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Chapter VII, Volume 20 A, PPR

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Acknowledgement

It has been difficult to give credit to specific individuals for their contributions which are included in this chapter. Some of the work was done at other sites and privately communicated to us.

Specifically, we are indebted to Dr. Wright Langham and associates for information concerning the cupferron-chloroform procedure, to Dr. K. G. Scott and his associates for the information on the hexone and T.T.A. extraction procedures and to Dr. M. D. Taylor, Mr. E. E. Motta, Mr. D. Revinson, Mr. Harold Delaney, Miss J. A. Jackson, Miss Cordelia Brown, and Miss Wilana Monroe, all of our group, for testing and working out most of the procedures.

J. J. Nickson, M.D.
E. R. Russell

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1. Introduction

Following the discovery of plutonium, the determination of its half life as 24,300 years, and the fact that the material is alpha active, it became obvious that elaborate precautions were necessary if the worker was to be protected from harm. Experience in the radium industry had indicated clearly that very small amounts of the radium element deposited in the body were capable of producing serious illness or death. As a result of these considerations, the conditions under which plutonium is handled in the laboratory have been ringed about with elaborate protective regulations and devices.

In addition, however, it seemed highly desirable, if not essential, to know as precisely as possible the amount of plutonium in the individual worker. Animal experimentation indicated that the plutonium content of the urine and feces would be a useful guide to the total amount of plutonium in the body. It was decided to use urine for the routine determination(3) primarily because of the greater ease in handling urine samples. As will be discussed below, it appears that in humans the amount of plutonium excreted per day is greater in the urine than in the feces.

Initially, a tentative maximum permissible body content of plutonium was established on an arbitrary basis. From purely physical considerations it seemed that plutonium,

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weight for weight, should be approximately one-fiftieth as toxic as radium. Since the tolerance amount of radium is generally accepted as 0.1 microgram in the body, the plutonium tolerance value was initially set at 5.0 micrograms in the body.

In order that one might estimate the plutonium content of the body through analysis of the urine, it was necessary first to establish the excretion rate. Preliminary experiments(1) with rabbits indicated that after the first two or three weeks of plutonium intake, approximately 0.01% of that retained in the body is excreted in a 24-hour urine specimen. Many excretion experiments with other animals and man have shown that this is nearly the correct value for the sub-acute excretion rate. Recent work discussed elsewhere indicates that this figure may be greater than the true excretion rate of plutonium which has been in the body for a year or more. It is possible that the figure of 0.01% may have to be reduced in the future.

If 5 micrograms is to be the body threshold, and 0.01% excretion is assumed, then analytical procedures capable of detecting 28 alpha counts per minute (plutonium) in a 24-hour urine specimen, or 2 counts per minute in a 100 ml specimen should be adequate. An adsorption procedure, described later, was designed specifically to assay 100 ml specimens. Any specimen showing less than 2 alpha counts per minute was not considered significant. This procedure

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served its purpose well. However, when it became apparent that the factor of fifty between radium and plutonium toxicity was too high, it was evident the method was not sufficiently sensitive. Comparative toxicity studies with these two elements showed that a factor of ten would be much safer and therefore the plutonium tolerance threshold was lowered to one microgram.

If the tolerance threshold is 1.0 microgram, the analytical procedure should detect at least 0.2 micrograms in the body, therefore 0.2×10^{-4} microgram in a 24-hour urine specimen would be significant. Since the average urine specimen used in Chicago is approximately 1/3 of a 24-hour sample, the method must then be sufficient to detect 0.7×10^{-5} microgram or 0.4 alpha counts per minute of plutonium. Smaller samples present an even more difficult problem.

The problem of detecting such small quantities of plutonium was mainly one to be solved by the development of adequate counters. Dr. Jesse and associates have produced counters with backgrounds of less than 0.1 count per minute. With such counters 0.2 counts per minute can be detected with fair accuracy. Counting times are long, of course.

It should be pointed out that contamination is one of the greatest sources of error in the determination of low alpha activity. This will be borne out very clearly in the results of the survey of project personnel. It is necessary that collection, handling and assaying of the urine be carried out under "sterile" conditions.

It is the purpose of this chapter to present a detailed description of the methods used in the detection of plutonium in humans and to briefly discuss the results. In closing, suggestions are given for the establishment and operation of a laboratory for the detection of plutonium in individuals working with or in areas contaminated by the element.

2. Estimation of Plutonium in the Body

2.1 Methods of Urine Analysis: A survey of the analytical methods for plutonium used by the chemistry division revealed that with certain modifications some of these might be used to assay urine. A direct lanthanum fluoride precipitation from a small volume of acidified urine is adequate for many purposes. Where the volume is large and the concentration of plutonium is exceedingly small, such a method is not applicable as too large a quantity of lanthanum is required. In addition, certain salts in the urine may cause difficulty.

