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DISTRIBUTION AND EXCRETION OF PLUTONIUM ADMINISTERED INTRAVENOUSLY TO MAN*

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I. INTRODUCTION

It is now a well established fact that the deposition of radioactive material (Ra, its isotopes and daughter products) in the skeletal system of radium dial painters was responsible for the bone necrosis, radiation osteitis, osteogenic sarcoma and other pathological changes in bone which characterize the condition commonly known as chronic radium poisoning.

Hamilton *et al.* (HaXX) were the first to demonstrate that plutonium, like radium, concentrates in the skeletal system of the rat. Numerous reports have emphasized that bone is a major site of plutonium deposition regardless of the animal species, the valence state of the material or the route of administration (La47; FiXX). Autoradiographic studies of the mode of deposition of plutonium in bone (BlXX; Ha47; Co47; CaXX) showed that it was deposited in a pattern quite different from that of radium. The latter element tends to be incorporated into the bone salts exclusively and becomes buried in the calcified structure in the manner to be expected from a member of the calcium family in the periodic table. Plutonium, however, shows some deposition in soft tissues (especially in the liver) and a remarkable affinity for the non-calcified, non-cartilaginous areas of bone. The material is highly localized in the epiphyseal line, the periosteum and the endosteum so that localization is predominately in regions of trabecular bone (see Fig. 1). The general conclusion was that the mode of deposition of plutonium made it potentially more hazardous than radium. Although there is only limited proof that the above conclusion is justified, it must be considered when evaluating the potential chronic toxicity of the material.

Subsequent experiments with rodents by Brues *et al.* (Br47) and others (CaXX) have demonstrated that plutonium is quite effective in producing pathological changes in bone including osteogenic sarcoma (see Fig. 2).

Brues (Br50) compared the relative chronic toxicity of equivalent microcurie amounts of plutonium and radium by following 1000 rats, 600 mice throughout life and 37 rabbits for over 400 days. A comparison of survival time, radiographically determined bone damage, pathological fractures and bone

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FIG. 1. Nuclear track autoradiograph showing localization of plutonium in the bone of the rat. (A. Williams, J. Wellnitz; Photomicrography by Los Alamos Photographic Laboratory.)

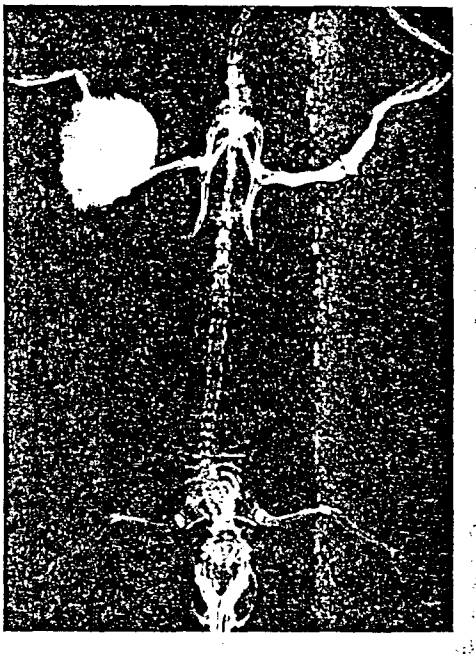

FIG. 2.

tumors in these animals appeared to bear out a plutonium–radium chronic toxicity ratio of 12-15/1 on the basis of injected dose or about 4-5/1 on the basis of retained material.

The above observations and the experiences of the radium dial industry have emphasized the necessity of employing extremely rigid control over all plutonium operations. The major health problem associated with plutonium processing is, of course, the possibility that small amounts of plutonium accumulated in the skeletal systems of workers may, over a period of from 10 to 30 years, cause bone changes similar to those observed in chronic radium poisoning. The possibility is serious enough to justify the adoption of a rigid maximum permissible body burden as is currently done with radium.

Only recently the subcommittee on internal radiation tolerances of the National Bureau of Standards established a tentative maximum permissible body content of 0.5 μg (0.032 μc) for plutonium. This value was adopted immediately by the Division of Biology and Medicine of the Atomic Energy Commission as the official maximum permissible tolerance for plant personnel (Wa50).

Adequate information as to the fixation and excretion of plutonium by man is essential to the evaluation and interpretation of the maximum permissible body tolerance. More specifically such studies seem highly important for the following purposes:

(1) To minimize the degree of uncertainty inherent in extrapolating the vast amount of animal experimental data to man.

(2) To provide the best possible quantitative basis for the diagnosis of degree of exposure of personnel to plutonium.

(3) To determine the degree of fixation of plutonium by man and establish criteria for the period of retirement from further exposure of workers having received a maximum permissible dose.

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(4) To provide more extensive and quantitative data on the deposition and excretion of plutonium by man as a basis for future consideration of maximum permissible body tolerance.

Need for the above information was recognized several years ago. It was also recognized that such information could be obtained only by administering small tracer amounts of plutonium to persons with a relatively short life expectancy. The first tracer study was initiated 10 April, 1945 (LaXX). Shortly thereafter, both the Chicago and Berkeley groups initiated similar studies (RuXX; HaXX).

This report is the final presentation of the results of twelve plutonium tracer cases studied as a joint project of the Los Alamos Scientific Laboratory of the University of California and the Atomic Energy Project of the University of Rochester School of Medicine and Dentistry.

The results of the studies conducted by the Berkeley and Chicago groups are correlated with the present ones providing a collection of data from sixteen cases.

In addition to the twelve tracer cases mentioned above, the Los Alamos Scientific Laboratory has had approx. 6 years experience with exposure problems associated with the processing of large amounts of plutonium.

Wherever applicable, the Laboratory's experiences with the exposure of personnel are used to enlarge and supplement the data collected from the plutonium tracer studies presented in this report.

2. METHODS

(A) *Selection and description of subjects*

The life expectancy of the individual was carefully considered as a basis of selection of subjects for study. As a rule, the subjects chosen were past 45 years of age and suffering from chronic disorders such that survival for 10 years was highly improbable. By adhering to these criteria, the possibility of late radiation effects developing would be avoided. Furthermore, an opportunity to obtain post-mortem material within a few months, or at most a few years, would be much greater.

Of twelve patients chosen, ten were past the age of 45. One was only 18-years-old, and has since died of Cushing's Syndrome. Up to the time of this report, and approx. 5 years since the initiation of the first study, five subjects are known to have died of their diagnosed illness. Autopsies and tissue samples were obtained from only three of the five terminated cases.

Brief summaries of the medical histories of the subjects of these studies are as follows:

Hp-1

This patient, a 67-year-old white male with a 9-year history of peptic ulcer, was admitted to the hospital following a severe gastrointestinal hemorrhage. The presence of a duodenal ulcer was confirmed by X-ray examination and a traction diverticulum of the esophagus was noted. Clinical diagnoses included duodenal ulcer, gastrointestinal hemorrhage with secondary anemia and esophageal diverticulum.

Hp-2

This patient, a 49-year-old white male, was a known hemophiliac and entered the hospital on this occasion for the thirty-eighth time. Symptoms referable to hypertension had been present for three years. Clinical diagnoses on this admission included hemophilia, essential hypertension with hypertensive cardiovascular disease and coronary insufficiency and chronic arthritis.

Hp-3

This patient, a 49-year-old white female, was admitted to the hospital with complaints of pigmentation of the skin, pruritic dermatitis and dependent edema. Initial clinical studies were carried out in November and December 1945, at which time diagnoses of hepatitis of unknown etiology and hypoproteinemia were made. She was admitted for follow-up examination in October 1946, when she appeared in good health.

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Hp-4

This patient, an 18-year-old white female, had a history of Cushing's Syndrome since 1941. Her admission in October 1945 was the fifth period of hospitalization. Chief complaints on this occasion were referable to hypertension and osteoporosis. The clinical diagnoses were basophile adenoma of the pituitary gland with hypertension, hypertensive heart disease, nephropathy with uremia, osteoporosis and a staphylococcic infection of the urinary tract. The patient ran a down hill course until death in uremia occurred in April 1947. Diagnoses at autopsy included basophile adenoma of the pituitary gland, atrophy of the thyroid gland, hypertrophy of the adrenals, hypertrophy of the left ventricle, hypoplasia of the uterus and ovaries, osteoporosis of the spine and pelvis, and chronic nephritis.

Hp-5

This patient, a 56-year-old white male, was admitted to the hospital in Novenber 1945 with complaints of generalized weakness and difficulty in walking and swallowing of 3-years duration. The clinical diagnosis was amyotrophic lateral sclerosis. Death occurred in April 1946. The diagnoses at autopsy included amytrophic lateral sclerosis, bronchopneumonia, generalized arteriosclerosis, renal cysts and adenoma of the right kidnev.

Hp-6

This patient, a 45-year-old white male with a history of Addison's disease since Jaunary 1945, was admitted to the hospital on 14 December 1945, for treatment of numerous infected lesions of the eyelids and toes. He responded to conservative treatment and studies began during convalescence. On readmission in June 1947, his condition was essentially unchanged.

Hp-7

This patient, a 59-year-old white female who had been previously treated for heart disease and hyperthyroidism, was hospitalized on 21 January 1946, for cardiac decompensation. The clinical diagnoses were rheumatic heart disease with mitral insufficiency and auricular fibrillation, and toxic nodular goiter. She expired in October 1946. Permission for autopsy was withheld, but the probable cause of death was lobar pneumonia.

Hp-8

This patient, a 41-year-old white female, had a history of scleroderma since January 1945, and a duodenal ulcer first diagnosed in 1944. The clinical diagnoses on this admission were scleroderma and duodenal ulcer.

Hp-9

This patient, a 66-year-old white male, was admitted to the hospital in March 1946 with a history of generalized dermatitis and weakness of eighteen months duration. A diagnosis of dermatomyositis was made. The patient expired in July 1947. Diagnoses at autopsy included generalized muscular atrophy, dermatitis, purulent bronchitis and bronchopneumonia, hypertrophy and dilatation of the heart and chronic passive congestion of the liver and spleen.

Hp-10

This patient, a 52-year-old negro male, was admitted to the hospital on 24 March 1946, in acute congestive heart failure. A history of heart disease since 1926 was obtained, and his history included both rheumatic fever and luetic infection. The clinical diagnoses on this admission included rheumatic heart disease, latent treated syphilis and ethmoidal and frontal sinusitis.

Hp-11

This patient, a 68-year-old white male with history of alcoholism and dietary inadequacies for many years, was admitted to the hospital on 12 December 1945, with complaints of dyspnea and abdominal swelling. He expired on 26 February 1946, and diagnoses at autopsy were cirrhosis of the liver, ascites and thrombosis of the portal vein.

Hp-12

This patient, a 53-year-old colored male, was hospitalized on 25 March 1945, following

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an automobile accident in which he sustained comminuted fractures of the left femur and right patella and a transverse fracture of the right radius and ulna. Physical findings of note included a left lenticular cataract and marked hypertrophic and atrophic arthritic changes in both knees, together with osteochondromatosis of the left knee.

(B) *Management of subjects and collection of samples*

Ten of the twelve patients were cared for in the special metabolic ward of Strong Memorial Hospital. The general management of the ward patients was as follows:

A control period of about 10 days was utilized to instruct the patient in the quantitative collection of urine and fecal specimens. During this period all necessary adjustments to ward routine and all necessary modifications in diet were completed. After the patient had proven himself capable of cooperation, a series of control urine and fecal samples were collected for the purpose of "blank" determinations by the method of plutonium analysis. Preceding the injection of plutonium and again at termination, physical and laboratory examinations were conducted on each subject.

Blood samples were drawn into dry sodium citrate as an anticoagulant. Samples of 15 ml were taken before administration of plutonium and at 4 hours, 1 day, 3 days, 6 days, 10 days, 15 days, etc. post injection.

Urine samples were collected directly into half-gallon fruit jars and preserved with formaldehyde. The urine was usually collected in 24-hour periods except on the day the plutonium was given. During the first day it was collected in two 12-hour periods.

Fecal samples were collected in 3 l. beakers. The patient was instructed to empty the bladder before defecation to avoid admixture of urine and feces. As a rule feces were pooled during intervals of four days, except immediately after the plutonium was given when the first two stools were collected separately. All samples were preserved by boiling for 10 min with 6 *N* HCl.

Tissue samples of from 25 to 150 g were obtained at autopsy and preserved in 80% alcohol.

(C) *Administration of plutonium*

The plutonium solution used in these studies was prepared by dissolving 5.0 mg of spectrographically pure plutonium metal in 1.0 ml of 2 *N* NHO_3. The solution was assayed for plutonium by α counting. An appropriate aliquot of the plutonium solution was placed in a 10 ml volumetric flask and diluted to volume with sterile 0.41% sodium citrate·$2H_2O$. The solution prepared in the above manner had a pH of approx. 5.5 and the plutonium was in the form of Pu^{+4}-complex.

The technique of injection and the method of assay of the injected dose were as follows:

One syringe was filled with sterile saline and a 22-gauge needle attached. The other syringe was filled with 0.5 ml of the plutonium solution and the needle used for filling the syringe was discarded. The needle of the syringe containing sterile saline was introduced into a cubital vein and the saline slowly injected to insure unrestricted entry into the vein. The syringe was then carefully detached from the needle, which was still in the vein, and the syringe containing the plutonium injection solution was substituted. The plutonium solution was injected rapidly after which the syringe was rinsed once by drawing it full of the patient's blood and discharging the blood back into the vein.

