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THE DISTRIBUTION AND EXCRETION OF PLUTONIUM IN TWO HUMAN SUBJECTS

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Assisted by

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[redacted] by law.

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Since people were of necessity exposed to some degree to plutonium and since plutonium is known to be very radiotoxic it was obviously desirable to have some method of determining whether or not a given person had any plutonium in him. It was equally desirable to be able to estimate as accurately as possible how much was deposited in any person. Animal experiments were used to procure as much data as possible. Some human studies were needed to see how to apply the animal data to the human problems. Hence, two people were selected whose life expectancy was such that they could not be endangered by injections of plutonium.

I. CASE HISTORIES

Case No. 1

A sixty-eight year old white male was admitted to the Billings Hospital in March, 1945 for surgical treatment of a recurrent epithelioma of the buccal mucosa. Upon admission to the Billings Hospital in March, 1945 the abnormal findings on physical examination were limited to the findings in the face and neck. The anterior portion of the mandible and contiguous area of the sub-mental triangle showed a large infected ulcerating area approximately seven centimeters in diameter. The anterior portion of the mandible was exposed in the depths of the lesion. The margins of both the buccal membrane and the cutaneous portions of the lesion were raised and hard. Bone was exposed in the central portion of the buccal and cutaneous surfaces.

X-ray examination of the chest revealed a metastatic lesion in the left upper lobe. The laboratory examinations were essentially negative except for a mild hyperchronic anemia. The Wasserman and Kahn were negative. Studies of histologic reactions from the excised tumor were diagnosed as epidermoid carcinoma. Definitive local surgery was performed on April 11, 1945 and April 28, 1945. On April 26, 1945 at 9:17 AM the patient was given an intravenous injection of 6.50 micrograms of +6 plutonium as a citrate salt in 0.9 per cent salt solution at a pH of 7. The volume of the injection was 8.05 cc. The patient remained in fair condition until August, 1945 when he complained of pain in the chest. X-ray evidence of extension of the pulmonary metastases was found. He expired on October 3, 1945.

The autopsy findings were weight, 168 pounds (76.4 kg.). An extensive postoperative recurrence of the epidermoid carcinoma of the mouth was found. There was extensive carcinomatous invasion of the structures of the sub-mental and submaxillary triangles. Bilateral pulmonary metastases were present. Associated findings of vascular thromboses, cavitation and abscess formation were noted. There was an acute bronchopneumonic process in the lower lobe of the left lung. No abnormality was noted on gross examination of the kidneys. Microscopic examination revealed "a mild focal interstitial nephritis, probably a pyelonephritis, as the arteries are only moderately sclerotic. Parenchymatous degeneration of the tubules is fairly marked and a few hyaline and calcified casts are seen".

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<u>Case No. 2</u>

A fifty-five year old white female was admitted to the Billings Hospital in December, 1945 for diagnosis and treatment. Six months previously (June, 1945), she had noted generalized lymphadenopathy. Two months later (August, 1945), pain, aggravated on motion, developed in the trunk. On admission to the Billings Hospital in December, 1945 the essential physical findings were the presence of bilateral non-tender, moderately enlarged lymph nodes in the cervical, axillary, and inguinal regions and generalized tenderness to pressure over the ribs. X-ray examination of the chest, pelvis, skull, and spine revealed many small, rounded areas of decreased density scattered throughout the bones examined. In addition, partial collapse and wedging of the last thoracic and first and second lumbar vertebrae with some associated calcification was noted.

Laboratory examinations were essentially negative except for a moderate hyperchromic anemia and leukocytosis. Wasserman and Kahn were negative. Study of sections of the tumor excised from the skull and left axilla revealed carcinomatous tissue. It was felt that the carcinoma probably originated in the left breast.

The patient's general condition was poor at the time of admission and deteriorated steadily throughout the period of hospitalization. On December 27, 1945 at 9:02 AM, 94.91 micrograms of +6 plutonium citrate were injected intravenously. The salt was contained in 4.4 cc of an isotonic saline solution 0.01 M in citrate at pH 6.5. The clinical course was not visibly altered following the injection. The patient expired on January 13, 1945.

The major autopsy findings were: (1) an adenocarcinoma probably arising in ectopic left axillary breast tissue with metastases to the liver, mesentery of the small intestine, lumbar vertebrae, ribs, skull and pelvis. Numerous healing pathological fractures of the ribs were found. (2) A lymphoblastoma involving the axillary, inguinal, peribronchial, periaortic, and pelvic lymph nodes. Thus the patient had two co-existing presumably independent tumors, an unusual finding. The weight at autopsy was recorded as 85 pounds (38.6 kg.).

Histologically, the bone marrow in all places examined was almost entirely replaced by tumor. The spleen showed a marked myeloid metaplasia. The kidneys showed many convoluted tubules filled with hyaline casts. The tubular epithelium showed evidence of degeneration and repair. Comparison of the biopsy sections with the post mortem sections shows no evident difference in the character of the tumor following the injection of plutonium. The cells characteristic of lymphoblastoma are also present in the biopsy sections.

II. <u>METHODS</u>

The control period in Case I was one week long and was used primarily to determine the approximate daily urinary output available for analytical purposes. In Case II the control period was somewhat shorter and was used for the same purpose.

In both cases the specimens were collected in the usual urinals and bed pans, the material being transferred in the case of the urine, to a gallon bottle to which 5 cc of concentrated hydrochloric acid had been added. The addition of the acid minimizes the liklihood of adsorption of plutonium by the container. The fecal specimens were transferred to "Seal-Fast" cardboard containers.

In Case II because of the condition of the patient, adequate separation of the urine and fecal specimens was not always possible. As a result adequate fecal excretion data could not be obtained.

Hematological studies made at frequent intervals in both cases included: hemoglobin in grams per ml; erythrocytes, leucocytes, platelets per cubic mm; reticulocytes in per cent; leucocyte differential; sedimentation rate (Westergren); and hematocrit reading. Liver function tests were performed in Case II by S. Schwartz using the cephalin flocculation and thymol turbidity tests and bilirubin determinations.

Specimens: The autopsies were performed by members of the Pathology Department of the School of Medicine of the University of Chicago. The specimens were placed in 95 per cent alcohol as experience elsewhere had shown that the usual ten per cent formalin preservative tends to leach plutonium out of the specimen. Insofar as possible the specimens were placed in individual containers.

RESULTS

Case I

Excretion of Plutonium in the Urine: For forty-eight hours following intravenous injection of the plutonium solution, each specimen of urine was collected and analyzed separately. The first voiding was approximately six hours after the injection. The results of the analyses are given in Tables I, II and III and Figure I. It is interesting to note that there is very little difference in the percent of the plutonium excreted in the third through the twelfth specimens though the unit concentration of plutonium in the urine varies widely. After forty-eight hours, the specimens voided in each 12 hour period were pooled for six days, followed by pooling of specimens for each twenty-four hour period for the duration of the experiment. The results are given in Tables III and IV. The twenty-four urine volumes ranged from 1500 ml to 3600 ml. There was little correlation between urinary volume and quantity of plutonium excreted.

The urinary excretion of plutonium in the first 24 hour period is very nearly 50 per cent of the total excreted in the urine throughout the entire period of observation, and is 36 per cent of the total excreted in both urine and feces. The rapidity with which the rate of excretion diminishes is remarkable. Within 24 hours, the excretion level had fallen to approximately one-hundredth of that noted during the first six hours. In approximately two weeks the excretion rate had fallen to approximately 0.004 times the initial rate.

Table I.

Percent of Plutonium Excreted in Urine in the First 38 Hours.
(Individual Specimens)

Specimen No.	Volume of Specimen (cc)	c/m per 100 ml urine	% of injected plutonium excreted
1 (6 hours)	152	6550	2.23
2	218	355	0.175
3	325	45	0.023
4	245	65	0.036
5	414	37	0.035
6 (24 hours)	182	78	0.032
7	108	138	0.033
8	122	137	0.022
9	73	95	0.020
10	97	92	0.030
11	148	67	0.024
12 (48 hours)	160	100	0.024

Table II.