In the development of analytical methods applicable to urine analysis the time element as well as manpower requirements to assay a given number of samples were considered. It was felt that an adsorption procedure would offer the greatest possibility of routinely assaying daily the largest number of specimens with a minimum of personnel. As was

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mentioned in the introduction the method developed was applicable only to 100 ml of urine. When larger volumes were used, difficulties were encountered.

The following section is devoted to brief description of some of the methods which have been tested. A detailed outline of the method finally adopted is given.

The adsorption procedure. In the development of a process for the extraction of plutonium from uranyl nitrate solutions, G. E. Boyd(2) and associates found that the Amberlite Resin IR-1 showed a strong tendency to adsorb plutonium. That this same resin could be used to concentrate the plutonium also was shown. It was thought that a similar procedure could be adapted to the removal of plutonium from urine. The procedure consisted essentially of diluting a 100 ml urine specimen with 50 ml of 0.3 M hydrochloric acid and percolating this solution through a glass column containing 2.5 grams of the IR-1 resin. Over 95% of the plutonium contained in the urine is adsorbed along with some of the inorganic cations and organic material. The adsorbed plutonium is washed free of the other adsorbed materials by percolating 150 ml of a 0.5 M hydrochloric acid solution through the column. Complete desorption of the plutonium is obtained with a 6 M hydrochloric acid elutriant. A 5 ml holdup is discarded and a 50 ml fraction is collected which contains about 85% of the adsorbed plutonium. This solution may be evaporated to 1 ml and transferred to a platinum plate for counting. Repeated use of the adsorbent causes accumulation of some organic material which decreases the adsorption of plutonium. In the development of an adsorption procedure for assaying large volumes of urine (1000 ml) Schubert(3) has shown that an alcohol wash between cycles will eliminate this decrease in adsorptive capacity.

There were 1048 individual specimens analyzed by this or a modification of this adsorption procedure. 85% of all the experimental tests showed better than 80% recovery of the plutonium. The method as applied to the routine survey of personnel was valuable only in detecting the presence of approximately 5 micrograms in the body.

Solvent extraction procedures. The solvent extraction procedures are mentioned here mainly because they are being used by other sites for the routine determination of plutonium in urine. W. Langham(4) at Los Alamos, has applied the cupferron-chloroform extraction procedure developed by G. Cowan(5) for assaying uranyl nitrate solutions for plutonium. K. G. Scott(6) at Berkeley has developed an extraction procedure making use of a benzene solution of thiophenyltrifluoracetone (T.T.A.) In our tests on these procedures, the recovery of plutonium has been above 80%. In blank tests we have always found some alpha activity which seems to be due to lanthanum impurities.

The cupferron-chloroform method.(4) The organic constituents of urine prohibit the direct extraction of plutonium into an immiscible solvent. Preliminary to the extraction it is necessary to either ash the urine or carry out a preliminary precipitation. It was found advisable to use a combination of both. After ashing, the residue is dissolved in dilute hydrochloric acid. Calcium phosphate is precipitated by neutralization of the solution with concentrated ammonium hydroxide. The precipitate which contains the plutonium is dissolved in 2 M hydrochloric acid, 1 mg of Fe^{+3} in 0.2 M hydrochloric acid is added and the solution neutralized to a pH slightly below that required to precipitate the iron. The plutonium is complexed by adding 1.5 ml of a 6% aqueous solution of cupferron. The plutonium is then extracted with 2 ml portions of chloroform until the last portion is colorless. The solvent is removed by evaporation, the organic matter destroyed with nitric and perchloric acids and a lanthanum fluoride precipitation carried out on a solution of the residue. This procedure may well have been altered recently. However, the essential features are the same.

The T.T.A. Procedure(6). This method is unique in that the final deposit on the platinum plate contains no visible solids which would reduce the alpha count by absorption. The procedure(12) as adopted for use at Hanford is given in detail here.

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"1. Place the sample in a two liter Erlenmayer (or beaker,) and evaporate to dryness in an oven at 160-200°C.

2. Take up the residue in 100 ml of 8 N nitric acid.

3. Heat this mixture in the oven for 30-60 minutes until the residue on the sides of the beaker is washed down.

4. Transfer the acid mixture to a small (100-250 ml) beaker. The size of this beaker depends upon the size of the muffle furnace available for step 6.

5. Evaporate the acid to dryness in the oven.

6. Place the beaker in a muffle furnace at 575°C. until the residue becomes white or only slightly gray. A considerable amount of urea may be present at this state.