The same syringe and needle used to inject the patient was used to measure 0.5 ml aliquots of the plutonium solution into each of four volumetric flasks. The washing of the syringe and the other essential steps of the injection technique were duplicated. The contents of each flask was diluted to volume with 2 *N* HCl and a suitable aliquot of each evaporated directly on platinum discs and assayed for α-activity. The average of the four assays was taken as the amount of plutonium administered to the patient. The average standard deviation for each set of four results was 3.0%. The amount of material received by each subject and the dates of injection are presented in Table 1.

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Table 1. Amount of plutonium administered to subjects via intravenous injection and the date of administration*

Designation of Subject	Date of Injection	μg Pu Injected**
Hp- 1	October 16, 1945	4.6
Hp- 2	October 23, 1945	5.1
Hp- 3	November 27, 1945	4.9
Hp- 4	November 27, 1945	4.9
Hp- 5	November 30, 1945	5.1
Hp- 6	February 1, 1946	5.3
Hp- 7	February 8, 1946	6.3
Hp- 8	March 9, 1946	6.5
Hp- 9	April 3, 1946	6.3
Hp-10	July 16, 1946	6.1
Hp-11	February 20, 1946	6.5
Hp-12	April 10, 1945	4.7

* Pu was administered as Pu^{+4}-citrate in 0.5 ml of 0.41% solution sodium citrate·$2H_2O$.

** Average standard deviation of determination of dose was 3.0 per cent.

(D) *Analytical procedures*

All urine samples were analyzed for plutonium using the cupferron extraction procedure developed at the Los Alamos Scientific Laboratory for the determination of exposure of laboratory personnel (LaXX).

Fecal samples were analyzed by a modification of the cupferron procedure published earlier (Ma48).

Blood and other tissue samples were "ashed" either in a muffle furnace or with conc. HNO_3 and H_2O_2. The ash solution was analyzed for plutonium by the cupferron extraction procedure in exactly the same manner employed for the analysis of urine ash solutions.

3. RESULTS

(A) *Clinical observations*

Acute toxic effects from the small doses of plutonium administered in these studies were neither expected nor observed.

As seen from the summaries of case histories, the subjects used in this study were suffering from a variety of conditions. In most cases, however, kidney and liver function appeared to be essentially normal. There were two notable exceptions.

Hp-4 was suffering from Cushing's Syndrome and chronic nephritis. The highly abnormal condition of this subject was accompanied by higher plutonium content in blood and urine and apparently a slower rate of plutonium fixation in bone. In fact, several of the urine analyses were ruled non-representative on the basis of the Chauvenet criterion.

Hp-11 was moribund at the time plutonium was administered. Therefore, no plutonium excretion values were obtained. Anatomical diagnosis revealed cirrhosis of the liver with associated ascites, which indicated marked impairment of liver function.

The data in Table 2 summarize some of the clinical laboratory observations. These data show no consistent trends in hemoglobin, red blood cell count, white blood cell count and differential count as a result of the injection of approx. 5 μg of plutonium. The rise in hemoglobin and red blood cell count in Hp-12 probably was a result of therapeutic measures. The observations in Table 2 were quite in accord with those made by Russell and Nickson (RuXX), who collected excellent clinical laboratory data from two cases following administration of plutonium. One individual received 6.5 μg of plutonium and was followed for 155 days. Another subject received 95 μg of plutonium and was followed for sixteen days. No alterations attributable to plutonium were found in the constituents of the peripheral blood of either patient.

In the present series clinical evidence suggestive of liver damage did not appear. While

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Table 2. Clinical data on subjects receiving intravenous injection of approx. 5 μg of plutonium as Pu^{++}*-citrate*

PATIENT CODE	SEX	AGE	WT. Kg.	Pu ADMIN AMT. μg	Pu ADMIN DATE	LABORATORY STUDIES* DATE	HGB g %	RBC x 10^{-6}	WBC x 10^{-3}	PMN %	LYMPHS %	EOS. %	BASO. %	MONO. %	UREA Cl. %	BUN	NPN
Hp- 1	M	67	70.3	4.6	10/16	10/4 10/19	13.9 13.7	4.47 4.55	7.1 7.0	71 54	19 34	1 4	0 1	9 7	96 90	21 23	- -
Hp- 2	M	49	69.0	5.1	10/23	10/6 11/7	15.0 14.5	4.7 4.1	9.05 7.85	57 68	28 22	8 8	0 0	2 2	58 48	25 23	- -
Hp-3	F	49	69.9	4.9	11/27	11/2 12/16	14.5 -	4.3 5.6	5.7 6.8	59 69	39 25	2 0	0 1	0 5	70 -	- -	34 31
Hp- 4	F	18	55.5	4.9	11/27	10/30 3/21	15.0 16.0	5.3 -	10.0 6.9	77 74	20 22	0 0	1 0	2 4	- -	- -	- -
Hp- 7	F	59	68.0	6.3	2/8	1/23 2/20	12.6 -	3.26 -	4.75 5.25	64 64	24 25	3 0	0 0	6 9	94 -	- -	26 -
Hp- 8	F	41	54.4	6.5	3/9	2/22 8/21	13.9 14.5	4.7 4.05	9.5 11.9	71 88	22 12	0 0	0 0	13 0	85 -	10 -	30 -
Hp- 9	M	66	63.0	6.3	4/3	3/13 1/25	12.3 12.3	3.9 4.1	6.25 7.3	70 61	17 9	0 12	0 1	13 17	72 -	- -	- -
Hp-10	M	52	71.0	6.1	7/16	7/9 8/13	13.3 -	5.5 -	5.65 -	31 42	52 46	5 3	2 2	7 8	87 82	11 -	22 -
Hp-12	M	53	-	4.7	4/9	4/4 7/3	8.9 13.5	2.85 4.51	5.6 4.3	74 32	18 64	- -	- -	6 4	- -	30 12	44 37

*Explanation of Symbols: HGB = Hemoglobin; RBC = Red Blood Cell Count; WBC = White Blood Cell Count; PMN = Polymorphonuclear Cells; LYMPHS = Lymphocytes; EOS. = Eosinophiles; BASO. = Basophiles; MONO. = Monocytes; BUN = Blood Urea Nitrogen; NPN = Non-Protein Nitrogen; UREA Cl. = Urea Excretion in Per Cent of Normal at One Hour.

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specific tests of liver function were not as a rule listed in the protocols, the possibility that injury to this organ might appear was considered.

Admittedly the observations made during this study provide no evidence of what may happen in 10–30 years. It may be said, however, that these studies and those of other investigators indicate that the intravenous injection of a single dose of 5–100 μg of plutonium was without acute subjective or objective clinical effects.

(B) *Deposition of plutonium in the body*

Since the beginning of this study, four of the subjects (Hp-4, 5, 7 and 9) have died as a result of their diagnosed illness. Another subject, Hp-11, was in the terminal phase at the time of injection. Autopsy and tissue samples were obtained in only three of the five cases. Two bone specimens were obtained from Hp-12 during open reduction of fractures and a number of his teeth were obtained at a later date. Blood samples were obtained from all subjects before plutonium injection and at frequent intervals thereafter. All tissue samples were analyzed for plutonium by the cupferron extraction procedure subsequent to ashing.

The data in Table 3 show the results of analyses of the various samples for plutonium. The results obtained by Russell and Nickson (RuXX) (referred to as Chi, I, II, III) and Hamilton *et al.* (HaXX) (referred to as Cal. I) are presented also. Two important points must be kept in mind when considering these data: (1) The samples of human tissues were, for obvious reasons, rather unsatisfactory. In most cases they were too small, poorly representative and were usually what could be obtained under the circumstances rather than what were desired; (2) The subjects were chronically ill and/or elderly and the results may not represent exactly the distribution of plutonium in tissues of healthy persons of average working age. These data, however, are all that are available and, therefore, must provide the basis for our present concept of the distribution of plutonium in the organs and tissues of man. They must also provide a basis for comparison with the results obtained from the numerous studies of plutonium deposition in experimental animals.

(1) *Deposition in the skeleton.* Animal experiments (HaXX; LaXX) reveal that approx. 60% of plutonium injected as PuO_{2++} and Pu^{+4}-citrate is localized in bone. If the vertebra, sternum and whole rib are taken as representative bones of the skeleton, and the average plutonium content (0.00657%/g), multiplied by the skeletal weight of the "Standard Man" (Li47), then 65.7% of the injected dose is the estimated amount of plutonium in the skeleton of a 70 kg man. Although the latter value was established rather arbitrarily, it is in good agreement with the value expected from animal experiments.

The data in Table 3 indicate a rather high plutonium content in bone marrow. The average of four determinations from three different laboratories was 0.0187% of the injected dose per gram of marrow. On the basis of 3000 g of bone marrow, there would be 56% of the injected dose concentrated in the marrow of a 70 kg man. Animal studies do not show appreciable concentrations of plutonium in the marrow. The major areas of plutonium concentration in rats and mice are the endosteum, periosteum and the epiphyseal line. It is quite possible that the samples of human marrow were too small to be representative, contained endosteum or spicules, or that the high deposition was an indication of an age factor related to the fact that the epiphyses of man unlike those of the rat unite at maturity.

(2) *Deposition in the liver.* The average plutonium deposition in the liver for the five cases was 0.0136% of the injected dose per g, which corresponds to 23.1% of the dose in a 1700 g liver (Standard Man). Table 4 presents the liver data in more detail, including the two cases reported by the Chicago investigators (RuXX).

Two cases (Hp-11 and Chi. -II) were in the terminal phase of illness at the time plutonium was administered. Both showed advanced liver disease. The values for plutonium deposition in the liver of these cases is highly questionable. The results in the other three cases, however, were rather

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Table 3. Distribution of plutonium in human tissues following intravenous injection of plutonium salts

Tissue[2]	Subject[1] and % of Injected Dose/g of Tissue								Rel. Pu Affinity[3]	Org. Wt./g[4]	Calc. %/Organ
	Hp-5	Hp-9	Hp-11	Chi. I	Chi. II	Hp-12	Cal. I	Av. %/g			
Bone Marrow	--	--	.0096	.0153	.0210	--	.0290	.0187	13.3	3,000	(56.1)[6]
Radius (Frag. head)	--	--	--	--	--	.0187	--	--	--	--	--
Liver	.0320	.0144	.0053	.0139	.0024	--	--	.0136	9.7	1,700	23.1
Rib (Cortex)	--	--	--	.0015	.0196	--	.0170	.0127	9.1	--	--
Patella	--	--	--	--	--	.0109	--	--	--	--	--
Vertebra	.0071	.0080	.0070	--	--	--	--	.0073	5.2	SKELETON	--
Sternum	.0070	--	.0100	.0044	--	--	--	.0071	5.1	10,000 →	65.7[5]
Rib (Whole)	.0050	.0038	.0068	--	--	--	--	.0052	3.7		--
Periosteum (Rib)	--	--	--	.0043	.0019	--	.0048	.0037	2.6	--	--
Spleen	.0007	.0015	.0048	.0024	.0014	--	.0019	.0021	1.5	200	0.4
Kidney	.0002	.0002	.0015	.0004	.0054	--	--	.0015	1.0	300	0.4
Thyroid	.0001	--	.0009	--	.0034	--	--	.0014	1.0	30	--
Adrenal	.0004	--	.0022	--	--	--	--	.0013	1.0	14	--
Lung	.0005	--	.0016	.0006	.0016	--	--	.0011	0.8	950	1.0
Pancreas	.0002	.0002	--	--	.0022	--	--	.0009	0.6	65	--
Gonads	.0003	--	.0012	.0005	.0009	--	--	.0007	0.5	--	--
Lymph Node	--	--	--	.0014	.0001	--	--	.0007	0.5	700	0.5
Teeth (Av. of 7)	--	--	--	--	--	.0003	--	--	--	--	--
Heart	.0000	.0000	--	.0003	.0011	--	--	.0003	0.2	350	0.1
Large Intestine	.0002	--	.0004	--	.0001	--	--	.0002	0.1	2,300	0.5
Small Intestine	.0001	--	.0005	--	.0001	--	--	.0002	0.1	--	--
Muscle and Skin	.0000	--	.0002	.0002	.0001	--	--	.0001	0.1	38,500	3.9
Blood	--	--	--	--	--	--	--	--	--	5,400	0.2[8]
Balance	--	--	--	--	--	--	--	.0001[7]	--	9,600	0.9
Total	--	--	--	--	--	--	--	--	--	70,000	96.7

(1) The various subjects received the following doses of plutonium: Hp-5 = 5 μg; Hp-9 = 6.3 μg; Hp-11 = 6.5 μg; Chi. I = 6.5 μg; Chi. II = 94.9 μg; Hp-12 = 4.7 μg; Cal. I = 103 μg.

(2) Tissues were obtained at the following times after injection: Hp-5 151 days; Hp-9 456 days; Hp-11 5 days; Chi. I 155 days; Chi. II 16 days; Hp-12 5 days; Cal. I 4 days.

(3) Calculated by dividing %/g of tissue by %/g of body weight if a unit dose of Pu was equally distr. in a 70 Kg. man.

(4) Hermann Lisco, Memorandum to AEC, July 21, 1947, Project Standard Man.

(5) Assumption made that vertebra, sternum and whole rib represent average bone of skeletal system.

