700099

III B 26 (21)

~~SECRET~~ ~~LIMITED~~ DECLASSIFIED

CN-3167
H-C

CLASSIFICATION CANCELLED 1/2/57
FOR ATOMIC ENERGY COMMISSION
BY
TECHNICAL INFORMATION SERVICE
AECD NUMBER None
TRB

Contract No. W-7405 eng-39

HEALTH DIVISION
R.S. Stone, Director

REPORT OF CONFERENCE ON PLUTONIUM - MAY 14th and 15th

edited by
J.J. Nickson

July 23, 1945

The designation "LIMITED" indicates a report dealing with information which is more restricted than the usual C reports are to persons receiving C reports to show them to other members of the project, even of the same laboratory, without specific authorization.

Report received: July 25, 1945
Issued: JUL 28 1945

DECLASSIFIED

This document contains information affecting the National defense of the United States within the meaning of the Espionage Act...

3389 01

0000879

~~SECRET~~ LIMITED

~~SECRET~~ ~~LIMITED~~

Table of Contents

3389 02

LIMITED

I Summary of Requests for Information Desired Concerning Plutonium

Drs. L. H. Hemplemann, S. T. Cantril, J. E. Wirth, J. J. Nickson and Mr. S. G. English wrote the letters on which this section is based. Immediate problems of importance about which further information is needed are emphasized.

I Diagnosis and Estimation of the Amount of Plutonium in the Human Body

A. Detection of amounts in the body in excess of the permissible level

1. Development of a satisfactory means of assay of urine and feces

a. Need more information on elimination rate as a function of time
b. Need more information on elimination rate as a function of route of intake

2. Determination of percentage of plutonium excreted daily by humans

3. Can blood samples be utilized for this purpose?

B. Detection of plutonium in the lung

1. Development of a satisfactory means of estimation of the amount of plutonium in the lung

2. Compounds of interest are +3, +4, nitrate in aqueous solution, +6 nitrate in ether solution, tetrafluoride, +4 oxide, +4 oxalate, +4 peroxide as slurry

C. Development of a method for detection and quantitation of plutonium in wounds

II Absorption

A. Skin

1. Need more information on absorption rate on various plutonium compounds through the intact skin

2. Is absorption influenced by use of potassium permanganate solution followed by sodium hypo-sulphide solution on the skin?

B. Gastro-Intestinal tract

1. Need more information on absorption rates of various plutonium compounds. Specific information is desired about those compounds mentioned under "diagnosis".

2. Can the elimination of plutonium be used in the event of gross intake to detect the amount that will be fixed in the bone?

C. Wounds

1. The rate of diffusion of plutonium from the wound area

2. The effect of different plutonium compounds on the rate of diffusion

3. How is the distribution pattern altered by having different sorts of wounds, e. g. puncture wounds as opposed to lacerations?

D. Lung

1. How much of the amount breathed is retained in the human lung?

2. How much material is absorbed from the lung to the blood and then to the skeleton?

III Permissible Levels of Plutonium

A. In the lung

B. In the bone

C. What is the minimum amount necessary to produce damage in the body?

D. Are the alpha rays from plutonium capable of producing damage to the skin?

IV Metabolism

A. Distribution pattern as a function of rate of intake

B. Distribution pattern as a function of diet

C. What is the rate of elimination of plutonium from bone?

D. Are the differing diets in the different laboratories effecting the results of animal experiments?

V Pathology

A. What is the nature of liver damage after intravenous administration of plutonium?

B. What is the nature of liver damage after sub-lethal doses given through other routes of entry?

C. Does pre existing kidney damage diminish the elimination of plutonium from the body? Should persons with kidney damage be excluded from working with plutonium?

VI Therapy

A. Development of methods of increasing elimination from the body

1. Effect of diet

2. Effect of injection of complexing or other agents

B. Methods of covering up material deposited in bone

C. Development of methods of therapy for plutonium in wounds (specific mention is made of those compounds mentioned under "diagnosis")

1. The effect of suction

2. The effect of increased venous flow

D. Formulation of a recommended procedure for treatment in case of a known over-dosage by inhalation, by mouth, or by wound

E. How much time can lapse before treatment must be instituted?

VII Protection

A. Is inactive dust in a work area an additional hazard in that it increases the probability of breathing plutonium?

B. Improvement of existing means of the physical protection of personnel from ingestion, inhalation or direct innoculation of plutonium

C. Development of a method for the rapid determination of the quantity of plutonium in the atmosphere

D. Development of a continuous monitoring device for atmospheric or dust borne plutonium which is effective in concentrations just above or at tolerance levels

E. Analysis of masks and respirators for percentage efficiency in filtering out various chemical forms of plutonium. Special mention was made of +4 and +6 nitrate, +3 and +6 sulphate, +3 and +4 chloride, +4, +5 and +6 carbonate.

F. Do various chemical structures play some part in the efficiency of respirators or is particle size the important factor?

VIII Plutonium-radium Ratios

A. What ratio for acute effects?

B. What ratio for chronic effects?

II Distribution of Injected Plutonium

R. D. Finkle

The distribution of plutonium in a dog 16 days after the administration of a lethal dose of plutonyl nitrate is shown in Table I. The skeleton contained 44% of the injected dose, (assumed 17% of body wgt.) liver 31%, muscle 8% and spleen 3.5%; 10% was excreted. The table with spleen at the top is arranged in order of decreasing amount of plutonium per gram of tissue, except for the bones which are the last three entries.

Femur, sternum and rib were the three bones sampled and were found to have the same concentration (0.033% of the injected dose per gram of tissue) within 17%, while a tooth was about 1/9 as active as bone. Marrow from the femur was 13 times more active than an equal weight of compact bone. 98% of the plutonium in the marrow was found in a fraction containing the spicules (Table II).

Plasma contains approximately 80% of the plutonium in samples of blood. Most of the metal in the plasma was attached to the globulins, probably largely on the beta globulin fraction.

The intravenous injection of plutonyl nitrate into mice yielded livers which retained over 27% even after 64 days. (Table III) This was not the case when plutonyl citrate was used. (Table IV) The liver content fell from 36% to 14% on the 31st day and to 7% on the 64th day. From the 4th to the 31st day the decrease was exponential with a half time value of 20 days. Mice which received plutonyl nitrate, intramuscularly, had liver retention which decreased exponentially and with a half time value of 20 days. Very little difference in metabolism at 33 days was found in the main series, with 0.5 mg/kilo and a group of four animals with 4.5 mg/kilo, except that the retention around the site of injection was somewhat greater with the higher dose. Dr. Hamilton's data (Tables VII and VIII) with plus 4 and plus 6 plutonium nitrates a administered intramuscularly to rats show relatively small concentration of the absorbed fraction in the liver except with plus six at four days.

Plutonyl citrate was injected into the peritoneal cavity of mice and was slowly absorbed in 64 days as indicated by the rise of the femur content to a value equivalent to 45-55% in the entire skeleton (Table VI). The livers contained over 30% of the dose, at first. Radio autographs demonstrated that the material was distributed throughout the liver in a normal manner rather than as a surface coating. Plutonyl nitrate, intraperitoneally, behaved similarly but was somewhat more slowly absorbed and, therefore, was retained longer by the liver.

The general biological reaction to administered plutonium appears to be a deposition of 50% of the material in skeleton and early retention of 20-40% by the liver. In most cases the amount in the liver decreases to 5-10% within 64 days.

Note: The concentration of plutonium in whole blood is presented in Table XIX.

Table I

DOG #33 - [DATA FROM RUSSELL]

DISTRIBUTION OF PLUTONIUM (+-NITRATE)

IN THE VARIOUS TISSUES 16 DAYS AFTER INJECTION (I.V.)

TISSUE	CONCENTRATION OF Pu/Gram	Per Cent of Injected Pu	Pu/Gram TISSUE / Pu/ml. BLOOD
Spleen	6.16 μg	3.560	560.
Liver	3.209	30.6	281.
B. Lymph Nodes	1.17	0.0218	106.4
Gall Bladder	0.93	0.031	84.5
Kidney	0.19	0.29	17.2
Adrenal	0.153	0.0034	13.9
Tooth	0.09	---	8.2
M. Lymph Nodes	0.085	0.085	7.7
Muscle	0.0808	---	7.35
Lung	0.06	0.129	5.45
S. Intestine	0.051	0.302	4.64
L. Ovary	0.051	0.009	4.64
Ureter	0.039	0.0003	3.55
Bladder	0.027	0.0025	2.45
Pancreas	0.027	0.0037	2.45
L. Intestines	0.0227	0.0263	2.07
Blood	0.011	---	1.00
Stomach	0.0097	0.0308	0.89
Pelvis of Kidney	0.009	0.0002	0.82
Heart	0.00875	0.0088	0.79
Brain	0.00182	0.0045	0.17
Bile	0.0000	0.0000	0.00
Femur	0.821	---	75.0
Sternum	1.07	---	97.0
Rib	1.14	---	103.6

Table II

DISTRIBUTION OF PLUTONIUM IN BONE

TISSUE	WEIGHT	TOTAL PLUTONIUM	CONCENTRATION Per Gram	Pu/Gram / Pu/ml.Blood	% of Injected Plutonium
1. Femur	37.30 μg	30.40 μg	0.821 μg	75.0	1.14%
(a) Periosteum	2.10	0.73	0.36	32.8	
(b) Marrow	0.176	0.11	0.625	56.9	
(c) Hard Bone from Diaphysis	2.41	0.155	0.064	5.8	
(d) Marrow	0.343	0.317	0.930	84.6	
(Spicules)		0.310	---	---	
(Cells)		0.0071	---	---	
2. Sternum (Parts)	7.80	8.32	1.07	97.3	
3. Rib (6th Right)	3.56	4.17	1.14	103.6	

3389 C8

000088b

Table III

The Distribution in Tissues Following an Intravenous Administration of Plutonyl (+6) Nitrate to Mice

% Per Organ of the Retained Portions
Average Values From Four Mice at Each Time

ORGAN	4th Day	8th Day	14th Day	31st Day	64th Day
Liver	36.3	37.8	33.1	30.1	27.5
Spleen	3.27	4.48	4.07	2.36	2.32
Kidney	1.02	0.72	added	0.41	0.36
Lung	0.57	0.52	to	1.01	0.72
Femur	1.33	1.69	carcass	1.69	2.21
Carcass	57.7	51.8	62.6	64.3	66.9

Table IV

The Distribution in Tissues Following an Intravenous Administration of Plutonyl (+6) Citrate to Mice

% Per Organ of the Retained Portions
Average Values From Four Mice at Each Time

ORGAN	4th Day	8th Day	16th Day	31st Day	64th Day
Liver	36.3	28.8	23.8	14.2	7.13
Spleen	2.78	2.93	3.45	2.44	1.52
Kidney	0.48	0.61	1.47	0.60	0.28
lung	1.09	0.76	0.71	0.69	0.22
Femur	4.36	4.29	2.48	2.48	3.05
Carcass	60.4	65.7	68.1	79.6	87.9

Table V

The Distribution in Tissues Following an Intra Muscular Administration of Plutonyl (+6) Nitrate to Mice

% Per Organ of the Absorbed and Retained Portions
Average Values From Four Mice

ORGAN	4th Day	8th Day	16th Day	33rd Day	64th Day	(4.5 mg/kilo) 33rd Day
Liver	19.4	20.9	15.2	7.90	3.92	13.7
Spleen	0.59	1.59	1.01	1.10	0.87	2.25
Kidney	0.81	3.45	0.87	——	——	——
Lung	0.68	——	0.69	——	——	——
Remaining Viscera	——	——	——	1.43	1.29	2.06
Femur	1.97	2.80	4.03	2.98	3.59	2.68
Carcass	73.9	68.1	70.2	76.6	84.8	74.3
	% of Total Retained Dose					
Site of Injection	65.4	62.4	57.9	63.6	45.2	88.1

Table VI

The Distribution in Tissues Following an Intraperitoneal Administration of Plutonyl (+6) Solutions to Mice

% Per Organ of the Retained Portions
Average Values From Two Mice

	Plutonyl Citrate			Plutonyl Nitrate		
ORGAN	4th Day	16th Day	64th Day	4th Day	16th Day	64th Day
Liver	33.8	41.7	8.70	32.4	37.4	21.5
Spleen	3.30	3.87	1.78	1.22	4.13	1.49
Kidney	0.98	0.66	0.64	0.18	0.74	0.15
Lung	0.17	0.24	0.22	0.27	0.36	0.65
Femur	0.66	1.23	1.81	0.48	1.00	1.72
Carcass	58.7	51.9	90.4	65.4	56.2	75.0

Table VII

"CORRECTED" DISTRIBUTION OF +4 PLUTONIUM IN RATS FOLLOWING INTRAMUSCULAR ADMINISTRATION (from Hamilton)

	FOUR DAYS		SIXTEEN DAYS		SIXTY-FOUR DAYS	
	% Per Organ	% Per Gram	% Per Organ	% Per Gram	% Per Organ	% Per Gram
Liver	3.52	0.30	5.24	0.80	2.62	0.35
Kidney	1.39	0.74	2.16	1.18	0.51	0.26
Testes			0.32	0.10		
Spleen	0.39	0.42	0.39	0.72	0.14	0.31
Muscle	1.36	0.015	2.76	0.036	2.81	0.032
Skin	9.23	0.22	2.28	0.055	0.79	0.029
Stomach	0.098	0.061	0.097	0.061	0.065	0.035
Sm & Lrg Intest.	2.43	0.24	1.24	0.12	0.51	0.044
Bone	70.7	3.42	59.4	2.76	64.0	4.31
Lungs	0.17	0.14	0.17	0.14	0.12	0.098
Brain	0.037	0.028	0.019	0.016	0.012	0.0089
Blood	2.38	0.17	0.16	0.011	0.25	0.015
Urine	0.65		1.05		3.23	
Feces	5.12		11.9		22.0	
Unab in Left Leg	95.7		87.6		68.1	