7. Dissolve the residue in 100 ml of a solution 2 N in nitric acid and 0.1 N in hydroxylamine hydrochloride.

8. Transfer the solution to two 100 ml centrifuge tubes (50 ml of solution to each.)

9. Add two ml of lanthanum nitrate solution (20 mg La^{+++}/ml) to each centrifuge tube and stir

10. Add 10 ml of 12 N hydrofluoric acid to each tube and stir.

11. Allow tubes to stand for five minutes.

12. Centrifuge at 2000 RPM for five minutes.

13. Decant supernatant liquid.

14. Break up cakes in the bottom of the centrifuge tubes and wash well with 10-20 ml of 1.5 N hydrofluoric acid.

15. Centrifuge at 2000 RPM for five minutes.

16. Decant wash liquor.

17. Dissolve the precipitates in a total of 50 ml of aluminum nitrate solution, meanwhile transferring all of the solution to one tube. Aluminum nitrate solution contains 3 pounds of hydrated aluminum nitrate dissolved in 195 ml of 2 N nitric acid and then diluted to a total of 1940 ml of solution.

18. Add 0.25 ml of sodium nitrite solution. (12 grams of sodium nitrite in 100 cc of water.)

19. Allow solution to stand for 15 minutes
20. Pour solution into a 100 ml separatory funnel.
21. Add 10 ml of T.T.A. solution. (5 grams of T.T.A. in 100 ml of benzene)
22. Shake for 10 minutes
23. Allow benzene to separate from the water layer.
24. Separate the water layer and discard.
25. Wash benzene layer twice with 10-20 ml of distilled water.
26. Add 10 ml of 8 N nitric acid.
27. Shake for 10 minutes
28. Evaporate nitric acid layer on 1-1½ inch diameter platinum or stainless steel plate.
29. Wash T.T.A. and funnel with 2-3 cc of distilled water.
30. Evaporate wash water on sample plate as in step 28.
31. Count the plate for alpha particles."

"<u>Experimental tests.</u> A number of samples spiked with 20 d/m of Pu have been carried from step 8 to determine the yield of the extraction process. These samples have given approximately 90% yield with fair consistency after the operator has had a little experience in handling the samples. Blanks (no Plutonium present) have given less than 0.2 c/m, even though the lanthanum used was contaminated with some alpha emitting material to the extent of 30 d/m per 40 mg of La^{+++}."

A few tests at Chicago have shown a minimum recovery of 80% with slight alpha contamination. The source of this contamination is not known.

<u>Precipitation methods of Analysis.</u> There are many cations which when precipitated in the presence of plutonium will act as a suitable carrier. The assumption is made that the cation

is precipitated with an anion which forms an insoluble compound with plutonium. Most of these carriers are not suitable for plutonium analysis simply because of the amount required for quantitative carrying. Lanthanum, which forms an insoluble fluoride is by far the most useful analytical carrier of plutonium. Because other ions which also form insoluble fluorides are also present in urine, a direct lanthanum fluoride precipitation is not satisfactory for analytical purposes. Often double precipitations are resorted to. For example, plutonium is precipitated with zirconium phosphate which separates it from the bulk of the salts. The plutonium is then separated from the zirconium by a lanthanum fluoride precipitation. The principle is a useful one, and forms the basis for the final procedure adopted.

The bismuth phosphate-lanthanum fluoride procedure. Plutonium may be extracted from the urine in either of two ways using a bismuth phosphate precipitation. The use of unashed urine was found to be quite time-consuming and required considerable equipment and manpower. As was pointed out by K. S. Scott, ashing the urine prior to analysis would make for much more reliable results.

The urine specimen commonly 1000 ml, though not limited to this volume, is acidfied with 100 ml of concentrated nitric acid which was previously used for washing out the collecting vessel. This washing is essential since it has been shown

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that adsorption of plutonium by glass from a natural urine solution is quite high. The specimen is then evaporated to near dryness on a medium temperature hot plate. The organic matter is destroyed with successive nitric acid treatments accompanied by heat. When the ashing is complete, as evidenced by the white residue, the sample is dried at a low temperature for about an hour.

The residue is now acidified with 2 ml of concentrated nitric acid and allowed to stand at room temperature to insure saturation. It is then dissolved in 35 ml of water and transferred to a 50 ml tapered centrifuge tube. Any insoluble residue is centrifuged out and the supernate transferred to a 90 ml pyrex centrifuge tube. The ashing container is washed out with 1 ml of nitric acid and 2 ml of water. This solution is transferred to the 50 ml centrifuge tube, thoroughly mixed with any residue present, centrifuged, and the supernate added to the solution in the 90 ml centrifuge tube. The solution in the 90 ml tube is then diluted to 80 ml. To this is added 2 ml of a saturated SO_2 solution. The solution is allowed to stand at least 20 minutes for reduction of the plutonium.