(6) Bone marrow not included in total recovery because bone samples were not freed of marrow before analysis.

(7) Balance assumed to have same Pu content as muscle.

(8) Value for blood taken at 30 day point, Fig. 3.

striking. As pointed out by Russell and Nickson (RuXX), the content of plutonium in the liver was much higher than was to be expected from results in experimental animals. Even though one of their cases survived 155 days after receiving plutonium in the +6 valence state (a form known to give low liver deposition in rats (HaXX; La47)), 28.5% of the injected dose was found in the liver. Subject Hp-5 had 42.8% of the plutonium injected as Pu^{+4}-citrate deposited in the liver after 151 days. The third case (Hp-9) survived 456 days and had 23.0% of the injected material deposited in the liver. Considering the elapsed time after injection, the plutonium content of the liver in the two

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Table 4. Liver deposition of plutonium administered intravenously to man

Subject	Days After Injection	Liver Wt. in Grams	% of Dose per Gram	% of Dose per Organ
Hp-5	151	1340	.0320	42.8
Hp-9	456	1600	.0144	23.0
Hp-II[1]	5	2325	.0053	12.3
Chi. I[3]	155	2050	.0139	28.5
Chi. II[2,3]	16	1110	.0024	2.7
AVERAGE	156	1641	.0136	21.9

[1] Hp-II was in terminal phase of illness; plutonium deposition probably low because of severe cirrhosis of the liver.

[2] Chi.-II was in terminal phase of adenocarcinoma; plutonium deposition probably low because of metastases to the liver.

[3] Russell, E.R. and Nickson, J.J. (13)

latter cases was even higher than that observed by Russell and Nickson (RuXX). The apparent higher deposition in the latter cases might indicate the destruction of the Pu^{+4}-citrate complex by the human liver. The results compare favorably with those obtained when rats were injected with uncomplexed quadrivalent plutonium ion (HaXX; La47; FiXX). The limited data presented in Table 4 indicated rather strongly that the retention of plutonium by the liver may be much greater for man than for rats and mice, and may be of the order of 20–40% of the injected dose during the first year. A comparison of the survival times and the amounts of plutonium deposited in the livers of Hp-5 and Hp-9 seems to indicate a "plutonium retention half-time" in the liver of one year or greater for man as compared to 40–60 days for rats.

(3) *Concentration in blood.* The data in Table 5 show the concentration of plutonium in blood at various times after the intravenous injection of approx. 5 μg of plutonium as Pu^{+4}-citrate. The results are expressed in percent of the injected dose in the total blood volume. The blood was assumed to be 7.71% of the total body weight (Li47).

The individual observations varied widely, especially during the first four days. The mean values, however, fell on a smooth curve (shown in Fig. 3).

The drop in blood plutonium content was very rapid at first, and reflected the very rapid rate of fixation of the material in the body. The mean blood concentration 4 hours after injection was 35.7%, at one day 15.7%, at 10 days 1.2%. Thirty days after injection the blood concentration of plutonium read from the curve in Fig. 3 was only 0.3% of the injected dose in the total blood volume. The extremely small amount of plutonium in the circulating blood eliminates blood analysis by the usual counting procedures as a means of diagnosing the degree of exposure of personnel. The application of techniques employing the counting of α-tracks registered by α-sensitive nuclear track photographic emulsions may prove possible.

(4) *Deposition in other organs.* The amounts of plutonium deposited in organs and tissues other than skeleton, liver and blood were rather small. When the percent per organ was calculated, based on the organ weight of the "Standard Man", the results were in reasonable agreement with what was anticipated from animal experiments. The data showing the percent of dose per g of organ and percent per organ are given in Table 3. The kidney and spleen each had an estimated average plutonium content of 0.4% of the injected dose per organ.

The relative affinity of the various tissues for plutonium was calculated by dividing the percent of the dose per g of organ by the

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Table 5. Plutonium content of blood samples following intravenous injection of approx. 5μg of plutonium as Pu^{+4}-citrate*

DAYS AFTER INJECTION	PATIENT CODE AND PER CENT OF INJECTED DOSE IN TOTAL BLOOD VOLUME*											AVERAGE
	Hp-1	Hp-2	Hp-3	Hp-4	Hp-5	Hp-6	Hp-7	Hp-8	Hp-9	Hp-10	Hp-12	
1/6	46.02	-	28.32	83.31	31.51	36.70	32.57	37.64	40.83	51.57	5.31	35.7
1	21.83	19.35	-	-	6.23	10.97	16.40	14.51	12.39	24.66	-	15.7
2	-	8.38	11.56	-	-	-	-	-	-	-	-	9.97
3	-	10.03	-	16.64	1.16	2.94	6.97	4.94	6.22	20.06	-	8.62
4	-	-	4.22	-	-	-	-	-	-	-	-	-
5	-	-	-	-	0.66	-	-	-	-	-	-	-
6	3.30	4.25	2.17	6.14	-	1.00	2.96	2.07	3.91	4.91	-	3.4
8	-	2.32	1.42	-	-	-	-	-	-	-	-	1.9
9	-	-	-	4.60	-	-	-	-	-	-	-	-
10	1.42	-	-	-	0.39	0.38	1.13	1.37	2.21	1.72	-	1.2
13	-	-	0.61	2.34	-	-	-	-	-	-	-	1.5
15	-	-	-	-	0.11	0.26	0.66	0.71	1.42	1.02	-	.70
17	-	-	0.51	1.45	-	-	-	-	-	-	-	1.0
22	-	0.70	-	-	0.18	0.25	-	-	-	-	-	.38
23	-	-	0.25	0.72	-	-	-	-	-	-	-	.48
29	-	-	-	-	-	-	0.37	-	-	-	-	-
30	-	-	-	-	-	-	-	-	-	0.36	-	-
31	-	-	-	-	-	-	-	-	-	-	0.51	-
36	-	-	-	-	-	-	-	-	0.42	-	-	-
42	-	-	-	-	-	-	-	0.17	-	-	-	-
46	-	-	-	-	-	-	-	-	-	-	0.45	-

*Total Weight of Blood Taken as 7.71% of Total Body Weight.

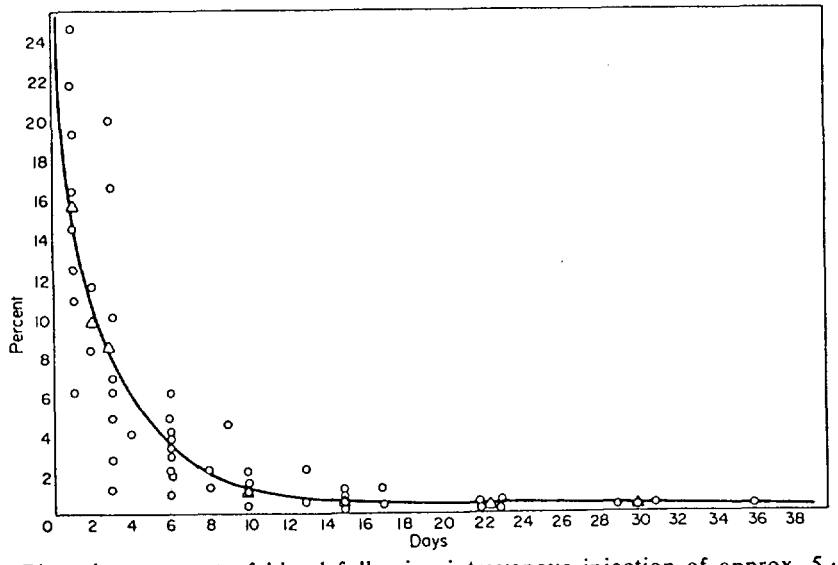

FIG. 3. Plutonium content of blood following intravenous injection of approx. 5 μg of plutonium as Pu^{+4}-citrate—10 cases percent of dose in total blood volume vs days after injection (weight of blood taken as 7.71% of body weight). ○ individual observations, △ observed mean.

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percent of the dose per g of body weight when the material was assumed to be equally distributed in a 70 kg man.

The bone, bone marrow and liver were the only tissues that showed a relative plutonium affinity appreciably greater than unity. The spleen was 1.5; all other tissues and samples were 1.0 or less. Obviously the skeletal system and liver are the tissues of major interest when considering the plutonium tolerance, as these two organs alone account for 90% or more of the total plutonium in the entire body.

(C) *Excretion of plutonium*

(1) *Urinary excretion.* The urinary excretion of plutonium was studied in eleven of the subjects following the intravenous injection of approx. 5 μg of plutonium as Pu^{+4} in 0.4% solution of sodium citrate·$2H_2O$. With the exception of the first day, urine from all subjects was collected in 24 hour samples through 22 days post injection. After 22 days the collection of 24 hour urine samples was continued as long as the patients were available for study. It was not possible to retain the subjects as long as was desired and the major weakness in these results is the short time interval over which the studies were continued. Two subjects were followed 22 days, one for 23 days, one for 27 and the remainder for 30 days or longer after injection. The Chicago cases (RuXX) were followed for 16, 140 and 186 days and the California case (HaXX) was followed for a period of 341 days. Because of the great importance of measurements at longer time intervals, the Chicago and California data have been incorporated with the data from these studies. The results of all urine analyses through 138 days post-injection are given in Table 6. Results are expressed as percent of injected dose excreted per day.

The means, revised means and standard deviations for the daily urinary excretion of plutonium from 0 to 138 days post-injection are given in Table 7. The equation of best fit for the observed means is a logarithmic function:

$$Y = aX^{-b} \qquad (1)$$

where Y is the amount of plutonium (expressed as percent of injected dose) excreted in a single day, X is the time of observation in days post-injection, and a and b are constants derived from the observed data by the method of least squares. Solution gives the following expression for the best curve of fit for the urinary excretion of plutonium utilizing all available data from 0 to 138 days post-injection:

$$Y_u = 0.23X^{-0.77}. \qquad (2)$$

The agreement between observed mean values and the derived expression for the urinary excretion of plutonium through 138 days post-injection is illustrated graphically in Fig. 4. In this graph the circles represent the observed means and the solid line represents the derived expression. The agreement is fairly good. The overall standard error of estimate, $\bar{S}_{YX}$ (determined by the usual methods of correlation analysis) was ±32%. The largest contributions to the standard error of estimate come from the 0 to 10 day portion of the curve and from the latter portion where there is an increased scatter of points because of the decrease in number of observations. Actually, attempts at curvilinear regression line fitting indicate that the function $Y = aX^{-1}$ is the best curve for the 0–10 day period rather than the logarithmic curve presented. We believe this difference in functional relationship may be due to the clearance of the injected plutonium from the blood during this early period after injection.

Extrapolation of the derived expression beyond 138 days introduces increasing uncertainty with increasing values of X. In order to interpret the excretion results in standard terms, i.e. "biological half-life", despite the fact that the data are not fitted by a single exponential curve, we have chosen to determine $T_{1/2}$ by assuming exponential excretion beyond the limits of observation and estimating $T_{1/2}$ from the last point on the excretion curve (a single value of the ordinate). One may then assume the slope of the excretion curve to be zero at this point and calculate an absolute minimum value for

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Table 6. Individual urinary excretion values of plutonium following intravenous administration[1] to human subjects (expressed as percent of dose excreted per day)