Table VIII

"CORRECTED" DISTRIBUTION OF +6 PLUTONIUM IN RATS FOLLOWING INTRAMUSCULAR ADMINISTRATION (from Hamilton)

	FOUR DAYS		SIXTEEN DAYS		SIXTY-FOUR DAYS	
	% Per Organ	% Per Gram	% Per Organ	% Per Gram	% Per Organ	% Per Gram
Liver	14.0	1.83	2.72	0.49	4.18	0.58
Kidney	1.95	1.13	0.68	0.40	1.70	0.90
Testes			0.14	0.051		
Spleen	0.37	0.63	0.32	0.58	0.52	0.88
Muscle	2.57	0.028	1.80	0.023	1.56	0.019
Skin	2.61	0.093	0.87	0.033	1.14	0.043
Stomach	0.66	0.19	0.082	0.042	0.15	0.075
Sm & Lrg Intest.	2.30	0.11	0.72	0.078	0.49	0.030
Bone	66.5	2.96	64.9	3.30	58.3	3.82
Lungs	0.33	0.25	0.14	0.12	0.16	0.11
Brain	0.031	0.023	0.012	0.0089	0.11	0.12
Blood	4.58	0.28	0.32	0.023	0.32	0.021
Urine	0.38		7.98		4.48	
Feces	7.58		19.3		26.3	
Unab in Left Leg	70.3		28.8		34.6	

III RETENTION OF INHALED PLUTONIUM

By Richard Abrams

The pertinent data are summarized in the accompanying tables. Tables IX and X apply to inhaled aerosols, and Table XI to intubated solutions.

Table IX is largely self-explanatory giving the types of compounds used, the methods of aerosol production, and the properties of the particles as observed in an electron microscope.

In Table X an attempt is made to indicate the fate of inhaled Pu aerosols. The column headed lung retention indicates the fraction of what is inhaled that deposits in the lung. Since the Pu in the lung is eliminated at a continuously decreasing rate it is impossible to give a single constant indicative of the rate; instead we have arbitrarily indicated the time needed for 50% and 90% elimination. The last two columns indicate the sites of greatest deposition. The liver reaches its maximum in 1 day and may then decrease somewhat. For the skeleton we have indicated what fraction of the originally retained dose is deposited and the time after exposure required to reach this maximum.

The final Table (XI) summarizes results on inhalation of solutions through tubes inserted in the trachea. For Pu (VI) and for Pu citrates elimination from the lung was rapid at first, followed by a sudden change to a slow rate (the latter presumably being characteristic of Pu IV). The half-times are given for each of these processes. It might be pointed out that the liver reaches a maximum in 1 day and may drop considerably thereafter, especially with Pu citrate. Also the fact is noted that citrate enormously accelerates the rate of transfer from lung to skeleton.

INHALATION OF PLUTONIUM AEROSOLS

TABLE IX

COMPOUND TYPE	AEROSOL PRODUCER	PARTICLES
NITRATES	Aqueous atomizer	Spherical, all below 0.2 µ
OXIDE	DC Carbon arc	Filamentous aggregate of 0.1 µ units (0.1 to 1.0 µ)
CUPFERRIDE	Freon bomb	

TABLE X

POUND	LUNG RETENTION	LUNG ELIMINATION TIME 50%	90%	LIVER MAXIMUM DEPOSITION (1 DAY)	SKELETON TIME	DEPOSITION
IV) nitrate	—	12 day	100 day	3%	> 20 day	25%
III) nitrate	7%	5	40	33	> 20	20
VI) nitrate	6	6	52	7	> 20	20
xide	8	20	—	—	—	—
(IV) cupferride	—	8	105	1	> 10 d	3

TABLE XI

TRACHEAL INTUBATION OF PLUTONIUM SOLUTIONS

OMPOUND	LUNG ELIMINATION HALF - TIME (DAYS) A	B	LIVER DEPOSITION 1 DAY	15 DAYS	SKELETON TIME	DEPOSITION
(IV) nitrate	12	- - -	1%	1%	15 days	4.5%
(VI) nitrate	1.8	20	5	2.5	15	20
(IV) citrate, (VI) citrate	0.7	15	20	7	>1	30

IV THE METABOLISM OF TISSUES OF PLUTONIUM TREATED RATS

E. S. Guzman Barron

It has been pointed out by Dr. Murray and by Dr. Brues that plutonium treated animals show great irregularity in their response to toxic doses of this substance. This irregular response might be due to the double action of plutonium as a heavy metal and as a radiation emitting substance. The radiation effects furthermore will be determined by the site of deposition of plutonium in the tissues.

The most constant effect of plutonium seems to be exerted on the blood-forming tissues. The spleen is considerably reduced in size in rats treated with intravenous injections of 2 mg plutonium per Kg. In these animals the size of the spleen has diminished by 70 per cent at the end of the 7th or 8th day after the injection (Figure III, 1). The diminution in size is accompanied with a diminution of the O_2 uptake of the tissue, (Figure III, 2) an indication that the substance has actually inhibited some mechanisms concerned with respiration in the spleen.

Another tissue in the rat constantly affected by plutonium is the thymus. The gland is considerably diminished in size and the QO_2 values go down day after day so that at the end of 9 to 10 days after injection they are only one third of the normal values (Figure III, 3).

The adrenals seem also to be profoundly affected by plutonium. On measuring the O_2 uptake, there is at first a sudden increase which subsides about the 5th day after injection to be replaced by extremely low values. In fact, 6 days after injection the QO_2 values decreased to 2.1 (forty per cent of normal) and remained constantly around this low value (Figure III, 4).

The inhibition of tissue respiration is not a general phenomenon. Thus, for example, the QO_2 values of the submaxillary glands remained little effected throughout the duration of the experiments (Figure III, 5). The same thing occurred on the respiration of heart muscle.

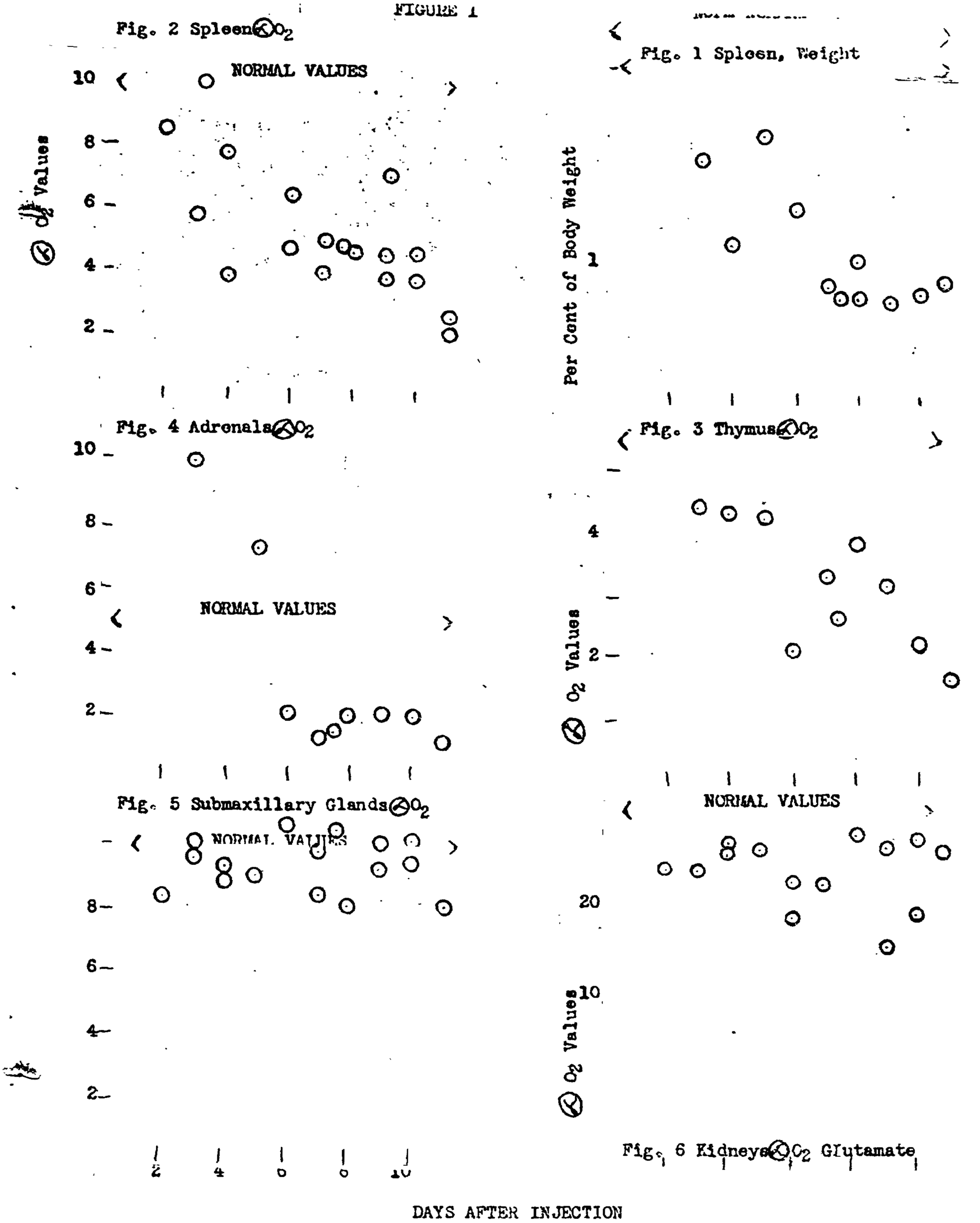
The response of the kidney to plutonium is variable. In some rats the kidneys were obviously damaged as shown by gross appearance and elevated blood NPN. In 31 rats treated with 2 mg of plutonium per Kg intravenously, NPN values from 50 to 60 mg per cent were found in 16 per cent; values from 60 to 80 in 20 per cent; finally, values above 80 in 16 per cent. Since normal NPN values in rats oscillate between 30 and 40 mg per cent, definitely high values (above 60) were found in 30 per cent of the treated rats. This kidney damage was confirmed by determining the rate of oxidation of glutamate (QO_2 glutamate) and of NH_3 formation. The QO_2 glutamate was generally lower than in control rats (Figure III, 6). The QNH_3 values were about half of the normal values (Figure IV, 7).

In the first experiments on tissue metabolism of plutonium treated rats we were struck by the remarkable appearance of the liver, which was yellow and quite friable. These tissues had almost lost the power of oxidizing pyruvic acid (marked with a cross in Figure IV, 8 and 9). These findings failed to appear in 23 rats treated in the same manner with plutonium. However, there was uniformly some inhibition of the

QO_2 pyruvate values (Figure IV, 8) as well as of the Q pyruvate values (Utilization of Pyruvate) (Figure IV, 9). The effect of product on the metabolism of fatty acids was irregular. In some cases there was an inhibition of the QO_2 butyrate values and the Q acetoacetate values (formation of acetoacetic from butyric acid) (Figure IV, 10) while in other animals these values were normal. There was also an inhibition of the anaerobic glycolysis (Figure IV, 11). If to these findings we add the changes observed in the electrophoretic pattern of the plasma proteins-low albumin and increased globulins it must be concluded that plutonium definitely produces liver lesions.

We have not yet determined the part played by the heavy metal and by radiation itself in these alterations.