The tube is suspended in a water bath at approximately 75°C. and stirred mechanically during the addition of 0.1 gram of bismuth from a stock solution containing 0.1 gram Bi^{+3} per ml of 10 M nitric acid. With continuous stirring, 1 ml of concentrated phosphoric acid is added over a period of approximately 5 minutes. The solution is allowed to digest for one hour at the elevated temperature. At the end of this period the precipitate is allowed to settle and the bulk of the supernate is removed. The residue is then washed with water into a 15 ml pyrex centrifuge tube and centrifuged, the supernate being discarded. The 90 ml tube is washed with two 2 ml portions of 1-1 hydrochloric acid. The washings are added to the 15 ml tube to dissolve the bismuth phosphate precipitate.

The hydrochloric acid solution is now diluted to 5 ml with water. 0.25 mg of lanthanum is added (stock solution 0.5 mg La^{+3} per ml in 0.1 M nitric acid.) The lanthanum is precipitated by stirring in 0.5 ml of 1-1 hydrofluoric acid. Stirring is continued for a short period. It is advisable to use platinum stirring rods as pyrex and bakelite rods increase the residue on the counting plates. After centrifugation at 2000 RPM for 5 minutes, the supernate is discarded. The lanthanum fluoride precipitate is slurried with a few drops of 5 M nitric acid and transferred to a platinum plate about two inches in diameter which is heated on a low temperature hot plate. Care must be taken to avoid spattering of the material. The centrifuge tube is washed several times with small portions of acid and the washings transferred to the platinum plate and evaporated. About 1 mg of solid is present and is spread evenly over the plate to minimize absorption of the alpha particles. Then the precipitate is

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dried, the plate flamed and counted.

This precipitation procedure was adopted as the method to be used to routinely analyze urine for plutonium for several reasons; (a) experimental tests by various technicians showed that over 90% of the plutonium added to a 1000 ml urine specimen could be recovered and that the reproducibility in this range was over 98%, (b) that large volumes of urine could be easily analyzed, (c) that the method would lend itself to routine operations, and (d) that the method does not depend on certain constituents of urine for its proper functioning.

Since the concentration of plutonium is extremely low (of the order 10^{-11} grams) it is necessary that long counting periods be used to obtain results that are significant. Most samples are counted for a minimum of three hours with a two-hour background count on a platinum plate. Control samples are usually counted for three hours prior to each sample count. Where appreciable activity is found in a sample, the plate is counted on several counters to eliminate the uncertainty of improper functioning of a single counter.

2.2 <u>Methods of Fecal Analysis</u>: There are to our knowledge no satisfactory analytical procedures by which inorganic cations are removed from untreated feces. The quantitative methods for the detection of plutonium in feces would involve some preliminary treatment of the material. Since the organic constituents will vary with the diet it would appear that many uncertainties would be present in a procedure where a solution of the natural specimen is assayed. Though a few specimens of this nature have been analysed with better than 80% recovery of the plutonium, many undesirable features were encountered which need not be enumerated. The problem of fecal analysis then resolves itself into devising suitable means for removing the organic matter from the sample. This is probably best accomplished by ashing.

Wet ashing. Wet ashing of feces can be accomplished by digesting the sample at elevated temperatures with oxidizing acids such sulfuric, perchloric, and nitric. For the purpose of plutonium analysis, nitric acid seems the most desirable. However, with this acid it is difficult to completely destroy all of the organic matter. Tests for plutonium recovery from nitric acid ashed feces have been erratic, probably due to incomplete ashing. The use of auxilliary oxidants, such as superoxol, have made for better recovery. Wet ashing under these conditions is quite time-consuming.

Dry ashing. Dry ashing consists of destroying the organic matter by heating the sample at high temperatures. Considerable losses of plutonium have been experienced in this procedure due to penetration of the plutonium into the walls of the ashing vessel. When preliminary drying is employed and the sample is separated from the walls of the ashing vessel with filter paper, such losses are avoided. Another difficulty is encountered due to a large insoluble

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residue which at times contains considerable plutonium.

The most satisfactory method which was found combines the two general procedures. It is emphasized that the method is not completely satisfactory at the present time.

Method for ashing feces for plutonium analysis. The fecal specimen contained in a Sealrite carton is dried at 110°C. for 24 hours or until the sample is brittle. The specimen is then transferred to a porcelain crucible which is lined with filter paper and ignited at 550-600°C. for 24 hours. After cooling, the ash is treated twice with fuming nitric acid and evaporated to dryness. The residue is dissolved in a minimal amount of hot 6 M nitric acid, heated for a short while and centrifuged. The remaining residue is washed with more hot 6 M nitric acid and centrifuged. The supernates are combined and diluted to 1.1 - 1.2 M in nitric acid.