Percent of Plutonium Excreted - 2nd to 8th Day.
12 Hour Urinary Output Analyzed

Days after Injection	Volume of Specimen (cc)	c/m per 100 ml urine	% of Injected Plutonium Excreted
2.4	258	77	0.045
3	415	41	0.139
3.5	630	54	0.085
4	540	39	0.048
4.5	515	10	0.012
5	430	20	0.020
5.5	660	15	0.012
6	485	16	0.017
6.5	600	10.5	0.014
7	380	11	0.0094
7.5	920	6.5	0.013
8	895	5	0.0095

Table III.

Percent of Plutonium Excreted - 9th to 155th Day.

Days after Injection	Volume of Specimen (cc)	c/m per 100 ml urine	% of Injected Plutonium Excreted
9	2510	5	0.027
10	3250	4.7	0.034
11	3275	6.6	0.047
12	2320	5.2	0.047
13	1490	5.4	0.018
14	2635	5.7	0.034
15	2480	4.7	0.026
16	2520	2.1	0.012
17	2650	4.5	0.028
18	2920	4.0	0.026
19	3300	2.1	0.015
20	3060	5.6	0.038
21-30 avg.	2723	8.2	0.045
31-40 avg.	3018	1.9	0.012
41-60 avg.	3346	2.2	0.017
61-80 avg.	3020	3.3	0.021
81-100 avg.	2505	2.9	0.015
101-125 avg.	2125	1.7	0.008
126-138 avg.	----	2.0	0.010
139-155 avg.	----	1.7	0.008

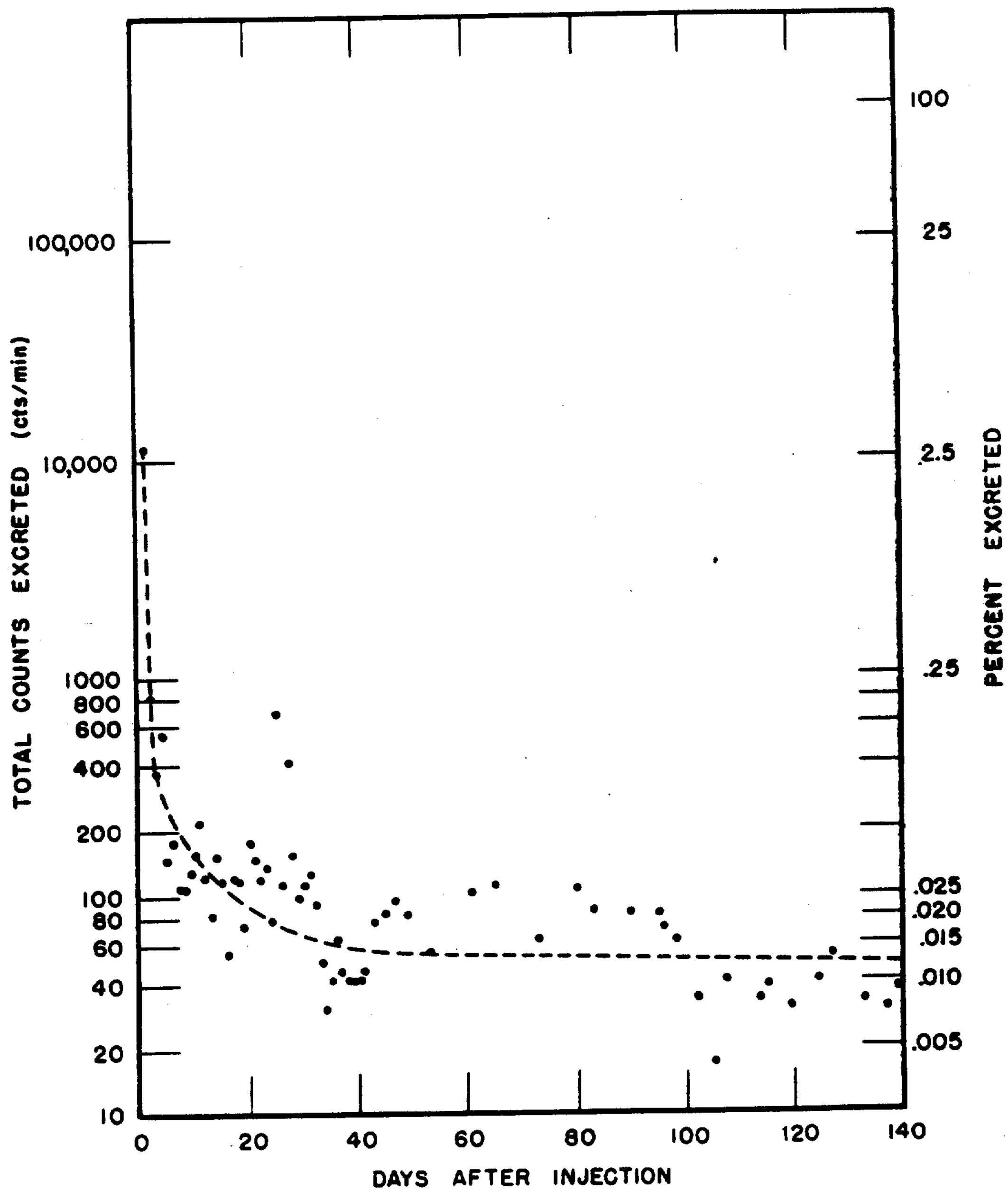


Figure I

Urinary excretion of plutonium in a sixty-eight year old white male following the injection of 6.50 micrograms of plutonium citrate.

Fecal Plutonium Excretion. During the first four days after injection seven individual fecal specimens were collected and analyzed for plutonium. Following this period the samples were collected at 24 hour intervals for several months and then 24 hour specimens were taken every four days until death. The results are given in Tables IV and V and Figure II.

Table IV.

Fecal Plutonium Excretion
Individual Fecal Specimens Collected in First 96 Hours.

Sample No.	Time of Collection after Injection	Weight of Specimens (gms)	c/m per gm of feces	% of Injected Plutonium Excreted
1	6 hours	13.0	26.0	0.076
2	28 hours	189.5	3.7	0.157
3	40 hours	45.5	16.2	0.161
4	51 hours	106.9	11.2	0.270
5	not recorded	141.5	6.2	0.195
6	not recorded	318.7	3.7	0.264
7	96 hours	76.2	9.1	0.154

Table V.