FIGURE 1



0000894

FIGURE II

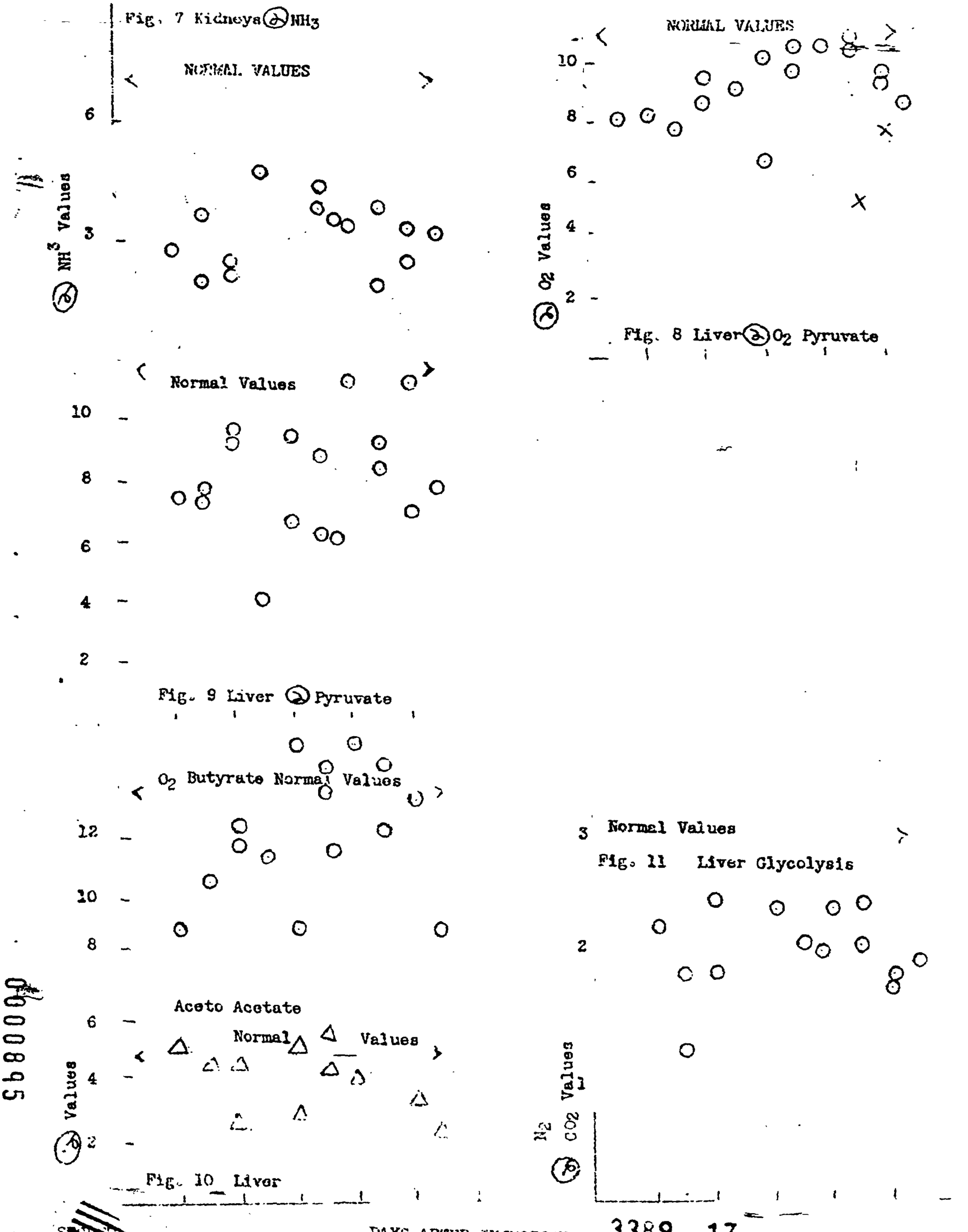


Fig. 7 Kidneys NH3
NORMAL VALUES
NH3 Values
6
3
NORMAL VALUES
10
8
6
4
2
O2 Values
Fig. 8 Liver O2 Pyruvate
Normal Values
10
8
6
4
2
Fig. 9 Liver Pyruvate
O2 Butyrate Normal Values
12
10
8
Aceto Acetate
Normal Values
6
4
2
Values
Fig. 10 Liver
3
Normal Values
Fig. 11 Liver Glycolysis
2
1
N2 CO2 Values
DAYS AFTER INJECTION

V Gross and Histopathology of Animals Treated with Plutonium

R. Murray

Animals autopsied after administration of plutonium fall into four groups, which showed the following gross pathological changes:

(a) Rats inhaling plutonium: Beyond changes in the lungs characteristic of acute pneumonia, there were no unusual effects.

(b) One dog treated intravenously with 0.36 $\mu g/gm$: The animal died after 16 days, but showed only pale bone marrow and hemorrhagic nodes.

(c) Mice and rats with intramuscular treatment: Those receiving high doses (2-12 $\mu g/gm$) of plutonium citrate had yellow, degenerated areas and punctate hemorrhages in the kidneys, particularly in the region of the cortico-medullary junction. All animals showed dry, ulcerated local lesions, which grew deeper with the duration of the experiment, in some cases reaching to the bone. The epithelium was proliferated at the margin of most ulcers. There were no other gross changes.

(d) Mice and rats with intravenous treatment: Spleens were noticeably smaller, weighing less than 50 mg in half the Carworth mice [redacted]

In the bone, there were two generally parallel changes: 1) The normal process of bone growth by cartilage hypertrophy stopped a few days after injection, when cartilage cells swelled abnormally, some osteocytes and osteoblasts died, other osteoblasts became inactive, and a loss of interdigitation between cartilage and spongy bone resulted. 2) At the same time, a little farther from the cartilage plate, the osteoblasts were over-active and laid down broad bands of hyperbasophilic bone without cartilagenous centers. Though this excessive bone-forming activity had apparently subsided somewhat at the 6-week interval, there was still practically no evidence of new interdigitation of bone and cartilage.

In the gastro-intestinal tract there was only very slight debris from occasional dead epithelial cells in the small intestine.

The lymphatic tissue of nodes, spleen and gastro-intestinal tract showed only mild nuclear changes, with no marked depletion of cells. The testis lost a considerable part of its spermatogenic elements at 6 weeks, though there was no change in the interstitial cells.

The spleen showed marked extramedullary erythropoiesis and some granulocytopoiesis, apparently in compensation for the depletion of bone marrow.

Changes after the intramuscular injection of 1.5 μg/gm appeared somewhat more slowly and were less severe than the otherwise very similar changes seen after the 1.25 μg/gm intravenous injection. At the injection site, the inflammatory cells pouring out from the vessels either were killed off or remained small and degenerated, thus inhibiting recovery by preventing the full course of inflammation. Muscle cells and tissue macrophages were killed also. Fibroblasts, though few were destroyed, became large and stained more deeply blue at late intervals.

In the few rats injected intravenously, the depletion of lymphatic tissue was marked at 2.0 μg/gm: thymus, node, and splenic white pulp were seriously depleted of lymphocytes, and peculiar changes were found in the reticular cells.

Perhaps the changes in the liver and adrenal of rats constitute the most striking difference between rats and mice in this experiment. In the liver, effects of treatment were observed as early as two weeks, and after several months were apparent even with doses as low as 0.5 μg/gm. The outer and middle portions of the lobule appeared to be the most severely damaged, containing swollen liver cells with nuclei many times enlarged. There were many mitoses and many dead cells, and the bile duct underwent intense hyperplasia. Some specimens at late intervals contained sharply demarcated areas of necrotic cells.

The variability of these findings should be especially noted. At the 6-week interval, for example, depletion of marrow in sacrificed animals ranged approximately from 30% to 95%, and the size of the testis varied from nearly normal to some 40% of normal. Similarly, livers in some rats

SECRET

were normal but in others severely damaged, though doses and intervals were the same. Many uncontrolled variables have not yet been taken into account.

Observations on autographic distribution will be included in a subsequent report.

VI. Clinical Picture Following Plutonium Administration

Austin M. Brues

This is a summarized account of the clinical picture of acute, subacute, and chronic plutonism as seen in animals. It includes data and observations from a large number of the investigators in the division, and includes observations on dogs, rats, rabbits, and mice.

The clinical picture of acute plutonium toxicity is best exemplified by the observations made in the dog given a lethal dose of the plus 6 nitrate intravenously (#33). Superficially at least, it is quite similar to the effect of a single lethal dose of total body x-ray. The initial x-ray sickness (depression and vomiting) ordinarily seen 1½ to 4 hours after total body x-ray, was lacking, but weight loss and refusal of food and water began within a few days and progressed steadily until death. A few days before death (around the tenth day) the dog entered the final "shock" phase, showing a rise in temperature (2°C), a corresponding rise in pulse rate, labored diaphragmatic breathing, salivation, hemorrhages into the skin and subcutaneous tissues, and evidence of slight bleeding from the bowel. The most marked clinical pathologic finding was the drop in white count, involving heterophiles and lymphocytes about equally. This began within the first two days and a level of about 500 white blood cells per mm^3 was reached at the end of the first week. A progressive anemia was observed throughout the course of the experiment, with an eventual 33% decrease in the red cell count. Albuminuria and microscopic hematuria were noted from the fourth to the seventh day. Other findings included a prolongation of clotting time, a sharp rise in sedimentation rate, a decline in plasma protein, and an increase in plasma α 2 and beta globulin. Certain findings relative to the pigments of blood and bile origin have been noted; the urinary urobilinogen rises in the early days, due probably to hepatic dysfunction; a green pigment occurs late in the course of acute toxicity in the urine, and is probably biliverdin. In addition, a decline in urinary coproporphyrin (isomer not yet determined) was seen during the first ten days. In the case of many of these findings, it is not yet possible to say categorically which are characteristic of plutonism as against acute x-ray toxicity.*

Certain findings made on other animals indicate (1) that there are certain dissimilarities between acute plutonism and the effects of total body x-ray, and (2) that there is great variability between the findings in one group of animals and in another.

* Terminally, a sharp drop in platelets has been observed and a further decline in the white count, with a terminal count below 100. Autopsy showed hemorrhages into many lymph nodes and hyperemia of certain parts of the gastrointestinal tract; the spleen was small, the liver and other organs appeared normal grossly and microscopically.

In the case of mice dying acutely (i.e., within two to four weeks), one strain (Carworth) showed only slight anemia, but one-half of the livers were grossly abnormal, being yellow and friable in consistency; many of these were entirely normal microscopically. ABC mice, on the other hand, showed profound anemia, with hemoglobin concentration down to 2 or 3 grams percent terminally. Spleens were all small and in many cases markedly atrophied. Gross examination showed the livers to be uniformly normal.

Although microscopic evidence of liver damage was not seen in the acutely poisoned dog, changes have been observed in rats and mice within the first month, but this has not been an entirely consistent observation. It has also been found that gross liver changes cannot consistently be obtained in successive experiments.

Gross renal damage also occasionally occurs following lethal doses of plutonium. This has occurred with intravenous citrate and nitrate (plus 6) and after intramuscular citrate. The lesions have been observed in rats, and mice consisting of a yellow area between the cortex and medulla, with yellow streaks extending down into the medulla, and with punctate hemorrhages in this area. No microscopic observations are yet available.

The acute lethal dose has varied between 0.4 mg/kilo (dog) and 1 mg/kilo (rodents), when nitrate and citrate were given intravenously. It is probably slightly higher when citrate is given intramuscularly. With intramuscular nitrate the acute lethal dose is above 4.5 mgs/kilo (mice) and with subcutaneous nitrate (mice) at about that level, although acute death has been seen in a few mice given 1.5 mgs/kilo.

In summary, acute plutonism is in many respects similar to acute total body radiation toxicity. In addition, the observations suggest that damage may occur more specifically in the liver, kidneys, and spleen and to erythropoiesis. These specific lesions have been extremely variable and difficult to reproduce. Their probable relation to the distribution of plutonium in the body is obvious.

Subacute plutonism might conveniently be defined as the state in which an animal gradually declines over a period of months, perhaps following evidence of recovery from acute intoxication. This was observed in another dog (#39) which survived 3 months after the injection intravenously of about 0.3 mgs/kilo of plus 6 citrate. This animal presented an acute picture similar to that following an acute lethal dose, except that it was in all respects less severe. Between the 10th and 16th day there was a slight rise in temperature and pulse, the dog was lethargic, and slight rectal bleeding occurred. The white count fell to 300 during this period and progressive anemia was occurring. At about the sixteenth day the symptoms improved rapidly and the white count began to increase. The white cell recovery was striking in the case of the heterophiles and only moderate in the lymphocytes. However, weight loss progressed steadily and the animal became gradually more anemic and emaciated. During the second month the white cell level again began to decline. Between the 79th day and death at 90 days there was a progressive increase in heart rate and body temperature. The gross findings at autopsy were similar to those seen acutely except that emaciation and anemia were much more marked.

Pathologic observations on other animals dying within four months indicate that we may expect damage to the blood-forming elements, liver, and bone. The commonest finding in the groups of rats dying in this period has been ascites and subcutaneous edema, nodular liver with necrotic areas, or with areas of hyperplasia of biliary tissue and, occasionally, hepatoma-like nodules.

Dr. C. J. Watson suggested in discussion of this point that similar hepatic lesions are known to occur in choline deficiency and allied states, and that methionine might be of therapeutic value. He pointed out that part or all of this picture might be secondary to the inanition which occurs, with resulting dietary deficiency. It seems important to investigate this, since liver carcinogenesis by azo dyes can be prevented by dietary means. It is worth pointing out that these regenerative processes might render the liver more liable to radiation damage.

Hematologic changes in the subacute range have been somewhat variable in the animals studied so far. When leukopenia occurs, it is usually most noticeable in the first few days, and this initial leukopenia is often sustained over a long period. In some groups of animals all doses down to 0.05 mg/kilo have resulted in a decrease in the white cell count to 25 to 50 per cent of normal; in other groups the first significant changes have occurred between 0.1 and 0.25 mg/kilo.

A third dog (#38) received 0.4 mg/kilo of plus 6 citrate intramuscularly and showed relatively milder acute and subacute changes. Weight loss has, however, continued through the third month. The laboratory data on the three dogs has been carefully tabulated by Dr. Prosser and is appended to this report. (Table XII)

Since little or no experimental work has extended over a period of more than six or seven months, one can only attempt to predict the picture of chronic plutonism on the basis of such data. Three bone tumors have been seen so far in rats and mice, two following intravenous and one following intramuscular treatment with plus 6 nitrate. In the latter case the tumor occurred in the femur near the site of the injection. In one instance extreme thinning of bone has been seen, with associated pathologic fracture. It remains to be seen to what extent these effects, and the anemia, leukopenia and hepatic changes, tend to be progressive or to extend to lower dosage levels.