The plutonium is now reduced by adding 2 ml of a saturated solution of SO_2 and allowing to stand at least 20 minutes. The bismuth phosphate precipitation which follows is identical to that described for urine analysis. In the experimental tests that have been carried out the recovery of plutonium has been about 80%. This compares favorably with recoveries obtained by the T.T.A. and cupferron procedures.

It was felt that the personnel involved in a routine

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may be of value in specific cases, however. This is particularly true if the question of ingestion can be eliminated. Under such conditions the amount in the feces represents either material excreted by the bowel or coughed up from the lungs. It may well be possible to gain an idea of the amount of plutonium in the lungs by study of the amount in the stools, under ideal conditions.

2.3 Methods for the Analysis of Tissues: The sudden demand for determining the concentration of plutonium in a large number of animal tissues made it necessary that a method of analysis be adopted with the minimum amount of experimental background. It was fortunate that the concentration of plutonium in these tissues, mostly from rats and mice, was sufficiently high that direct counts could be made and compared with the precipitation or extraction procedure adopted. The solution of the ashed tissue contained only small amounts of inorganic salts and little difficulty was encountered in making a direct lanthanum fluoride precipitation; the method gave 85% recovery. When lower concentrations of plutonium in large specimens were subsequently encountered it was obvious that such a method could not be used.

R. Abram(7) modified the zirconium phosphate-lanthanum fluoride procedure developed by G. E. Boyd(8) and associates, to assay small samples, mostly from rats and mice. This method was shown to give an average of 85% recovery, though various technicians have reported much higher and lower results.

This procedure has been used to assay human tissues, however, parallel tests were made with rabbit tissues containing an equivalent amount of ash per ml which showed only 60% recovery of the plutonium. In another case involving human tissues,(9) a direct lanthanum fluoride precipitation was used. This was possible since only soft tissues were assayed and the calcium content of the ash was small. It is obvious that neither of these procedures is a suitable method for assaying large amounts of tissue containing extremely small amounts of plutonium.

One of the main difficulties which was encountered in the development of a procedure for assaying tissues was obtaining complete solution of the ashed residue. In the case of liver samples the residue remaining after ashing contained as much as 30% of the plutonium. It was found that the amount of residue is reduced considerably if the specimen is not heated to dryness after a peroxide treatment. Superoxol is generally used in the ashing of tissues.

M. D. Taylor(10) spent considerable effort in devising means of ashing tissues which would give either a residue completely soluble in dilute nitric acid or leave a residue which did not contain any of the plutonium. One method using ammonium nitrate was quite satisfactory from the standpoint of solution of the ash but was rather hazardous. The method finally adopted made use of fuming nitric acid.

The tissue specimen is completely dried at 110°C for 24 to 48 hours and is transferred to a kjeldahl flask and heated

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alternately with small portions of fuming nitric acid and superoxol until a completely white residue is obtained. It is essential to avoid vigorous heating of the residue as etching of the vessel will occur. The sample is then difficult to remove. When ashing is complete the residue is dried over a very low flame for a short while and then allowed to cool. The residue is warmed with 3 ml of concentrated nitric acid, diluted to 25 ml and transferred to a 50 ml centrifuge tube. The sides of the kjeldahl flask are washed down with 3 ml of concentrated nitric acid. This is washed into the 50 ml centrifuge tube with 17 ml of water. If any residue is present, it is centrifuged out and the supernate transferred to a 90 ml centrifuge tube and diluted to 80 ml. The plutonium is reduced by allowing to stand 20 minutes after the addition of 2 ml of saturated SO_2 water. The bismuth phosphate-lanthanum fluoride procedure described above is followed. This procedure is applicable to a 75 gram bone specimen or to approximately a 400 gram soft tissue specimen. When larger samples are to be assayed, proportional increase in the reagents required to dissolve the ash is necessary. Equivalent amounts of bismuth are required but the final amount of lanthanum used need not exceed 0.5 mg.

Experiments have shown that better than 90% of the plutonium can be coprecipitated with 0.5 mg lanthanum as the fluoride from a 5 M hydrochloric acid solution containing 1 gram of bismuth in 15 ml of solution. Washing of the lanthanum fluoride precipitate with a hydrochloric-hydrofluoric acid mixture is necessary to eliminate the bismuth from the precipitate only where the maximum amount of bismuth is used. This method has been applied to human tissues to which known amounts of plutonium were added and the recovery has been above 88% in all cases.

3. Results of the Routine Urine Surveys

3.1 Chicago: The results which were obtained on the personnel of the Metallurgical Laboratory may be divided into two groups: (1) results obtained with IR-1 adsorption procedure, and (2) results obtained by employing the bismuth phosphate-lanthanum fluoride procedure. In Group I the results are further divided into three groups: (1) those obtained during the period August, 1944 to October, 1944, (2) between October, 1944 and April, 1945, and (3) between April, 1945 and October, 1945. The Group II results were all obtained under identical conditions. The division of Group I results is on the basis of changes in either the procedure of analysis, method of sample collections, shifting of laboratory equipment, or changes in equipment. The results in Group I have one thing in common, they are all on the basis of analysis of 100 ml urine specimens.

