



PROVENANCE

REPOSITORY: OFFICE OF HUMAN RADIATION  
EXPERIMENTS (OHRE)

COLLECTION: PLUTONIUM INJECTION INVESTIGATION  
FILES (OHRE 1)

BOX: 2

FOLDER: PLUTONIUM INJECTIONS - ROCHESTER -  
GEN INFORMATION

1145074A

## II. Methods

### A. Clinical

#### 1. Selection of subjects

The individuals chosen as subjects for the experiment were a miscellaneous group of male and female hospital patients for the most part with well established diagnoses. Preference was given to those who might reasonably gain from continued residence in the hospital for a month or more. Special treatments and other therapy thought to be of benefit to the patients were carried out in the usual manner. The necessity of studying urinary and fecal rates of excretion of Pu automatically excluded cases of advanced renal disease or disturbance in the function of the gastrointestinal tract. Patients with malignant disease were also omitted from the group on the grounds that their metabolism might be affected in an unknown manner.

The life expectancy of the individual was carefully considered. As a rule, the subject chosen was past 45 years of age and suffering from a chronic disorder such that chance of survival for ten years or more was improbable. By adhering to these criteria it was hoped

(a) That the possibility of late radiation effects developing in the course of ten or fifteen years would be avoided.

(b) That an opportunity would present itself to obtain post mortem material within a period of months or at most a few years.

Of eleven patients in the Rochester group, ten were past the age of 45. One was only 15 years old but has since died of Cushing's Syndrome; a woman aged 49 years may have a greater life expectancy than originally anticipated due to an error in the provisional diagnosis. Up to the time of compilation of this report and approximately two years since the initiation of the study, five subjects have died of their disease. Complete autopsies with tissue analyses for Pu were obtained

in three instances; one death occurred in another institution with a complete post mortem but no analyses of tissues; one subject died in another hospital and permission for autopsy could not be obtained.

## 2. Management of patients

Ten of the twelve subjects were cared for in the special medical ward of the hospital where they were continuously under observations of the physician in charge of the experimental work and of a specially trained staff of nurses. One patient HP-11, remained on the general ward. No collections could be made because he was in the terminal phase of his illness when the Pu was injected. Material from the subject HP-12 was obtained at Oak Ridge.

The general plan of procedure with patients resident in the medical ward was as follows:

During a control period the subject was carefully instructed in the quantitative collection of urine and fecal specimens. He became adjusted to ward routine and any necessary modifications in diet, medication, etc., were made. The period of indoctrination usually required about ten days. After the subject had proven himself capable of cooperation, control specimens of urine and feces were collected.

The period of observation following the injection was originally set at 22 days, however, as the work progressed, it became evident that more prolonged studies were desirable. Whenever possible these have been carried out and include a longer initial period of observation as well as follow-up studies made a year or more after the injection. Details are given in the case histories (Section III) and in Section IV.

Preceding the injection of Pu, the physical examination was re-evaluated, blood counts, urea clearances, and blood chemistry were obtained. (Details are given in Section III).

~~SECRET~~

Routine for collection of blood, urine, and feces

Blood

Blood was drawn into dry sodium citrate as an anticoagulant. Exactly 15 ml of well mixed whole blood was pipetted into a glass ampoule and sealed. At first formalin was added as a preservative but later this was omitted because of the precipitation of protein with the attendant difficulty in removing the material from the ampoule. Specimens were drawn before the injection of Pu and at stated intervals thereafter. The schedule evolved was one control specimen and post injection specimens at 4 hours, 24 hours, 3 days, 6 days, 10 days, 15 days, and at the termination of the period of hospitalization. The number of samples contributed by each subject and time relation to injection of Pu appear in the protocol of Section IV.

Urine

Urine was collected by having the subject void directly into a new half gallon fruit jar. The usual collection period for urine was 24 hours except for the day on which the Pu was given, when it was collected in two 12 hour periods. At the completion of each collection a label was affixed to the jar giving the subject's number and the dates and hours of collections. Fifteen ml of 40% formalin was added as a preservative and the specimen heated on the steam bath for about two hours. This sufficed to expel much of the air from the jar which was then sealed and cooled to room temperature. Enough reduction in pressure was obtained in the jar to hold the lid firmly in place and prevent loss in transit. As a further precaution, an adhesive marker was placed at the top level of the liquid in the jar in order that any leakage which might have occurred would be revealed to the person receiving the urine for analysis. The system worked very satisfactorily and losses were negligible.

1145077

~~SECRET~~



Feces

Feces were passed into large (3000 ml) weighed Pyrex beakers that had not been used previously for any other purpose. To avoid admixture of urine with feces the patient was required to empty his bladder as completely as possible prior to defecation. The weight of the fecal specimen was obtained by difference and the date and hour recorded. As a rule the feces were pooled during intervals of four days. Canine markers were not used. The fresh stool was covered with 6N HCl and boiled for about ten minutes. This method of preservation had several advantages; most of the fecal material disintegrated, bacterial decomposition was stopped, and transfer of the resultant suspension to a half gallon fruit jar was readily accomplished. Usually one jar sufficed for all the stools in a four day period. Sealing and marking of the specimen jars was accomplished as described in the case of the urine. Following the administration of Pu the first two or three stools were saved separately rather than in a pool in order that the time of appearance of the tracer in the feces might be determined more accurately.

3. Method of Administration of Plutonium

(a) Preparation and nature of solutions.

The standard solution of Pu for use in human tracer studies was obtained from Dr. Wright Langham of Los Alamos and consisted of 5 mg of Pu as nitrate dissolved in  $2\text{H-NO}_3$ , valence +4. The material was received in a volume of one ml in a sealed glass ampoule. The content of the ampoule was transferred to a small rubber stoppered vial which in the following text will be referred to as Solution A. As a general check on methods and procedure, a preliminary experiment was carried out on rats.

Rat Experiment

Six hundredths of a cubic centimeter (0.06 ml) of Solution A were measured with a 0.1 ml pipette into a 10 ml volumetric flask and made to

~~SECRET~~



~~SECRET~~  
-5b-

Note to Dr. W. Lundquist

The only animal experiments made with the plutonium solution received in Rochester for the HP work are those recounted on pages 5 and 6. Both Bob Fink and I realize that these are at variance with some of the work you have done and that reported elsewhere. We see no particular reason for its inclusion except that you may wish to mention briefly the range of Pu concentration in the livers of animals as it was known to you when we first started our cooperative study. Please feel free to modify this section of the report in any way you see fit.