Greying of the hair in brown ADC mice treated intravenously with plus 6 nitrate, has appeared progressively at lower doses; it was first noted at two months in the group given 0.5 mg/kilo; it was seen at three months in those given 0.2, at four months in those given 0.1, and is just noticeable at that time in those given 0.05 mg/kilo. This has been most noticeable around the thorax and has in all cases progressively intensified.

Testicular atrophy has been watched for in rats given intravenous citrate. It was observed six weeks after administration of 0.1 mg/kilo, but had not become clinically noticeable at that time after 0.05 mg/kilo.

From what we know at the present time, it seems reasonable to expect malignancy to occur following the administration of plutonium, as is seen after prolonged radiation in general, and to expect that bone may be a favorable site for plutonium carcinogenesis. Thresholds for this and other forms of chronic damage cannot be estimated at the present time except by analogy with radium, which of course presents certain difficulties.

The best information regarding the production of local damage by plutonium has been obtained in the course of experiments on mice receiving plus 6 nitrate intramuscularly and subcutaneously. Occasional brown mice have shown local greying of hair at the injection site 100 days after the injection of 1 microgram; ulceration of the skin has occurred 20 days after the subcutaneous injection of 4 micrograms and 40 days after the intramuscular injection of 10 micrograms. It is reasonable to suppose that these effects have been produced by the local presence of a fraction of these total doses, and that ulceration might under favorable conditions be caused by amounts near 1 microgram deposited locally. Ulceration has been dry, indolent, and has become progressively wider and deeper over periods of many weeks. Keratotic overgrowths have occurred but no malignancies have been seen within the first five or six months. This is interesting in view of the great susceptibility of mice to skin carcinogenesis by hydrocarbons.

Table XII.

CLINICAL PICTURE OF Pu TOXICITY IN THREE DOGS

	33	38	39
Dose mg/kg	0.36	0.404	0.286
Salt	+ 6 nitrate	+ 6 citrate	+ 6 citrate
Route	I. V.	I. M.	I. V.
Survival	Died 16 days	Alive 3 months	Died 90 days
Pu in Blood	90% drop in 30 min., after 10 days 0.01 γ g/ml	1.2 γ g/ml. 3½ hrs. 0.5 γ g/ml 24 hrs. 0.01 γ g/ml 14 d.	60% drop in 1 hour, 0.005 γ g/ml 14 d.
Pl. protein picture	low albumen, very high α 2 globulin, high β globulin and fibrinogen	some increase in β globulin.	high α 2 and β globulin
Pu localisation in blood	mostly on β globulin	on β globulin	mainly β globulin
Urine albumen		++ on 5-7th days -thereafter	++ 5-7th days -thereafter
Urine sp. gr.	no systematic change	no change	no change
Urine pH	constant		
Urinary Cl	normal until food cons. dropped.		
Gross changes	emaciated, weak		emaciated, lumps outside abdomen 80-85th days.
Heart rate	+37% 12-16 days	no significant change	transitory rise 10-16 days; progressive increase 79-90 days
Rect. temp.	+2°C 12-16 days	no significant change	same as heart rate
Bl. Press.	-16% (13th d.)		
Pl. Vol	+23% 8th day	+3.1% 12th day	+14.6 12th day
		+3.1% 36th day	+16.2 36th day

SECRET

3389 25

0000903

~~SECRET~~

	33	38	39
Bl. Vol	+14.7% 8th day	-26.5% 12th day	-15.1 12th day
		-26.0 36th day	-20.0 36th day
Weight	lost 11.67% wt. in 16 days	slow decline, 17.5% loss by 79 days	slow decline, 20% loss by 2½ months
Food Cons.	declined to few gms/day	slightly below control level continually	low 12 days; nearly normal afterward
Histamine	decreased	high 8 days, declining thereafter	high 8 days, declined thereafter
Plasma protein	28% increase by 15th day	slow increase, + 8% 50th day	+ 12% on 12th & 50th days
Serum protein	20% increase by 15th day	slow increase, + 19% 50th day	+ 11% on 50th day
Hematocrit			
control	40	46	45
minimum	32 on 15th day, -20%	29 on 29th day, -37%	17 on 72nd day, -62%
change	terminal hemoconcentration	37 on 72nd day	13 on 83rd day, -71%
RBC			
control	6,000,000	6,850,000	6,000,000
minimum	4,100,000 on 15th day	4,300,000 on 20th day	2,500,000 on 40th, 51st days
	4,890,000 on day of death	recovered to 6,050,000 on 51st day	2,200,000 on 72nd day
Hemoglobin			
control	14 gms %	16 gms %	15 gms %
	11 gms % 15th day	9.8 gms % 15th day	8.9 gms % on 15th day
			6.0 gms % on 72nd day

0000904

3369 29

	33	38	39
WBC			
control	20,000	9,500	11,700
minimum	200 on 16th day	400 on 13th day	300 on 13th day
Recovery	none	recovered to 4,900 on 51st day decreased to 2,600 on 66th day	800 on 40- 51st days 500 on 72nd day
Heterophiles			
control	11,000	7,200	8,500
minimum	900 on 8th day	150 on 13th day	120 on 13th day
change	none seen on 15th day no recovery	recovered to 3,600 on 51st day	1,650 on 29th day 450 on 51st day
Lymphs			
control	7,000	1,500	1,800
minimum	180 mm^3 on 7th day	200 on 13th and 29th day recovered to 600 on 51st day	150 on 20-51st days
Reticulocytes	0.1% on 16th day	decreased from 14th to 29th days	decreased from 3rd to 14th day
Platelets	decreased	decreased in early days - recovered late	decreased in late days
Sed. Rate	increased 5x	control 1mm/hour, increased to 52 on 29th day recovered to [illegible] on 80th day	control 9mm/hour, increased to 60 on 10th day, 75 on 72nd day.
Red cell fragility	unaltered		

	33	38	39
Clotting		no significant change	increased by 13th day decreased 15-65th days increased 85th day
Proth. time	unaltered		
Pigment exc.			
fecal urobilinogen	normal	no samples 1st 2 wks., 3rd & 4th wks.	normal values
urine urobilinogen		possibly early rise; irregular.	elevated first few days; irregular thereafter
urine coproporphyrin	terminal rise	50% decrease 2-4th wks., normal 5th-6 wks., below normal thereafter	50% decrease 2-4th wks., normal 5-6th wks., low thereafter
green urinary pigment		+ +	+ +
N. P. N. (blood)	moderate rise terminally	maintained 40% decrease	slight decrease second month only
amino N	unchanged		
creatine N		50% decrease	60% decrease
creatinine N		50% decrease	60% decrease
urea N		definite rise	questionable rise
Autopsy	hemorrhagic cervical lymph nodes & kidney liver, etc. grossly normal		hemorrhagic nodes, marrow; small hemorrhages in duodenum and myocardium.

VII Excretion Studies

Wright Langham

The primary interest of our health department is the immediate development of a method of monitoring personnel for internal body contamination with plutonium. The obvious purpose of a monitoring plan is to enable us to retire individuals from further contact with the material before they have absorbed harmful amounts. The execution of such a plan depends on the establishment of a number of factors among which are the following:

1) The development of a method of determining exceedingly small amounts of plutonium in some body fluid or excrement;

2) The establishment of the relationship between the body fluid or excrement and the amount of plutonium contained in the human body;

3) The development of a sampling system which excludes the possibility of external contamination of the sample.

This report summarizes our attempts to establish some of the above factors. The urine has been chosen as the source of the sample for study.

Method of Sampling and Analysis:

Because of the extreme difficulty of detecting small amounts of internal contamination with plutonium, and because of the great possibility of external contamination of the sample, the practice has been to collect 24-hour samples under very rigorous conditions. The subject is directed to stay away from work and preferably away from the Site for a 48-hour period preceding the period of collection of the sample to be analyzed. All persons are asked to wear freshly laundered clothing during this preliminary period and to bathe and wash their hands frequently.

The subject is asked to report to the hospital at eight o'clock in the morning at the close of the 48-hour preliminary period. He is given hospital clothing and after taking a shower, is admitted to a special room provided for collecting the 24-hour urine sample. He is asked to remain in this room for the entire 24-hour period. It is requested that the subject restrict his fluid intake to one cup or glass of fluid per meal to avoid an abnormally large sample.

A hand counter is available in the room and a note is made as to whether or not the individual has a hand count. The subject is instructed to wash his hands each time before he voids and to wear white cotton gloves during voiding, thus preventing epithelial scales of the hands from falling into the flask and contaminating the sample. The voidings are collected in a 2 liter erlenmeyer flask which is placed at such a height that it is not necessary for the person to touch the flask or the funnel while urinating. When the collection is completed, the subject dresses and leaves the hospital leaving his specimen where it was collected. The sample is picked up and delivered to the laboratory by a member of the group doing the analyses.

Rigid adherence to the procedure described above should permit the collection of a 24-hour urine sample as nearly free from external contamination as possible.

The effectiveness of the above method is indicated by the data in Table XIII which gives a comparison of the analyses of samples consisting of two overnight specimens collected in the individuals' homes with 24-hour samples collected from the same individuals by the above hospital method. The average counts per minute obtained in the samples collected at home was 20 as compared to 2.2 counts per minute per sample when collected under hospital conditions. The most probable explanation of this great difference is that external contamination was avoided in the latter case.

The samples collected in the hospital are analyzed by the following method: The entire 24-hour specimen is evaporated almost to dryness and the residue wetashed using one addition of conc. HCl and repeated additions of conc. HNO_3 and 30% H_2O_2. The ashing is continued until a white solid almost completely free of organic matter is all that remains. The residue is taken up in 2 N HCl and a complete hydroxide precipitation carried out. The hydroxide precipitate is dissolved in 2 N HCl, the solution is adjusted to a pH = 0.3-0.5 and the Pu, plus 1 mg. of ferric iron as a carrier, is extracted into chloroform using cupferron. The chloroform is evaporated off and the cupferron residue digested off with nitric and perchloric acids. The Pu is then carried out of the perchloric acid solution with lanthanum fluoride. The lanthanum fluoride precipitate is transferred to a platinum disc and counted for 30 minutes in an alpha counter.

The data reported in Table XIV give some idea as to the performance of this method when applied to spiked urine samples and to mock urine ash solutions. Blank determinations were made on 24 samples of urine from persons never having worked with Pu. These samples ranged in size from 800 to 1200 ml. The average of all blank determinations was 0.5 c/m per sample with a spread of 0-1.2 c/m.

Results of Personnel Monitoring:

Thirty-six members of the staff were chosen for the first test of the above monitoring method. These people were chosen to represent high, moderate, and low or no exposure groups. The number in each group was too few to give any definite significance to the classification. The results are indicative, however, and are summarized in Table XV. It may be significant that all individuals showing a positive count in the urine had had one or more high nose counts on record since joining the project. A high nose count is recorded against an individual when a moist filter-paper swab inserted into the nostril and rotated shows 50 c/m or greater when counted in an alpha counter.

Urinary Excretion of Plutonium by the Human:

If urinary excretion values are to be used to establish the actual amount of internal body contamination it is essential to know the relation between the amount of Pu in the human system and that excreted in the urine per 24 hours. On April 10, 1945, an attempt was made to establish this relationship by injecting a human subject intravenously with 4.7γ of +4 Pu which was complexed with sodium citrate(0.3% solution) and adjusted to a pH of 6.0.

The subject was an elderly male whose age and general health was such that there is little or no possibility that the injection can have any effect on the normal course of his life. The patient might not have been an ideal subject in that his kidney function may not have been completely normal at the time of injection as indicated by slight albuminuria and a low urine specific gravity.

The +4 citrate complex was used in order to produce the maximum deposition in the bone. This presumably would produce an excretion rate comparable to that of a worker having absorbed the material at a slow rate thereby depositing a maximum amount in the bone where it is probably the most damaging.

The results obtained for the first 18 days after injection are presented graphically in Figure 1 by blocking in the per cent of the total injected dose excreted per day.

These data show the excretion during the first day was surprisingly low and that the leveling off of the excretion rate was much slower than with rats. The most probable explanation of these observations is that they represent some metabolic abnormality of the subject. It is possible, however, that the stability of the +4 citrate complex is a factor. A blood sample taken 4 hours after the injection showed that about 50 per cent of the injected dose was still in the circulating blood. The calculation, however, was based on the assumption that there had been a complete mixing of the material throughout the total blood volume.

A rather favorable excretion rate is indicated by the observation that the leveling off point seems to be about 0.02 per cent instead of 0.01 per cent as observed for rats.

The Effect of Size of Dose on Urinary Excretion of 49:

A number of fundamental assumptions must be made in regard to the metabolism of Pu if a limited amount of human tracer data are to form the basis of a method of diagnosing internal body contamination. (1) It is necessary to assume that, once absorbed, all valence states and all compounds of Pu are metabolized by the animal organism in essentially the same way. (2) It is necessary to assume that Pu is metabolized in the same way regardless of the route of absorption or administration. (3) It is also necessary to assume that the fraction deposited and therefore the fraction excreted is independent of the size of the dose administered or absorbed.

Hamilton (CN-2383) has reported a limited amount of information in support of the validity of the first two assumptions. The following experiment was performed to test the validity of the third.

Five groups of mature male rats were injected with 0.032γ (2250 c/m), 1.1γ, 5.3γ, 15.0γ, and 52.0γ of Pu respectively. The material was administered as +4 citrate complex in a solution 0.5 per cent with respect to sodium citrate. The pH of the solution was 6.0. The urine and feces were collected daily for five days from each group and analyzed for 49. The results of the urine analyses are given in Table XVI. These data show rather conclusively that the per cent of the total injected dose excreted in the urine of the rat under the above conditions is independent of the size of the dose administered.