DAYS POST INJECTION	PER CENT OF INJECTED DOSE EXCRETED PER DAY														
	Hp-1	Hp-2	Hp-3	Hp-4	Hp-5	Hp-6	Hp-7	Hp-8	Hp-9	Hp-10	Hp-12	Chi.-I[2]	Chi.-II[2]	Chi.-III[2]	Cal.-I[3]
1	.181	.472	.569	.440	.296	-	.217	.377	.160	.414	.101	.857	2.531*	.152	.480
2	.146	.294	.289	.236	.166	.218	.212	.232	.085	.330	.103	.182	.153	.167	.150
3	.114	.174	.112	.221	.077	.127	.137	.128	.069	.218	.088	.063	.184	.067	.120
4	.094	.123	.107	.132	.052	.111	.096	.140	.066	.170	.078	.077	.133	.033	.031
5	.069	.116	.078	.116	.030	.076	.069	.083	.047	.089	.068	.026	.032	.042	.037
6	.066	.061	.043	.119*	.020	.057	.059	.078	.052	.060	.044	.0256	.029	.042	-
7	.062	.062	.043	.077	.033	.044	.045	.066	.050	.079	.069	.0234	.024	.024	-
8	.055	.048	.049	.081	.026	.043	.037	.057	.032	.065	.080	.0227	.023	.025	.016
9	.051	.046	.022	.095*	.027	.032	.033	.047	.032	.051	.043	-	.027	.019	.069
10	.045	.038	.027	.081*	.022	.031	.023	.050	.035	.044	.038	.0082*	.034	.030	.026
11	.040	.048	.027	.075*	.021	-	.018	.044	.026	.041	.038	.0097	.047	.019	.036
12	.038	.039	.015	.072*	.026	.024	.019	.023	.030	.038	.027	.0095	.047	.014	.029
13	.034	.045	.020	.067*	.023	.023	.019	.037	.027	.029	.030	.0236	.018	.034	-
14	.035	.036	.020	.058*	.018	.020	.013	.035	.030	.029	.039	.007	.034	.009	-
15	.034	.039	.028	.050	.015	.022	.012	.035	.030	.025	.029	.0059	.026	.016	.013
16	.026	.024	.024	.033	.020	.017	.012	.036	.049*	.021	.023	.0109	.012	.004	.016
17	.027	.027	.021	.032	.020	.013	.011	.032	.038	.023	.029	-	.028	-	.0056
18	.026	.020	.017	.037	.020	.015	.011	.029	.027	.021	.026	-	.026	-	.010
19	.025	.019	.018	.032	.018	.015	.010	.031	.029	.017	.029	.0022	.015	-	.006
20	.017	.021	.012	.025	.021	.013	.008	.032	.029	.018	.032	.0093	.038	-	.0048
21	.017	.017	.019	.029	.020	.012	.010	.029	.032	.022	.025	.0076	.032	-	.0017
22	.016	.015	.014	.035	.018	.012	.013	.021	.032	.016	.025	.0145	.027	-	.0050
23	.025	.018	.014	.014	-	-	.008	.021	.032	.019	.039	.0151	.029	-	.0091
24	.021	.014	-	-	-	-	.008	.025	.032	.016	.023	.0128	.020	-	.0076
25	.013	.014	-	.011	-	-	.008	.023	.029	.016	.021	.0128	.148*	-	.011
26	-	.017	-	.011	-	-	.007	.022	.032	.016	.023	.0175	.024	-	.0022
27	-	.008	-	.008	-	-	.008	.028	.032	.014	.017	.0151	.043*	-	.0044
28	-	.009	-	-	-	-	.008	.023	.024	.013	.024	.0197	.034	-	.0074
29	-	.009	-	-	-	-	.008	.019	.025	.014	.023	.0138	.022	-	.0043
30	-	.008	-	-	-	-	.006	.021	.023	.014	.021	.0151	.024	-	.0069
31	-	.007	-	-	-	-	.005	.017	.025	-	.021	.010	.027	-	.0077
32	-	.007	-	-	-	-	.007	.016	.024	-	.012	.010	.020	-	.0063
33	-	.009	-	-	-	-	.006	.015	.022	-	.037*	.017	.011	-	.0073
34	-	.009	-	-	-	-	.006	.015	.020	-	.020	.0139	.008	-	.0084
35	-	-	-	-	-	-	.006	-	.022	-	.026	.0127	.009	-	.0069
36	-	-	-	-	-	-	.006	.015	.022	-	.018	.0165	.015	-	.0079
37	-	-	-	-	-	-	.006	.011	-	-	.023*	.0111	.011	-	.0063
38	-	-	-	-	-	-	-	.016	-	-	.018	.0174	.009	-	.0085
39	-	-	-	-	-	-	-	.012	-	-	.021	.0112	.009	-	.0064
40	-	-	-	-	-	-	-	.017	-	-	.019	.0072	.009	-	.0072
41	-	-	-	-	-	-	-	.019	-	-	.013	.0092	.011	-	.0080
42	-	-	-	-	-	-	-	.014	-	-	.013	.0127	-	-	.0081
43	-	-	-	-	-	-	-	.016	-	-	.015	.0095	.017	-	.0076
44	-	-	-	-	-	-	-	.014	-	-	.015	.0031	-	-	.0055
45	-	-	-	-	-	-	-	.013	-	-	.017	.013	.018	-	.0063
46	-	-	-	-	-	-	-	.015	-	-	-	.012	-	-	.0073
47	-	-	-	-	-	-	-	.014	-	-	.015	-	.020	-	.0059
48	-	-	-	-	-	-	-	.014	-	-	.017	.0064	-	-	.0059
49	-	-	-	-	-	-	-	.018	-	-	.015	.0063	-	-	.0063
50	-	-	-	-	-	-	-	.014	-	-	-	.0054	.018	-	.0078
51	-	-	-	-	-	-	-	.013	-	-	-	.007	-	-	.0082
52	-	-	-	-	-	-	-	-	-	-	.035	.0073	-	-	.0098
53	-	-	-	-	-	-	-	.013	-	-	.019	.0023	-	-	.0074
54	-	-	-	-	-	-	-	.013	-	-	.043	-	-	-	.0077
55	-	-	-	-	-	-	-	.015	-	-	.043*	.0073	.014	-	.0096
56	-	-	-	-	-	-	-	.013	-	-	.036	.003	-	-	.0064
57	-	-	-	-	-	-	-	.012	-	-	.018	.0075	-	-	.0050
58	-	-	-	-	-	-	-	.013	-	-	.036	.0094	-	-	.0058
59	-	-	-	-	-	-	-	.012	-	-	-	.011	-	-	.0098
60	-	-	-	-	-	-	-	.011	-	-	-	.0063	.022	-	.0067
61	-	-	-	-	-	-	-	.012	-	-	-	.0068	-	-	.0066
62	-	-	-	-	-	-	-	.010	-	-	-	.0092	-	-	.0058
63	-	-	-	-	-	-	-	.009	-	-	-	.0094	-	-	.0077
64	-	-	-	-	-	-	-	.012	-	-	-	.0071	-	-	.0042
65	-	-	-	-	-	-	-	.011	-	-	-	.0099	.024	-	.0042
66	-	-	-	-	-	-	-	-	-	-	-	.014	-	-	.0047
67	-	-	-	-	-	-	-	-	-	-	-	.014	-	-	.0064
68	-	-	-	-	-	-	-	-	-	-	-	.011	-	-	.0068
69	-	-	-	-	-	-	-	-	-	-	-	.011	-	-	.0070
70	-	-	-	-	-	-	-	-	-	-	-	.014	-	-	.0100
71	-	-	-	-	-	-	-	-	-	-	-	.0096	-	-	.0072
72	-	-	-	-	-	-	-	-	-	-	-	.0089	.014	-	.0092
73	-	-	-	-	-	-	-	-	-	-	-	.0083	-	-	.0069

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Table 6. (Contd.)

DAYS POST INJECTION	PER CENT OF INJECTED DOSE EXCRETED PER DAY														
	Hp-1	Hp-2	Hp-3	Hp-4	Hp-5	Hp-6	Hp-7	Hp-8	Hp-9	Hp-10	Hp-12	Chi.-I[2]	Chi.-II[2]	Chi.-III[2]	Cal.-I[3]
74	-	-	-	-	-	-	-	-	-	-	-	.010	-	-	.0079
75	-	-	-	-	-	-	-	-	-	-	-	.013	-	-	.0051
76	-	-	-	-	-	-	-	-	-	-	-	.0081	-	-	.0041
77	-	-	-	-	-	-	-	-	-	-	-	.0043	-	-	.0065
78	-	-	-	-	-	-	-	-	-	-	-	.014	-	-	.0074
79	-	-	-	-	-	-	-	-	-	-	-	.0052	-	-	.0066
80	-	-	-	-	-	-	-	-	-	-	-	.0046	.024	-	.0048
81	-	-	-	-	-	-	-	-	-	-	-	.0042	-	-	.0055
82	-	-	-	-	-	-	-	-	-	-	-	.002	.018	-	.0080
83	-	-	-	-	-	-	-	-	-	-	-	.0041	-	-	.0068
84	-	-	-	-	-	-	-	-	-	-	-	.0029	-	-	.0022
85	-	-	-	-	-	-	-	-	-	-	-	.007	-	-	-
86	-	-	-	-	-	-	-	-	-	-	-	.0046	-	-	.0100
87	-	-	-	-	-	-	-	-	-	-	-	.0076	-	-	.0079
88	-	-	-	-	-	-	-	-	-	-	-	.0086	-	-	.0037
89	-	-	-	-	-	-	-	-	-	-	-	.0049	-	-	.0071
90	-	-	-	-	-	-	-	-	-	-	-	.0032	.017	-	.0077
91	-	-	-	-	-	-	-	-	-	-	-	.0075	-	-	.0088
92	-	-	-	-	-	-	-	-	-	-	-	.014	-	-	.0071
93	-	-	-	-	-	-	-	-	-	-	-	.006	-	-	.0060
94	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.0071
95	-	-	-	-	-	-	-	-	-	-	-	.0093	.017	-	.0052
96	-	-	-	-	-	-	-	-	-	-	-	.011	.015	-	.0042
97	-	-	-	-	-	-	-	-	-	-	-	.0083	-	-	.0057
98	-	-	-	-	-	-	-	-	-	-	-	.012	.013	-	.0053
99	-	-	-	-	-	-	-	-	-	-	-	.006	-	-	.0070
100	-	-	-	-	-	-	-	-	-	-	-	.0096	-	-	.0061
101	-	-	-	-	-	-	-	-	-	-	-	.005	-	-	.0052
102	-	-	-	-	-	-	-	-	-	-	-	.009	.008	-	.0040
103	-	-	-	-	-	-	-	-	-	-	-	.006	-	-	.0070
104	-	-	-	-	-	-	-	-	-	-	-	.0086	-	-	.0051
105	-	-	-	-	-	-	-	-	-	-	-	.019	-	-	.0058
106	-	-	-	-	-	-	-	-	-	-	-	.0075	-	-	.0046
107	-	-	-	-	-	-	-	-	-	-	-	.0098	-	-	.0060
108	-	-	-	-	-	-	-	-	-	-	-	.0063	.009	-	.0052
109	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.0044
110	-	-	-	-	-	-	-	-	-	-	-	.0056	-	-	.0015
111	-	-	-	-	-	-	-	-	-	-	-	.0085	-	-	.0042
112	-	-	-	-	-	-	-	-	-	-	-	.015	-	-	.0051
113	-	-	-	-	-	-	-	-	-	-	-	.0095	.007	-	.0056
114	-	-	-	-	-	-	-	-	-	-	-	.011	-	-	.0029
115	-	-	-	-	-	-	-	-	-	-	-	.0145	.009	-	.0053
116	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.0047
117	-	-	-	-	-	-	-	-	-	-	-	.0069	-	-	.0023
118	-	-	-	-	-	-	-	-	-	-	-	.0035	-	-	.0039
119	-	-	-	-	-	-	-	-	-	-	-	.0066	-	-	.0036
120	-	-	-	-	-	-	-	-	-	-	-	.0051	.007	-	.0025
121	-	-	-	-	-	-	-	-	-	-	-	.0041	-	-	.0047
122	-	-	-	-	-	-	-	-	-	-	-	-	-	-	.0039
123	-	-	-	-	-	-	-	-	-	-	-	.0115	-	-	.0014
124	-	-	-	-	-	-	-	-	-	-	-	.0086	-	-	.0039
125	-	-	-	-	-	-	-	-	-	-	-	.0106	.009	-	.0036
126	-	-	-	-	-	-	-	-	-	-	-	.0037	-	-	.0032
127	-	-	-	-	-	-	-	-	-	-	-	.008	.011	-	.0040
128	-	-	-	-	-	-	-	-	-	-	-	.0073	-	-	.0019
129	-	-	-	-	-	-	-	-	-	-	-	.0052	-	-	.0024
130	-	-	-	-	-	-	-	-	-	-	-	.0054	-	-	.0014
131	-	-	-	-	-	-	-	-	-	-	-	.0075	-	-	.0011
132	-	-	-	-	-	-	-	-	-	-	-	.0055	.008	-	.0038
133	-	-	-	-	-	-	-	-	-	-	-	.0088	-	-	.0037
134	-	-	-	-	-	-	-	-	-	-	-	.0091	-	-	.0027
135	-	-	-	-	-	-	-	-	-	-	-	.011	.007	-	.0029
136	-	-	-	-	-	-	-	-	-	-	-	.0056	-	-	.0026
137	-	-	-	-	-	-	-	-	-	-	-	.0075	-	-	.0032
138	-	-	-	-	-	-	-	-	-	-	-	.0073	.009	-	.0010

* Values eliminated from revised mean on basis of the Chauvenet Criterion.

(1) All cases except Chi-1, 2, 3 and Cal-1 received Pu^{+4} in .4 per cent $Na_3C_6H_5O_7 \cdot 2H_2O$ solution. The latter cases received PuO_2^{++}.

(2) Russell, E. R., Nickson, J. J., Argonne National Laboratory Report CH-3607 and unpublished data.

(3) Hamilton, J. G., et al, Report No. CH-3589.

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the "biological half-time". For the above reasons it is important to supplement the urinary excretion data beyond 138 days to the greatest possible extent. Three additional groups of samples were obtained from two of the cases after the close of the experiment. One group of four consecutive daily urine samples was obtained from Hp-6 beginning on the 523rd day and another group beginning on the 1610th day after injection. The average daily urinary excretion of plutonium at 523 days was 0.002% and at 1610 days 0.0011% of the injected dose. Four daily samples collected from Hp-3 beginning at 1645 days after injection showed an average daily urinary excretion of 0.0008% of the injected dose.

In addition to the three groups of samples mentioned above a number of urine plutonium assays were made on workers at the Los Alamos Laboratory. A few of these individuals accumulated measurable amounts of plutonium during wartime operations.