1145079

~~SECRET~~

volume with 0.41% sodium citrate • 2H<sub>2</sub>O (This diluted plutonium solution is referred to as Solution B). Three rats weighing respectively 233, 222, and 236 grams were injected intravenously in the tail vein with 0.5 ml of Solution B. At the same time, three dummy solutions were prepared, each of which consisted of 0.5 ml of Solution B diluted to a volume of 100 ml in a volumetric flask with 2N-HCL. Counts were made from these dummies by evaporating 0.1 ml from each on 1 cm<sup>2</sup> silver foil. The rats showed no evidence of toxicity and were killed at four days. Their livers were digested in a mixture of nitric acid and hydrogen peroxide and the digest made to a volume of 25 ml in volumetric flasks. 0.1 ml portions of the liver digests were evaporated on 1 cm<sup>2</sup> platinum foil and counted. The total number of counts on the individual dummy solutions in terms of 0.5 ml of Solution B (or 15% Pu) were:

	<u>c/p/m</u>
Dummy #1	1,180,000
" #2	1,100,000
" #3	1,060,000
Average	<u>1,113,000</u>

Counts on the rat livers as total counts per liver were:

	<u>c/p/m</u>
#1 (233 gm)	22,800 or 1.9%
#2 (222 gm)	20,000 or 1.8%
#3 (236 gm)	30,500 or 2.9%

It is clear that only a comparatively small localization of Pu occurred in the liver which suggested that the Pu remained in a soluble state (probably as a citrate complex) at least temporarily after the injection and had time for good distribution throughout the body. This was felt to be important from the standpoint of the human tracer studies where because of possible radiation hazard, it was hoped that the Pu would not be taken up in high concentration by a single organ such as the liver.

(b) Choice of size of dose

There are no altogether satisfactory criteria at present for estimating the tolerance dose of 94 Pu<sup>239</sup>. The problem may be approached



from several points of view. None of these is free from some criticism since certain assumptions have to be made without support of experimental evidence.

One may start with the premise that the maximum permissible dose of radium is 0.1 microgram (1) (2). The alpha particles which are responsible for its chief biological effects are derived not only from radium but also the "daughter" nuclei of the radium series. In the primary step the radium yields  $2.21 \times 10^5$  disintegrations per minute or 0.1 microcurie. About 45 per cent of the radon thus formed is lost through the lungs but the alpha radiation of the remainder is absorbed in the body together with the alpha particles of the radium A and C' disintegration series. The total energy absorbed in the body from the radium series is, therefore, about 14.23 Mev as compared with about 4.79 Mev for radium alone. The ratio of the biologically effective energy liberated by 0.1 microcurie of radium to that derived from 0.1 microcurie of plutonium is the ratio of the energies of the alpha particles derived from each; i. e.  $\frac{14.23}{5.15} = 2.76$ .

An amount of Pu, that with the same distribution will be biologically comparable to 0.1 microgram of Ra will be 4.47 micrograms and may be calculated from the expression:

$$\frac{2.43 \times 10^4}{1.59 \times 10^3} \times \frac{239}{226} \times 2.76 \times 0.1 = 4.47$$

\* Constants employed in making these calculations are as follows (3):

	<u>Energy of Alpha particle</u>	<u>Half Life</u>	<u>Atomic Wt.</u>
Ra	4.791 Mev	$1.59 \times 10^3$ yrs	226
Rn	3.486 "	3.825 days	222
Ra A	5.998 "	3.05 min.	218
Ra B	.....	.....	...
Ra C	.....	.....	...



Another and highly practical consideration, however, enters the choice of the dose. While the rate of excretion in man could not be predicted in advance, there was every reason to believe on the basis of animal experiments and one human case, that injected plutonium would be largely retained (4). It was considered probable, moreover, that the rate of elimination in urine and feces would prove to be a function of the total amount deposited in the body. If the quantity injected was too small, the absolute amount eliminated would be less than could be measured with reasonable accuracy by current analytical procedures. It was estimated that the necessary data could be obtained with a dose of 1 microgram. The dilemma of possible late radiation hazard was met by the choice of subjects believed to have short life expectancies.

A second method of approximation is to consider the maximum allowable exposure to radiation from an alpha emitting isotope. The alpha particles travel but a short distance, exert their maximum effect locally and are absorbed almost completely by the soft tissues. It has been customary for this reason

\*Constants employed in making these calculations are as follows (3): (Continued)

	<u>Energy of Alpha Particle</u>	<u>Half-life</u>	<u>Atomic</u>
Ra C'	7.680 Mev	$1.5 \times 10^{-4}$ sec	214
RaD	.....	.....	...
Ra E	.....	.....	...
Pu	5.15 Mev	$2.43 \times 10^4$ yrs	239

The sum of the energies of the alpha particles of radon, radium A and radium C is 17.164 Mev. However, because of the loss of radon gas through the lungs, only 45 per cent is absorbed by the tissues or  $17.164 \times 0.45 = 7.724$  Mev. The total energy absorbed by the tissues from the alpha radiation of the series is 9.44 Mev (from "daughter" nuclei) + 4.79 Mev (from radium) = 14.23 Mev.

SECRET



tolerance at such a level that not more than 0.01 roentgen equivalent physical alpha radiation will be received per unit of tissue per day. A dose of this magnitude appears to carry little likelihood of injury to cells (2).

The rate at which energy is received per day from one millicurie of an alpha emitter distributed through one gram of tissue may be expressed as follows:

$$2.60 \times 10^4 (\text{alpha particle energy in Mev}) \times 24 \quad (6)$$

or

$$6.72 \times 10^4 (\text{p.e. in Mev}) = \text{rep/day}$$

Since 1 mg of radium yields one millicurie or  $2.21 \times 10^9$  disintegrations per minute one may calculate the quantity of plutonium required to produce an equal number of disintegrations from the expression:

$$\frac{2.43 \times 10^4}{1.59 \times 10^9} \times \frac{239}{226} \times 1 = 16.1 \text{ mg of Pu (approximately)}$$

The energy of the alpha particle of Pu is 5.15 Mev (3). Thus 16.1 mg of Pu will yield if distributed in one gm of tissue:

$$6.72 \times 10^4 \times 5.15 = 3.46 \times 10^5 \text{ rep/day}$$

or if evenly distributed in a 70 Kg man, the dose would be:

$$\frac{3.46 \times 10^5}{7 \times 10^4} = 4.94 \text{ rep/gm/day}$$

The amount of Pu which will emit tolerance radiation of 0.01 rep/day is:

$$\frac{0.01}{4.94} \times 16.1 = 0.0326 \text{ mg or } 32.6 \text{ micrograms}$$

The fallacy in any such reasoning is that Pu (as in the case of many other radioactive isotopes) is not evenly distributed throughout the body, but having gained access to the blood stream, is ultimately deposited largely in the bones. Moreover, early localization of a large fraction of the dose in the liver if given intravenously is a distinct possibility (7).

