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PROGRESS REPORT FOR THE MONTH OF JUNE 1945

CONTRACT # W-7405-eng-48-A

Joseph G. Hamilton, M.D.

June 14, 1945

CLASSIFICATION CANCELLED
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PART I

SUMMARY

A. METABOLIC STUDIES OF FISSION PRODUCTS

The soil and plant studies have been concluded for the present and a final report is being prepared. The long term aerosol studies are being continued. A special series of smoke studies appear in a separate report. A method for the isolation of Pa^{233} free from fission products, uranium, and thorium is being developed.

B. METABOLIC STUDIES OF PRODUCT

The retention of Plutonium by the lungs of rats exposed to the inhalation of PUO_2 smokes was found to be approximately 5% of the originally inhaled activity, 256 days after exposure. The rate of elimination of the retained activity in the lungs at the end of this 8½ months interval was approximately 0.5% per day. The behavior of both Plutonium and fission products following inhalation of PUO_2 smoke containing fission product was found to be very similar 64 days after exposure.

A patient suffering from carcinoma of the stomach, received, by intravenous injection, approximately 5 gms of plutonium as $PUO_2(NO_3)_2$, enriched with Pu^{238} so that the activity was equivalent to 50 μgms of Pu^{239}. Four days later, as a result of surgery, specimens of bone, spleen, tumor, omentum, and skin were obtained. The distribution pattern of these tissues were very similar to that observed in rats. The highest degree of deposition within the bone was present in the trabecular portion of the marrow. The rate of urine elimination was low falling below 0.1 percent per day at the end of 16 days.

A new method for the relatively rapid analysis of large specimens of urine and feces has been developed, whereby it would be possible to detect 5×10^{-6} gms of plutonium in each days output of urine or feces. A detailed description of this method is being forwarded to the appropriate parties in all operating areas.

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PART II [redacted]

SECTION A.

TECHNICAL PROGRESS REPORT ON THE METABOLIC STUDIES OF PRODUCT

1. Radioautographic Studies

Additional bone radioautographs, including samples from a rib of a human subject, are in various states of preparation. A large series of specimens from animals subjected to the decalcification-calcification cycle of treatment will soon be available for radioautographic study.

2. Tracer Studies

The two animals exposed to PUO_2 smoke were sacrificed 256 days later and the results obtained with these two animals appear below. More animals exposed both to PUO_2 smokes and $PUO_2(NO_3)_2$ aerosols are being carried along. Since with only two animals, these results can only be considered qualitative in character.

TABLE I

The Percent Distribution of Plutonium in Two Rats 256 Days After Inhalation of PUO_2 Smoke

Tissue	Rat #1	Rat #2	Average
Lungs	6.18	3.38	4.78
Liver	.014	.042	.028
Kidney	.0015	.0005	.001
Spleen	.0023	.0039	.0031
G. I.	.022	.0070	.015
Head	< .05	< .05	< .05
Skeleton	.16	< .20	< .20
Balance	.032	.014	.023
Urine	2.34	2.42	2.38
Feces	91.2	93.8	92.5

In Table II there is presented the rate of excretion per day of the activity remaining in the animals at the indicated time intervals.

TABLE II

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TABLE II (con.)

The Percent Excretion of Retained Plutonium From the Rats at the Indicated Time Intervals.

Day	Total Excretion Per Day*	Lung Activity*	Percent Excreted Per Day
8 (4-16)	139.9	2604	5.25%
16 (8-24)	59.5	1896	3.14%
32 (24-40)	11.9	1531	.78%
64 (40-80)	10.77	1244	.87%
96 (72-112)	7.53	918	.82%
128 (103-144)	7.20	737	.98%
192 (144-224)	2.47	446	.55%
256 (200-256)	1.29	362	.36%

*Indicated as the average number of counts per second for the two animals.

The three most significant facts to be noted in this experiment are as follows: First, a very significant amount of the originally inhaled PUO_2 is retained by the lungs after eight and one-half months in the rat. Second, there is only a very slight degree of absorption from the lungs, with deposition in other tissues. Third, a very significant rate of loss of material from the lungs continued at a diminishing rate for the 256 day interval. More precise evaluation of the values for lung retention and rates of excretion at this prolonged interval will be available later. However, I doubt if the present figures for the rat will have to be revised at that time by more than a factor of two.

The results are now available from a group of three rats sacrificed 64 days following exposure to PUO_2 smoke prepared from neutron irradiated plutonium metal and the salient facts are summarized in the following table.

TABLE III

The Distribution of Plutonium and Long-lived Fission Products in the Same Rats 64 Days after Exposure to PUO_2 Smoke Prepared from Neutron Irradiated Plutonium Metal.