Table 7. Means, revised means and standard deviations of urinary, fecal and urinary plus fecal excretion of plutonium following intravenous administration to human subjects (expressed as percent of injected dose)*

DAYS POST INJECTION	URINARY EXCRETION Mean %/Day	URINARY EXCRETION Revised Mean %/Day	URINARY EXCRETION Standard Deviation	FECAL EXCRETION Mean %/Day	FECAL EXCRETION Revised Mean %/Day	FECAL EXCRETION Standard Deviation	URINARY & FECAL EXC. Mean %/Day
1	.5176	.3628	.614	.1553	.1988	.1168	.5616
2	.1974	-	.070	.2458	-	.1230	.4252
3	.1266	-	.052	.2275	-	.0905	.3541
4	.0962	-	.041	.1842	-	.1135	.2804
5	.0652	-	.030	.1582	-	.0857	.2234
6	.0540	.0490	.026	.1096	-	.0440	.1586
7	.0501	-	.022	.0766	-	.0401	.1267
8	.0440	-	.022	.0717	-	.0412	.1157
9	.0424	.0384	.023	.0647	-	.0415	.1031
10	.0355	.0341	.018	.0538	-	.0385	.0860
11	.0350	.0319	.018	.0566	-	.0360	.0885
12	.0300	.0270	.016	.0568	-	.0351	.0838
13	.0307	.0279	.013	.0512	-	.0354	.0791
14	.0274	.0250	.014	.0453	.0386	.0301	.0636
15	.0253	-	.012	.0438	.0370	.0286	.0623
16	.0219	.0199	.011	.0617	.0296	.1090	.0495
17	.0236	-	.0092	.0402	.0285	.0411	.0521
18	.0219	-	.0076	.0377	.0268	.0394	.0487
19	.0190	-	.0081	.0278	-	.0168	.0468
20	.0200	-	.0101	.0274	-	.0169	.0474
21	.0195	-	.0093	.0263	-	.0183	.0458
22	.0188	-	.0083	.0243	-	.0182	.0431
23	.0203	-	.0105	.0224	-	.0156	.0427
24	.0179	-	.0077	.0211	.0167	.0141	.0346
25	.0279	.0159	.0142	.0199	.0145	.0160	.0304
26	.0172	-	.0088	.0211	.0160	.0156	.0332
27	.0178	.0149	.0126	.0163	.0119	.0129	.0268
28	.0180	-	.0092	.0153	.0122	.0140	.0302
29	.0153	-	.0074	.0180	-	.0146	.0333
30	.0154	-	.0072	.0179	-	.069	.0333
31	.0150	-	.0086	.0191	-	.0119	.0341
32	.0128	-	.0067	.0188	-	.021	.0316
33	.0155	.0125	.0102	.0192	-	.011	.0317
34	.0125	-	.0056	.0192	-	.011	.0317
35	.0138	-	.0083	.0201	-	.012	.0339
36	.0143	-	.0056	.0151	-	.0091	.0294
37	.0114	.0091	.0062	.0183	-	.0119	.0274
38	.0138	-	.0043	.0181	-	.0121	.0319
39	.0119	-	.0055	.0079	-	.0044	.0198
40	.0119	-	.0058	.0088	-	.0031	.0207
41	.0120	-	.0044	.0087	-	.0032	.0207
42	.0120	-	.0027	.0082	-	.0040	.0202
43	.0130	-	.0040	.0079	-	.0031	.0209
44	.0094	-	.0059	.0094	-	.0015	.0188
45	.0135	-	.0050	.0087	-	.0049	.0222
46	.0114	-	.0041	.0088	-	.0053	.0202
47	.0137	-	.0058	.0084	-	.0072	.0221

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Table 7. (Contd)

DAYS POST INJECTION	URINARY EXCRETION Mean %/Day	URINARY EXCRETION Revised Mean %/Day	URINARY EXCRETION Standard Deviation	FECAL EXCRETION Mean %/Day	FECAL EXCRETION Revised Mean %/Day	FECAL EXCRETION Standard Deviation	URINARY & FECAL EXC. Mean %/Day
48	.0108	-	.0056	.0067	-	.0018	.0175
49	.0114	-	.0062	.0064	-	.0026	.0178
50	.0113	-	.0059	.0060	-	.0028	.0173
51	.0094	-	.0032	.008	-	-	.0174
52	.0173	-	.0154	.010	-	-	.0273
53	.0104	-	.0074	.010	-	-	.0204
54	.0212	-	.0189	.0069	-	.0047	.0281
55	.0178	.0115	.0144	.010	-	-	.0215
56	.0146	-	.0149	.010	-	-	.0246
57	.0106	-	.0056	.0070	-	-	.0176
58	.0161	-	.0136	.0057	-	.0019	.0217
59	.0109	-	.010	.0070	-	-	.0179
60	.0115	-	.0074	.0070	-	-	.0185
61	.0085	-	.0029	.0080	-	-	.0165
62	.0083	-	.0021	.0064	-	.0023	.0147
63	.0087	-	.0007	.008	-	-	.0167
64	.0078	-	.0041	.008	-	-	.0158
68	.0089	-	.0028	.0063	-	-	.0152
70	.0120	-	.0028	.0045	-	-	.0165
74	.0090	-	.0022	.0050	-	-	.0140
78	.0107	-	.0050	.0033	-	-	.0140
79	.0059	-	.0022	.0055	-	.0007	.0114
80	.0111	-	.0110	.0055	-	.0007	.0166
81	.0048	-	.0010	.0055	-	.0007	.0103
82	.0093	-	.0081	.0051	-	.0009	.0144
83	.0055	-	.0022	.0060	-	-	.0115
84	.0026	-	.0010	.0060	-	-	.0086
85	.0070	-	-	.0060	-	-	.0130
86	.0073	-	.0036	.0050	-	-	.0123
90	.0093	-	.0071	.0042	-	-	.0133
94	.0071	-	-	.0040	-	-	.0111
98	.0101	-	.0044	.0050	-	-	.0151
100	.0079	-	.0028	.0056	-	-	.0135
102	.0070	-	.0026	.0038	-	-	.0108
106	.0061	-	.0022	.0043	-	-	.0104
108	.0068	-	.0021	.0038	-	-	.0106
112	.0101	-	.0071	.0021	-	-	.0122
116	.0047	-	-	.0029	-	-	.0076
120	.0039	-	.0023	.0032	-	-	.0071
126	.0035	-	.0010	.0030	-	-	.0065
130	.0034	-	.0028	.0037	-	-	.0071
136	.0041	-	.0022	.0034	-	-	.0075
138	.0058	-	.0042	.0025	-	-	.0083

*Cases of Russell and Nickson and Hamilton, et al used in computing means where applicable.

They were removed from further exposure to plutonium and occasional urine assays were made over a period of the next several months. The urine assays on three members of this group are given in Table 8. Since these individuals received unknown exposure doses via the usual routes of entry over an indefinite time, the results are not analogous to a single intravenous injection of a known amount of plutonium. However, the inclusion of these individuals has been attempted in order to extend the excretion curve. An attempt has been made to interpret the chronic variable exposure dose in terms of an *effective* single dose given at some *effective* time between the limits of exposure. This interpretation was accomplished by fitting the slopes of the urinary excretion curves of these individuals to the slope of the 138-day curve in the following manner: if $Y_u = 0.23X^{-0.77}$ gives the percent (Yu) of a single dose excreted on day X, then $0.0023\ DX^{-0.77}$ is the expression for the measured activity, i.e. counts per min, excreted on day X when the single dose (D) is expressed in the same units. If the assumption is made that *a*

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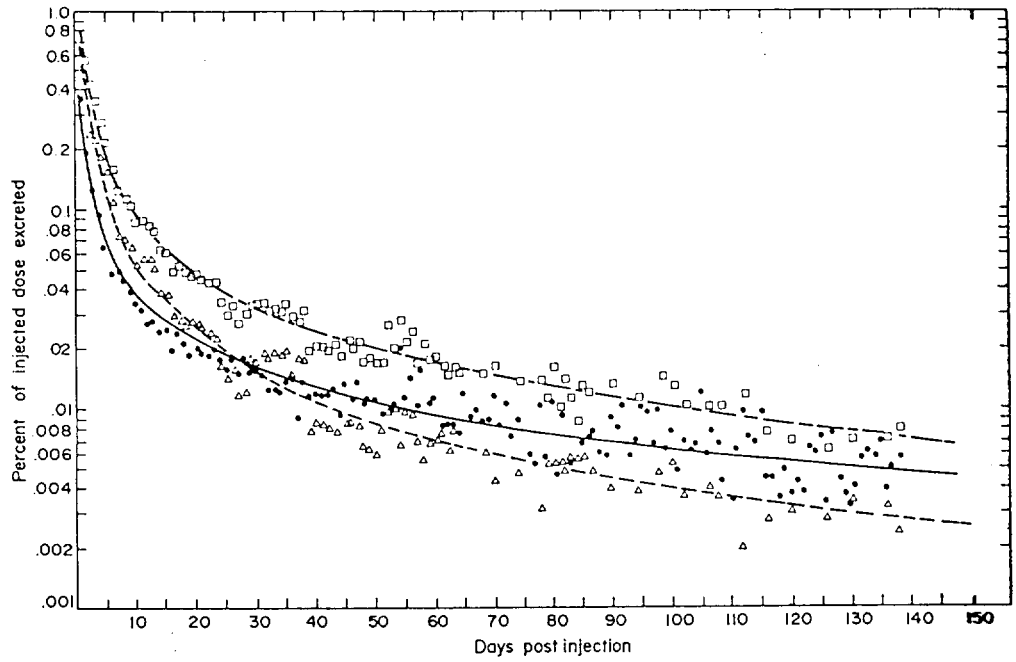

FIG. 4. Observed means for urinary, fecal and urinary & fecal excretion of plutonium following intravenous injection, compared with their derived expressions. □——Urinary & fecal excretion $Yu+f = 0.79\,X^{-0.94}$ ●——Urinary excretion----$Yu = 0.23\,X^{-0.77}$. △----Fecal excretion----$Yf = 0.63\,X^{-1.09}$.

chronic variable exposure dose may be represented by *a single effective dose* (D_E) then the activity (Y_q) in the sample excreted q *effective* days after this single dose is given by the expression

$$Y_q = 0.0023\,D_E q^{-0.77}. \tag{3}$$

The activity (Y_{q+a}) of the sample excreted on $q+a$ days after the single dose (there being no exposure between q and $q+a$) is given by the expression

$$Y_{q+a} = 0.0023\,D_E(q+a)^{-0.77}. \tag{4}$$

Dividing 3 by 4 and solving for q gives

$$q = \frac{a}{\left(\frac{Y_q}{Y_{q+a}}\right)^{1.30} - 1}, \tag{5}$$

q then is the *effective* time of exposure and its substitution in (3) gives the effective dose D_E, as follows:

$$Y_q = 0.0023\,D_E\left[\frac{a}{\left(\frac{Y_q}{Y_{q+a}}\right)^{1/0.77} - 1}\right]^{-0.77}$$

$$D_E = 434.8\,Y_q\left[\frac{a}{\left(\frac{Y_q}{Y_{q+a}}\right)^{1.30} - 1}\right]^{0.77}. \tag{6}$$

This expression gives an approximation of the total body burden of a person chronically exposed to plutonium. The body burden is expressed in terms of a single *effective* dose as determined from two urinary excretion measurements (Y_q and Y_{q+a}) taken sufficiently far apart (with no exposure between) so that the two measurements are significantly different.

The method of interpretation given above was applied to the urinary plutonium excretion data from the Los Alamos personnel and their average total plutonium body

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Table 8. Plutonium urine assays on Los Alamos personnel after removal from further plutonium exposure

W.B.G.			W.A.B.			D.L.W.		
Days[1]	c/m/24-hr.[2]	P.Error[3]	Days[1]	c/m/24-hr.[2]	P.Error[3]	Days[1]	c/m/24-hr.[2]	P.Error[3]
1	9.4	0.53	1	21.3	0.60	1	13.8	0.55
27	6.9	0.51	20	11.6	0.54	21	8.4	0.52
104	5.5	0.50	45	8.2	0.52	94	3.9	0.48
205	6.4	0.51	193	7.7	0.51	118	3.5	0.48
281	4.6	0.49	370	6.7	0.50	195	3.2	0.48
315	3.7	0.48	1460[4]	1.2	0.17			
387	3.8	0.48						
450	3.3	0.48						
498	2.4	0.47						
652	1.4	0.46						
707	1.9	0.47						
734	1.4	0.46						
798	0.9	0.46						
831	1.3	0.46						
947	2.1	0.47						
1022	0.9	0.46						
1044	1.9	0.47						
1103	1.3	0.46						
1203	1.1	0.46						
1294	1.3	0.47						
1322	0.8	0.46						
1348	0.8	0.46						
1379	0.7	0.46						
1448	0.7	0.46						
1574	0.3	0.45						
1638	0.6	0.46						
1698	1.1	0.46						

W.A.B. - D_E[5] = 1.2 μg
W.B.G. - D_E = 1.3 μg
D.L.W. - D_E = 1.0 μg

(1) Days after removal from further plutonium exposure.

(2) Alpha counts per minute per 24-hour urine sample at 50 per cent counting geometry.

(3) Probable error calculated from empirical formula derived specifically for the cupferron extraction procedure for determining plutonium in urine (15).

(4) Result due to H. M. Parker in private communication to N. E. Bradbury, July 7, 1949.