Because of its negligible excretion and very slow rate of decay, once deposited in the skeleton, it must continue to irradiate the local tissues



with little abatement in intensity during the entire life of the individual. If one considers the skeleton alone as the area subjected to irradiation and computes the tolerable dose on the basis of skeletal mass, one arrives at a much smaller value. What value one should take for skeletal weight is a matter for further debate since the gross (wet) weight of the human skeleton has been measured on but few occasions (8). If we assume the skeleton to be 16 per cent of the total weight of the body, then  $32.6 \times 0.16 = 5.2$  micrograms of Pu that could be given safely to our man of 70 Kg.

Unfortunately radioautographs reveal a far from uniform distribution of plutonium in bone (9). Deposition appears to occur in the uncalcified matrix, in the subperiosteal region, and in the periosteum. The skeleton cannot be assumed to receive uniformly distributed irradiation. It is quite possible that the total weight of tissue in which plutonium is concentrated may be of the order of 1000 gm. Should this prove to be the case, our hypothetical subject would be receiving  $\alpha$  radiation from five micrograms of Pu at the rate of 0.11 rep/day in certain areas and little or none elsewhere. These may be, in fact, highly critical regions. For example; excessive irradiation of the red bone marrow is known to cause anemia and agranulocytosis; disturbances of cell function in the periosteum initiated by deposits of plutonium have been found to produce metaplasia and bone sarcoma in rats (7) (10). Because of the unique distribution of the isotope, it is clear that even for the skeleton the limit of 0.01 rep/day may be too high if the dose is calculated on the assumption of uniform distribution throughout skeletal tissues.

The several imponderables mentioned in the preceding paragraphs have been a source of concern to those who were responsible for the pursuit of this experiment. The data submitted in Section IV supply partial answers to rates of excretion and tissue distribution but leave unanswered the fundamental question of tolerance<sup>†</sup>.

† The provisional allowable deposition of plutonium (accumulated total) in the body of workers was set by the Manhattan District at 1.0 microgram (2).

SECRET

1145064



~~SECRET~~

(c) Technique of Injection

Blank solution for Human Injection - In order that the staff might be familiar with all details of the procedure of injection, material was assembled two or three days prior to the actual administration of Pu and a blank injection was given.

Apparatus Required:

Sterile	0.1 ml pipette
"	0.41 per cent $K_2$ citrate $\cdot H_2O$
"	$Zn - HNO_3$
"	20 mb syringe with #20 needle attached
"	30 ml syringe with #20 needle
"	1 ml tuberculin syringes (two)
"	25 ml volumetric flask
"	#20 and #22 needles
"	20 ml rubber capped vial
"	0.85 per cent solution of sodium chloride

Using aseptic precautions 0.05 ml of the  $Zn-HNO_3$  was transferred to the volumetric flask and diluted to volume with citrate buffer. After mixing 20 ml were transferred to the rubber capped vial. This vial with two tuberculin syringes, sterile needles, sterile saline, etc., was taken to the patient's bed. One tuberculin syringe was filled with sterile saline and a #22 needle  $1\frac{1}{2}$  inches long attached. The other tuberculin syringe which simulated the one to be used in the actual injection of Pu was filled to the 0.5 ml mark from the vial with citrate. The needle used to withdraw the citrate was discarded and the syringe placed carefully in a convenient position. The needle attached to the saline containing syringe was introduced into the patient's median basilic vein and the saline injected slowly to make sure that there was no failure to enter the vein. The syringe was now carefully detached from the needle and the one with the 0.5 ml of citrate solution was substituted. At this

1145065

~~SECRET~~

point about 0.1 ml of blood usually entered the syringe and gave further evidence of free connection with the vein. The solution was then injected rapidly and the plunger slowly withdrawn until blood filled the barrel to the 0.5 ml mark. The blood rinsed the syringe and was returned to the vein after a moment or two. The needle was withdrawn and firm pressure applied for a minute to the site of injection.

#### Injection of Plutonium Solution

The same apparatus and routine were used in the injection of the plutonium complex. In this case, however, 0.05 ml of Solution A was transferred to sterile 25 ml volumetric flask and diluted to the mark with 0.41 per cent citrate + H<sub>2</sub>O solution. Five tenths of a cubic centimeter of this solution (hereinafter referred to as Solution C) was the amount injected. It contained approximately five micrograms of Pu +4 as citrate complex. Prior to injection the strength of the solution was assayed on the basis of its alpha activity. Dummies were prepared by withdrawing 0.5 ml portions of Solution C into a 1 ml tuberculin syringe fitted with a #22 needle and ejecting into a 25 ml volumetric flask containing 2N-HCl. Counts were made on 0.1 ml portions of the dummy dried on 1 cm<sup>2</sup> silver foil. The actual number of micrograms given to the subject was approximated on the basis of count of post injection dummies prepared by one of the group in attendance at the time of the injection. This individual took careful note of the amount of Solution C withdrawn into tuberculin syringe and watched the technique of injection. In preparation of the dummies the procedure was duplicated in exact detail except that 0.85 per cent NaCl was substituted for the patient's blood. In brief, after injection the syringe and needle used for that purpose was cleaned and dried. The needle was filled with saline to simulate the patient's blood. Solution C was drawn to the 0.5 ml mark through another needle and the latter removed. The needle with saline was attached and a very small amount of saline drawn into the syringe. The plutonium solution was ejected into a 25 ml volumetric flask and the tip of the needle dipped



into fresh 0.85 per cent NaCl solution. The saline was drawn to the 0.5 ml mark to rinse the barrel of the syringe once and also ejected into the volumetric flask. The flask was filled to the mark with 21-HCL. Four or five dummies were prepared and counted. The average count was taken as an index of the amount of Pu received by the subject. Counts were made both in Rochester and Los Alamos.