Fecal Plutonium Excretion
Daily Specimens from the 5th to the 138th Day

Days after Injection	Weight of Specimen (gms)	c/m per gram feces	% of Injected Plutonium Excreted
5	49.5	19.3	0.214
6	57.0	8.7	0.109
7	54.2	6.3	0.076
8	64.4	7.3	0.105
10	278.3	3.2	0.200
12	129.9	2.8	0.082
13	144.7	1.2	0.040
14	70.1	2.8	0.044
15	166.7	1.0	0.042
1[illegible]	122.7	1.1	0.029
18	232.1	0.6	0.031
19	128.9	0.9	0.027
20	130.0	0.53	0.0154
21-30 avg.	112.4	0.59	0.0[illegible]45
31-40 avg.	115.5	0.29	0.0068
41-60 avg.	123.0	0.18	0.0038
60-100 avg.	143.6	0.21	0.0043
101-138 avg.	88.2	0.16	0.0031

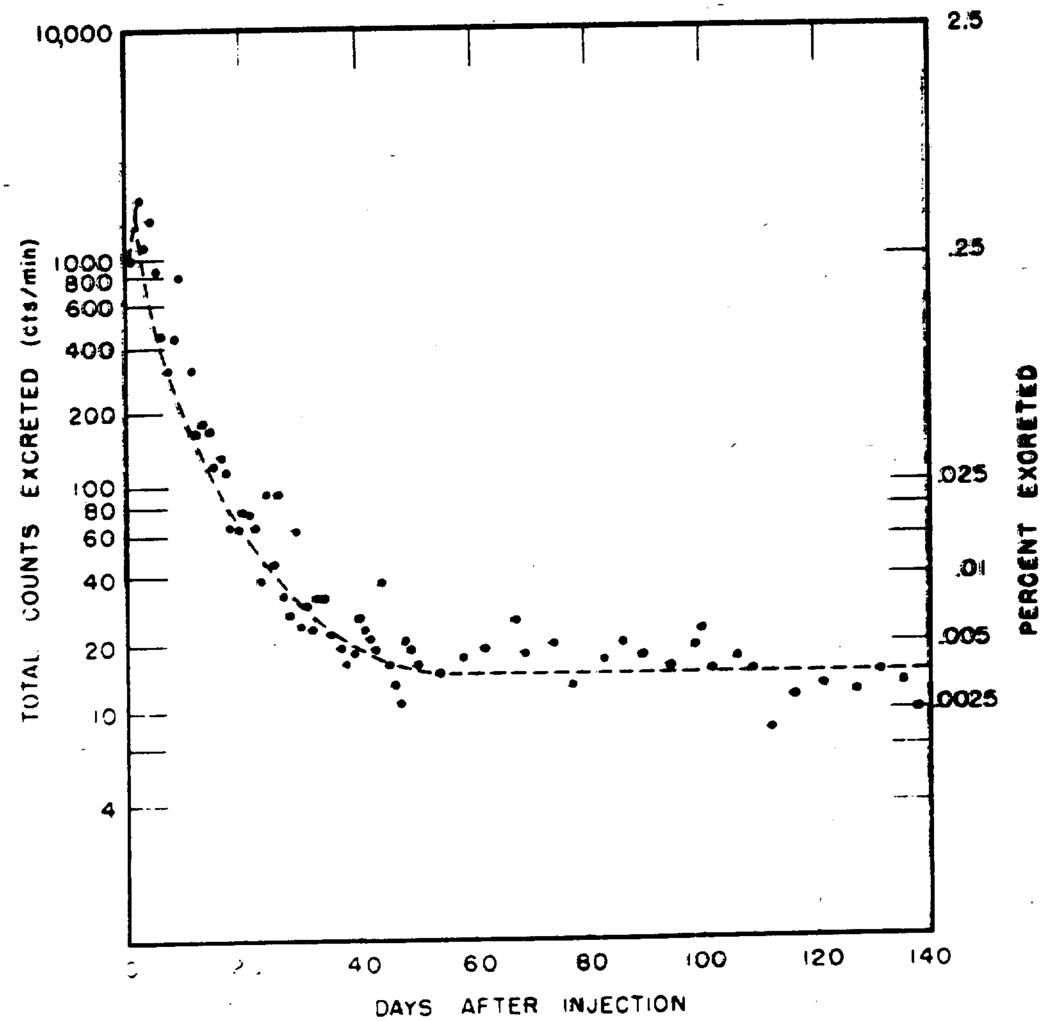


Figure II

Excretion of plutonium in the feces of a sixty-eight year old white male following intravenous injection of 6.50 micrograms of plutonium citrate.

Total excretion of plutonium for 138 days is estimated as 8.18 percent of the injected dose. The urinary excretion is estimated as 5.24 percent of the injected dose, the fecal excretion as 2.90 percent of the injected dose. The average excretion figures are multiplied by the appropriate factor in arriving at the above estimates, since average figures only are given throughout much of the period of study.

Clinical Studies of Peripheral Blood. No changes were observed in the hemotological constituents of the peripheral blood which could be attributed to the action of the isotope administered. These data are recorded in Table VI and in Figures III, IV and V.

Table VI.

Blood Findings - Case I

	Hgb. gms. %	RBC M/cu. mm.	Hematocrit cc/100 cc	Reticulocytes %	Platelets/ cu. mm.	PMN %	PMN Absolute	Lymphocytes %	Lymphocytes Absolute	Monocytes %	Eosinophils %	Basophils %	Sed Rate 60" (uncorrected) (Westegren)
4-24-45	10.6	2.97	34	1.0	499,400	77	7238	17	1598	4	1		106
4-24-45	9.7	3.64		1.4	591,000	77	8046	15	1560	6	1	1	
4-26-45	10.9	3.56	35	1.6	332,200	69	5741	27	2403	7	2	1	106
4-26-45	Intravenous injection of 6.50 micrograms of plutonium												
4-27-45	10.5	3.61	34.5	1.5	480,700	79	10191	15	1935	4	1	1	100
4-28-45	10.5	3.71		1.5		81	7857	15	1455	4			
4-30-45	10.3	3.90		1.2		64	4256	21	1396	8	2	1	
5- 1-45	10.0	3.52	31	1.5	298,100	66	4323	23	1506	11	9	1	113
5- 2-45	9.5	3.66		1.7	292,000	63	4221	28	1876	5	4		
5- 3-45	9.5	3.14		3.2	299,200	63	3969	24	1377	6	7		
5- 4-45	9.7	3.71	32	2.4	436,700	70	5250	20	1500	3	6	1	116
5- 5-45	10.4	3.77		1.5		76	4832	14	895	6	4		
5- 7-45	9.7	3.79		3.0	350,900	70	5460	23	1784	5	2		
5- 8-45	9.8	3.80		3.0	294,800	82	9635	16	1870	1		1	
5- 9-45	9.2	3.54	30	3.0		70	5355	17	1300	7	6		60
5-10-45	9.3	3.54		2.1	244,200	64	4096	18	1152	6	11	1	
5-11-45	9.1	3.30	29	2.6		60	4800	26	2080	5	9		93
5-15-45	9.0	3.52	31	1.5	361,900	62	4867	22	1716	9	7		109
5-19-45	9.5	3.14	31	1.6	317,800	61	3355	35	2185	3		1	94
5-22-45	9.2	3.69	28.5	2.0	346,500	55	4812	26	2275	7	11	1	103
5-25-45	8.5	3.09	28	3.3	334,400	62	4495	28	2030	4	6		99
5-29-45	10.0	3.78	34	1.9	323,400	80	8120	13	1319	5	1	1	78
6- 1-45	9.6	3.34	31.5	1.7	141,900	62	4643	20	1530	6	12	1	84
6- 5-45	10.1	3.70	32	1.0	283,800	65	6337	29	2827	4	2		83
6- 8-45	9.8	3.60	32	1.0	272,800	71	5254	2[illegible]	1554	6	1	1	85
6-12-45	9.7	3.57	33	1.8	282,700	55	3685	38	2546	5	2		80
6-29-45	10.0	4.07	33	1.1	238,700	69	6658	24	2316	5	1	1	110