Table XIII

Effect of Method of Collecting
Sample on Counts Found in the Urine

Person	c/m and Place of Collection of Sample At Home*	In Hospital**
D. W.	10.1	2.2
W. A. B.	41.6	4.3
W. B. G.	16.1	3.4
W. G. T.	2.8	0.1
J. P.	17.8	—
D. D.	30.6	2.2
Average:	20.0	2.2

* Samples collected at home were two overnight voidings collected by the individual after thorough bathing and washing of hands.

** Samples collected in hospital were 24-hour samples collected under the rigorous hospital plan after a two day leave from the Site.

Table XIV

Recovery of Known Amounts of Pu
From Regular and Mock Urine Samples

No. of Detns.	Nature of Samples	Amt. of Spike c/m	Recovery %	Spread %
24	Blanks (reg. urine)	0.	(ave. 0.5 c/m)	(0-1.2 c/m)
4	mock urine sol.	29.2	94	88-100%
11	" " "	10.0	93	85-101%
12	reg. urine	10.0	88	73-104%
3	reg. urine	4.5	95	81-105%

Table XV

Results of Monitoring Site Personnel

Classification	No. of Persons	Ave. c/m/24 hr. urine sample*
Highly exposed	5	2.2
Moderately exposed	23	0.4
Low or no exposure	8	0.2
Those having high nose counts** recorded	14	1.2
Those having no high nose counts recorded	22	0.2

* 0.5 c/m was subtracted from each value as a blank.

** A high nose count is recorded against an individual when a moist filter-paper swab inserted into the nostril and rotated shows a count of 50 c/m or greater when counted in an alpha counter.

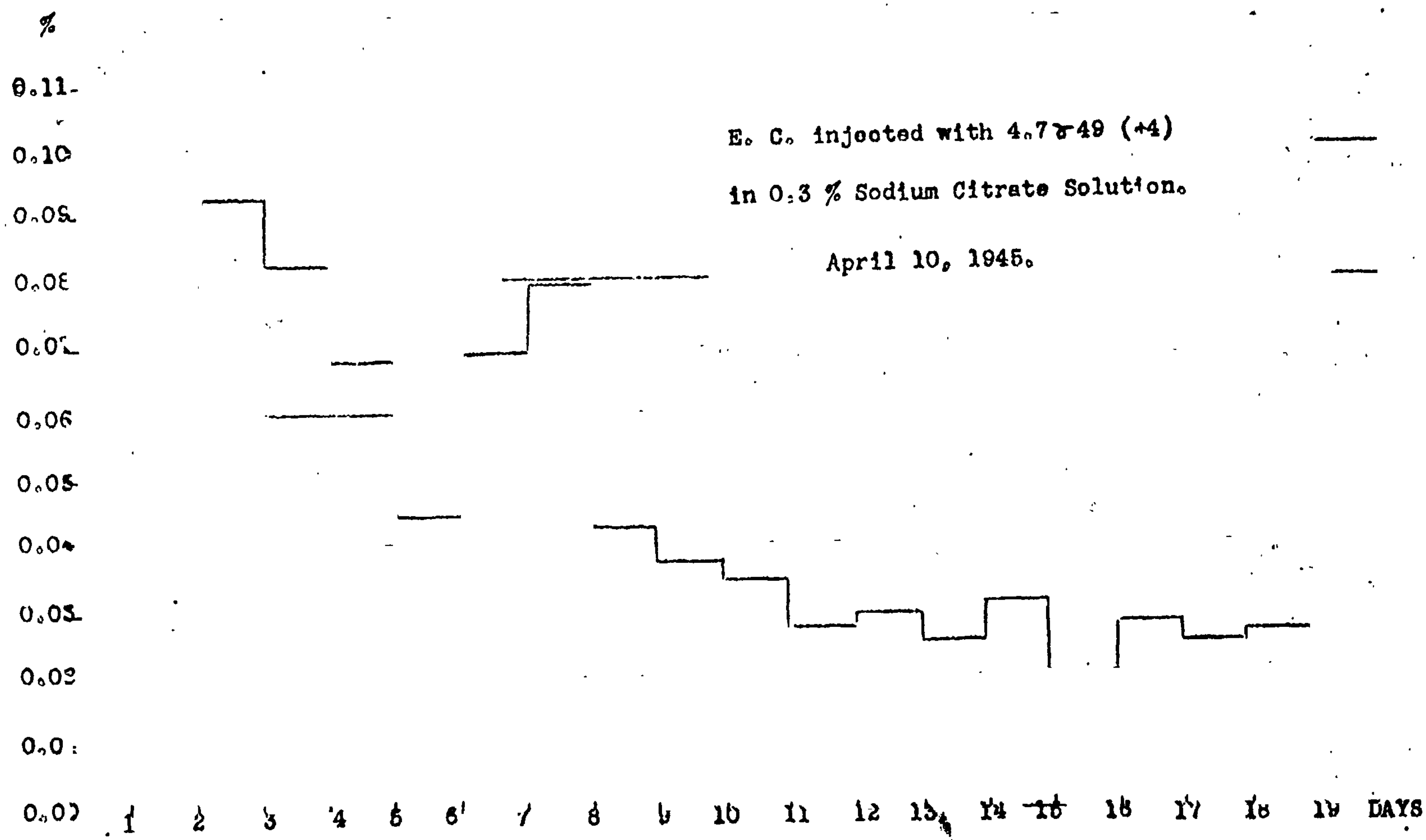
Table XVI

Effect of Dosage on Per Cent Excretion of Pu (+4) Citrate in the Urine of the Rat

Period after Inj. - Days:	% of Inj. Dose Excreted per Day Dosage γ				
	0.032	1.1	5.3	15	52
1st	0.72	0.71	0.73	0.57	0.77
2nd	0.27	0.22	0.31	0.20	0.26
3rd	0.22	0.12	0.18	0.16	0.19
4th	0.15	0.11	0.13	0.13	0.17
5th	0.14	----	----	0.12	----

FIG. III - EXCRETION OF Pu IN THE URINE OF THE HUMAN

GRAPHED AS PERCENT OF TOTAL INJECTED DOSE EXCRETED PER DAY



SECRET

0000913

3389 35

SECRET

E. R. Russell

Tables showing the excretion of product by various animals are presented. The question was raised as to what value could be set as the probable minimum daily urinary product excretion from this data. 0.01% of the material retained in the body would appear to be a fair estimate. The question has arisen as to why dog 38 (table on page 2) showed a much lower excretion than 0.01% per day. On the basis that only 65% of the material is absorbed from the muscle and that 20% has been excreted, the 0.01% would also apply to this animal. The data in the tables for all animals, rats, dogs, and rabbits, show from 0.01% to 0.03% daily excretion when constancy is reached.

Dr. Stone has asked what comparisons have been made between the concentration of plutonium in the blood and the urinary excretion. Comparisons of 7-and 14-day blood concentrations and urinary excretion indicate that little definite information can be gained. Comparisons of dogs 38 and 39 at 40 days after injection shows that while dog 38 had an estimated 2.72 µg of plutonium in the circulating blood the 24 hour urinary excretion was only 0.123 µg. Dog 39 had but 0.685 µg of Pu in the circulating blood and excreted 0.163 µg. Thus, though the blood level of Pu in dog 39 was ¼ that of dog 38, the amount excreted in the urine was slightly greater.

The fecal product excretion for all animals studied has been shown to be from 3 to 4 times higher than the excretion from urine collected during corresponding periods. (Tables XIV-XX). It was suggested that stools be assayed to establish the product content in humans. The difficulties encountered in analyzing stools and the comparison of human fecal product excretion to that of dogs would lead one not to rely on this procedure. Dr. Hamilton stated that he is working on a method for stool analyses that should be published very shortly.

Table XVII is presented to show the value of dog excretion studies to the interpretation of data accumulated on humans. The excretion of Pu for these dogs is compared with that of a single male human following IV injection with 6.5 µg of +6 plutonium citrate.

Table XVII

Period	% Excreted-Man / % Excreted-Px-33	% Excreted-Man / % Excreted-Px-38	% Excreted-Man / % Excreted-Px-39
	URINE		
1st 24 hrs.	0.4	0.3	0.2
2nd "	1.5	0.44	0.3
3rd "	2.6	0.38	0.6
4th "	5.0	1.1	0.65
5th "	1.1	0.29	0.22
6th "	1.7	0.99	0.47
7th "	0.99	0.63	0.47
8th "	1.0	0.92	0.59
9th "	1.4	1.3	0.29
	FECES		
1st 24 hrs.	0.015	0.0068	0.0032
2nd "	0.187	0.063	0.023
3rd "	0.062	0.073	0.053

If we are to place any weight on our animal studies it is quite clear from the above figures that the urinary excretion of dogs and man is more comparable than fecal excretion. Data presented by Mr. Langham on a human tracer experiment using 4.7 μg of the ~~4~~-4 citrate shows good correlation with our results. He also reported low fecal excretion. In his discussion he also pointed out that 50% of the injected plutonium was present in the circulating blood four hours after the injection. Our data showed that at the end of 45 minutes only 15% of the plutonium remained in the circulating blood.

It has been asked whether the IR-1 or the IR-4 resin adsorption method would be more suitable for detecting low activities in the urine. Since the IR-1 column procedure was designed to detect approximately 1 count per minute in a 100 ml specimen and the tolerance has been set at a level approximately 10 times smaller, the method now being done is certainly not adequate for 0.1 count per minute. It is suggested that less frequent analyses and larger volumes be used for each specimen. The IR-4 method which has been used for 500 to 1000 ml specimens has shown considerable variation and needs further investigation. Specimens of 2 to 3 liters have been assayed by evaporation and precipitation with LaF_3. This is to be avoided if possible because of the time consumed.

It was suggested during the discussion that the plutonium blood concentration be followed more closely and compared with urinary excretion to see if there is any definite relationship. A minimum of two animals should be studied inasmuch as the difference between dogs 38 and 39 was so great.

It is felt that the rabbit fecal product excretion is much closer than other animals studied to that of man for the period shortly after injection. Data beyond four days after injection for man was not available. (Table XXIII).

The question of controls was mentioned by Mr. English. The data collected by our group have shown very few controls. The values range from 0-1X 10^{-5} µg per 500 ml specimens. It was suggested that future work should include a number of control specimens.

In discussing a tolerance limit for plutonium contained in the body the question again arose as to what fraction of a day's urine should be analyzed in order to calculate the retained plutonium. Morning specimens have always shown a higher unit activity and any retention calculated from these analyses would tend to be too high. For accurate data, the entire 24-hour specimen or a large fraction thereof must be assayed. If the tolerance limit is to be set at 0.7 µg and 0.01% taken as the amount excreted then a maximum 4.8 α counts per day must be detected. Detection of one count per minute from the dog's excretion would indicate a deposition in the body of 0.6 µg. If we are to detect lower activities than the fraction of the daily urine to be assayed it should be correspondingly larger. The discussion was concluded with the following suggestions:

1. That larger volumes of urine be assayed for plutonium, preferably portions of 24-hour specimens.

2. That a large number of control specimens be run.

SECRET

Table XVIII

Plutonium Excretion

HUMAN

6.5 μg 46 Citrate I.V. pH-7.0

URINE

Period	% Excreted [1]
1st 24 hrs.	2.540
2nd "	0.153
3rd "	0.084
4th "	0.133
5th "	0.032
6th "	0.038
7th "	0.023
8th "	0.023
9th "	0.027
10th "	0.034
11th "	0.047
12th "	0.028
13th "	0.018
14th "	0.034
15th "	0.026
16th "	0.012
17th "	0.028
18th "	0.026
19th "	0.015
20th "	0.038
21st "	0.034

FECES

Period	% Excreted [1]
1st 24 hrs.	0.010
2nd "	0.103
3rd "	0.067

Blood Changes

After Injection	Conl. per ml	% of Inj*
10 min.	3.2×10^{-4} μg	20%
45 min.	2.5×10^{-4} μg	15%

* Assume 4000 ml blood

1. of amount injected.

From the above data we should expect higher urinary product excretion from humans than from dogs.