Sample Calculation of Dose, Subject HP-2

Counts were made with Simpson Counter #38021. Dummy prepared as outlined on page 12. Volume of Dummy-25 ml containing 0.5 ml of Solution C. All plates were counted for two periods of fifteen minutes each. At least two plates were made of each sample. Volume of dummy dried on each plate - 0.1 ml.

<u>Dummy No.</u>	<u>Volume Counted</u>	<u>Average Count Per Minute</u>
1	0.1 ml	1408
2	0.1 ml	1410
2	0.1 ml	1340
4	0.1 ml	1447
4	0.1 ml	1339
Total average count per minute		<u>1401</u>

Since each count represents two disintegrations, the total number of disintegrations per minute in the average dummy was:

$$1401 \times 250 \times 2 = 700,500 \text{ disintegrations}$$

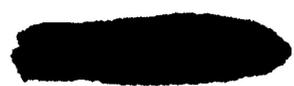
This was taken as the alpha activity of 0.5 ml of Solution C - the quantity injected.

The amount of Pu required to yield this activity may be calculated as follows:

$$16.1 \mu \text{ gm Pu} \rightleftharpoons 1 \text{ microcurie or } 2.21 \times 10^6 \text{ d.p.m.}$$

$$\text{then } \frac{7 \times 10^5 \text{ (activity of Pu injected)}}{2.21 \times 10^6} \times \frac{16.1}{1} = 5.1 \mu \text{ gm Pu}$$

5.1  $\mu$  gm of Pu were contained in the volume of Solution C injected.



III. Description of Subjects.

A. Introduction

The material in this section is a resume of the clinical history and recent status of the subjects. Where follow-up studies have been completed any pertinent change in the physical condition is mentioned and laboratory data of interest have been included. Death of the individual is indicated by the sign following the HP number. When known, the anatomical diagnosis is given. If no comment on change in physical status appears in the report, it may be assumed that there has been no material change in condition up to the time of preparation of manuscript.

Intravenous injection of 4.6  $\gamma$  of <sup>HP-1</sup>Fu +4 as citrate complex on Oct. 16, 1945

Case History

White male of 67 years with a nine year history of peptic ulcer. Entered hospital on September 20, 1945 following a hemorrhage so severe as to require transfusion. X-ray examination revealed a duodenal ulcer and traction diverticulum of the esophagus at the level of the tracheal bifurcation.

Examination

T=37 C; P = 72; R = 18; B.P. = 115/70 Ht. - Wt. 70.3 Kg.

Generally well preserved for his years. Some pallor of mucous membranes inconstant rales at the bases of lungs; moderate tenderness in the midepigastrium without spasm. No other findings of note. Studies were conducted during convalescence from October 2, 1945 to December 10, 1945.

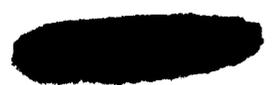
Laboratory Data

Before Injection

After Injection

- Urine - Negative except for trace of protein
- Stool - Positive guaiac reaction at first but later negative.
- Blood Wasserman Reaction - Negative

GLC



EE-1 (continued)

Before Injection

After Injection

Blood Counts - Oct. 4, 1945

Blood Counts - Oct. 19, 1945

Red Blood Cells -	4.47 x 10 <sup>6</sup> per cmm .....	4.55 x 10 <sup>6</sup> per cmm.
Hemoglobin	13.9 gm/100 cc .....	13.7 gm/100 cc
White Blood Cells	7,100 .....	7,000
Differential:		
Polymorphs	71 per cent .....	54 per cent
Small Lymphs	17 per cent .....	9 per cent
Inter. Lymphs	2 per cent .....	25 per cent
Monocytes	9 per cent .....	7 per cent
Eosinophiles	1 per cent .....	4 per cent
Basophiles	.....	1 per cent

Blood Non-protein Nitrogen 31 mg. %  
 Total plasma 6.2 gms. %

Urea Clearance - Oct. 10, 1945

Urea Clearance - Oct. 22, 1945

1st Hour Standard	52 cc/minute or 96% of Normal ...	48 cc/minute or 90% of Normal ...
2nd Hour Standard	54 cc/minute or 100% of Normal...	57 cc/minute or 105% of Normal...
Blood Urea Nitrogen	21 mg. % .....	23.5 mg. %

Clinical Diagnosis

- Ulcer, Duodenal
- Hemorrhage, gastrointestinal
- Anemia, secondary to hemorrhage
- Diverticulum of the esophagus

Intavenous injection of 5.1% of <sup>Fe-2</sup>Pu +4 as citrate complex on Oct. 23, 1945

Case History

White male of 49 years with a history of hemophilia. Entered hospital on October 5, 1945 for the 38th time for special blood studies, previous admissions having been for episodes of bleeding and complaints referable to hypertension which was first noted in 1929, but produced no marked symptoms until 1943.

Examination

T = 36.9 C; P = 96; R = 20; Ht. 161 cm.; Wt. 69 Kg.; B.P. 20/120. Well developed, well nourished male. Eyes show slight arteriolar narrowing. Heart is enlarged with an apical systolic murmur. There are scattered basilar rales.

HP-2 (continued)

bilaterally which clear on coughing. External hemorrhoidal tags are present. There is a deformity of the left hip, and joint changes are present in both arms and legs. Studies were conducted from October 10, 1945 to November 19, 1945 while on program for hemophilic studies and therapy. A follow-up period occurred January 5, 1946 to January 14, 1946 while bleeding from the intestinal tract.