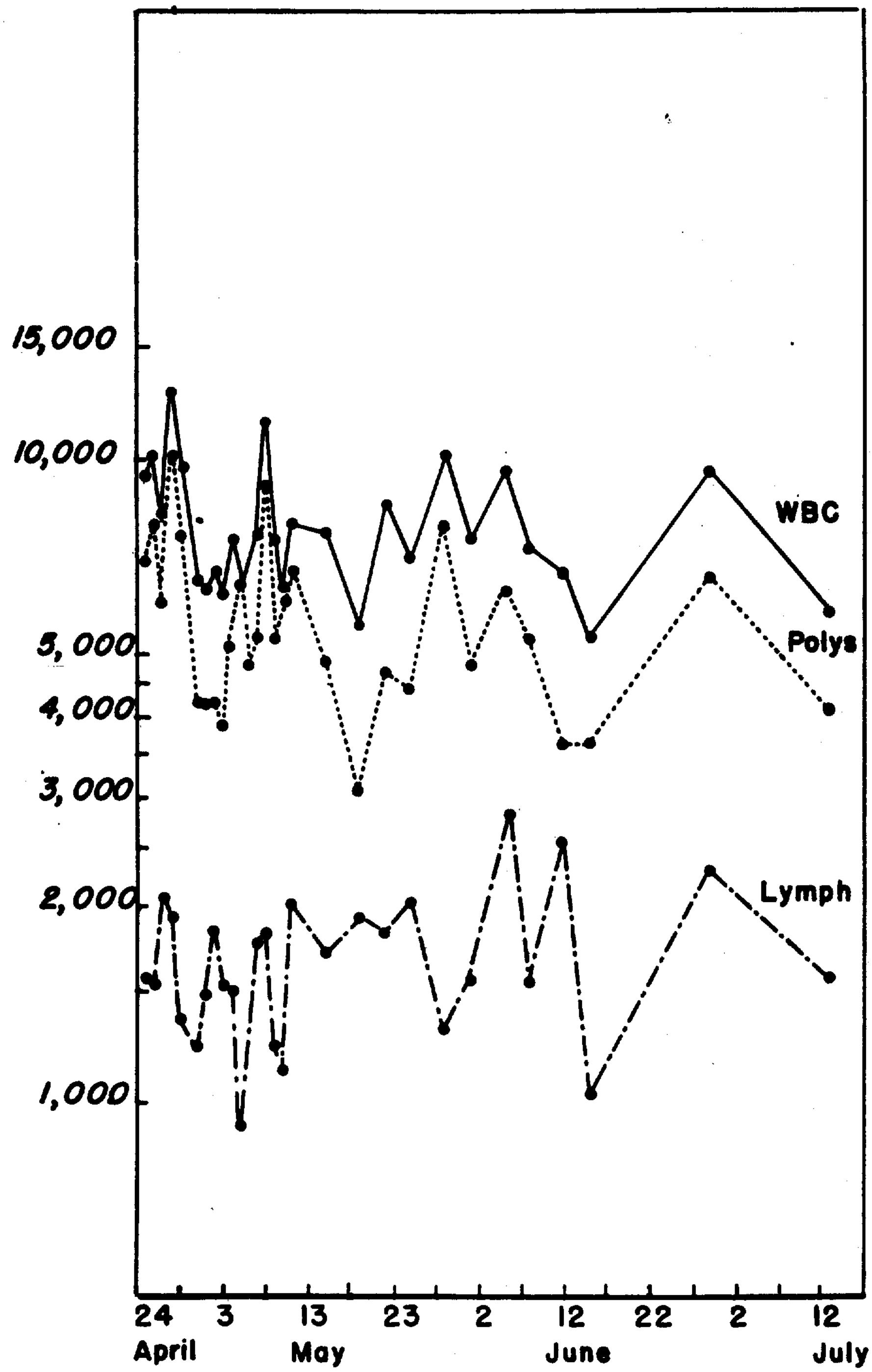


Figure III

Total white blood cell, polymorphonuclear cell, and lymph cell counts per cubic millimeter, in Case I.

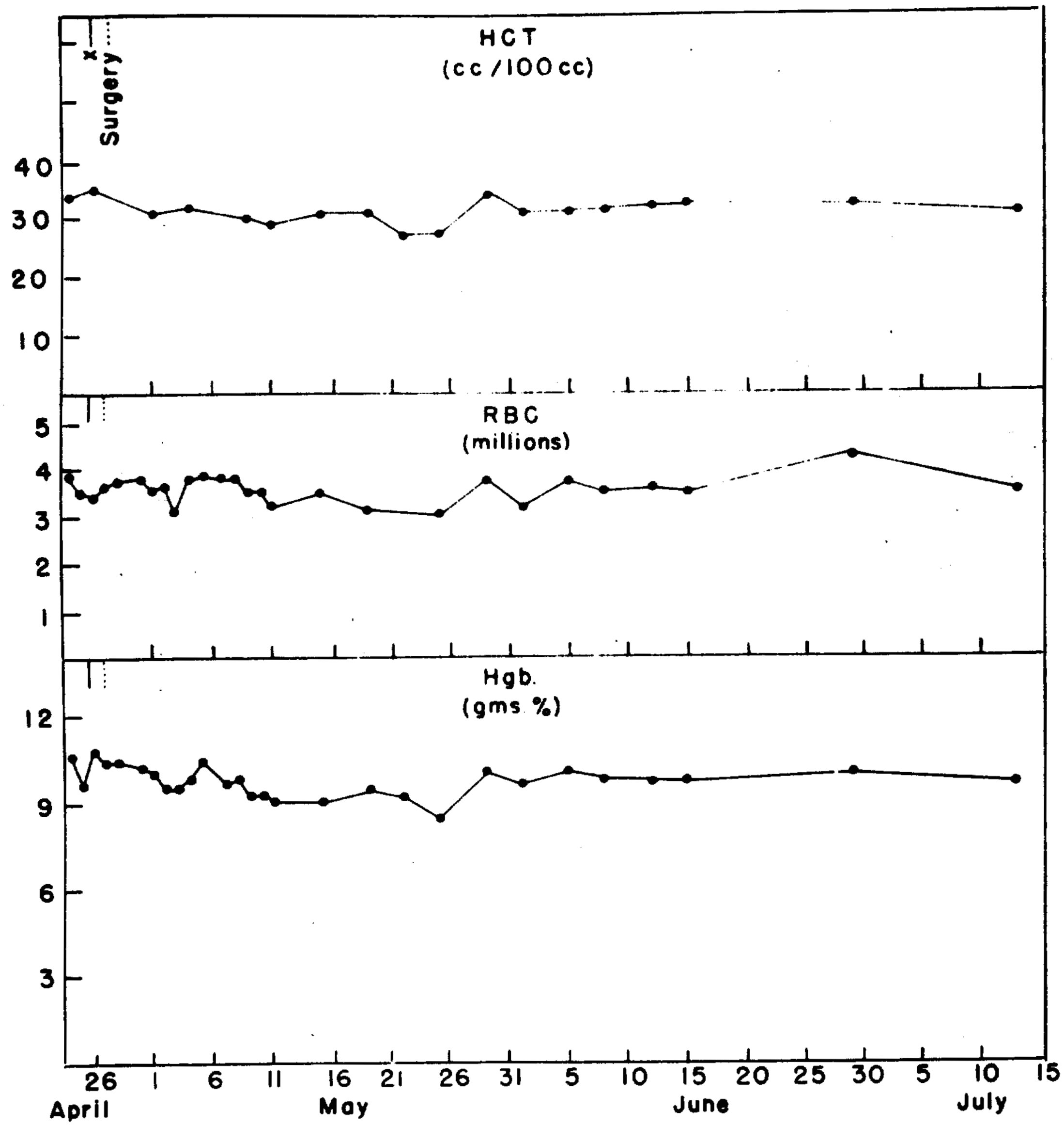
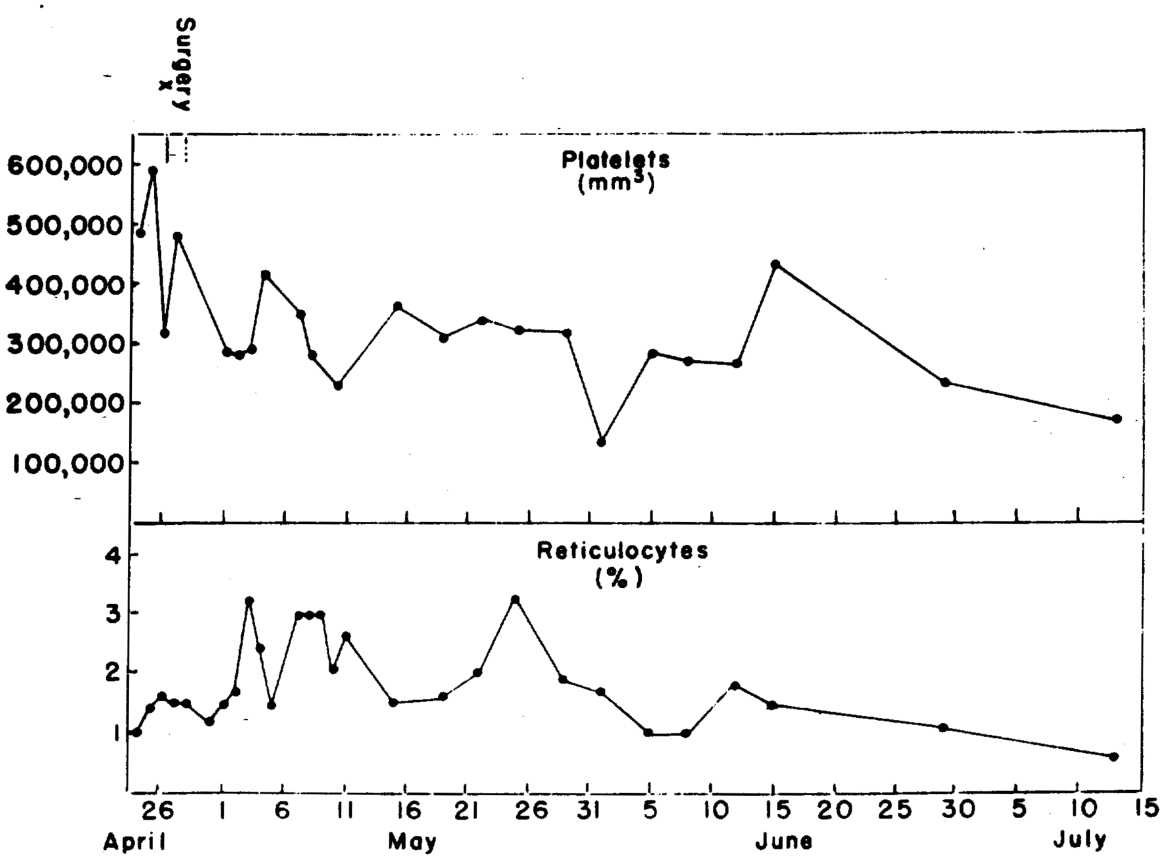