SECRET

0000917

Table XIX

Plutonium Concentration Changes in Blood

Dog Px-33 I.V. Injection-2669.7 ug +6 Nitrate		Dog Px-38 I.M. Injection-2963 ug +6 Citrate		Dog Px-39 I.V. Injection-1630 ug +6 Citrate	
Time After Injection	ug Pu/ml Whole Blood	Time After Injection	ug Pu/ml Whole Blood	Time After Injection	ug Pu/ml Whole Blood
0.5 hrs	0.56	3.5 hrs	1.20	5 min	1.371
24 "	0.193	5.75 "	0.96	20 "	1.204
72 "	0.039	24 "	0.54	80 "	1.086
168 "	0.016	72 "	0.084	24 hrs	0.106
240 "	0.011	168 "	0.023	168 "	0.008
336 "	0.011	336 "	0.010	336 "	0.005
384 "	0.010	696 "	0.005	696 "	0.002
		960 "	0.004	960 "	0.0015
		1752 "	0.0057	1752 "	0.0006
		1848 "	0.0031	1848 "	0.0005

Injection Data

Animal	Blood Volume	Vol. of Pu Solution	mg Pu/Kilo
Px-33	483 ml	4.840 ml	0.358
Px-38	680 ml	1.118 ml	0.404
Px-39	450 ml	0.615 ml	0.29

Table XXIII

Plutonium Excretion

Rabbits

Period	Animal 1641 (0.1 mg/Kg) % in Urine	% in Feces	Animal 1794 (0.02 mg/Kg) % in Urine	% in Feces
1st day	0.31	0.84	0.18	0.82
6th "	0.04	0.17	0.01	0.12
14th "	0.026	0.053	0.20	0.19
21st "	0.029	0.028	0.17	0.14
28th "	0.021	0.063	0.06	0.02
35th "	0.027	0.10	0.02	0.10
42nd "	0.030	0.04	0.05	0.10

SECRET

Table XXIV

Rats--Accumulated Excretion

% of Total Dose

Period Days	0.125 mg/Kilo 4438 U	4438 F	4439 U	4439 F	4400 U	4400 F	4435 U	4435 F	0.50 mg/Kilo 4436 U	4436 F	4437 U	4437 F
3	2.8	5.1	5.7	3.5	7.9	4.5	6.8	3.0	9.0	2.5	7.0	3.6
7	3.0	9.6	5.9	7.2	8.3	7.9	7.0	8.1	9.5	6.2	7.4	7.8
14	3.3	17.3	6.2	12.3	8.7	13.0	7.3	12.0	9.8	9.3	7.6	11.6
28	3.7	20.9	6.6	16.3	8.2	16.5	7.5	12.5	10.0	10.1	7.7	14.2
42	3.9	30.6	6.8	18.7	9.1	19.8	7.6	13.1	10.2	10.5	7.9	17.3
57	4.2	31.5	6.9	19.9	10.1	20.9	7.7	13.7	10.3	11.0	8.0	17.9
	Average daily excretion after 14 days											
%/day	.021	.33	.016	.177	.032	.183	.010	.040	.011	.040	.010	.148

Period Days	2.0 mg/Kilo 4431 U	4431 F	4432 U	4432 F	4433 U	4433 F	4434 U	4434 F	4441 U	4441 F
3	1.5	4.1	2.7	4.7	3.0	4.6	2.5	2.7	4.1	3.7
7	1.6	9.3	2.8	8.9	3.1	6.9	2.6	7.4	4.2	7.1
9	---	---	3.2	9.5	3.7	9.8	2.7	9.7	---	---
10	---	---	---	---	---	---	---	---	4.6	9.0
11	2.8	12.1	---	---	---	---	---	---	---	---

Table XXV

ED Experiments

Average % Plutonium Excreted Per Mouse

I. V. Injection-0.25-1 ug/gm

Period	1	2	3	4	5	6	7	8	9	10	11	12
	Groups											
2 days	--	--	--	--	--	--	3.5	4.2	6.7	5.0	--	--
4 "	--	--	--	--	--	--	5.4	6.3	9.5	6.7	--	--
5 "	--	4.5	--	--	--	--	--	--	--	--	--	--
7 "	17.8	--	[illegible]	10.2	3.3	7.9	7.3	7.8	14.3	8.6	9.5	12.6
10 "	--	--	--	--	--	8.5	--	--	--	--	--	--
11 "	--	--	14.4	--	--	--	--	--	--	--	--	--
12 "	--	--	--	10.9	--	--	--	--	--	--	--	--
14 "	--	--	--	--	3.9	--	9.4	9.6	20.6	12.3	15.2	18.2
22 "	--	--	--	--	--	--	9.6	10.5	23.2	13.7	17.9	21.5
23 "	--	--	--	--	6.2	--	--	--	--	--	--	--
24 "	--	--	--	--	--	--	--	10.7	--	--	--	--
28 "	--	--	--	--	--	--	11.3	--	25.3	15.0	19.4	24.9
35 "	--	--	--	--	--	--	--	--	26.5	16.2	21.8	26.9
36 "	--	--	--	--	--	--	12.1	--	--	--	--	--
56 "	--	--	--	--	--	--	--	--	27.7	16.6	23.3	29.3
72 "	--	--	--	--	--	--	--	--	29.0	17.9	24.0	30.4
	ABC	CF_1	ABC	CF_1	ABC	CF_1	ABC	ABC	CF_1	CF_1	ABC	CF_1
	Average daily excretion						22 days to					
36 days	--	--	--	--	--	--	0.18	0.2	0.25	0.19	0.30	0.41
72 days	--	--	--	--	--	--	--	--	0.11	0.08	0.12	0.18

SECRET

0000921

3389 46

Table XX

Daily Urinary Plutonium Excretion
Dog

I.V. +6 Nitrate		I.M. +6 Citrate		I.V. +6 Citrate	
Px-33		Px-38		Px-39	
Sample	% Excreted	Sample	% Excreted	Sample	% Excreted
1	6.37	1	8.54	1	12.66
2	0.094	2	0.343	2	0.495
3	0.0325	3	0.219	3	0.139
4	0.0274	4	0.116	4	0.205
5	0.0292	5	0.109	5	0.147
6	0.0022	6	0.039	6	0.081
7	0.024	7	0.037	7	0.049
8	0.0225	8	0.025	8	0.039
9	0.0191	9	0.020	9	0.034
10	0.0187	10	0.015	10	0.032
11	0.0187	11	0.019	11	0.029
12	0.0165	12	0.011	12	0.025
13	0.0067	13	0.0112	13	0.017
14	0.0296	14	0.0109	14	0.020
15	0.0292	15	0.012	15	0.022
16	0.0180	16	0.0125	16	0.013
		average daily excretion for 5 day intervals			
		17	0.009	17	0.0143
		18	0.0059	18	0.010
		19	0.0047	19	0.0075
		20	0.0053	20	0.0088
		21	0.0042	21	0.0099
		22	0.0047	Average 14-day intervals	
		Average daily during oral citrate 10 days	0.0057	22	0.0063
		Average daily during I.V. citrate 7 days	0.0063	23	0.0071
		Average daily after citrate 7 days	0.0042		

Table XXI

Daily Fecal Plutonium Excretion
Dog

Px-33 Sample	Px-33 % Excreted	Px-38 Sample	Px-38 % Excreted	Px-39 Sample	Px-39 % Excreted
1	.648	1	1.48	1	3.07
2	.551	2	1.64	2	4.39
3	1.080	3	.920	3	1.26
4	.299	4	.595	4	----
5	.065	5	.296	5	1.00
6	.100	6	.129	6	.044
7	.063	7	.148	7	----
8	.209	8	.104	8	.175
9	.081	9	.132	9	.101
10	.056	10	----	10	.187
11	.038	11	.186	11	.047
12	.041	12	.053	12	.113
13	.039	13	.034	13	.070
14	.057	14	.054	14	.043
		15	.035	15	.062
		16	.031	16	.044
		17	.067	17	.134
		18	.028	18	.039
		19	.013	19	.036
		20	----		
		21	.022		
		22	.021		

SECRET

Table XXII

Comparative Plutonium Excretion

Total

Series	Animal	Dose (ug)	Period	% Product Excreted Urine	Feces	Number Animals	High Urine	High Feces	Low Urine	Low Feces
FA	Rats	8.1	4 days	5.7	7.1	5	7.2%	7.8%	3.3%	6.1%
FC	Rats	13.5	5 days	0.11	85.2	6				
FP	Rats	50	24 hrs	1.3	1.1					
FP	Rats	50	14 days	4.4	10.1					
FA_2	Mice	11	17 hrs	M 13.5		10				
CX	Mice	--	6 wks	M 10.5		--		12%		9%
CX	Rats	--	6 days	M 8.5		--		12%		5%

FA-- +6 I.C., FC-- +4 and +6 Oral FP and FA_2-- +6 I.V.

0000924 3369-43

Table XXVI

Plutonium Concentration in Whole Blood

J		K				F G	
Rabbit 302 ug		Rabbit 37.4 ug					
Time after Injection	ug/ml W. B.	Time after Injection	ug/ml W. B.	Rat	Dose	Time after Injection	ug/ml W. B.
22 hrs	.076	23 hrs	.014	4432	2 mg/K	9 days	.036
8 days		7 days	.001	4433	"	"	.014
15 "	.031	14 "	.019	4441	"	10 "	.025
22 "		21 "	.0012	4461	1 mg/K	17 "	.019
29 "	.0067	28 "	.003	4466	"	16 "	.017
36 "	.010	35 "	.0007	4406	.125 mg/K	18 "	.005
43 "	.001	42 "	.0013	4402	"	19 "	.003
Plus 6 Nitrate I.C.				Plus 6 Nitrate I.V.			

1387 Rabbit 20 ug		2031 Rabbit 20 ug		4893 C X Mouse 3.85 ug		4894 Mouse 3.85 ug	
Time after Injection	ug/ml W. B.	Time after Injection	ug/ml W. B.	Time after Injection	ug/ml W. B.	Time after Injection	ug/ml W. B.
8 hrs	.005	8 hrs	---	1 hr	.065	1 hr	.336
23 "	.0007	23 "	---	5 "	.066	5 "	.069
144 "	---	144 "	.0023	23 "	.016	23 "	.011
				95 "	.0042	95 "	.0045
				197 "	.0092	197 "	.010

Plus 4 Nitrate I.C.

Plus 4 Nitrate I.C.

VIII - Ra-Pu, Po-Pu Ratios

R. E. Fink

Data on some preliminary "range-finding" experiments in progress concerning the acute toxicity of radium, plutonium, and polonium in rats are presented in the form of dosage-survival time charts. These data are combined on a semilogarithmic scale in Figure II.

The polonium was administered intravenously as the chloride in approximately neutral isotonic NaCl. The dosage level ranged from 170 to 50 microcuries (0.0375 to 0.0085 micrograms) per kilogram body weight, and killed all animals in from 5 to 20 days. Four animals which received 15 uc/kg for tracer studies were sacrificed at 50 days. No deaths occurred in the control group.

The plutonium was prepared for injection by neutralizing the 1 N HCl stock solution with an equal volume of 1 N sodium citrate and diluting to isotonicity. About 50 moles of citrate were used for each mole of plutonium present. Injections of 19 to 190 microcuries (300 to 3000 micrograms) per kilogram of body weight were made via a tail vein. The first deaths occurred twelve days after the injection. A number at the lower dosages are still living after 77 days. One control animal died a few minutes after injection of the NaCl-citrate solution, but the remainder are still alive and well.

Three separate experiments have been carried out with radium. In the first experiment the dosages ranged from 20 to 200 microcuries per kilogram, using a preparation about seven months old, in which the polonium had reached about 0.5% of its equilibrium value, i.e., one microcurie of polonium was injected with each 200 microcuries of radium. The amount of polonium in the preparation was determined by the method used regularly in our biological tracer work, stirring an HCl solution (0.1 to 3N) of the preparation with a silver foil in a hot water bath for two hours or more, then washing the foil with HCl and H_2O and measuring the activity deposited. The radium was injected intravenously as the chloride in isotonic saline. The 20, 40, and 70 uc/kg doses were made with slightly alkaline reaction (pH 7-8), while the remainder were slightly acid (pH 6-7). The majority of the animals of this first radium group are still living 170 days after the injection though there were three early deaths at the 70 and 110 uc/kg levels.

The second radium experiment was carried out in the same manner as the first except that the dosages ranged from 300 to 1400 uc/kg. The data show a wide scatter in this group, so that there was no marked difference in average survival time in the range of 500 to 1400 uc/kg in this small group of animals. The animal which died 9 days after receiving 500 uc/kg apparently succumbed to an overdose of D.D.T. used for controlling lice. These animals received from 1.5 to 7 microcuries of polonium per kilogram as a contamination in the radium preparation, and while those dosages of polonium are probably sub-lethal they may have constituted an additional insult to the organism sufficient to complicate the results of the experiment.

In the third radium experiment the dosages were 1000, 2000, 4000, and 8000 microcuries per kg. For these dosages it was necessary to remove the polonium from the preparation even though its age was only a few months, for at the highest dosage levels the polonium present would have been sufficient to kill the animals without any assistance from the massive dose of radium present. The amount of polonium present was lowered to 0.05% of its equilibrium value by stirring the 1 N HCl solution of the preparation (10 ml) with a cylinder of silver foil in a test tube for six hours at room temperature. The injections were made in slightly acid (pH 6-7) isotonic saline as before, but in order to avoid possible complications from chemical toxicity the 8000 dose was split into four, and the 4000 dose into two equal daily injections. The survival times shown on the chart are given as days after the first injection. The animals which received 8000 uc of radium plus 4 uc of polonium per kg both died in 11 days. Those receiving 4000 uc of radium + 2 uc of polonium died at 15 and 24 days, while those receiving 2000 and 1000 uc/kg are still living 36 days after the injection. It seems likely at this stage of the experiment that these lower dosages will show the low-polonium preparation to be less toxic than that used in the second experiment. The problem of comparing the acute toxicity of radium in rats with its long-term toxicity in humans is considerably complicated by the question of the age of the preparation involved. The 20-day LD50 for radium in equilibrium with all its products is probably not higher than 50 uc/kg while the figure for freshly prepared radium is probably over 4000 uc/kg. On the other hand, the long term effects might bear little or no relation to the age of the radium preparation at the time of its incorporation into the body. None of the control animals for the radium experiments have died.