Laboratory Data

Before Injection

After Injection

Oct. 5, 1945

Jan 5 - 14, 1946

Urine - Negative except for small amount of albumin.	For casts plus albumin in follow up period.
Stool - Negative during 1st period of study	Gross blood during follow-up.
Blood Wasserman Reaction - Negative	

Blood Counts - Oct. 6, 1945

Blood Counts - Nov. 7, 1945

Red Blood cells -	4.7 x 10 <sup>6</sup> per cmm.	4.08 x 10 <sup>6</sup> per cmm.
Hemoglobin -	15 grams/100 cc	14.5 grams/100 cc.
White Blood cells -	9,050	7,850
Differential		
Polymorphs -	57 per cent	68 per cent
Small Lymphs -	20 per cent	4 per cent
Inter. Lymphs -	8 per cent	18 per cent
Monocytes -	2 per cent	2 per cent
Eosinophiles -	8 per cent	8 per cent

Blood Non-protein Nitrogen 42 mg. %  
 Total Protein 6.1 grams %

Urea Clearance - Oct. 11, 1945

Urea Clearance - Oct 31, 1945

1st hour maximum	56 cc/minute or 71% of normal	24 cc/minute or 44% of normal
2nd hour standard	23 cc/minute or 43% of normal	28 cc/minute or 52% of normal
Blood Urea Nitrogen	25 mg. %	23 mg. %

Clinical Diagnoses

- Hemophilia
- Hypertension, essential
- Heart Disease, Hypertensive
- Coronary Inefficiency
- Arthritis, Chronic

This man has been hospitalized on several occasions since January 14, 1946 because of



HP-2 (continued)

Severe hemorrhages from the intestinal tract. In each case he has recovered  
ing multiple transfusions. He is in regular attendance at the out patient c  
and his condition otherwise remains essentially unchanged.

Intravenous injection of 4.9% of <sup>HP-1</sup> Pu +4 citrate complex on November 27, 1945

Case History

White woman of 49 years, complaining of acneform pruritic eru  
over thighs, buttocks, trunk, and face; pigmentation of the skin, puffiness  
the face and swelling of the ankles and feet. Diet has been of rather poor  
for a considerable period. No history of alcoholism.

Examination

T = 37.0; P = 80; R = 20; B.P. = 120/80; Ht. 157.5 cm.; Wt. 60  
Skin of dark tan color with some increased pigmentation in the creases of the  
palms; many small papulo-pustular lesions on the chest, abdomen, back, upper  
and thighs; liver edge at right costal margin; slight pretibial and pedal  
Initial studies were carried out between November 13, 1945 and December 18, 1945.  
Readmitted for follow-up studies on October 13, 1946 to October 18, 1946.

Laboratory Data

Before Injection

After Injection

Urine - No abnormalities noted  
Stool - Bile pigment present  
Blood Wasserman Reaction - Negative

Blood Counts - Nov. 2, 1945

Blood Counts - Oct.

Red Blood Cells	4.3 x 10 <sup>6</sup> per cmm	.....	5.6 x 10 <sup>6</sup> per cm	.....
Hemoglobin	14.5 gms/100 cc	.....	.....	.....
White Blood Cells	5,700	.....	6,800	.....
Differential				
Polymorphs	59 per cent	.....	69 per cent	.....
Lymphs	39 per cent	.....	25 per cent	.....
Eosinophils	2 per cent	.....	.....	.....
Monocytes	.....	.....	5 per cent	.....
Basophiles	.....	.....	1 per cent	.....

EP-3 (continued)

<u>Before Injection</u>		<u>After Injection</u>
Non-protein Nitrogen	34 mg. % .....	31 mg. %
Total Protein	4.8 gm. % .....	5.8 gm. %
Alb/Glob	3.4/1.4 .....	4.3/1.5
Icterus Index	18 .....	7
P. S. P.	15 min. 35 per cent .....	
	2 hrs. 70 per cent total .....	

Urea Clearance

1st Hour Standard	38 cc/minute or 70% of normal .....
2nd Hour Standard	35 cc/minute or 64% of normal .....

Geph. Flocc. - negative  
 Thymol Turbidity - 250  
 Alkaline Phosphatase -  
 Bodansky Units

Clinical Diagnoses

Hepatitis etiology (unknown)  
 Hypoproteinemias  
 Dermatitis (cause unknown)

When last examined in October 1946, she appeared to be in excellent health.

---

Intravenous injection of 4.9 g of Pu <sup>H<sub>2</sub>O</sup> as citrate complex on November 27, 1945

Case History

Eighteen year old white girl with a history of Cushing's Syndrome since 1941. Entered hospital on October 29, 1945 for the fifth time for further treatment of that condition. Chief complaints this time were headaches and back pain referable to her hypertension and osteoporosis. Studies were carried out between October 29, 1945 and December 20, 1945 with follow-up periods on February 11, 1946 to February 17, 1946 when she was given penicillin for a urinary tract infection, and March 13, 1947 to March 29, 1947 while under treatment for heart fail

HP-4 (continued)

Examination

T = 36.9 C; P = 100; R = 22; B.P. = 205/130; Ht. 145.5 cm.  
 Short heavy set female with florid complexion, buffalo type obesity, dry, thin skin with purple striae over trunk and back and multiple purpuric areas on extremities. Marked hirsutism over face, sparse pubic, axillary, and scalp. Ophthalmoscopic exam shows narrowed and tortuous vessels. Heart is enlarged. Tenderness over spine and in right lower quadrant of abdomen.

Laboratory Data

Before Injection - Oct. 29, 1945

Urine - Alb 0; 2-10 WBC and occasional granular cast  
 Stool - Guaiac negative

After Injection - Mar

Alb 3+  
 Hyalin and granular cr

Blood Wassermann Reaction - Negative

Blood Counts - Oct. 30, 1945

June 30, '46

Dec. 31, '46

Red Blood Cells -	5.3 million per cmm.	.....	.....
Hemoglobin	15 gms per 100 cc	.....	16 gm/100 ml
White Blood Cells	10,000	6,900	.....
Differential			
Polymorphs	77 per cent	74 per cent	.....
Lymphs	20 per cent	22 per cent	.....
Monocytes	2 per cent	4 per cent	.....
Eosinophiles	1 per cent	.....	.....

Hemat. 47% R.P.C.

Nov. 1, 1945

Serum Prot. 5.5%  
March 29, 1947

Blood Protein (plasma) 6.3 gm. %  
 Blood Non-protein Nitrogen 35 mg. %

.....  
64 mg. %

Urea Clearance - Nov. 1, 1945

March 26, 1947

Normal Val

1st Hour Max.	29 cc/minute or 38% of Normal	Renal blood flow	44.5/min	50%
2nd Hour Max.	39 cc/minute or 52% of Normal	Glomerular Filtr.	17.1	117%
		Maximum tubular capacity	2.88	77%

P. S. P. Test 60% in two hours



HP-4 (continued)

Clinical Diagnoses

- Cushing's Syndrome (Basophile adenoma of the pituitary gland)
- Hypertension
- Heart Disease, Hypertensive
- Osteoporosis
- Urinary Tract Infection S. albus
- Nephropathy, Hypertensive
- Uremia

The course was progressively downward during the one and a half years following administration of Pu. Heart failure and uremia characterized the terminal of her illness. Our final collections of urine were made during March 1947, at time the urine contained sufficient protein to give a 3+ reaction. Death in uremia on April 29, 1947.