(5) Estimated by equation [6] Page 29.

content approximated in terms of an *effective* dose at some *effective* time (q). The effective doses for W.B.G., W.A.B. and D.L.W. were estimated at 1.3 1.2 and 1.0 μg respectively at respective effective times of 37, 53 and 42 days before the first urine assay used in the calculation. Assuming the above doses, all urinary excretion data (Table 8) collected from these persons were used to adjust the experimental urinary excretion curve (2) extending it to 1750 days again using least squares analysis. The adjusted expression is

$$Y_{ua} = 0.20\, X^{-0.74}. \qquad (7)$$

Figure 5 shows the adjusted curve through 1750 days represented as a heavy broken line. The points representing the three sets of data collected from Hp-3 and Hp-6 beyond 138 days after injection are shown on the graph as triangles. Points originating from the urine assays of the three Los Alamos workers are shown as circles and the theoretical curve (2) through 138 days is given as a heavy solid line for comparison. The standard error of

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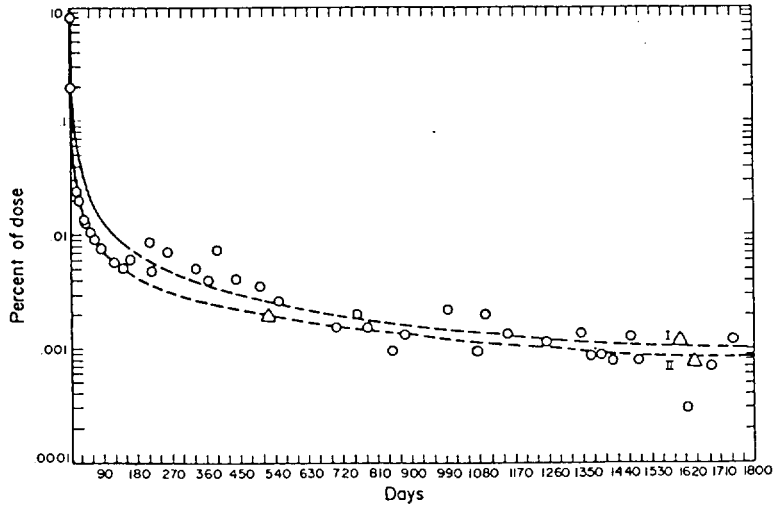

FIG. 5. Adjusted urinary and fecal excretion curves through 1750 days.
I. Fecal plus urinary excretion $Y_{ua} + f = 0.20\,X^{-0.74} + 0.63\,X^{-1.09}$.
II. Urinary excretion $Y_{ua} = 0.20\,X^{-0.74}$.
—Portion of curve based on experimental observations through 138 days.
--Adjusted portion of curve through 1750 days.
○Points established from urinary excretion values for Los Alamos Laboratory personnel.
△Average of four consecutive daily values from a single experimental case.

estimate for the adjusted expression is 42% due largely to the poorer fit during the first few days and to the small number of observations during the later time period.

Integration of the expression $Y_{ua} = 0.20\,X^{-0.74}$ between the limits of $X = 1/2$ and $X = (n + 1/2)$ gives the area (A_{ua}) under the urinary excretion curve which represents the total percent of the injected dose of plutonium excreted in the urine up to and including the nth day after injection.

$$A_{ua} = 0.20 \int_{1/2}^{n+1/2} X^{-0.74}\,\mathrm{d}X$$

$$= \frac{0.20}{0.26}\left[(n + 1/2)^{0.26} - (1/2)^{0.26}\right]$$

$$= 0.77\,(n + 1/2)^{0.26} - 0.64. \qquad (8)$$

When $n = 1750$ days, A_{ua} (the total amount of plutonium excreted in the urine through 1750 days) is only 6.3% of the total injected dose.

(2) *Fecal excretion.* The same cases used for urinary excretion studies were used for the study of fecal elimination of plutonium following intravenous administration of Pu^{+4}-citrate. Fecal samples were collected daily for the first few days. Later stools were pooled at 4-day intervals because of the uncertainty of obtaining representative 24-hour samples. Plutonium analyses were made on aliquots of each specimen using methods described earlier. The results of analysis of individual fecal specimens are given in Table 9. Results are expressed as percent of the administered dose excreted per day. Fecal excretion data could be obtained for only one of the cases (Chi. -I) reported by Russell and Nickson (RuXX). The original data were no longer available and it was necessary to read individual values from the graph given in their report. The original fecal excretion data were not available for the one case studied by Hamilton *et al.* (HaXX) and it was not feasible to include their results. The present report of the fecal elimination of plutonium is, therefore, confined to twelve cases.

The means, revised means, and standard

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deviations for the daily fecal excretion of plutonium from 0 to 138 days post injection are given in Table 7. The best curve of fit for the observed means was established by the method of least squares and was found to be:

$$Y_f = 0.63\ X^{-1.09}, \qquad (9)$$

with a standard error of estimate of 28%. In the above expression Y_f is the amount of plutonium excreted in the feces on a specific day (expressed as percent of the injected dose) and X is the day of measurement in days after injection. The agreement between the observed values and the derived expression is shown graphically in Fig. 4. In this figure the derived expression is represented by a heavy broken line and the observed points are represented as open triangles. The fecal excretion of plutonium in percent of the injected dose excreted per day is plotted against time in days.

No representative fecal excretion data beyond 138 days were available from Los Alamos personnel because of small but significant contamination of feces from swal-

Table 9. Individual fecal excretion values of plutonium following intravenous administration[1] to human subjects (expressed as percent of dose excreted per day)

DAYS POST INJECTION	PER CENT OF INJECTED DOSE EXCRETED PER DAY											
	Hp-1	Hp-2	Hp-3	Hp-4	Hp-5	Hp-6	Hp-7	Hp-8	Hp-9	Hp-10	Hp-12	Chi-1[2]
1	.052*	.204	.018*	.134	.004*	.085	.147	.178	.333	.087	.370	.250
2	.221	.204	.157	.274	.311	.085	.120	.266	.389	.087	.370	.465
3	.241	.204	.157	.274	.311	.179	.087	.210	.389	.087	.297	.294
4	.050	.317	.095	.306	.185	.179	.080	.080	.131	.110	.297	.380
5	.105	.317	.099	.306	.110	.179	.055	.080	.131	.110	.183	.223
6	.046	-	.070	.126	.110	.179	.055	.080	.131	.110	.183	.116
7	.021	-	.070	.126	.110	.037	.055	.080	.131	.110	.020	.083
8	.021	.120	.070	.126	.064	.037	.055	.070	.131	.034	.020	.112
9	.021	.120	.070	.126	.051	.037	.032	.070	.131	.034	.020	-
10	.021	.084	.027	.117	.051	.037	.032	.070	.131	.034	.020	.021
11	.046	.084	.027	.117	.052	.023	.032	.070	.118	.034	.020	-
12	.046	.084	.027	.117	.052	.023	.032	.045	.118	.034	.020	.083
13	.046	.084	.027	.117	.032	.023	.023	.045	.118	.034	.020	.045
14	.046	.062	.023	.085	.032	.023	.023	.045	.118*	.022	.020	.044
15	.035	.062	.023	.085	.032	.015	.023	.045	.118*	.022	.023	.042
16	.035	.062	.023	.040	.017	.015	.023	.032	.414*	.022	.023	.034
17	.035	.062	.023	.040	.017	.015	.016	.032	.157*	.022	.023	-
18	.035	.055	.016	.040	.017	.015	.016	.025	.157*	.022	.023	.031
19	.015	.055	.016	.028	.017	.015	.016	.025	.055	.012	.053	.027
20	.015	.055	.016	.028	.020	.015	.016	.025	.055	.012	.053	.019
21	.015	.055	.016	.028	.020	.010	.008	.025	.055	.012	.053	.019
22	.015	.022	.006	.028	.020	.010	.008	.045	.055	.012	.053	.018
23	.017	.022	.006	.026	-	-	.008	.045	.052	.012	.026	.010
24	.017	.022	-	-	-	-	.008	.009	.052*	.012	.026	.023
25	-	.022	-	-	-	-	.011	.009	.052*	.006	.026	.013
26	-	.021	-	-	-	-	.011	.009	.052*	.006	.026	.023
27	-	.021	-	-	-	-	.011	.009	.043*	.006	.016	.0083
28	-	-	-	-	-	-	.011	.009	.043*	.006	.016	.0069
29	-	-	-	-	-	-	-	.009	.043	.006	.016	.0158
30	-	-	-	-	-	-	-	.018	.043	.006	.016	.0063
31	-	-	-	-	-	-	-	.018	.035	-	.016	.0074
32	-	-	-	-	-	-	-	.018	.035	-	.016	.0062
33	-	-	-	-	-	-	-	.018	.035	-	.016	.0079
34	-	-	-	-	-	-	-	.018	.035	-	.016	.0079
35	-	-	-	-	-	-	-	.018	.035	-	.022	.0054
36	-	-	-	-	-	-	-	.018	-	-	.022	.0054
37	-	-	-	-	-	-	-	.028	-	-	.022	.0050
38	-	-	-	-	-	-	-	.028	-	-	.022	.0042
39	-	-	-	-	-	-	-	.011	-	-	-	.0047
40	-	-	-	-	-	-	-	.011	-	-	-	.0066
41	-	-	-	-	-	-	-	.011	-	-	-	.0064
42	-	-	-	-	-	-	-	.011	-	-	-	.0053
43	-	-	-	-	-	-	-	.011	-	-	.008	.0047
44	-	-	-	-	-	-	-	.011	-	-	.008	.0092
45	-	-	-	-	-	-	-	.014	-	-	.008	.0042
46	-	-	-	-	-	-	-	.014	-	-	.008	.0033
47	-	-	-	-	-	-	-	.014	-	-	-	.0028

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Table 9. (Contd.)

DAYS POST INJECTION	PER CENT OF INJECTED DOSE EXCRETED PER DAY											
	Hp-1	Hp-2	Hp-3	Hp-4	Hp-5	Hp-6	Hp-7	Hp-8	Hp-9	Hp-10	Hp-12	Chi-1[2]
48	-	-	-	-	-	-	-	.008	-	-	-	.0054
49	-	-	-	-	-	-	-	.008	-	-	-	.0047
50	-	-	-	-	-	-	-	.008	-	-	-	.0040
51	-	-	-	-	-	-	-	.008	-	-	-	-
52	-	-	-	-	-	-	-	.010	-	-	-	-
53	-	-	-	-	-	-	-	.010	-	-	-	-
54	-	-	-	-	-	-	-	.010	-	-	-	.0038
55	-	-	-	-	-	-	-	.010	-	-	-	-
56	-	-	-	-	-	-	-	.010	-	-	-	-
57	-	-	-	-	-	-	-	.007	-	-	-	-
58	-	-	-	-	-	-	-	.007	-	-	-	.0043
59	-	-	-	-	-	-	-	.007	-	-	-	-
60	-	-	-	-	-	-	-	.007	-	-	-	-
61	-	-	-	-	-	-	-	.008	-	-	-	-
62	-	-	-	-	-	-	-	.008	-	-	-	.0048
63	-	-	-	-	-	-	-	.008	-	-	-	-
64	-	-	-	-	-	-	-	.008	-	-	-	-
68	-	-	-	-	-	-	-	-	-	-	-	.0063
70	-	-	-	-	-	-	-	-	-	-	-	.0045
74	-	-	-	-	-	-	-	-	-	-	-	.0050
78	-	-	-	-	-	-	-	-	-	-	-	.0033
79	-	-	-	.006	-	-	.005	-	-	-	-	-
80	-	-	-	.006	-	-	.005	-	-	-	-	-
81	-	-	-	.006	-	-	.005	-	-	-	-	-
82	-	-	-	.006	-	-	.005	-	-	-	-	.0042
83	-	-	-	-	-	-	.006	-	-	-	-	-
84	-	-	-	-	-	-	.006	-	-	-	-	-
85	-	-	-	-	-	-	.006	-	-	-	-	-
86	-	-	-	-	-	-	-	-	-	-	-	.0050
90	-	-	-	-	-	-	-	-	-	-	-	.0042
94	-	-	-	-	-	-	-	-	-	-	-	.0040
98	-	-	-	-	-	-	-	-	-	-	-	.0050
100	-	-	-	-	-	-	-	-	-	-	-	.0056
102	-	-	-	-	-	-	-	-	-	-	-	.0038
106	-	-	-	-	-	-	-	-	-	-	-	.0043
108	-	-	-	-	-	-	-	-	-	-	-	.0038
112	-	-	-	-	-	-	-	-	-	-	-	.0021
116	-	-	-	-	-	-	-	-	-	-	-	.0029
120	-	-	-	-	-	-	-	-	-	-	-	.0032
126	-	-	-	-	-	-	-	-	-	-	-	.0030
130	-	-	-	-	-	-	-	-	-	-	-	.0037
136	-	-	-	-	-	-	-	-	-	-	-	.0034
138	-	-	-	-	-	-	-	-	-	-	-	.0025

*Values eliminated from revised mean on basis of the Chauvenet Criterion.

(1) All cases except Chi-1 received Pu^{+4} in 0.4 per cent $Na_3C_6H_5O_7 \cdot 2d_2O$ Solution.

(2) Russell, E. R., Nickson, J. J., Argonne National Laboratory Report CH-3607.

lowed material removed from the lungs of the workers by ciliary action. One may ask why the small amount of lung contamination does not prevent the use of the urinary excretion results from these workers to adjust the 138 day urinary excretion curve to 1750 days. This material does not reach the absorbing area of the lung and is not absorbed appreciably from the gastrointestinal tract (probably less than 0.01%). The small amount of material which has reached the alveoli is being absorbed into the blood at an infinitesimal rate. Of the amount absorbed only a fraction of a percent contributes to the daily urinary excretion.