Figure IV

Hematocrit reading, red blood cell count, hemoglobin determination in Case I. The injection was given on April 26, 1945.

Figure V

Platelet and reticulocyte counts in Case I.



<u>Post Mortem Findings</u>. The patient died 155 days after the injection of plutonium. The analytical data is recorded in Table VII. The specimen of marrow and spicules showed the greatest activity per gram of tissue. The plutonium content per gram of liver was nearly as great. The activity of the cortex of the rib was one-tenth that of the bone marrow. No activity could be detected in the sample of bile analyzed. The effects of plutonium on normal and tumor tissue was looked for in the post mortem material by H. Lisco. He found no changes which he felt could be attributed to the action of the plutonium.

Table VII.

Distribution of plutonium in tissues of Case I, 155 days after the injection of 6.5 microgram of plutonium.

Tissue	Weights of Organs (gms)	Gms of Tissue Analyzed	Observed Counts per/min.	Cts/gm of Tissue per/min.	ug/gm of Tissue (x 10^{-3})	Relative Affinity for Plutonium*
Marrow + Spicules		0.8292	58.8	70.9	1.043	10.13
Liver	2050	34.11	2040.0	59.8	0.880	8.54
Sternum		4.38	111.1[1]	20.6	0.303	2.94
Periosteum (rib)		0.1215	2.12	20.0	0.299	2.86
Spleen	260	32.12	354.9	11.1	0.164	1.59
Lung Tumor		2.03	14.8	7.4	0.109	1.06
Cancer Tissue		2.87	20.9	7.2	0.106	1.03
Rib (cortex)		1.0125	6.06[1]	7.0	0.103	1.00
L. Nodes (aortic)		0.63	4.17	6.7	0.099	0.96
Lungs	1950	15.39	40.7	2.6	0.038	0.37
Testicle (gl. portion)		4.3425	10.0	2.3	0.034	0.33
Kidneys	340	27.35	53.3	1.7	0.025	0.24
Heart		4.9435	6.0	1.2	0.018	0.17
Diaphragm		35.73	33.3	1.0	0.015	0.14
Fat (abd.)		17.05	3.4	0.2	0.003	0.03
Bile		8 cc	2.6	?	0.000	----

* Counts per gram/counts per gram assuming uniform distribution of plutonium.
1 90% correction factor applied to observed counts to give actual counts/gm.

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Case II.

Excretion Studies. The urinary excretion data is listed in Table VIII and plotted in Figure VI. Unfortunately no comparison of fecal and urinary excretion can be made in this case. The collection of separate urine and stool samples was impossible. In fact the graph of urine excretion in Figure VI might with greater truth be called the graph of total product excretion.

The 24 hour excretion rate was 0.152 percent of the amount injected. This represents an excretion of 0.144 micrograms of the 94.9 micrograms injected. Following the initial 24 hour period the excretion rate was comparable to that in the other cases studied. The total known excretion was 0.684 percent of the amount injected, or 0.[illegible]9 micrograms.

Table VIII.

Daily Plutonium Urinary Excretion, Case II.

Days after Injection	24-hour Volume	Alpha Counts/min/ 100 cc.	% of Injected Dose Excreted
1	1660 ml	594	0.152
2	1725	622	0.167
3	1750	250	0.067
4	1150	186	0.033
5	2020	134	0.042
6	1300	207	0.042
7	1190	132	0.0243
8	1500	110	0.0254
9	1400	89	0.019
10	1280	154	0.030
11	1120	108	0.019
12	940	100	0.014
13	875	251	0.034
14	630	99	0.009
15	830	124	0.016
16	150	164	0.004

Studies of the Peripheral Blood: No alterations in the hematological constituents of the peripheral blood occurred following the administration of 97.2 micrograms of plutonium which could be attributed to the presence of the element. The interpretation of changes in the thymol turbidity and cephalin flocculation tests, and in the amount of bilirubin in the blood serum was not possible because of the terminal state of the subject. These data are presented in Table IX and in Figure VII.