Anatomical Diagnoses

- Basophilic adenoma of pituitary gland
- Hypertrophy of the left ventricle
- Atrophy of thyroid gland
- Hypertrophy of adrenal glands
- Hypoplasia of uterus and ovaries
- Osteoporosis of spine and pelvis
- Chronic Nephritis

No tissues were obtained for analysis for Pu since death occurred in another

HE-5 \*

Intravenous injection of 5.18 of Pu <sup>44</sup> as a citrate complex on Nov. 30, 1945

Case History

White male of 56 years with a three year history of increasing generalized weakness and difficulty in walking and swallowing. Entered hospital on November 19, 1945 for study

Examination

T = 35.6 C; P = 72; R = 32; B.P. = 126/92; Ht. 172.9 cm; Tall thin man with tremor of hands, slow speech, and obvious muscular fasciculation. Bilateral Babinski's with hyperactive deep tendon reflexes. No other findings of note. Studies were carried out on November 19, 1945 to December 22, 1945.

HP-5 ° (continued)

Laboratory Data

Before Injection

After Injection

Urine - No abnormalities found

Stool - Guaiac Negative

Blood Wasserman Reaction - Negative

Blood Counts

Red Blood Cells -  $4.6 \times 10^6$  per cmm.

Hemoglobin - 16.3 gm./100 cc.

White Blood Cells- 7,400

Urea Clearance - Nov. 29, 1945

1st hour standard 52 cc/minute or 96% of normal

2nd hour standard 37 cc/minute or 69% of normal

Blood Urea Nitrogen 14.6 mg. %

B. N. R. - 12%; -28%

Clinical Diagnoses

Atrophic Lateral Sclerosis

Death occurred on April 29, 1946

Anatomical Diagnoses

Atrophic lateral sclerosis  
Bronchopneumonia, bilateral  
Emaciation extreme  
Atrophy of viscera  
Arteriosclerosis, general  
Renal cysts  
Adenoma of right kidney  
Decubitus ulcers  
Thrombi of periprostatic vessels

HP-6

Intravenous injection of 5.3% of  $Pu^{+4}$  as citrate complex on Feb. 1, 1946

Case History

White male of 45 years with a history of Addison's Disease since January, 1945. Had pellets of desoxycorticosterone implanted on October 31, 1945.

HP-6 (continued)

Admitted to hospital again on December 14, 1945 because of multiple staphylococcus infections on eyelids and toes.

Examination

T = 36.7C; P = 60; R = 20; B.P. 122/78; Ht. 170 cm.; Wt. 49 Kg.

Well developed but thin male with deeply pigmented skin; generalized lymphadenopathy; both lids of left eye red and swollen with scaling; conjunctivae markedly injected; Right big toe nail ingrown on medial aspect with swelling, redness, and heat in surrounding area; purulent discharge in corner of nail bed. Other toes developed evidence of infection and all were treated with compresses and surgical excision of nails. While convalescing, studies were carried out from January 21, 1946 to February 23, 1946. Follow-up studies during June, 1947. Condition was unchanged.

Laboratory Data

Before Injection

After Injection

Urine - Negative except for 10 WBC per high powers field.  
Stool - Guaiac Negative  
Wasserman Reaction - Negative

Blood Counts

Red Blood Cells - 3.98 million/cmm.  
Hemoglobin - 13 gms. %  
White Blood Cells- 3,300  
Differential  
Polymorphs 38 per cent  
Lymphs 48 per cent  
Eosinophiles 11 per cent  
Monocytes 3 per cent

Urea clearance - January 29, 1946

1st hour Standard 56 cc/minute or 103% of Normal  
2nd hour Standard 51 cc/minute or 95% of Normal

Blood Urea Nitrogen 14.5 mg. %  
Blood Non-protein Nitrogen 27 mg. %

Clinical Diagnosis

Addison's Disease



Intravenous injection of 6.3 of Pu <sup>HP-1</sup> as citrate complex on Feb. 8, 1946

Case History

White female of 59 years with a history of Rheumatic heart disease for twenty years and an overactive thyroid since 1944. She had been treated in this hospital during April and November, 1945 and was readmitted on January 21, 1946 for further treatment because of heart failure.

Examination

T = 36.6 C; P = 76; R = 22; B.P. = 128/60; Ht. 163.3 cm.; Wt. 68 Kg.

Well developed, fairly well nourished woman who is dyspneic and coughs frequently; Neck vessels are distended with visible pulsations; marked pitting edema from feet to hips; Prominent nodule above sternal end of right clavicle; heart is markedly enlarged to left, rhythm is totally irregular with a systolic murmur audible over all of precordium. P2 is accentuated; Signs of fluid at right lung base; Liver is palpated 2-3 cm. below costal margin and is tender.

Laboratory Data

Before Injection

After Injection

Urine - Alb. 1 plus; no RBC or Casts  
Stool - Guaiac Negative  
Wasserman Reaction - Negative

Blood Counts - January 23, 1946

February 20, 1946

Red Blood Cells - 3.25 x 10 <sup>6</sup> per cmm	.....
Hemoglobin - 12.6 gm. %	.....
White Blood Cells 4,750	.....5,250.....
Differential	
Polymorphs 64 per cent	64 per cent
S. Lymphs 19 per cent	22 per cent
L. Lymphs 5 per cent	I.L. 3 per cent
Monocytes 6 per cent	9 per cent
Eosinophiles 3 per cent	.....
Regenerated 3 per cent	2 per cent

Blood Non-Protein Nitrogen 26 mg. %  
Total Plasma Protein 6.5 %  
R.H.F. plus 6% plus 7 %

WBC ranged from 3,400 -6,100 during hospital stay. Differential remained essentially as reported.



HP-7 \* (continued)

Brea Clearance - Feb. 6, 1946

1st Hour Standard 51 cc/minute or 94% of Normal  
2nd Hour Standard 52 cc/minute or 96% of Normal

Clinical Diagnoses

Rheumatic Heart Disease  
Toxic Nodular Goiter  
Myocardial Insufficiency  
Mitral Insufficiency  
Auricular Fibrillation

Death occurred on October 27, 1946 in another hospital. No post mortem could be obtained. Probable cause of death - Lobar Pneumonia.