Group I Results. August, 1944-October, 1944: During this period it was not realized that working in contaminated areas would be such a serious factor. Especial care was taken to see that all apparatus was free of alpha contamination. During this period 222 individual urine specimens were analysed. Nearly 60% indicated a body content of plutonium greater than 5 micrograms, 30% between 1 and 5 micrograms and the remainder less than 1 microgram. It was recognized that adjacent rooms in which large quantities of alpha-active substances were handled contributed greatly to the abnormally high results. This was quite clearly demonstrated when a solution containing plutonium was spilled in the adjacent laboratory and the analytical results on the urines became abnormally high. In order to avoid a recurrence of such contamination, the analytical lab was moved to another site where little plutonium was handled in nearby rooms.

October, 1944 - April, 1945. During this period 628 individual urine specimens were analysed. 1% indicated a body content of over 5 micrograms of plutonium, 26% between 1 and 5 micrograms and the remainder less than 1 microgram. This tremendous drop in the overall activity of the specimens indicated very clearly that extreme care must be taken to avoid contamination if any significance is to be attached to the results. In addition to avoiding contamination in the analysis area it was found that very special care should be exercised by the individual in collecting the sample. Work at Los Alamos showed this very clearly.

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<u>April, 1945 - October, 1945.</u> It was during this period that further efforts were made to minimize contamination. Definite procedures for collecting and handling the specimens were adopted. In the 208 individual specimens analysed, less than 1% showed a body content of greater than 1 microgram, 13% between 0.2-1 microgram and the remainder below 0.2 microgram. Ten of the specimens that were analysed were discarded as having been definitely contaminated. The incident occurred when several milligrams of plutonium (oxide powder) was transported in the hall by the analytical laboratory personnel. The results obtained on that day were exceedingly high.

<u>Group II Results.</u> It became apparent during the above periods that four things must be done for accurate and significant urine analysis. (1) An isolated laboratory free of alpha contamination must be provided for the analysis.

(2) The analytical method must be altered so that large volumes of urine could be routinely assayed.

(3) Alpha counting instruments must be provided capable of detecting 0.1 alpha count per minute.

(4) Very definite rules of collecting and handling the specimens must be followed.

As a compromise, some of the rooms in the south end of the New Chemistry Annex were renovated to meet as nearly as possible the specifications of a non-contaminated and isolated laboratory. In November, 1945, routine analysis of the urines began as nearly as possible under the conditions as outlined above. As of February 1, 1945, 216 individual urine specimens have been analysed. Less than 1% have indicated a body content of plutonium greater than 0.4 microgram, 6.5% between 0.1-0.4 microgram and the remainder less than 0.1 microgram. Twelve controls of 1000 ml each were run which showed as a maximum a body content of 0.02 microgram, assuming the activity to be from plutonium. This may be regarded as the lower limit of sensitivity of the method as described above.

3.2 Clinton Laboratories: During the one-year period ending February, 1945, 325 urine specimens from the Clinton Laboratories were assayed for plutonium. These specimens represent only a small group of persons working under Dr. S. G. English. As in the case of the Chicago survey, the specimens are grouped according to certain changes which were made in the analytical procedure or changes in the conditions of analysis.

Group I Results. This group consists of the first 178 specimens assayed for plutonium. The samples were acidified with hydrochloric acid and the plutonium adsorbed onto an anion exchange resin, IR-4, by shaking in contact with the resin for several hours. The plutonium was then eluted from the resin with 6 M hydrochloric acid. Plutonium was coprecipitated with lanthanum fluoride and counted in the usual manner.

The results of the first 118 specimens were complicated by the fact that a lanthanum blank was not used in the background determinations. Over 93% of these specimens showed an estimated body content above 0.2 microgram, the average being 1.12 micrograms. This is obviously due to alpha contaminants in the lanthanum as well as possible contamination from the source of collection.

The source of the alpha activity in the various specimens of lanthanum has not been determined. Some samples have been found to contain as much as 1.6 alpha counts per minute per milligram. This activity is coprecipitated with lanthanum fluoride, and is partially extracted from lanthanum solutions with chloroform when complexed with cupferron. In general, the alpha activity associated with lanthanum will follow plutonium in the lower oxidation state. It is of interest that only a small fraction of the activity is extracted with plutonium into a benzene solution of thiophenyltrifluoroacetone.