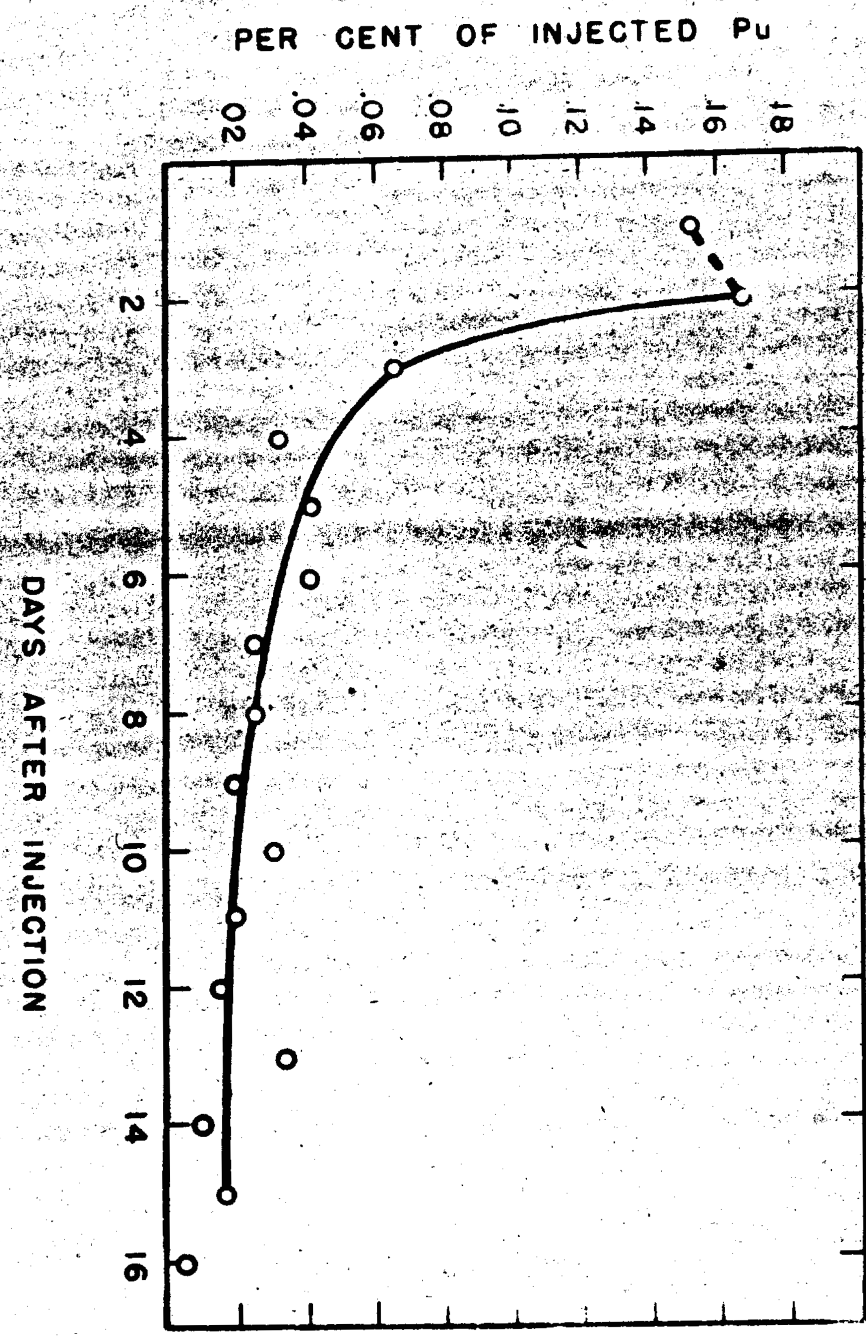
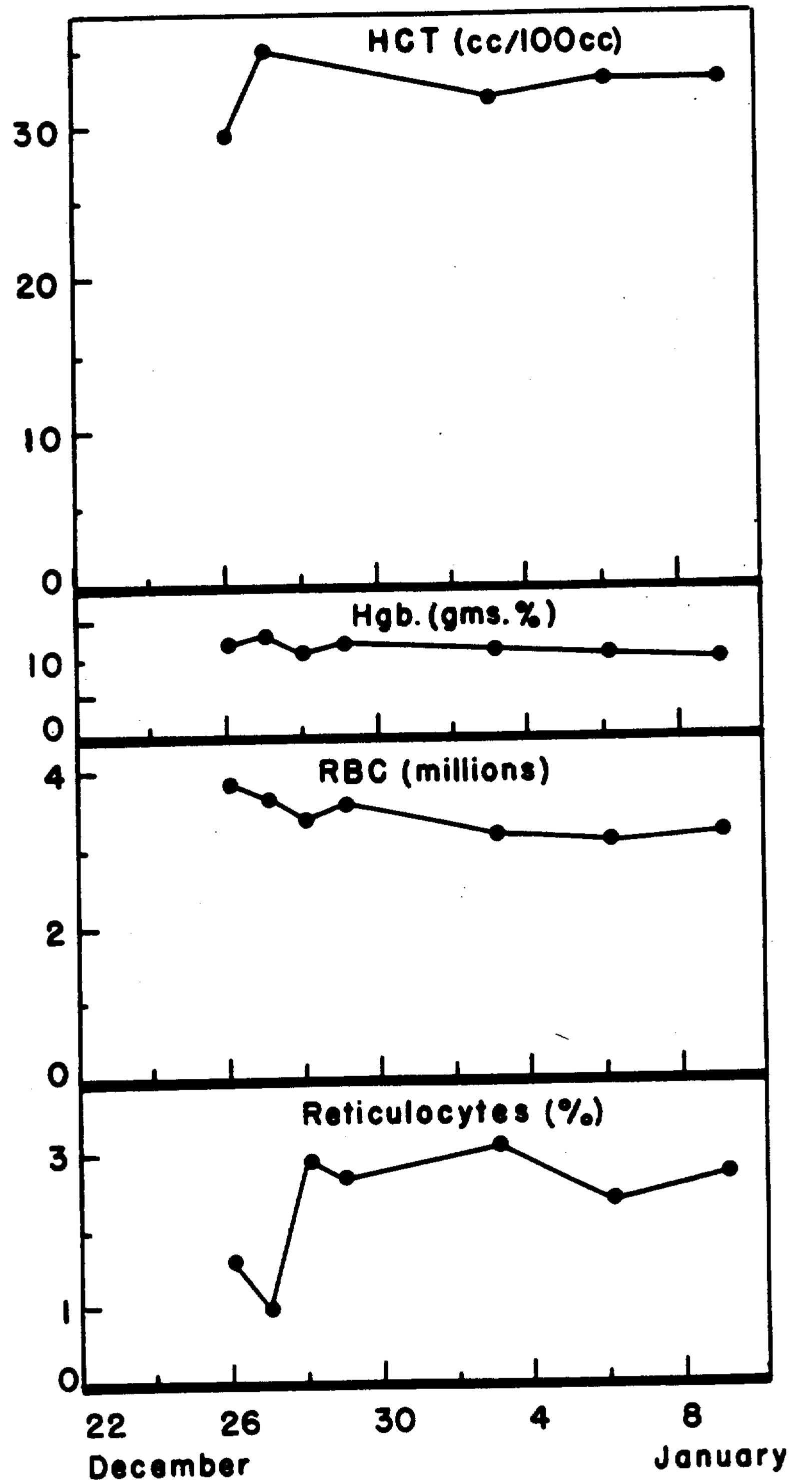


Figure VI

Excretion of plutonium in the urine following the injection of 94.9 micrograms of plutonium citrate.



<u>Figure VII</u>

Hematocrit, hemoglobin, red blood cell and reticulocyte findings in Case II.

Table IX

Blood Findings in Case II

Date	12/26/45	12/27/45*	12/28/45	12/29/45	1/2/46	1/5/46	1/8/46	1/12/46
Hb	12.1	12.9	11.8 gm	1[illegible].[illegible] gm	11.[illegible]	11.0	10.5	11.0
RBC	3.96	3.72	3.47	3.65	3.37	3.25	3.32	3.36
Hematocrit	29	35			32	33	33	33
WBC	17,250	20,950	16,550	18,300	17,900	18,950	20,500	20,950
Reticulocytes	1.6%	1.0	2.9%	2.7%	3.2	2.4	2.8	1.9
Sed Rate	115	101			59		58	57
Neutrophiles, %	83	75	77	71	81	82	80	85
Neutrophiles, No.	14,276	15,675	12,705	12,993	14,499	15,498	16,400	17,765
Eosinophiles, %	5	2	4	3	2	1	2	12
Basophiles, %			1					
Lymphocytes, %	12	15	11	15	10	13	13	12
Lymphocytes, No.	2,064	3,135	1,815	2,745	1,790	2,457	2,665	2,508
Monocytes, %	2	8	7	10	7	4	5	3
Stabs				1%				
Metamyelocytes, %					2			
Polychromasia			sl.	sl.	sl.	sl.		sl.
Hypochromasia	sl.	sl.					sl.	
Anisocytosis	sl.	sl.	sl.	sl.	sl.	sl.	sl.	sl.
Normoblasts								2
Polys. toxic	x							x
Cephalin Flocculation		1+	2+	1+	1+	1+	2+	1+
Serum Bilirubin 15 min.		0.48	0.42	0.42	0.63	0.36	0.58	0.38
Total		1.0	0.72	0.76	1.04	0.56	1.00	0.64
Thymol Turbidity		90	88	89	89^{2}	89^{1}	86^{2}	90

* Injection of plutonium on this day following the withdrawal of blood for study.