---

Intravenous injection of 6.5% of <sup>HP-8</sup>Tu 44 as citrate complex on March 9, 1946

Case History

White female of 41 years with a history of scleroderma since January 1945. In addition she has suffered from peptic ulcer, proven by X-ray to be in the duodenum, at intervals since May 1944. Entered this hospital for treatment on February 19, 1946. Studies were carried out from February 19, 1946 to May 13, 1946.

Examination

T = 36.5 C; P = 82; R = 20; B.P. = 128/76; Ht. 163.5 cm.; Wt. 48 kg.  
Thin and pale female with important findings limited to the skin; On the face is a loss of the nasolabial folds, eyelids are tight and the skin is drawn across the mouth. Over the sternal and clavicular regions, it is thick and pigmented particularly about the sites of the bilateral scalenotomies. Skin over hands and fingers is thick and tightly stretched so that approximation of fingers to thumb is impossible, and there is blanching over bony prominences. Similar condition but to lesser extent exists over lower extremities.

SECRET

1175098

H7-8 (continued)

Laboratory Data

Before Injection

After Injection

Urine - Negative except for a rare hyaline cast

Stool - Guaiac Negative

Blood Wasserman Reaction - Negative

Blood Counts - Feb. 22, 1946

Blood Counts - Aug. 21,

Red Blood Cells	- 4.7 x 10 <sup>6</sup> cmm. (per) .....	4.05 million per cmm
Hemoglobin	- 13.9 gms. % .....	14.5 gms. %
White Blood Cells	- 9,500 .....	11,900
<u>Differential</u>		
Polymorphs	- 71 per cent .....	88 per cent
S. Lymphs	- 8 per cent .....	.....
L. Lymphs	- 14 per cent .....	12 per cent
Eosinophiles	- 1 per cent .....	.....
Monocytes	- 6 per cent .....	.....

Total Plasma Proteins	6.3 gms. %
Blood Non-protein Nitrogen	30.0 mg. %
Blood Urea Nitrogen	10.0 mg. %
Calcium	10.0 mg. %
Phosphorus	3.0 mg. %

Urea Clearance - Feb. 22, 1946

1st Hour Standard	41 cc/minute or 76% of Normal
2nd Hour Standard	51 cc/minute or 94% of Normal

Clinical Diagnoses

- Scleroderma
- Ulcer, duodenal, chronic

Intravenous injection of 6.3  $\gamma$  Pu <sup>H<sub>2</sub>O</sup> +4 as citrate complex on April 3, 1946

Case History

White male of 66 years with history of generalized dermatitis and increasing muscle weakness since fall of 1945. All attempts at therapy produced no permanent benefit.



HP-9 (continued)

Examination

T = 36.4 C; P = 84; R = 20; B.P. = 128/76; Ht. 169 cm.; Wt. 63 Kg.

Man appears chronically ill, skin is dry and loose with many rough, reddened papular areas on trunk, neck and extremities, face is red, and eyelids and ears are red and edematous. Extremities show diminished muscle power with some degree of atrophy. Initial studies carried out March 11, 1946 to May 9, 1946. Follow-up on May 1, 1947 to May 27, 1947.

Laboratory Data

Before Injection

After Injection

Urine - No abnormalities found

Stool - Guaiac Negative

Wasserman Reaction - Negative

Blood Counts - March 13, 1946

Blood Counts - January 25, 1947

Red Blood Cells	- 3.9 x 10 <sup>6</sup> per cmm.	4.1 x 10 <sup>6</sup> cmm.
Hemoglobin	- 12.3 gms. %	12.2 gm/100 ml
White Blood Cells	- 6,250	7,300 cmm.
Differential		
Polymorphs	- 70 per cent	61 per cent
S. Lymphs	- 12 per cent	( 9 per cent )
L. Lymphs	- 5 per cent	( total )
Monocytes	- 13 per cent	17 per cent
Eosinophiles	0	12 per cent
Basophiles	0	1 per cent
		Platelets in smear abundant

Urea Clearance - March 16, 1946

1st Hour Max 54 cc/minute or 72% of Normal  
2nd Hour Standard 20 cc/minute or 37% of Normal

(Patient had difficulty in voiding for last specimen)

Clinical Diagnoses

Dermatomyositis

Death on July 2, 1947 from aspiration pneumonia

Anatomical Diagnoses

Generalized muscular atrophy  
Dermatitis

1005100

SECRET





HP-10 (continued)

Blood Counts - July 9, 1946

Blood Counts - Aug. 13,

Red Blood Cells	- 5.49 million per cmm.	.....	.....
Hemoglobin	- 13.3 gms. per 100 cc	.....	.....
White Blood Cells	- 5,650	.....	.....
<b>Differential</b>			
Polymorphs	31 per cent	.....	42 per cent
S. Lymphs	46 per cent	.....	23 per cent
L. Lymphs	6 per cent	.....	17 per cent
Eosinophiles	5 per cent	.....	3 per cent
Basophiles	2 per cent	.....	2 per cent
Monocytes	7 per cent	.....	8 per cent
Degenerated	3 per cent	.....	.....

Urea Clearance - July 9, 1946

Urea Clearance - Aug. 1,

1st Hour Max.	67.4 cc/minute or 90% of Normal	.....	1st Hour Standard
			40 cc/min or
2nd Hour Max.	62.4 cc/minute or 84% of Normal	.....	66.9 cc/minute or

Non-protein Nitrogen 22 mg. %

Urea N. 11 mg. %

Clinical Diagnoses

- Heart Disease, probably rheumatic
- Syphilis, latent, treated
- Sinusitis, ethmoid and frontal
- Dental caries
- luetic

HP-11 •

Intravenous injection of 6.5% of Pu +4 as citrate complex on Feb. 20, 1946

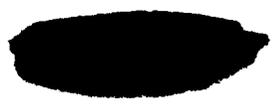
Case History

White male of 63 years with a history of alcoholism along with inadequate diet dating back many years and possible cardiac disease for several months. Entered the hospital December 12, 1945 because of persistent difficulty in breathing and increase in the size of his abdomen.