Studies of the excretion of plutonium by mice, rats, rabbits and dogs (HaXX; La47; FiXX; RuXX) showed the urinary excretion of all species was quite uniform. The plutonium excretion in the urine 30–50 days after injection was 0.01–0.02% of the administered dose per day. The urinary/fecal excretion ratio varied widely, however, for the various species. The ratio was 1/10–15 for the rat and only 1/2–3 for the dog.

Russell and Nickson (RuXX) reported a

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plutonium urinary/fecal excretion ratio of 3/1 in man based on the observation of one case through 140 days. The California group (HaXX) reported an excretion ratio of 3–4/1 by one subject followed for 341 days.

The adjusted urinary excretion for 0–1750 days and the fecal excretion curve for 0–138 days may be solved for the urinary to fecal excretion ratio:

$$\frac{Y_{ua}}{Y_f} = \frac{0.20\,X^{-0.74}}{0.63\,X^{-1.09}} = 0.32\,X^{0.35}. \qquad (10)$$

The urinary/fecal ratio is 1.8/1 at 138 days post injection and 4.4/1 at 1750 days when calculated from the above expression. Unfortunately no applicable fecal excretion data are available from the Los Alamos personnel to permit adjustment of the expression for fecal excretion beyond 138 days. If the urinary/fecal ratios at 138 and 1750 days are calculated from the unadjusted expressions (Y_u and Y_f) for both urinary and fecal excretion, the values are 1.7/1 and 3.9/1 respectively. Although extrapolation beyond 138 days is subject to increasing uncertainty with increasing values of X, the above values lead to the conclusion that the urinary/fecal plutonium excretion ratio is not constant, over the range (0–138 days) measured, but approaches 4/1 as a limit at some later time. The results obtained by Hamilton (HaXX) on the case followed for 341 days seem to support the above conclusion.

The expression $Y_f = 0.63\,X^{-1.09}$ gives the amount of plutonium (expressed as percent of injected dose) excreted in the feces on a particular day (X) after injection. Integration of the expression between the limits of $X = 1/2$ and $X = n + 1/2$ gives the total percent (A_f) of the injected dose excreted through day n:

$$\begin{aligned} A_f &= 0.63 \int_{1/2}^{n+1/2} X^{-1.09}\,dX \\ &= -7.00\,[(n+1/2)^{-0.09} - (1/2)^{-0.09}] \\ &= -7.00(n+1/2)^{-0.09} + 7.45. \qquad (11) \end{aligned}$$

From the above expression $A_f = 2.96\%$ through the first 138 days.

(3) *Total excretion (urine plus feces)*. From the practical point of view the total urinary plus fecal excretion rate of plutonium is extremely important. The summed elimination rate determines how long a worker should avoid further exposure to plutonium after having reached an accepted maximum permissible body level.

The observed mean urinary plus fecal plutonium excretion values are given in Table 7. Results are expressed as percent of injected dose excreted per day. The means were obtained from the individual urinary excretion data from fifteen cases and the individual fecal excretion data from eleven. The results reported by the Chicago and California groups were used when available and applicable.

Application of the method of least squares gives the expression

$$Y_{u+f} = 0.79\,X^{-0.94} \qquad (12)$$

as the best curve of fit for the urinary plus fecal excretion data for 0–138 days. The standard error of estimate of the computation is 17%. Y_{u+f} is the total plutonium excreted in feces plus urine on a particular day (expressed as percent of injected dose) and X is the time after injection in days.

The observed means and derived expressions are compared graphically in Fig. 4. Observed values are represented by squares and the derived expression by the heavy broken line designated Y_{u+f}.

The expression $Y_{u+f} = 0.79\,X^{-0.94}$ represents the total excretion of plutonium only through the 138th day. Adjustment can be made, however, for urinary excretion measurements through 1750 days by summing the expression for fecal elimination (9) and the adjusted expression for urinary excretion (7).

$$Y_{ua+f} = Y_{ua} + Y_f = 0.20\,X^{-0.74} + 0.63\,X^{-1.09}. \qquad (13)$$

This equation is adjusted to include all urinary excretion results from Los Alamos Laboratory personnel through 1750 days, and gives the total percent of an injected dose of

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plutonium which may be excreted on a given day (X) after the time of injection.

The adjusted expression for total elimination rate (Y_{ua+f}) through approx. 5 years and the observed means are presented graphically in Fig. 5 for comparison with the adjusted urinary excretion rate (Y_{ua}) for the same time interval.

Integration of the adjusted expression for total elimination rate between $X = 1/2$ and $X = n + 1/2$ days, gives the total amount of plutonium expected to be excreted up to and including day n

$$A_{ua+f} = 0.20 \int_{1/2}^{n+1/2} X^{-0.74}\,\mathrm{d}X + 0.63 \int_{1/2}^{n+1/2} X^{-1.09}\,\mathrm{d}X$$

$$= 0.77(n + 1/2)^{0.26} - 7.00(n + 1/2)^{-0.09} + 6.81. \quad (14)$$

Table 10 compares the observed and calculated values of total plutonium excretion for various time intervals using the integrated expression (14).

These results emphasize the relatively slow rate of elimination of systemically deposited plutonium by man. According to these data only 8.7% of a single injected dose is excreted in 1750 days (approx. 5 years).

4. DISCUSSION

(A) *Distribution of plutonium in tissues and organs of man*

Table 3 contains all available data (up to the time of this report) on the distribution of plutonium in the tissues and organs of man. These data were the results of analysis of a miscellaneous group of samples collected from seven human subjects. The subjects were elderly persons or persons suffering from an incurable chronic disease. The samples were often small and poorly representative and not obtained from the seven cases at comparable times after injection of the plutonium. These unavoidable difficulties must be recognized and accepted when considering the results. Despite the above difficulties, the data are extremely valuable as a supplement to a much greater and more reliable mass of data concerning the distribution of plutonium in the tissues and organs of laboratory animals. The data on man are in good agreement with results of similar studies in rats, mice, rabbits and dogs. The good agreement permits the conclusion that there are no *major* differences in the quantitative distribution of plutonium in the tissues and organs of man and those of common laboratory animals with perhaps one exception—the liver. The results indicate that the retention of plutonium in the liver following its intravenous injection as Pu^{+4}-citrate complex and as plutonyl ion may be 20–40% for man as compared to 10% or less for rats. The "biological half-time" of plutonium in the liver of man is probably much greater than that for rats.

The average amount of plutonium found in vertebra, sternum and rib was 0.0066% of the injected dose per gram of whole bone. Assuming vertebra, sternum and rib as representative of the entire skeleton, 66% of the injected dose would be deposited in a 10 kg skeletal system (7 kg of bone, 3 kg of marrow) of a 70 kg man.

The observed concentration of plutonium in bone may be used to estimate the radiation dose received per g of skeletal system when a "standard man" has accumulated the official maximum permissible plutonium body content of 0.5 μg (0.032 μc). Using the dosage rate formula: rep/day = 54 CE (where C = concentration of radioisotope in μc/g, E = energy of the radiation in MeV, and the rep = 93 ergs/g), the radiation dosage received per g of skeleton from 0.032 μc of plutonium is as follows:

$$\text{rep/day} = 54 \times 6.6 \times 10^{-5} \times 0.032\ \mu\text{c} \times 5.15\ \text{MeV} = 0.00057.$$

A similar calculation for the official maximum permissible radium content of 0.1 μc may be made for comparison. If 50% of the radon from radium decay is retained in the body, then approx. 15 MeV of energy will be released in the body by the α-particles per decay. If 100% of the radium is deposited in a 10 kg skeletal system, then the radiation dosage in rep per day is given as follows:

$$\text{rep/day} = 54 \times 1 \times 10^{-5} \times 15 = 0.0081.$$

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Table 10. Observed and derived total urinary plus fecal plutonium excretion values for various times after administration of a single dose of plutonium to man

TIME AFTER INJECTION	PER CENT OF INJECTED DOSE	
	Observed	Calculated*
10 days	2.43	2.56
20 days	3.06	3.17
30 days	3.41	3.53
40 days	3.70	3.81
50 days	3.90	4.03
60 days	4.11	4.21
70 days	4.27	4.36
80 days	4.42	4.50
90 days	4.54	4.62
100 days	4.67	4.74
120 days	4.87	4.93
140 days	5.01	5.10
1 year		6.26
2 years		7.22
3 years		7.83
4 years		8.30
5 years		8.68
10 years		9.96
20 years		12.17

*Calculated from the integrated expression for adjusted urinary plus fecal excretion [14]. The calculated values appear higher than the observed values by a constant amount because of the decision to accept a poor curve fit during the first ten days (See Page 23).

According to the above calculation, the radiation dosage per g of skeleton delivered by 0.1 μg of radium would be 14 times that delivered by the maximum permissible dose of plutonium if the two materials were distributed in a comparable manner in the skeleton. Autoradiographic studies show conclusively, however, that radium and plutonium do not distribute in a comparable manner. Plutonium is more localized and concentrates in the endosteal and periosteal surfaces. The choice of a more conservative body tolerance dose for plutonium was made to allow for its more specific localization in the skeletal system. It should be noted, however, that radium does not distribute uniformly throughout bone and Evans has reported that analyses of bone samples from radium cases showed the radium to be unevenly distributed by as much as a factor of 10. It may be necessary, therefore, for plutonium to be concentrated by a factor of 140 over radium in order that 0.5 μg will give radiation intensities comparable to that which may occur with 0.1 μg of radium. Evans (Ev50b) has also pointed out that the presence of mesothorium in the radium responsible for the early radium poisoning cases may account for an additional safety factor of 5 in the 0.1 μg radium tolerance.

The above discussion supports the possibility that the 0.5 μg maximum permissible tolerance dose for plutonium is extremely conservative.

(B) "*Biological half-time*" *of plutonium in man*

The "biological half-time" of plutonium in man can be estimated from the excretion data presented in this report. Although the adjusted urinary plus fecal excretion curve is (empirically at least) logarithmic in nature, it appears that the curve approaches an exponential for longer times. Such an exponential curve would be in keeping with the assumption that metabolic processes are primarily first order reactions. Whatever the true process is, from the data and curves given in this report, it is possible to calculate the absolute minimum half-time of plutonium in the body. It is assumed (not unreasonably) that the excretion of the plutonium measured in terms of the amount in the body at a given time does not increase at some time. If one

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takes the last point on the combined urinary plus fecal excretion curve (a single value of the ordinate in Fig. 5) and assumes exponential excretion thereafter, an absolute minimum value is obtained for the biological half-time. On this figure, which is a plot of $\Delta C/C_0$ vs Δt exponential excretion would be represented by a straight line with zero slope. Examination of the adjusted curve shows that $0.001 \pm 0.00035\%$ per day is excreted at 1750 days (approx. 5 years) after exposure. Up to 5 years 8.7% of the total has been excreted. The time required to excrete an additional 41.3% (assuming exponential excretion beyond 1750 days) is

$$\frac{41.3}{0.001 \pm 0.00035} = 41{,}300 \text{ days} = 113 \text{ years with limits of 84 and 175 years.}$$

Thus, the mean minimal biological half-time estimate is 118 years. From the above, one may conclude that the excretion coefficient is too small to be of any practical significance in elevating the maximum permissible dose of plutonium or in permitting the return to work of an individual who has reached the maximum permissible body burden. Once a worker is retired from work with plutonium because of a maximum tolerance exposure, it must be assumed that he is retired from such work for the balance of his lifetime.

(C) *Determination of plutonium body burden from urinary excretion*

It the determination of exposure doses by the use of excretion data, one is primarily concerned with three different situations. First is the case of a single acute exposure dose occurring at a known time. Second is the case of a variable chronic or subacute dose with only the total exposure time being known. Third is the case of a chronic invariant (usually low level) exposure dose with the time limits known.

The evaluation of the single acute exposure dose occurring at a known time is the basis of this paper. A urinary excretion curve through 138 days after a single acute exposure is given in Fig. 4. This curve has been extended beyond the observation limit to 1750 days (Fig. 5) by applying data collected on exposed personnel from the Los Alamos Laboratory. The method used to apply these data was explained earlier. It is worth noting that the difference between the adjusted curve and the extrapolated 138-day curve at 1750 days is less than the standard error of estimate of the former. This finding allows more confidence in further extrapolation beyond 1750 days post exposure. The calculation of the body burden from a single acute exposure is simple.

Since

$$Y_{ua}(\%) = 0.20\, X^{-0.74}$$

$$Y(c/m) = 0.0020\, D_E X^{-0.74},$$

then

$$D_E = 500\, Y(c/m) X^{0.74}. \qquad (15)$$

Thus, a single urine count, Y, made X days after an unknown single acute exposure, D_E, determines D_E in counts per min. The exposure dose in μc or μg is easily determined if the counting geometry, etc. is known.