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<u>Distribution of Plutonium in the Tissues.</u> The Plutonium content of the tissues analyzed is listed in Table X. The marrow and rib specimens showed the highest specific activity, as would be expected from the animal work. The plutonium content per gram of liver tissue was roughly one-tenth that of the bone marrow. The specific activities per gram of muscle and fat were respectively one-twentieth and one-thirty-fifth that of the bone marrow. H. Lisco reviewed the histological material for evidence of changes similar to that attributed to plutonium in the experimental animals. No such change was observed. It should be pointed out that the amounts per gram of body weight were greater in the animals in which changes were seen.

Table X.

Plutonium Distribution in Tissue 16 Days after Injection.

Tissue	Weight of Organ (gms)	Weight of Sample (gms)	Total Counts[1] in Sample	Counts[1]/ gm of Tissue	Micrograms Plutonium/ gram of tissue ($x 10^{-3}$)	Relative Affinity for Plutonium[2]
Marrow (Rib)		0.2065	289	1399	20	8.49
Rib (Cortex)		0.430	558	1299	18.6	7.88
Callus and Bone		0.1933	160	828	11.2	5.02
Callus (bone free)		0.262	140	534	7.7	3.17
Kidney	190	6.00	2162	360	5.1	2.18
Thyroid		2.64	597	226	3.2	1.37
Contents (lower bowel)		10.05	1833	183	2.6	1.11
Liver	1110	8.70	1405	162	2.3	1.00
Pancreas	60	6.045	893	148	2.1	0.90
Periosteum		0.461	57	123	1.7	0.75
Lung	490	14.40	1533	107	1.5	0.65
Fat, Mesenteric		5.850	560	96	1.2	0.58
Spleen	85	10.850	1021	94	1.2	0.57
Tumor (Liver)		1.970	140	71	1.0	0.43
Heart	250	9.40	660	70	1.0	0.42
Ovary, L.		1.975	122	63	0.90	0.38
Lymph Node (abd.)		1.53	73	48	0.70	0.29
Intestines (small)		3.40	151	45	0.64	0.27
Intestines (large)		6.87	291	43	0.60	0.26
Muscle (Str.)		15.32	613	40	0.57	0.24
Blood (Heart Clot)		1.835	40	22	0.31	0.13

1 - Alpha counts per minute from plutonium.

2 - Counts/gram found divided by counts/gram assuming equal distribution of the plutonium.

DISCUSSION

It must be emphasized that the data discussed above, while obtained on humans, may not be applicable to the population with which we are mostly concerned. The majority of occupationally exposed persons are in the 20-40 year age group and are in good general health. The persons discussed above both had carcinomas, one of which had widespread metastases. In case #2, the injection was made but seventeen days before death and the terminal state may have influenced the metabolic behavior of the element. In case #1 no gross evidence of other than local disease, except for the metastasis to the lung, was noted at the time of injection. Thus, barring alterations due to age, the early distribution of the plutonium was presumably a "physiological" one. However, it must be pointed out that we have no information on the early distribution pattern of the plutonium in this case. The data given in TableVII represents the distribution of the injectate 155 days later, after profound metabolic disturbances, causing his death, had occurred. It is impossible to say what influence this may have had in altering the early distribution pattern.

As is well-known, the biological behavior of a given agent varies greatly from one species of mammal to another. Hence, experience with humans injected with plutonium was vital to any interpretation of the data obtained from animals. The rate of plutonium excretion in rats(2), mice(2), rabbits(3) and dogs(4) varies widely. The route of excretion varies from species to species(2,4). Since our estimate of the body content, and hence ultimately of the desirability of removing a given worker from his job, depended upon the excretion rate of plutonium in the human, it became necessary to determine that rate directly in the species concerned. Knowledge of the distribution of the element as well as its rate and route of elimination from the human body provided information which could be correlated with the more extensive experimental investigation in animals and provided information which made possible the estimation of the amount of plutonium already deposited in the workers by the determination of the daily plutonium excretion rate of the individual concerned.

<u>Clinical Picture</u>. Insofar as can be determined the clinical course in neither of the two cases was influenced by the injection of plutonium. In Case #1, the concentration of that material was 0.085 micrograms per kilogram of body weight immediately following the injection. In the second case the concentration of plutonium was 2.46 micrograms per kilogram of body weight.

That the amount of plutonium injected in these subjects produced no appreciable clinical effect is likely in view of the fact that the amount of plutonium necessary to produce damage is far greater. Table XI lists some of the experimental values(2).

Table XI.

Comparison of Dose Levels of +6 Plutonium in Animals and Their Effects.

	ug/kg	Effects	Time
Rats	700 - 1000	LD 50% in	30 Days
Rats	200 - 600	LD 50% in	150 Days
Rats	10	None	420 Days

It will be seen that the level of 10 micrograms per kilogram is approximately 117 times the dosage level in Case I and 4 times the dosage level in Case II.

Haematological Studies. No hematological changes of the peripheral blood were observed in either subject. In view of the very slow excretion rate and long half-life of deposited plutonium it might be assumed however that a condition comparable to that described by Martland(5), Castle(8) and Bomford and Rhoads(9) in individuals with chronic radium poisoning (severe anemia, leukopenia and thrombocytopenia with or without bone sarcoma) might well develop in either case were it possible to observe subjects over extended periods of time. The difficulty which arises in attempting to extrapolate from the radium damage data on the human to the expected effect of plutonium is, among other things, due to the difference in the excretion pattern and the impossibility of estimating what the ingested dose might have been in the individuals who have succumbed to radium poisoning. While bone sarcomas have been reported in individuals with a total of 0.5 μg of radium in the body at death, little information is available as to the amount which was in the body initially and this initial dose may be the critical amount.

Case I

Excretion Studies. The fact that the rate of excretion of plutonium apparently had not reached a constant even 100 days after injection deserves emphasis. The rate of fall is slight but definite. This point deserves emphasis as it may indicate that the excretion rate 1000 days after exposure may be even less than the average of 0.012 per cent found after 150 days in this case. Evidence for continued diminution in the excretion rate of plutonium 238 (isotope of plutonium 239) is found in the patient studied by the University of California group which is described in the biology volumes of this report. In this patient, 158 days after injection, the daily excretion rate is approximately 0.0015 per cent of the injected dose(6), a figure definitely lower than our figure of 0.012 per cent one hundred and fifty days after injection.

Should the lower figure prove to be the more correct one the difficulty of detecting tolerance concentrations of plutonium by means of the urinary excretion of that element is materially increased.

It is interesting to note the totals of urinary and fecal excretion for the time periods of 0-24 hours, 2-10 days, and 11-100 days. Table XII gives these data for Case I in terms of per cent of the injected dose:

Table XII

Summary of Plutonium Excretion for Indicated Time Periods, Case I

Time	Urine	Stool	Total
0-24 hours	2.53%	0.233%	2.764%
2-10 days	0.638%	1.748%	2.386%
11-100 days	1.902%	0.767%	2.669%

It is apparent that the total excretion is roughly equal for each of the various periods. One might speculate that the next order of magnitude, that is 101-1000 days, might also show a total plutonium excretion of approximately 2.5 percent. If this percentage excretion for the 101-1000th days period is subsequently borne out by experimental observation, it would paint a rather discouraging picture from the point of view of the normal excretion rate for plutonium.

