

Observations

No pyrogenicity or other sign of toxicity from the injectant was noted. After 28 days about 0.027% of the administered radionuclide is in the circulating blood. The disappearance of ^{143}Pm from the blood appears to follow a power function (Figure 1) where concentration as percent of injected dose per gram blood is given by the expression

$$c = 59 \times 10^{-5} t^{-0.58}$$

FIGURE 1. Disappearance of ^{143}Pm from the Blood of a Pig

This expression will be more precisely defined as more data become available.

Excretion data are shown in Figure 2. About 10% of the injected promethium is accounted for in the excreta up to the twenty-eighth day

Urinary excretion was unusual in that this pig did not urinate for the first 3 days of the experiment.

Whole-body counting data, as shown in Figure 3, are not in good agreement with the excretion data, indicating nearly 25% removal by the

FIGURE 2. Daily Excretion of Intravenously Injected ^{143}Pm (No samples were collected between 14 and 21 days, and between 21 and 28 days.)

FIGURE 3. Retention of Intravenously Injected ^{143}Pm in a Pig as Determined by Whole-Body Counting

twenty-eighth day. The first day value for total-body count was no doubt influenced by the unusual excretory behavior of this pig. Otherwise, the data agree well with those of Stuart for retention of intravenously injected $^{148\text{m}}\text{Pm}$ in dogs (Annual Report, 1963).

Conclusions

The injectant elicited no pyrogenicity and from that standpoint

appears safe for human use. No other toxic effects have been noted. This particular isotope appears well suited for fairly long-term metabolism studies, although the blood disappearance is rapid enough that radioanalyses become difficult after the first week, even with doses of $0.13 \mu\text{Ci/kg}$. Based on measurements taken thus far, the $10\text{-}\mu\text{Ci}$ dose of ^{143}Pm appears to be a good choice for further animal metabolism studies.

PRODUCTION AND DOSIMETRY OF EXPERIMENTAL QUANTITIES OF ^{237}Pu

Plutonium-237, an electron capture isotope which emits a 60 keV gamma ray and $K\alpha$ and $K\beta$ X rays of ^{237}Np , was produced in experimental quantities. This material is being investigated for use in plutonium metabolic studies in animals with possible extension to use in human testing.

Investigators:

*I. C. Nelson**
*A. J. Haverfield**
*W. W. Schultz***

Plutonium-237 has been demonstrated as a tracer in animal studies of plutonium metabolism and excretion.⁽¹⁾ Its potential usefulness in human studies is suggested by the fact that its decay is accompanied by photon emissions easily measured from outside of the body, when injected at levels which would result in a very small radiation dose to the body. In practice, however, the production of ^{237}Pu is accompanied by the production of contaminating, long-lived, alpha-emitting isotopes. To investigate the suitability of ^{237}Pu for animal and human studies, a small amount of the material was produced for testing and evaluation.

Observations

The ^{237}Pu was formed by the ^{235}U (a, 2n) ^{237}Pu reaction produced by irradiating a 93% enriched ^{235}U foil with 27.5 MeV helium ions in the 88 in. cyclotron at the Lawrence Radiation Laboratory, Berkeley, California.

The bombardment consisted of 84.0 μA hr at a rate of 10 $\mu\text{A/hr}$.

The solution of the irradiated target in HNO_3 was subjected to two cycles of anion resin purification. The final product, on August 31, 1967, consisted of 5.1 μCi ^{237}Pu and 1.1 nCi alpha-emitting contaminants contained in 1.6 ml of nitrate solution. The contaminants are identified in Table I.

The photon spectrum of the purified product, as obtained using a Ge(Li) detector, is shown in Figure 1. All of the peaks shown were identified as the ^{237}Pu gamma or as X rays from the ^{237}Np daughter. No higher energy peaks were observed. The absolute emission rate of the photon radiation, calculated from the work of Hoffman and Dropesky,⁽²⁾ is given in Table II. The half-life was previously established as 45.6 days.⁽³⁾

The decay of ^{237}Pu is also accomplished by emission of an alpha particle, 3.3×10^{-6} of the time, to ^{233}U , which has a half-life of 1.6×10^5 years. This mode of decay is sufficiently infrequent to be neglected in dose calculations. The energy Q of the electron capture mode of decay is 0.22 MeV.

* *Biophysical Sciences Section,
 Environmental and Radiological
 Sciences Department*

** *Materials and Process Chemistry
 Section, Chemistry Department*

TABLE I. Plutonium-237 Contaminants

Radionuclide	Percent Abundance	pCi/ μ Ci ^{237}Pu
^{236}Pu	42.60	91
^{238}Pu	24.88	53
^{239}Pu and/ or ^{240}Pu	15.09	32
^{233}U and/or ^{234}U	2.96	6.3
^{228}Th	4.83	10.3
^{224}Ra	2.41	5.1
^{220}Rn	2.41	5.1
^{216}Po	2.41	5.1
^{212}Bi	0.80	1.7
^{212}Po	1.61	3.4

Because plutonium is a bone seeker, it was assumed that bone constituted the critical organ of interest and the dose to that organ was calculated. Calculations were based on standard man parameters and on an intravenous injection of $1 \mu\text{Ci } ^{237}\text{Pu}$ as it was constituted on August 31, 1967. Dose calculations were made with reference to radium wherein one maximum permissible body burden sustained delivers 0.56 rem/week to bone. The results of the dose calculations are shown in Table III. Contributions from ^{236}Pu , ^{238}Pu , ^{239}Pu , ^{233}U , and ^{228}Th in addition to ^{237}Pu were considered. The dose from the other alpha-emitting contaminants was negligible.

The total dose contributed by the ^{237}Pu itself was less than 100 mrem. The principal dose after 20 years is contributed by ^{238}Pu and ^{239}Pu .

FIGURE 1. Plutonium-237 Photon Spectrum, Ge(Li) Detector (20 cm^3)

TABLE II. Principal Photon Emission-Plutonium-237

Photon	Approximate Energy, keV	Approximate No. of Photons/100 Dis.
Neptunium L X-rays	17	30
Neptunium K X-rays	100	40
Unconverted gamma rays	60	5

TABLE III. Calculated Dose to Bone From $1 \mu\text{Ci } ^{237}\text{Pu}$ Plus Contaminants Injected Intravenously

Year, Post-injection	Dose Rate, mrem/year	Accumulated Dose, rem
1	220	0.22
2	109	0.33
3	96	0.42
4	85	0.51
5	79	0.59
10	60	0.94
15	53	1.2
20	49	1.5

Conclusions

This experiment showed that it is possible to produce ^{237}Pu in microcurie amounts without significant gamma-emitting contaminants. There are formed, however, measurable amounts of alpha-emitting contaminants. It is estimated that the longer lived of these contaminants would deliver about 50 mrem/year to bone per microcurie ^{237}Pu injected. Another irradiation will be scheduled at a lower helium ion energy, but for a longer total irradiation time,

in an effort to reduce the proportion of longer-lived alpha contaminants.

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