Inasmuch as the data collected to date are rather scanty for standard LD50 calculations, the toxicities of the three substances under study were compared roughly on the basis of average survival curves drawn free-hand as shown in Figure II. The numerical comparison data taken from the survival curves are shown in the accompanying table, which indicates that for short survival periods polonium may be about three times as toxic as plutonium and that plutonium, in turn, may be about thirty times as toxic as radium when all are expressed in terms of microcuries. The fact that neither of the radium animals at the 2000 uc/kg level have died in the ten days since the survival curves were drawn makes it appear probable that the average lethal dose values shown in the table for radium at the 30 and 40 day periods are too low with respect to polonium-free radium preparations, and that there is accordingly a greater difference between the toxicity of radium and plutonium for 30 and 40 day periods than is indicated in the table.

A rough calculation involving the lethal dose data, the area under the retention curves for plutonium, radium and the daughter elements of radium, and the relative energies of the alpha particles involved indicates that the plutonium: Radium toxicity ratios based on the amount of alpha ray energy given off in the tissues are about the same as those based on the original dose in microcuries (the amount of radium energy lost due to excretion during the first few weeks being approximately balanced, in the rat, by the energy of the daughter elements retained in the body). When polonium and plutonium are compared on the same basis the polonium is found to be about twice as toxic as plutonium per unit of alpha-ray energy dissipated in the body during a ten day survival period, about five times as toxic for a 20-day period, and perhaps as high as ten times for 30-day periods.

Thus, even on the basis of equivalent alpha-ray energies in the tissues there appear to be real differences of the order of tenfold and 100-fold between the acute toxicities of the three substances under study. The most probable explanation of these differences appears to lie in their different distributions in the body, a large proportion of the radium apparently burying itself deep in bony structures where it is relatively innocuous from the standpoint of acute toxicity, the plutonium concentrating in the endosteal layers of bone close to the marrow and (at least to a greater extent than radium) in soft tissues, and the polonium concentrating in highly radio-sensitive soft tissues such as the hematopoietic and lymphatic tissues themselves.

Data on the effect of the three substances on growth, hematological, and pathological pictures are in the process of being analyzed and will be reported in detail later. A preliminary inspection indicates that the weight curves may be fairly sensitive indicators of toxicity in the case of low dosages and that the hematological and pathological data show an overwhelming insult to the white and red blood cell forming structures.

~~SECRET~~

Table XXVII

Lethal Dose Studies

Days after Injection

Substance	10	20	30	40	
Radium	8000	4000	2300	1400	Approximate dose in microcuries per kg required to kill an "average" rat at time indicated
Plutonium	200	140	110	90	
Polonium	110	45	30(?)	?	
Radium	1/40	1/29	1/21	1/16	Approximate relative toxicity in terms of microcuries (no correction for daughter products of radium)
Plutonium	1	1	1	1	
Polonium	1.8	3.1	3.7(?)	?	
Radium	8000	4000	2300	1400	Approximate dose in micrograms per kg required to kill an "average" rat at time indicated
Plutonium	3000	2200	1700	1400	
Polonium	0.024	0.010	0.007	?	
Radium	1/2.7	1/1.8	1/1.4	1/1.0	Approximate relative toxicity in terms of micrograms
Plutonium	1	1	1	1	
Polonium	120,000	220,000	260,000?	?	

SECRET

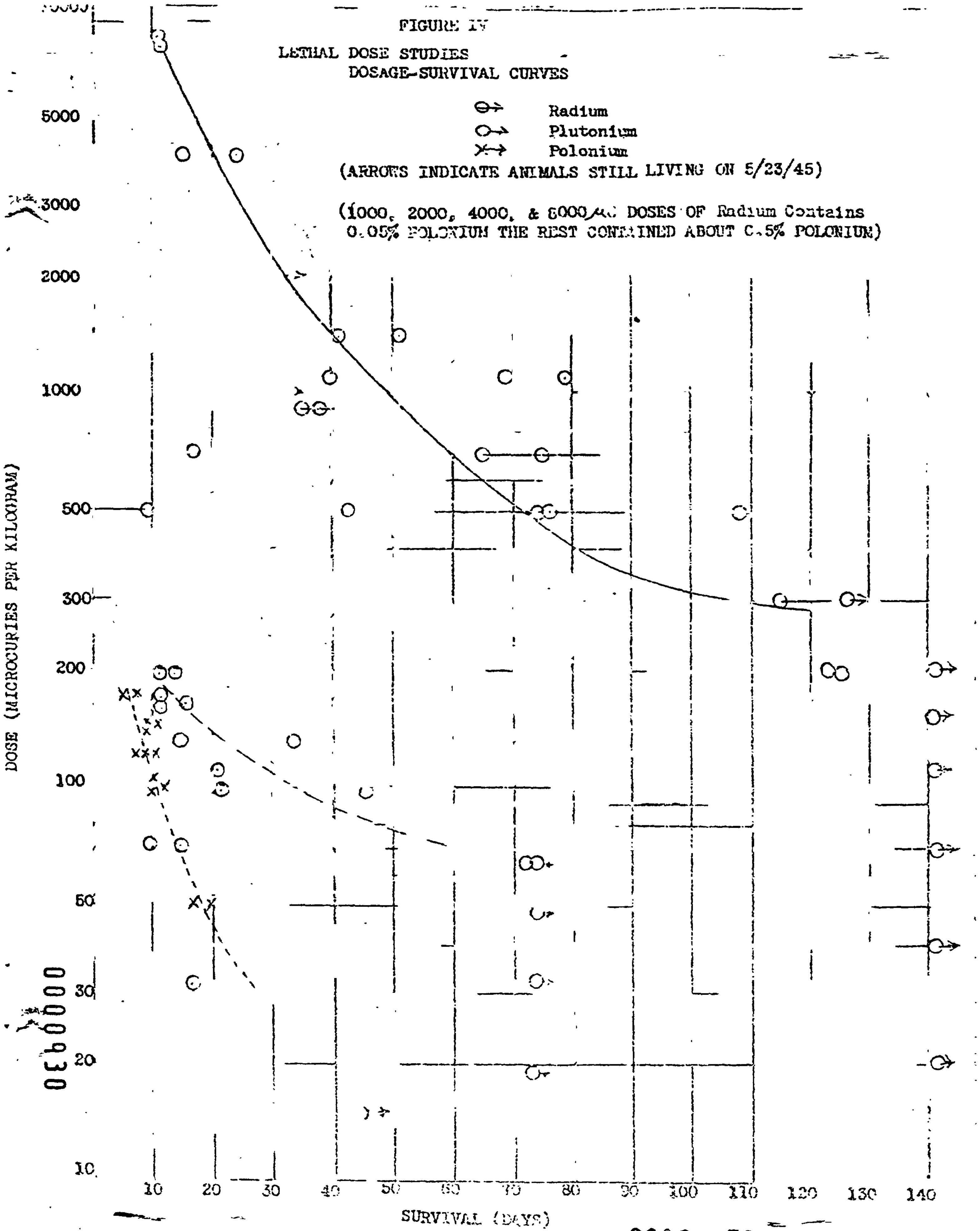


FIGURE IV
LETHAL DOSE STUDIES
DOSAGE-SURVIVAL CURVES
Radium
Plutonium
Polonium
(ARROWS INDICATE ANIMALS STILL LIVING ON 5/23/45)
(1000, 2000, 4000, & 8000 μc DOSES OF Radium Contains 0.05% POLONIUM THE REST CONTAINED ABOUT 0.5% POLONIUM)
DOSE (MICROCURIES PER KILOGRAM)
5000
3000
2000
1000
500
300
200
100
50
30
20
10
10
20
30
40
50
60
70
80
90
100
110
120
130
140
SURVIVAL (DAYS)

The toxicities of plutonium have been determined and are tabulated for some combinations of:

(1) intravenous (IV), intramuscular (IM) and subcutaneous (SC) administrations;
(2) nitrates and citrate complexes;
(3) Mice, rats, rabbits and dogs;
(4) acute and semi-acute 50% killing (MLD), histological, hematological and weight effects.

The plutonium toxicities are compared with those of radium and X-rays in an attempt to utilize both the experimental and clinical background and the tolerance levels which have been set for these older hazards.

It has been found, in general, that for periods of less than thirty days the ratio of administered doses of plutonium to radium (Pu/Ra - on a weight basis) for similar effects is approximately unity. But as the experimental interval has been extended to 150 days at present time this ratio, Pu/Ra, has increased and reached a maximum value of seven in one case.

By comparison with the X-ray data it is seen that, although the retention in the body is high, the lethal effect of plutonium is similar to that of a single irradiation by X-ray. On the other hand, in spite of the more rapid elimination of radium the lethal effect increases more rapidly with time for it than for daily irradiation by X-ray. This effect is in the direction to be expected from an increasing retention of disintegration products.

Comparison of Pu, Ra and X-rays Upon Survival

Table XXVIII

	MLD μg/gm			Retention in %	MLD *μc Retained/gm		
	30 d.	90 d.	150 d.	15-90 day	30 d.	90 d.	150 d.
Pu Mice IV.	1.0	1.0	1.0	60	0.038	0.038	0.038
Ra Mice IP.	1.00	0.35	0.20	40	0.56	0.2	0.12
X Mice	80μ/day	40μ/day	30μ/day	——	——	——	——
X - Single dose CF. Mice ABC Mice	 450r 425r	 425r 425r	 385r 425r				
Pu Rats IV.	1.25	1.00	0.75	70	0.055	0.044	0.033
Ra Rats IP. (&IV)	1.0	0.5	——	40	0.56	0.28	——
X Rats	55μ/day	35μ/day	30μ/day	——	——	——	——
X - Single dose Rats	 600 r						
Po Rats IV. (?)	0.90×10^{-5} (0.40 μc/g) 3.5×10^{-5} (IV or IP)	——	2.2×10^{-5} (IV or Sub Q) 0.1 μc/g) (0.16 μc/g)	?			

Pu - Citrate - Mice IV	0.75	60	Probable
Pu - " - Rats IV	1.0	70	"
Pu - " - Mice IM	< 1.5	> 50	"
Pu - " - Rats IM	1.0	> 50	"
Pu - Nitrate - Rats IM	> 4.5	< 20	"
Pu - " - Mice Sub Q	3.0	?	

* Pu - 1μg = 0.063μc

Po - 1μg = 4500μc

For radium 1μgm = 1.4μc, (20% retention of 2 daughters).

0000932

SECRET

~~SECRET~~

0000933

Table XXIX

Comparison of Plutonium, Radium and Single Doses of X-Rays Upon Hematological Changes

		RBC		HEMOGLOBIN		LYMPHOCYTES		HETEROPHILES	
		Detectable	50% Fall	Detectable	50% Fall	Detectable	50% Fall	Detectable	50% Fall
RABBIT	X-Ray	<800 r	<800 r	<500 r	<800 r	<25 r	100 r	25 r	300 r
	RADIUM	>20 μc/kg <100 μc/kg	>100 μc/kg	<100 μc/kg	>100 μc/kg	>20 μc/kg <100 μc/kg	>100 μc/kg	>20 μc/kg <10 μc/kg	>100 μc/kg
	Plutonium	>100 μg/kg	>100 μg/kg	>100 μg/kg	>100 μg/kg	>20 μg/kg <100 μg/kg	>100 μg/kg	>100 μg/kg	>100 μg/kg
RAT	X-Ray	>300 r	>300 r	>300 r	>300 r	<300 r	<300 r	<300 r	~300 r
	RADIUM	<20 μc/kg	>500 μc/kg <1000 μc/kg	<60 μc/kg	>500 μc/kg <1000 μc/kg	<20 μc/kg	~60 μc/kg	<20 μc/kg	~20 μc/kg
	Plutonium	<250 μg/kg	>1000 μg/kg <2000 μg/kg	<250 μg/kg	>1000 μg/kg <2000 μg/kg	<250 μg/kg	<250 μg/kg	<250 μg/kg	<250 μg/kg
MOUSE	X-Ray	—	—	—	—	—	—	—	—
	RADIUM	<165 μc/kg	>165 μc/kg	<165 μc/kg	>165 μc/kg	<165 μc/kg	ca 165 μc/kg	<165 μc/kg	~165 μc/kg
	Plutonium	>180 μg/kg	?	>180 μg/kg	?	>18 μg/kg	<180 μg/kg	<18 μg/kg	<180 μg/kg

SECRET

Table XXX

Comparison of Effects of Pu and Ra Upon Weight

Literal	Species, strain	Agents	Route of Administration	Levelling dose $\mu g/gm$ (30-150 da.)	Interpolated Estimate
FD	ABC	Pu	IV	>0.5 <1.25	1.0
	CF_1	Pu	IV	>0.5 <1.25	1.0
FK	ABC	Pu	IV	1.0	1.0
FF	ABC	Ra	IP	0.25 0.5	0.25
	CF_1	Ra	IP	>0.10 <0.25	0.15
CW	Mouse	Ra	IP	0.15	0.15
CW	Rat	Ra	IP	0.165	0.16
CX	Mouse	Pu	IC	> 0.2 < 2.0	1.0
	Rat	Pu	IC	> 0.25 —	
JK	Rabbit	Ra Pu		100 μg Ra > 100 μg Pu	

SECRET

0000934

[illegible]

The numbers 1-10 refer to degree of damage from 10% to virtually 100% destruction. All [illegible]. The letters [illegible] refer to the extent of recovery [illegible]. The letter n indicates complete recovery. Under "Spleen myelopoiesis - stimulation" the figures are relative only and do not indicate multiples of the normal. The letters under this heading indicate return to normal [illegible] from damage. Other signs have the following meaning:

+ change incapable of quantitation ? insufficient data
± questionable change - not examined

0 no change

ESTIMATES COMPARING HISTOPATHOLOGY OF X-RAY, STRONTIUM, PLUTONIUM AND RADIUM IN MICE

Agent	X-Ray	Sr(89) IP	Plutonium IV	Plutonium IV	Plutonium IV	Radium IP
Dose	350 r	1.0 μc/g	[illegible]	[illegible] c/g	[illegible]	[illegible]
Range of Intervals	4h-21d	1d-5mo.	[illegible]	1d-[illegible]	1d-[illegible]	[illegible]
Bone Marrow - Dep	10a	10b	[illegible]	4d	[illegible]	10?
Bone Marrow - Grow.	9a	9b	[illegible]	6e	4e	9e
Bone Growth - Damage	0	2e	4e	4e	4e	8e
Gut Epithelium	4a	0	0	0	0	±
Gut Lymphatic	3n	-	2a	4e	4e	6e
Mes. Lymph Node	3n	0	2a	4e	4e	6e
Skin	0	-	-	-	-	-
Spleen Lymphatic - Damage	2a	0	4e	4e	4e	6e
Spleen Myelopoiesis - Damage	0a	0	6b	0	0	0
Spleen Myelopoiesis - Stim.	6n	4n	6e	4e	6e	2e
Testis	0	-	6e	0	6e	9e
Ovary	2e	-	?	-	-	-
Thymus	4n	-	4e	0	0	4e
Liver	0	-	4e	0	0	0
Other Organs	0	-	0	0	0	0

0000935

SECRET

Interpretation of Histology Table

Although doses of 1.0 μc/g of Sr and 1.25 μg/g of plutonium are alike in their approximation to the 30-day survival median lethal dose in mice for these substances, the damage to all organs is perhaps several times greater with Sr than with plutonium.