Examination

T = 36.5 C; P = 90; R = 20; B.P. = 130/80; Ht. 171 cm.; Wt 73

Poorly nourished, weak, thin male who is slightly confused; some generalized



HP-11 • (Continued)

lymphadenopathy; few basilar rales bilaterally; liver down 7-9 fingerbreadths below costal margin, tender, knobby, with blunt edge; no other findings of note

Laboratory Data

Before Injection

After Injection

Urine - Dark in color with no abnormal findings

Stool - Guaiac negative on admission

Blood Counts

Red Blood Cells - 4.62 million per cmm.  
 Hemoglobin - 14.8 gms. per 100 cc.  
 White Blood Cells- 9,400  
 Differential  
   Polymorphs           75 per cent  
   Lymphs               20 per cent  
   Monocytes            4 per cent  
   Basophiles           1 per cent

Blood Non-protein Nitrogen   49 mg. %  
 Total Plasma Protein        6.7 gm. %  
 Alb/Glob                    3.2/3.5  
   II                         4  
 BSP dye retained            72 per cent

Death on February 26, 1946 at 4:50 A. M.

Anatomical Diagnoses  
(Autopsy done 5 hours after death)

Cirrhosis of the liver  
 Ascites  
 Thrombosis of Portal Vein

IV. Results

E. Clinical Results

Acute toxic effects from the small dose of Pu administered were neither expected nor observed. Because of specific localization of the metal in the liver and skeleton, these are the tissues most likely to be affected. There was no evidence that anemia developed or that the white blood cell count was altered. With regard to ultimate effects, it is too early to predict what may occur.

~~SECRET~~



Clinical evidence suggestive of liver damage has not appeared. The specific tests of liver function have not as a rule been listed in the protocol. The possibility that injury to this organ might appear has been considered. The margin of safety in the liver is so large that so-called liver function tests usually do not give positive results until there is actual evidence of hepatic decompensation. Symptoms and signs are often as reliable as other methods of assessment. Two of our subjects undoubtedly had liver damage prior to injection (HP-3 and HP-7). HP-3, a woman, was recovering from a low grade hepatitis, was injected and continued to make satisfactory recovery afterward. Subject HP-7, also a woman, died without an autopsy but from the clinical history, there is but little doubt that she suffered from chronic passive congestion of the liver and probably had cardiac cirrhosis. She remained under close observation until shortly before death and no signs suggestive of a deterioration in her hepatic status were noted.

Admittedly this is no proof that plutonium in the amount given failed to inflict further damage on already diseased livers, but there was certainly no acute or severe insult to that organ. In summary, it may be stated that within a period of two years, the intravenous injection of a single dose of 5 to 6 grams of Pu +4 complexed with citrate was without subjective or objective clinical effects.



REFERENCES

1. Cantril, S. E. and Parker, E. M.  
The Tolerance Dose  
Health Division Reports # CH-2512
2. Cantril, Simeon E.  
Biological Bases for Maximum Permissible Exposures  
Health Division Reports #CH-3571, August 9, 1946
3. Project Handbook  
CH - 697, Chapter 3
4. Langham, Wright  
Report of Conference on Plutonium  
#CH - 3176, Page 27 et seq., May 14-15, 1945
5. Russell, R. R. and Hickson, J. J.  
Distribution and Excretion of Plutonium  
Chapter VII, Vol. 20A - PPR
6. Hale, William F.  
Isotopes - Dosage Measurements and Calculations for  
Therapeutic Purposes  
Radiology and Biophysics Seminars,  
University of Rochester, January 15, 1947
7. Finkle, Raymond D., Jacobson, Leon O., Kistalicki, Walter,  
Lawrence, Elsie, Simmons, Eric L., and Snyder, Robert H.  
The Toxicity and Metabolism of Plutonium in Laboratory  
Animals  
CH - 3763
8. Shohl, Alfred E.  
Mineral Metabolism  
American Chemical Monograph Series #62  
Reinhold Pub. Corp., 1939
9. Axelrod, Dorothy, Cogg, B. R., and Hamilton, J. G.  
The Deposition of Plutonium and Actin Lanthan Products in  
Bone as a Decontamination Problem  
#CH - 3591, Chapter VII
10. Frenser, C., Ladd, Painter, E. E., Lisco, Corran, Bruce, Austin M.,  
Jacobson, Leon O. and Swift, M. H.  
The Clinical Sequences of Physiological Effects of Ionizing  
Radiation in Animals.  
#CH - 3752, Argonne National Laboratory

SECRET

EXCRETION OF PLUTONIUM ADMINISTERED INTRAVENOUSLY TO MAN. RATE OF EXCRETION AND FECES WITH TWO OBSERVATIONS OF DISTRIBUTION IN TISSUES.

I. Introduction

II. Methods

A. Clinical

1. Selection of patients

2. <sup>Management</sup> ~~Handling~~ of patients

a. Control period

b. Observation period

c. Routine tests

(1) Blood tests

(2) Urine and kidney function tests, etc.

d. Collection and preservation of samples (blood feces and urine)

3. Method of Administration of Plutonium

a. Preparation and nature of solutions

b. Choice of size of dose

c. Technique of Injection

(1) Discussion of actual injection procedure

(2) "Dummy" injection for evaluating amount of plutonium given

B. <sup>Chemical</sup> Clinical Methods

1. Blood analysis

2. Feces analysis

3. Urine analysis

4. Tissue analysis

III. Description of Subjects (case reports). Short paragraph about each of 12 subjects giving

A. History

B. Physical

C. Laboratory

D. Diagnosis (if known)

SECRET



SECRET

~~SECRET~~

IV. Results

- A. Concentration of Plutonium in blood following intravenous administration as  $\text{Pu}^{+4}$  Citrate.
- B. Excretion of Plutonium in the urine following intravenous administration as  $\text{Pu}^{+4}$  Citrate.
- C. Excretion of Plutonium in feces following intravenous administration as  $\text{Pu}^{+4}$  Citrate.
- D. Deposition of Plutonium in tissues following intravenous administration as  $\text{Pu}^{+4}$  Citrate.
- E. Clinical Results

V. Discussion and Conclusions

- A. Correlation between blood concentration and urinary and fecal excretion of Plutonium.
  - 1. Possible significance of one abnormal case.
- B. Half-time of Plutonium in the body.
- C. Choice of urinary excretion value for diagnosing Plutonium exposure by urine assay.
- D. Discussion of results in relation to tolerance amount of Plutonium in the body.
- E. Discussion of results in relation to Chicago and California experiments of man.
- F. Discussion of results in relation to experiments on mice, rats and dogs.

VI. Summary or Abstract

1105107

~~SECRET~~