The fecal excretion pattern is similar to that described for the excretion in the urine. No sharp early peak in the excretion rate is noted however. On the other hand, the rapidity with which the rate falls is not so marked. Indeed, the total plutonium excreted from the second to the tenth day is greater in the feces. However, as pointed out above, the fecal excretion after the twentieth day is distinctly less than the urinary excretion.

It will be noted that throughout this paper the excretory rate is given as "percent per day of the injected dose". It would be more accurate to speak of the percent per day of the amount in the body. Because of the low rate of excretion of plutonium the correction factor is small and it is felt that the small inaccuracy introduced by this practice is justifiable, particularly in preliminary studies.

Distribution of plutonium in the Body. It may be useful to compare the relative concentrations of plutonium in the various organs in the two cases. It is recognized that such comparisons cannot be pushed too far because of the many uncontrolled variables.

For ease of comparison, the values from Case I in Table XIII are adjusted to an injection amount of 94.91 micrograms, the amount injected in Case II, assuming the same distribution would occur with the larger dose.

In both cases the bone marrow shows the greatest concentration of plutonium per gram of tissue. On the basis of animal experimentation it is felt that the plutonium probably initially localizes in the osteoblastic and collagenous tissue surrounding the spicules, forming the endosteum. Since the proportion of this tissue is greatest in the marrow specimen, it shows the highest activity. It is of interest also to note the much higher proportional activity of the bone cortex in Case II, where the cortex shows almost as much activity as the marrow. The decalcification of the bones noted in this case would result in a greater proportion of plutonium-containing tissue than found in the comparable specimens in Case I, where the calcium content of the bones was apparently normal. The specimen of callus from the rib in Case II did not show as high concentration as the cortex or marrow specimens do. Since the callus represents a healing pathologic fracture, it is entirely possible that the uptake of plutonium was abnormally low.

Table XIII

Comparison of the concentration of plutonium per gram of tissue. For ease of comparison the values from Case I are adjusted to an injection amount of 94.91 micrograms, the amount injected in Case II.

Tissue	Case I Gm Pu/gr tissue ($x 10^{-3}$)	Case II Gm Pu/gm tissue ($x 10^{-3}$)
Bone Marrow + Spicules	15.2	20.0
Bone Cortex	1.50	18.6
Kidney	0.36	5.1
Liver	12.8	2.3
Lung	0.55	1.7
Fat	.04	1.5
Spleen	2.39	1.2
Tumor	1.59	1.0
Heart	0.26	1.0
Ovary		0.90
Testicle	0.50	
L. Nodes	1.44	0.70
Muscle, striated	0.22	0.57

The amounts in the livers are of considerable interest. The reasons for the wide discrepancy shown are not known at the present time. In Case I the liver content at death, some 150 days after injection, constituted approximately one-third of the injected amount. This value is far higher than the data from experimental animals would lead one to anticipate(2). It is true that early values comparable to the one listed here may be found in the experimental animal. Amost uniformly, however, the initial high value has dropped by a factor of five or ten by the hundredth day(2). Why, in this instance, the liver should have retained plutonium so tenaciously is not understood. Indeed, it must be admitted that we cannot rule out the possibility that the amount in the liver was at one time lower than the final value. Liver biopsies would be extremely useful in following the plutonium content of that organ over a wide time range.

In Case II the content of plutonium in the liver was approximately one-sixth of the amount noted in Case I and constituted approximately one percent of the amount injected. This figure is, if anything, somewhat lower than one would expect the concentration in the liver to be on the 16th day after injection, judging again from the results of animal experiments.(2)

The concentration of plutonium in the spleen in Case I, which showed some congestion but no other evidence of pathologic change, was distinctly greater than the concentration in the spleen in Case II where a marked myeloid metaplasia was observed. The relative concentration of plutonium in the spleen observed in these two cases given here are distinctly less than those observed in experimental animals, particularly in dogs(4). In most instances the plutonium concentration in the spleen compares favorably with that of the bone marrow. Certainly the difference noted between the results in the two human cases are far less than the difference between species(2,4). Again no explanation for this fact can be given at this time.

It is interesting to note that in both cases the primary tumors, two carcinomas and a lymphosarcoma, did not concentrate plutonium to a significant degree. While it is impossible to generalize from two cases, it seems unlikely that plutonium will be of any value in the treatment of carcinomas in humans. As a general principle any radioactive agent injected for therapeutic purposes must concentrate to a greater degree in the tumor than elsewhere.

There is a marked difference in the concentration of plutonium in the kidneys of the two cases. The higher value is found in Case II. Two factors may reasonably be expected to operate in the direction of producing a higher concentration of plutonium in this case. First, and probably more important, is the fact that the death occurred shortly after the injection. The data obtained from animal experiments indicates that the kidney concentration is higher shortly after injection(2). In both cases evidence of degenerative changes in the tubules of the kidneys was noted in the tissue sections. In addition, in Case I changes suggestive of a pyelonephritic lesion were noted. It is possible that the urinary excretion data will be found subsequently to be too low because of the presence of disease in the kidneys. Evidence obtained elsewhere, however, would indicate that the figures for urinary excretion given here are not seriously in error(7).

The lack of plutonium in the bile is of considerable interest. Within the limits of the method (approximately 10^{-4} micrograms of plutonium per gram of tissue) none was found. Similar findings were noted in the plutonium injected dogs(4).

The relative activity of the contents of the lower bowel in Case II are higher than would be anticipated from the results of the analysis of the feces. Further, the value is four times higher than that obtained for specimens of the tissue of the large and small intestine in this case. If the assumption is made that the amount of plutonium in the bile was negligible as in Case I, it would seem then that plutonium is being excreted by the large or small intestine. Since other heavy metals are excreted by the large intestine it seems reasonable to tentatively assume that plutonium is also excreted by this route. The assumption cannot be verified until further experimental data is available.

In general the relative amount of plutonium per gram of tissue tends to be higher in Case II than in Case I. It is possible that the explanation lies in the comparative lack of fatty tissue in Case II so that the organs and tissues studied tend to have a greater proportion of plutonium than was noted in Case I. The total fat is difficult to estimate from the data at hand and therefore the total amount of plutonium absorbed in the fat. In spite of the lower unit concentration in the fat in Case I, it may be that the proportional amount of plutonium in the total fat was greater in Case I than in Case II.

Summary and Conclusions. Distribution and excretion studies have been made of plutonium 239 +6 citrate in two human subjects given total intravenous doses of 5 and 94.91 micrograms of plutonium respectively. No clinical effect was noted which could be attributed to the biological action of the element in 155 and 16 days of observation respectively. Such changes as occurred in the hemotological picture and in liver functions can be attributed to the terminal state of the subject, to the underlying disease, or both.

It is difficult to make other than very tentative generalizations because of the considerations mentioned above and because of the fact that only two cases are reported here. From what is known from the cases reported here (and from other

cases reported elsewhere) the following tentative conclusions may be drawn. It must be recognized clearly that these are not in the true sense of the word conclusions but are only working hypotheses that must be confirmed and elaborated upon by subsequent investigations.

(1) The urinary rate of excretion of plutonium in humans is exceedingly low. The best evidence available at this time would indicate that the "chronic" (150th day) excretion rate does not exceed 0.01 percent per day of the amount fixed in the body.

(2) The fecal rate of excretion of plutonium fixed in the body is lower than the urinary rate by a factor of approximately three. What evidence we have would indicate that the rate of fecal excretion does not exceed 0.003 percent per day of the amount in the body.

(3) The highest concentration of the plutonium fixed in the body is found in the bone marrow. The liver concentration has varied so widely in the two cases here reported that it is impossible to predict on a reasoned basis what the general picture might be.

(4) The concentration of plutonium in the neoplastic tissue of these cases was not high.

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