Effects of varying modes of injection of plutonium differ only in the spleen, where the red pulp is more severely damaged by I-V than by I-M administration. Even here, however, subsequent hyperactivity is the same for both methods.

The 1.0 μc/gm (1/5 M. L. D.) strontium series results in as great damage to bone marrow as is seen with plutonium at the median lethal dose.

SECRET

[illegible]

J. J. [illegible]

It is emphasized that the remarks and values given here are not to be regarded as the results of anything other than preliminary work. Neither time nor personnel has permitted anything other than a very tentative evaluation of the problem under discussion.

The problem of wound contamination has been one which has excited considerable discussion throughout the project. Unfortunately the amount of work which has arisen out of this discussion is not in proportion to the volume of words. Numerous individuals have pointed out that the entrance of plutonium into the body, via wounds, constitutes a very serious hazard. With the maximum permissible level set at approximately 1 microgram fixed in the body, it would be quite easy in one accident to introduce a far greater amount.

The problem of wound treatment can be approached from two points of view. The first entails excision of the possibly contaminated area. The excision must necessarily include a margin of uncontaminated tissue if the treatment is to be successful. For large, grossly contaminated wounds on the hand, the satisfaction of the dictates of this method of treatment might well necessitate the amputation of the hand.

The second approach to the problem is to attempt to decontaminate the wound area. It is with this approach that the majority of the work reported here has been done. Preliminary studies were directed at a study of the rate of absorption of plutonium from the site of injury. It is obvious that if the material is 100% absorbed from the injured area in one second, no attempt at decontamination will be useful. Hence it was felt that it was necessary to obtain information on this point before other studies were done. As a base line for evaluating other decontaminating agents it was decided to use ordinary distilled water.

Method of Performing the Experiment

Rats were used. Lacerations one to two centimeters long were made in the skin of either the thigh or upper lateral abdomen. Frequently two incisions were made on the same animal. The manipulations were performed under intra-peritoneal nembutal anesthesia. The plutonium was introduced into the wound as the 49 nitrate. Five gamma of a 2 g/L solution, pH 2.0-2.5 was used. The analyses were done by members of Dr. Cole's section. In some of the experiments the residual body content of plutonium was not determined. Thus, in Figure VI the uppermost line represents a difference figure and not a figure fixed by analysis. This, of course, means that this part of the graph must be considered tentative.

The wash solution analyses were done in conjunction with wound site analysis. The wash was done by placing the solutions in an ordinary 100 cc buret. The time of washing was approximately three minutes in most of the experiments. Results of these experiments are summarized:

1) The amount of plutonium fixed at the site of injury falls in 24 hours to approximately 30% of the amount placed in the wound.

2) The amount found in the leg and abdominal wound sites shows a persistent difference at all time intervals. The explanation for this is not known. It has been suggested that the amount of bleeding in the two areas may possibly account for the difference. This point has not been tested up to the present time.

3) Examination of the data indicates that the time of washing after the introduction of plutonium into the wound is critical. Approximately 80% of the material can be removed if the wound is washed with plain water one minute after contamination. This percentage drops to approximately 30% five minutes after contamination with plutonium. At 5 seconds approximately 90% of the plutonium can be removed.

   Other agents than water were investigated. These are 0.2% lanthanum nitrate solutions, 0.5% thorium nitrate solution, 5% citric acid solution at pH of 6.05, and 1.25 M potassium bi-sulphate. None of these agents gave as good decontamination at the five minute interval as water gives at the one minute interval.

4) An experiment was performed in which the wash solution was fractionated, the first 30 cc being kept separate from the remainder of the wash. 95% of the activity was present in the 30 cc fraction.

5) To investigate the possibility that lymphatic drainage was playing a large role in the removal of plutonium from the wound sites, several inguinal nodes were removed from animals who had thigh lacerations. The nodes were removed at 6 hours, 24 hours and 4 days. In no instance did the percentage of activity in the nodes exceed 0.5% of the amount placed in the wound.

Some work on the rate of movement of plutonium following intramuscular injection has been done. The work is too tentative to discuss in detail. However, it would appear that the movement of plutonium following intramuscular injection is in large measure determined by the connective tissue surrounding muscle fibers and muscle bundles. This also was carried out by injecting the material. It is possible that the force necessary to do the injection is in large measure responsible for the disposition of the material along the fascial planes.

Discussion: Insofar as one is permitted to evaluate preliminary results, it is felt that the following inferences can be drawn:

1) Time after the introduction of plutonium into a wound is perhaps the most important single condition which affects the ability to remove the material. In consequence, any agent

which is to be used to decontaminate wounds must be present in any laboratory in which plutonium is to be used. It must be applied as soon as possible after known or suspected contamination.

2) The universal presence of water in laboratories together with the absence of any strikingly better agent suggests the use of water as the decontaminating agent of preference.

3) The slope of absorption of plutonium from wounds in graph VI would indicate that the problem of excision could be delayed for approximately 1/2 hour without serious prejudice to the patient. It is suggested that more detailed experiments may lengthen this time interval.

4) It is emphasized that the above conclusions and the following suggested procedure for handling contaminated wounds is based on and applied solely to lacerations. It is not felt that any finding or conclusion based on lacerations have necessarily any implications for puncture wounds. It is also felt that puncture wounds are a far more serious problem than are lacerations from the decontamination point of view.

Suggested Routine for Handling Plutonium Contaminated Wounds.

1) Following known or suspected contamination wounds should be washed in a strong stream of running water for not less than three minutes. Bleeding of the wound area should be encouraged.

2) A light tourniquet might be applied to increase venous flow.

3) The first 100 cc or so of wound washings should be collected for future analysis in an attempt to estimate the amount of plutonium that could be in the wound.

4) The individual, after washing the wound, should go or be taken directly to the nearest medical aid station. A physician should be informed of the fact that a plutonium contaminated wound is coming in.

5) The question of whether or not to excise the wound area must naturally be left to the physician's judgement. Parenthetically, it would be extremely helpful to have a rapid, precise means of determining the amount of plutonium in a wound area.

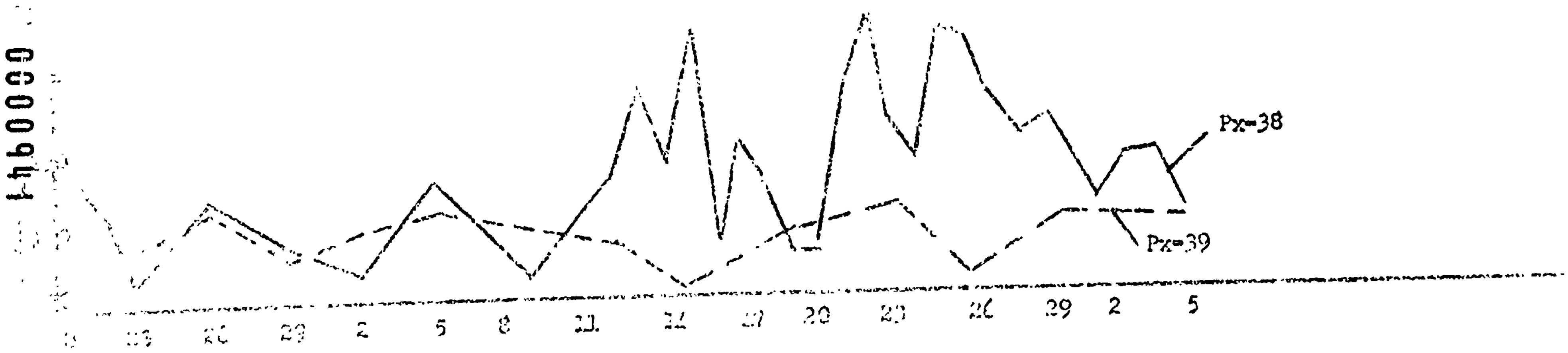
During the course of study of dogs injected with plutonium, the opportunity presented itself in dogs PX-38 and PX-39 to investigate the effect of the citrate ion on plutonium excretion. This data is presented in Figure V. PX-38 received both oral and intravenous citrate. The average excretion rate during the intravenous citrate administration was increased from a base of 0.0045% to an average of 0.0065% of the amount injected. At the same time the average amount of urine excreted per day also increased. To test whether or not the slight increase in excretion was merely a result of the increased urine volume, the dog was given 20 cc of 20% sodium chloride solution intravenously daily for five days. The urine excretion increased but the amount of plutonium excreted per day was unaltered. This latter information is not found in Figure V.

It is emphasized that the effect of citrate administration on the excretion of plutonium in the feces is not available at this time. It is, of course, possible that the fecal excretion of plutonium was altered.

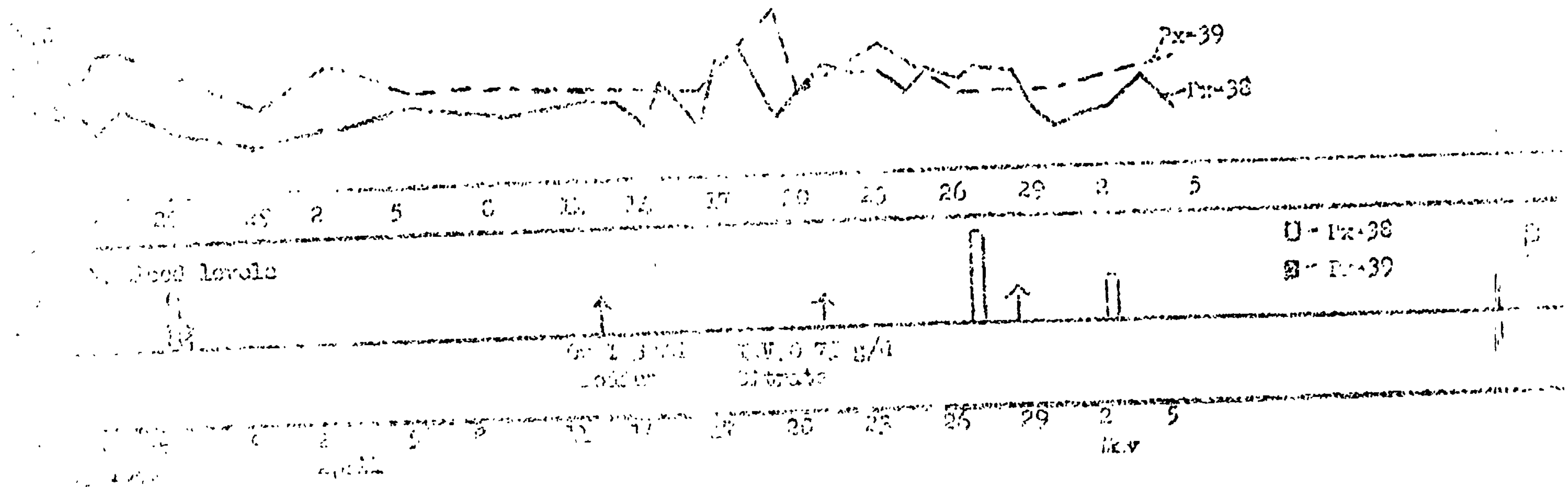
The amount of plutonium in the blood of the two animals is also given on graph V. It is of interest to note that the concentration per unit volume in the two animals is quite different yet the amount being excreted per day in the urine does not. No explanation for this fact is available at this time.

SECRET

0000940



Px = 38   % Pu excreted per day: Control period: 0.0045
Oral citrate: 0.0056
I.V. citrate: 0.0065
Px=39 % Pu excreted per day: 0.0077



0000941

0000942

PLUTONIUM

Table VI

Rats

Wound site no wash - abdomen ......
Wound site no wash - leg..........
Wash solution analysis - abdomen...
Wash solution analysis - leg.......

64