Tissue	Plutonium	Fission Products
Lungs	8.38%	9.51%
Liver	< .01%	.028%
Kidney	< .01%	.033%
G. I. Tract	.09%	.088%
Spleen	< .01%	.014%
Head	< .20%	.20%
Skeleton	< .50%	.27%
Balance	< .20%	.12%
Urine	1.20%	3.09%
Feces	90.40%	87.60%

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It is interesting to compare these results with the corres-ng data for the 0, 4, and 16 day intervals which appear in the April 1945 thly Report. One inconsistency appears in the relatively lower skeleton alues at the 64 day interval for fission product deposition. Otherwise the pattern is consistent and the distribution of the two types of active material remained quite similar. The rates of excretion (chiefly lung activity) per day were .29% for plutonium and 1.90% for fission products of the corresponding material remaining in the body at the end of the 64 day interval. The plutonium excretion rate, at the same interval, was greater in the other experiments noted above. Those figures in Table III indicate the similarity between the two types of active material but certain qualitative differences, such as the greater degree of absorption through the lungs, and more rapid excretion of the fission products are evident.

Longer term animals exposed to this type of PUO_2 smoke are on hand and will be sacrificed at the appropriate intervals.

May 14, 1945, a human subject, suffering from a carcinoma of the stomach, received approximately 5 gm of plutonium as $PUO_2(NO_3)_2$ by intravenous injection in a solution of isotonic NaCl at Ph4. This sample of plutonium contained sufficient Pu^{238} to increase the specific activity of the injected material to the equivalent of 50 gms of Pu^{239}. Four days later, the patient was operated upon and specimens of rib, spleen, tumor, omentum, subcutaneous tissue, and skin were obtained. At the same time, a sample of blood was also secured. Unfortunately, the surgeon failed to secure a specimen of liver. The patient is a 50 year old male, weighs 58.1 kilograms, and is in good general physical condition, aside from the tumor. All excreta has been collected at daily intervals since the time of injection of the plutonium.

The content of plutonium in the different tissues in terms of percent of the administered dose is given in the following table together with the excretion per day. Due to the surgical procedure, the patient was on a very restricted diet with the result that for the first two and one-half weeks, little fecal elimination took place. The per organ content of skeleton and blood were taken on the basis of these structures, representing 15% and 10% respectively of the patient's weight. The sample of rib was carefully slit open, the marrow removed by gentle washing with normal saline and then the trabecular bone and endosteum were scraped away from the cortex. The periosteum was likewise removed from the cortical bone and all four components assayed for their plutonium content.

The relatively high content of plutonium in the separated trabecular material from the specimen of rib, which also contained the endosteal tissue, is correlated with the radioautographic studies in animals. It will be recalled that bone radioautographs showed the bulk of the plutonium to be concentrated in the endosteal region and about the trabecular bone. The relatively low values for cortical bone and periosteum likewise follow the pattern indicated by the animal studies. However, the high plutonium content of the marrow in man was surprising since no indication of this fact was evident from our animal studies. The possibility of entrapment of plutonium in the colloidal state by the phagocytic cells in the marrow is ruled out in our opinion for two reasons. First, animal studies done concurrently by intravenous injection of aliquots from the same solution of plutonium given

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patient showed no excessively high concentration in either the liver nor the spleen. When the material is colloidal in character, very high uptake values for these two organs have been consistently observed. Second, the plutonium content of the spleen of the patient was quite low. The possibility of leaching of the plutonium from the endosteum, when the marrow was washed out from the bone, is very unlikely due to the fact that under the far more rigorous conditions surrounding decalcification of bone with dilute acid, very little leaching takes place. We have not received radioautographs from rats receiving plutonium by intravenous injection and further more, all bone radioautographs available at present from Berkeley have been from animals that had received the material two months or longer before they were sacrificed. During this interval, the plutonium may have migrated from the marrow to the trabecular bone and the endosteum. Because of these two gaps in the picture, we cannot state that under the conditions of this human study, the same type of marrow concentration does not exist in the rat. We are now going to secure bone radioautographs from rats under comparable conditions in an attempt to settle this point.

TABLE IV

The Distribution of Approximately 5 gms of Plutonium in a Human Patient, 4 Days Following the Intravenous Administration of the Material as $PuO_2(NO_3)_2$. The Excretion Data for the First 18 Days Following Administration is Included.