The next 60 specimens showed a decided decrease in the plutonium body content. From the sample count was subtracted the background of a lanthanum blank. Nearly 35% of the samples showed negative results. A little more than 65% showed zero or positive results. The average estimated body content, excluding the negative results, was 0.101 microgram.

Such a marked decrease, from 1.12 to 0.101, in the average estimated plutonium body content made it necessary that,

(1) either an analytical method be devised whereby plutonium would be free of lanthanum, or (2) that extreme care be taken in the selection of the lanthanum as a carrying agent. In addition, counters capable of detecting low alpha counts were necessary. The maximum counting time for the above samples was 20 minutes. This is far from adequate to give significant counts below 0.5 counts per minute.

<u>Group II Results</u>. 105 specimens are included in this group. The method of analysis as well as counting time constitute the major changes made. The urine was ashed according to the procedure described previously. The residue was dissolved in 0.1 M hydrochloric acid and the plutonium extracted by the IR-1 adsorption procedure.

Over 12% showed negative counts and the remainder zero or positive results. Excluding the negative results, the average estimated body content was 0.036 microgram, which is again a significant decrease.

In the preliminary tests on the analytical method used here, it was shown that about 80% of the plutonium was recovered. However, later tests showed that the results were not consistent and that the results obtained may probably be low.

<u>Group III Results</u>. 43 specimens are included in this group. The specimens were assayed by the bismuth phosphate-lanthanum fluoride procedure under conditions identical to Group II Chicago samples. 30% showed negative counts which

did not fall below -0.1 count per minute and 19% showed significant positive counts. Again excluding the negative results, the average estimated body content was 0.063 micrograms. This is nearly a two-fold increase over the previous group, however, it was pointed out that the Group II results may be low.

It should be emphasized here that in the case of Group II Chicago and Group III Clinton results that frequent controls were run. The results on the controls ranged from 0.01 to 0.08 alpha counts per minute per 1000 ml of urine. Such counts are not significant but indicate that (1) the reagents used in the analyses do not contribute to contamination, (2) that external contamination is reduced considerable, and (3) that the consistency of the results on the controls would lend weight to high results obtained on the specimens. One control has shown a high count (0.4 cts/min.) No reason can be given for this high result as a control run simultaneously was normal.

4. Experimental Studies

The development and use of an analytical procedure to determine the concentration of a substance in the excreta has little meaning unless this information can be used to determine either certain body functions or the amount of the substance in the body which may be injurious. The latter is the more important factor here as it will afford a means of detecting a harmful substance, here plutonium, before it reaches toxic concentrations in the body.

It was previously mentioned that plutonium is eliminated from the body in the urine at a fairly constant rate--the rate being approximately 0.01% per day. This figure was proposed on the basis of some very preliminary excretion studies on rabbits(1). Subsequent experiments on mice, rats, and dogs showed that the excretion rate may vary by a factor of five in the different species(11). It was felt necessary to establish independently the excretion rate of humans.

The fecal plutonium excretion, however, varied as much as a thousand fold from species to species. This made it difficult to assign any rate for human fecal plutonium excretion.

4.1 Results of Human Excretion Studies:

Urinary excretion of plutonium. Three experiments were begun within a few weeks (one at Chicago) in which plutonium was injected into a human and the plutonium excretion followed daily. During the first 15 days of the experiments there was less than 10% difference between the daily urinary plutonium excretion of the individual studied by Dr. W. Langham and associates at Los Alamos and the individual studied by Dr. J. J. Nickson, E. R. Russell and associates at Chicago. The individual studied by Dr. J. G. Hamilton at Berkeley showed a slightly lower excretion but not by a factor of 2. Following the initial period where a rapid decrease in the excretion rate is observed, there was a slight divergence in the results obtained from the three subjects. The individual

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studied at Los Alamos showed an average daily excretion of slightly less than 0.02%, the one at Chicago slightly above 0.012% and the individual at Berkeley slightly less than 0.006%. These values persisted over a 100-day period. Since these experiments were completed, two additional studies have been made at Chicago. The excretion rate of one of these individuals after the first two weeks has remained between 0.010 and 0.015% per day. The other individual was not available for further study after the 16th day.

In view of the fact that the majority of the urinary plutonium excretion studies on humans have indicated that a sub-acute excretion rate of 0.01% per day is very nearly correct, this value appears to be at this time a reasonable one to use in determining the concentration of plutonium in the body of workers. It may be pointed out that the urinary plutonium excretion of dogs(13) parallels that of man.

Fecal excretion of plutonium. In addition to following the urinary excretion of plutonium of the above individuals, the plutonium content of the daily fecal specimens was also determined. It has been predicted by several workers on the basis of animal excretion studies, that the plutonium fecal excretion rate would be greater than the urinary excretion rate. It therefore appeared that stool determinations would be easier to interpret. All of the human studies that have been made have failed to confirm this thesis. Plutonium in a 24-hour fecal specimen is from 2 to 4 times less than that in a corresponding 24-hour urine specimen.