In the Los Alamos exposures, we have an illustration of the variable chronic exposure case with known time of exposure. Only under conditions of stress when safety factors of design may be exceeded will this type of exposure be seen. There are three methods of estimating the total exposure dose under such conditions. Past practice at the Los Alamos Laboratory was to assume that an individual contracted his total exposure dose on the last day of the exposure period. His total body burden was then determined by substitution in the urinary excretion formula as shown above. In this case, zero time is the last day of exposure. Obviously this method gives too low a value for the exposure dose as the estimated dose is directly proportional to time. A second method which has been used is exactly the same as the previous one except that zero time is taken as the first day of exposure which assumes that all of the dose was accumulated on exposure day one. It is evident that this estimate of total exposure is too high. The third method,

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which was used in this paper to determine the adjusted urinary excretion curve, is believed to more closely approximate the true situation. In this method it has been assumed that the total exposure dose may be represented by a single *effective* dose occurring at some *effective* time intermediate to the limits of exposure. The equations and steps to be followed with this method are shown on pages 1153 and 1159. Ordinarily the first urine count is used to determine whether an individual should or should not be withdrawn from exposure. It is not used as one of the two significantly different dose determining counts. This due to the fact that the initial withdrawl count may reflect the high urinary excretion resulting from the previous ten days exposure, and to the relatively high percent excretion during the first 10 days post-exposure period. The high rate of elimination resulting therefrom may relatively obscure any exposure doses accumulated previous to that time.

The case of chronic invariant exposure is probably of primary interest. This is the type of exposure (within limits) that occurs in processing procedures in the plutonium industry in which air concentrations, etc. are rigidly controlled and the work is routine. An analysis of the general case is presented as follows:

If m = time of exposure in days and n = days from the beginning of an exposure to the time a urine analysis is made with $n > m$ (preferably by more than 10 days) then the counts per min in the urine excreted on day n is:

$$Y_n = 0.0020\,[D_1 n^{-0.74} + D_2(n-1)^{-0.74} + D_3(n-2)^{-0.74} + \ldots + D_m[n-(m-1)]^{-0.74}]$$

where

D_1 is the exposure dose in counts per min on exposure day 1,

D_2 is the exposure dose in counts per min on exposure day 2,

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D_m is the exposure dose in counts per min on exposure day m.

Considering the case in which we are interested, namely, $D_1 = D_2 \ldots = D_m = D_j$ (the constant daily exposure dose), then

$$Y_n = 0.002\,D_j[n^{-0.74} + (n-1)^{-0.74} + \ldots + [n-(m-2)]^{-0.74} + [n-(m-1)]^{-0.74}]$$

Thus

$$D_j = \frac{Y_n}{0.0020\,[n^{-0.74} + (n-1)^{-0.74} + \ldots + [n-(m-2)]^{-0.74} + [n-(m-1)]^{-0.74}]}$$

Considering the bracketed term in the denominator:

$$n^{-0.74} + (n-1)^{-0.74} + \ldots + [n-(m-1)]^{-0.74} = (n-m+1)^{-0.74} + (n-m+2)^{-0.74} + \ldots + n^{-0.74}.$$

This term is similar to the infinite series r^t where r has the limiting values $(n-m+1)$ and (n) and $t = -0.74$. The sum of the series $r^{-0.74}$ may be written:

$$\sum_{r=1}^{r=R} \frac{1}{r^{-0.74}} = \frac{1}{1^{0.74}} + \frac{1}{2^{0.74}} + \frac{1}{3^{0.74}} + \cdots + \frac{1}{R^{0.74}}.$$

Thus we may write:

$$(n-m+1)^{-0.74} + (n-m+2)^{-0.74} + \cdots + n^{-0.74} = \sum_{r=(n-m+1)}^{r=n} \frac{1}{r^{0.74}}$$

$$= \sum_{r=1}^{r=n} \frac{1}{r^{0.74}} - \sum_{r=1}^{r=(n-m)} \frac{1}{r^{0.74}} = \sigma(n) - \sigma(n-m)$$

and on substitution

$$D_j = \frac{Y_n}{0.002\,[\sigma(n) - \sigma(n-m)]}.$$

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The following empirical formula* is good to 2 parts in 50 for $r = 1$ and to better than 1 part in 1000 for $r > 5$:

$$\sigma(r) = 3.8462(r + 1/2)^{0.26} - 3.2880. \quad (16)$$

Thus, on substitution we have:

$$D_j = \frac{Y_n}{0.002[3.8462(n + 1/2)^{0.26} - 3.8462(n - m + 1/2)^{0.26}]}$$

or

$$D_j = \frac{130\ Y_n}{[(n + 1/2)^{0.26} - (n - m + 1/2)^{0.26}]}.$$

Since the total exposure dose $= mD_j = T_{D_m}$

$$T_{D_m} = \frac{130\ mY_n}{[(n + 1/2)^{0.26} - (n - m + 1/2)^{0.26}]}. \quad (17)$$

In addition to the empirical formula for $\sigma(r)$ a plot of the real values of $\sigma(r)$ vs (r) for values of r up to 90 days has been included (Fig. 6) from which the values of the sums may be read directly.

In the equation for T_{D_m} 7 exposure days per week are assumed. The formula for T_{D_m} may be adjusted for 6 exposure days per week as follows:

We assume that exposure begins on the first working day of a week for simplicity.

Obviously the only days not contributing to exposure are those on which $D_j = 0$. In the 6 day week, therefore, $D_7 = D_{14} = D_{21} = \cdots D_{7a} = 0$ where a = number of weeks worked by the subject. Thus, the terms corresponding to D_7, D_{14}, $D_{21} \cdots$ etc. must be subtracted from the dose equation. Hence:

$$D_j = \frac{Y_n}{0.002\{[\sigma(n) - \sigma(n - m)] - [(n - 6)^{-0.74} + (n - 13)^{-0.74} + (n - 20)^{-0.74} + \cdots + (n - 7a + 1)^{-0.74}]\}}.$$

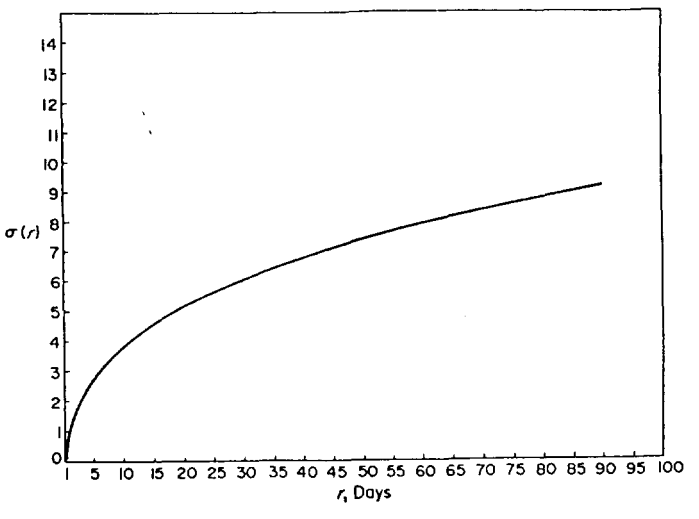

FIG. 6. Plot of $\sigma(r) = 3.8462\ (r + 1/2)^{0.26} - 3.2880$.

*Determined by Bengt Carlson of the Los Alamos Theoretical Division.

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and designating the total exposure dose for the 6 day week as $T_{D_{m_6}}$ then

$$T_{D_{m_6}} = [500\, m Y_n/3.8462[(n+1/2)^{0.26} - (n-m+1/2)^{0.26}] - [(n-6)^{-0.74} + (n-13)^{-0.74} + (n-20)^{-0.74} + \cdots + (n-7a+1)^{-0.74}]]. \quad (18)$$

Similarly for 5 exposure days per week

$$D_6 = D_7 = D_{13} = D_{14} = D_{20} = D_{21} = \cdots D_{7a-1} = D_{7a} = 0$$

the total exposure dose

$$T_{D_{m_5}} = 500\, m Y_n/3.8462[(n+1/2)^{0.26} - (n-m+1/2)^{0.26}] - [(n-5)^{-0.74} + (n-6)^{-0.74} + (n-12)^{-0.74} + (n-13)^{-0.74} + \cdots + (n-7a+2)^{-0.74} + (n-7a+1)^{-0.74}].$$

In the preceding formulae exposure conditions were assumed to consist of an equal and constant daily exposure dose D_j equivalent to a single injected dose. Also, the constants 0.0020 and −0.74 were empirically established on the basis of data available at the time of this report. These values may change as more data become available.

A specific example of the application of the above dosage calculation is given below, using the expression for 7 exposure days per week. In fact, the 7-day exposure formula may be valid for either the 5- or 6-day week. Such would be the case if one considers that absorption from the lung is the primary source of contamination and that the equilibrium between the alveolar and blood plutonium concentration is not radically altered by the one or two day period of no exposure each week.

For purposes of presenting a specific example we may assume the following conditions:

Duration of exposure (m) = 330 days
Duration of time from beginning of exposure until urine sample taken (n) = 360 days
Counts per min of urine sample (Y_n) = 2 c/m
The total body dose T_{D_m} may be calculated from the formula:

$$T_{D_m} = \frac{130 \times m \times Y_n}{[(n-1/2)^{0.26} - (n-m-1/2)^{0.26}]}.$$

On substitution:

$$T_{D_m} = \frac{130 + 330 \times 2}{[(360.5)^{0.26} - (30.5)^{0.26}]} = \frac{8.58 \times 10^4}{2.19} = 3.9 \times 10^4\ c/m.$$

Assuming a 50% counting geometry was used ($1\ \mu g = 7 \times 10^4\ c/m$)

$$T_{D_m} = 0.56\ \mu g.$$

5. SUMMARY

The distribution and excretion of plutonium administered intravenously to man has been studied. The data from twelve subjects have been correlated with similar data collected by other investigators, making a total of 16 cases considered. The data have been supplemented further with observations made on three Los Alamos Laboratory personnel who absorbed measurable amounts of plutonium in the course of their work. The results of these studies may be summarized as follows:

(1) Clinical observations and clinical data collected on the various subjects indicate that the intravenous injection of a single dose of 5–100 μg of plutonium is without acute subjective or objective clinical effects.

(2) The analysis of tissues following the intravenous injection of plutonium showed that there was little difference in the mode of deposition of plutonium in man and in the common laboratory animals. As in the case of

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rats and other laboratory animals the skeletal system was the major site of plutonium deposition. Retention of plutonium by the liver of man seemed to be higher and the "biological half-time" in liver longer than for the more common laboratory animals.

(3) Concentration of plutonium in the blood following intravenous injection drops very rapidly; only 0.3% of the total injected dose was fixed in the total blood volume 30 days after injection.

(4) The urinary excretion of intravenously administered plutonium was not exponential. Curvilinear regression line fitting showed that the urinary excretion through 138 days was best expressed by the fractional logarithmic function

$$Y_u = 0.23\, X^{-0.77}.$$

In this expression Y_u is the percent of the injected dose excreted in a single day and X is the time of observation in days post-injection. The standard error of estimate is 32%.

(5) The above expression for the urinary excretion through 138 days was adjusted by including data collected on Los Alamos Laboratory personnel. This adjustment permitted the development of an expression for the urinary excretion of plutonium through 1750 days. The adjusted expression is:

$$Y_{ua} = 0.20\, X^{-0.74}.$$

The standard error of estimate of the adjusted expression is 42%.

(6) The excretion of plutonium in the feces likewise was not exponential. Application of the method of least squares showed the best curve of fit for the fecal excretion of plutonium through 138 days was:

$$Y_f = 0.63\, X^{-1.09}.$$

In this expression Y_f is the percent of the injected dose excreted on a specific day and X is the time of measurement in days post-injection. The standard error of estimate of the above expression is 28%.

(7) The urinary to fecal plutonium excretion ratio obtained by solution of the above expressions for urinary and fecal excretion showed the urinary to fecal ratio was not constant. It was essentially 1:1 at 30 days and approached 4:1 at approx. 5 years.

(8) The total (urine and fecal excretion) through 138 days was best expressed by the equation:

$$Y_{u+f} = 0.79\, X^{-0.94}.$$

(9) The total urine plus fecal excretion through 1750 days could be approximated by adding the expression for the fecal excretion through 138 days and the adjusted expression for the urinary excretion through 1750 days. The expression for the combined excretion is:

$$Y_{ua+f} = 0.20\, X^{-0.74} + 0.63\, X^{-1.09}$$

in which Y_{ua+f} represents the percent of the injected dose excreted in the urine plus feces on a specific day, and X designates the time of observation in days post-injection.

(10) Integration of the above expression between the limits of 1/2 and $n + 1/2$ days post-injection gives the following expression:

$$A_{ua+f} = 0.77\,(n + 1/2)^{0.26} - 7.00(n + 1/2)^{0.09} + 6.81,$$

which represents the integrated amount of plutonium in percent of the injected dose (A_{ua+f}) excreted up to and including the nth day after injection. Substitution in this expression showed that only 8.7% of a single injected dose was excreted in approx. 5 years.

(11) Application of the data of this report to the calculation of the "biological half-time" of plutonium in man gives a mean minimal "biological half-time" estimate of 118 years, with a variation of from 84 to 175 years.

(12) The urinary excretion data of this report were applied to the diagnosis of exposure of personnel to plutonium. Three sets of exposure conditions were considered:

(a) The application of plutonium urine analysis to estimate the total body dose fol-

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lowing a single acute exposure occurring at a known time;

(b) The application of plutonium urine analysis to estimate the total body burden of plutonium following variable chronic or subacute exposure with only the total exposure time being known and;

(c) The application of urine analysis to estimate the total body burden following chronic invariant exposure (such as may occur in a carefully controlled routine plant process) with time of exposure known.

Expressions for the calculation of body dose under the conditions set forth in (a), (b) and (c) are included in this report.

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