	% per Organ	% per gram
Cortex		.0072
Marrow		.019
Spicules		.032
Periosteum		.0048
Whole Bone	87.2	.010
Spleen	.22	.0019
Tumor		.0011
Omentum		.00043
Skin		.00048
Subcutaneous Tissue		.00037
Blood	7.49	.0013
Plasma		.0023
RBC		.00028

Excretion Data

	1	2	3	4	5	6	7	8	9	10	11
Urine	.48	.15	.12	.031	.057	.014	.014	.016	.068	.026	.036
Feces				.31					.0092		

	12	13	14	15	16	17	18	19
Urine	.029	.017	.017	.013	.016	.0056	.010	.0062
Feces							.017	.010

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The human excretion data indicates that the rate of urinary elimination is almost the same for rats given a portion of the same solution

tonium, see Table V.

TABLE V

A Comparison of the Rates of Excretion of Plutonium in the Rat and Man Following the Intravenous Administration of $PUO_2(NO_3)_2$

Day	RAT % Dose per Day		MAN % Dose per Day	
	Urine	Feces	Urine	Feces
0 - 1	.32%	1.39%	.48%	
1 - 2	.15%	2.83%	.15%	.076%
2 - 3	.061%	1.54%	.12%	
3 - 4	.033%	1.92%	.031%	
5 - 8	.023%	1.35%	.020%	
9 - 16	.031%	———	.028%	.0026%*

* Also includes feces through 19 days.

The fecal excretion in the patient was far less but perhaps is related to his operation and subsequent lack of fecal output. More specimens will have to be accumulated before any conclusive opinion can be reached in regard to the rate of fecal excretion of plutonium by this patient.

It is planned to continue the daily collections of both urine and feces from this patient for an indefinite period. In addition, there is enough PU^{238} for another human study when a suitable patient is available. It should be pointed out that we feel the use of Pu^{238} as a tracer for a limited number of selected patients is desirable since it is possible to use from 1 to 5 , gms of plutonium, which is the range of dosage in man that is of greatest interest, due to the high specific activity of this material.

Mr. Scott has recently developed a method for the reasonably rapid and quantitative extraction of plutonium from 24 hour collections of both urine and feces. The material is ashed and then the plutonium extracted from the ash by means of Hexone. From 75% to 80% recovery has been consistantly obtained. The entire procedure of ashing, extraction, and counting can be done with an average expenditure of 2 hours per sample, providing adequate facilities for ashing are available. This method is readily adapted to handling up to ten days accumulation of urine. The final precipitate is mounted on platinum dishes 5 centimeters in diameter to reduce self-absorption but even under these conditions our background of the counter is approximately one count per minute. On the basis of using 10 day urine samples, it should be possible to detect a daily excretion of 2×10^{-6} gms per day. Difficulty of securing alpha particle free reagents, particularly zirconium and lanthanum, presents a serious problem and must be kept in mind. Mackay's Lanthanum and Zirconium are particularly bad in this respect. The alpha activity from these

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resents follows very closely the chemistry of plutonium in this type of separation.

Our work with plutonium has been greatly facilitated by the extensive cooperation given to us by the different members of Doctor Latimer's group and in particular, by Doctor Connick who supervised the preparation of the sample of Pu^{238} and assisted Mr. Scott in developing his method for assaying large samples of urine and feces.

3. Decontamination Studies

Preliminary results indicate that the technique of overlayering the endosteal region of the bone by the decalcification-calcification cycle, described in an earlier report may be successful. Additional data to either substantiate or deny this most hopeful procedure will shortly be available.

4. Soil Studies

Experiments were conducted to determine the degree of fixation of product in its three valence states, on clay. For preliminary experiments, a hudrogen clay (Death Valley Bentonite) was suspended in distilled water at Ph 4.5. Although product in the +3 and +4 states tends to precipitate at the hydrogen ion concentrations used, it is believed that the data nonetheless show pronounced adsorption of these states on the clay. The percentage adsorption of the three valence states on hydrogen clay suspensions of various strengths is given in the following table:

Percent Conc. of Clay	Percent Fixation of +3	Percent Fixation of +4	Percent Fixation of +6
.01	94.2	66.0	18.6
.05	98.5	94.5	68.0
.10	98.7	----	95.0
.50	99.0	----	99.1
1.00	99.3	----	99.4

Additional experiments are being carried out to determine the fixation of product on clay under conditions of greater acidity and electrolyte concentration. It is of interest to note that a pronounced difference in the behavior of +3 and +6 plutonium exists in the higher dilutions of clay which then vanishes at the higher clay concentrations. The lower affinity of clay for +6 plutonium is probably due to the fact that +6 plutonium exists in solution as the plutonyl (PUO_2^{++}) ion while in the +3 state, it exists as Pu^{+++}. The affinity of clay for cations is proportional to the number of positive charges carried by the ions in solution.

Experiments are in progress to ascertain the availability of the three valence states of product to plants.

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5. Projected Studies

The tracer, soil, plant, smoke, radioautographic and human studies are to be continued for the next two months.