The average daily fecal plutonium excretion for the four cases studied is 0.003% ranging from 0.001% to 0.006% of that contained in the body. From the difficulties encountered in detecting 2 x 10^{-5} micrograms of plutonium, it would appear that surveys of personnel through fecal analysis would be difficult.

4.2 Distribution of Plutonium in the Body: The development and understanding of any satisfactory means of plutonium therapy is dependent upon a knowledge of the distribution of the element in the organism. Since nearly 90% of the plutonium finding its way in the body is retained there for many years it is vitally important that we week some means of increasing the excretion rate. The first step in devising means of therapy is to learn in what organs the plutonium is concentrated.

There have been many experiments involving animals in which plutonium was injected and at some later date its distribution determined. The majority of these tests have shown that the liver, spleen, bone marrow, and lymph nodes are the principle sites of deposition. The same general distribution has been found for the one fairly normal human which was studied. The distribution data is given in Table I. In addition the distribution of plutonium in a female containing

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approximately 90 micrograms was determined (see Table II.) This individual had many abnormally functioning organs and therefore the distribution may not be representative. It is interesting to note that even under these conditions the marrow and bone are among the principle sites of deposition.

Table I

Distribution of Plutonium in a 68-year, White Male
(155 days after injection of 6.5 ug of plutonium as the citrate)

Tissue	Grams of tissue analysed	✓Cts/gram of tissue	*Relative Affinity for Plutonium
Marrow (rib)	0.8292	70.9	10.13
Liver	34.11	59.8	8.54
Sternum	5.38	20.6	2.94
Periosteum	0.1215	20.0	2.86
Spleen	32.12	11.1	1.59
Tumor (lung)	2.03	7.4	1.06
Cancer Tissue	2.87	7.2	1.03
Rib (cortex)	1.0125	7.0	1.00
L.Nodes (aorta)	0.63	6.7	0.96
Lung	15.39	2.6	0.37
Testicle (glandular)	4.3425	2.3	0.33
Kidney	27.38	1.7	0.24
Heart	4.9435	1.2	0.17
Diaphragm	35.73	1.0	0.14
Abdominal Fat	17.05	0.2	0.03
Bile	8 cc	?	---

* = cts/gram found ÷ cts/gram assuming equal distribution throughout the body.

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Table II

Distribution of Plutonium in a 54-year, White Female (16 days after injection of 94.91 µg of plutonium citrate)

Tissue	Grams of tissue Analysed	αcts/gram of tissue	*Relative Affinity for Plutonium
Marrow (rib	0.2065	1399	8.49
Rib (cortex)	0.430	1299	7.88
Callus and bone	0.1933	828	5.02
Callus (bone free)	0.262	534	3.17
Kidney	6.00	360	2.18
Thyroid	2.64	226	1.37
Contents (lower bowel)	10.05	183	1.11
Liver	8.70	162	1.00
Pancreas	6.045	148	0.90
Periosteum (rib)	0.461	123	0.75
Lung	14.40	107	0.65
Fat	5.850	96	0.58
Spleen	10.850	94	0.57
Tumor (liver)	1.97	71	0.43
Heart	3.40	70	0.42
Ovary (l.)	1.975	63	0.38
L. Node (abd.)	1.53	48	0.29
Intestines (small)	3.40	45	0.27
Intestines (large)	6.87	43	0.26
Muscle (striated)	15.32	40	0.24
Blood (heart clot)	1.835	22	0.13

* = cts/gram found ÷ cts/gram assuming equal distribution throughout the body.

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5. Summary and Suggestions

A brief survey of the method employed in the detection of plutonium in humans has been given with emphasis on the method now being used to survey the personnel of the Metallurgical Laboratory. The information may be of value to any organization contemplating the use of plutonium.

There are several important factors briefly mentioned in the text which must be considered in order that a laboratory may effectively detect very small amounts of plutonium:

(1) The specimen, urine or feces, must be collected under conditions where there is very little chance of contamination. This is probably done by:

- (a) Having the individual remove all garments possibly exposed to plutonium,
- (b) Thoroughly cleansing himself
- (c) Using uncontaminated vessels for collecting the specimen, and
- (d) Keeping the specimen out of contaminated areas.

(2) The analytical laboratory should be remote from all contaminated areas.

(3) The air entering this laboratory should be filtered.

(4) The analyst should not be allowed to wear street clothes in the laboratory and should be required to cleanse himself thoroughly before entering, and the clothing should be changed.

(5) Continued control analyses should be made.

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(6) Repeated use of collecting vessels should be avoided. If these factors and other minor points are adhered to, any positive results that are obtained should carry considerable weight.

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