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BIOLOGICAL STUDIES WITH POLONIUM, RADIUM, AND PLUTONIUM

Edited by

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PREFACE

This volume is one of a series which has been prepared as a record of the research work done under the Manhattan Project and the Atomic Energy Commission. The name Manhattan Project was assigned by the Corps of Engineers, War Department, to the far-flung scientific and engineering activities which had as their objective the utilization of atomic energy for military purposes. In the attainment of this objective, there were many developments in scientific and technical fields which are of general interest. The National Nuclear Energy Series (Manhattan Project Technical Section) is a record of these scientific and technical contributions, as well as of the developments in these fields which are being sponsored by the Atomic Energy Commission.

The declassified portion of the National Nuclear Energy Series, when completed, is expected to consist of some 60 volumes. These will be grouped into eight divisions, as follows:

Division I — Electromagnetic Separation Project
Division II — Gaseous Diffusion Project
Division III — Special Separations Project
Division IV — Plutonium Project
Division V — Los Alamos Project
Division VI — University of Rochester Project
Division VII — Materials Procurement Project
Division VIII — Manhattan Project

Soon after the close of the war the Manhattan Project was able to give its attention to the preparation of a complete record of the research work accomplished under Project contracts. Writing programs were authorized at all laboratories, with the object of obtaining complete coverage of Project results. Each major installation was requested to designate one or more representatives to make up a committee, which was first called the Manhattan Project Editorial Advisory Board, and later, after the sponsorship of the Series was assumed by the Atomic Energy Commission, the Project Editorial Advisory Board. This group made plans to coordinate the writing programs at all the installations, and acted as an advisory group in all matters affecting the Project-wide writing program. Its last meeting was held on Feb. 9, 1948, when it recommended the publisher for the Series.

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The names of the Board members and of the installations which they represented are given below.

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* Represented Madison Square Area of the Manhattan District.

† The Y-12 plant at Oak Ridge was operated by Tennessee Eastman Corporation until May 4, 1947, at which time operations were taken over by Carbide & Carbon Chemicals Corporation.

‡ Clinton Laboratories was the former name of the Oak Ridge National Laboratory.

§ SAM (Substitute Alloy Materials) was the code name for the laboratories operated by Columbia University in New York under the direction of Dr. H. C. Urey, where much of the experimental work on isotope separation was done. On Feb. 1, 1945, the administration of these laboratories became the responsibility of Carbide & Carbon Chemicals Corporation. Research in progress there was transferred to the K-25 plant at Oak Ridge in June, 1946, and the New York laboratories were then closed.

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Many difficulties were encountered in preparing a unified account of Atomic Energy Project work. For example, the Project Editorial Advisory Board was the first committee ever organized with representatives from every major installation of the Atomic Energy Project. Compartmentation for security was so rigorous during the war that it had been considered necessary to allow a certain amount of duplication of effort rather than to permit unrestricted circulation of research information between certain installations. As a result, the writing programs of different installations inevitably overlap markedly in many scientific fields. The Editorial Advisory Board has exerted itself to reduce duplication in so far as possible and to eliminate discrepancies in factual data included in the volumes of the NNES. In particular, unified Project-wide volumes have been prepared on Uranium Chemistry and on the Analysis of Project Materials. Nevertheless, the reader will find many instances of differences in results or conclusions on similar subject matter prepared by different authors. This has not seemed wholly undesirable for several reasons. First of all, such divergencies are not unnatural and stimulate investigation. Second, promptness of publication has seemed more important than the removal of all discrepancies. Finally, many Project scientists completed their contributions some time ago and have become engrossed in other activities so that their time has not been available for a detailed review of their work in relation to similar work done at other installations.

The completion of the various individual volumes of the Series has also been beset with difficulties. Many of the key authors and editors have had important responsibilities in planning the future of atomic energy research. Under these circumstances, the completion of this technical series has been delayed longer than its editors wished. The volumes are being released in their present form in the interest of presenting the material as promptly as possible to those who can make use of it.

The Editorial Advisory Board

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The Manhattan Project Technical Section of the National Nuclear Energy Series is intended to be a comprehensive account of the scientific and technical achievements of the United States program for the development of atomic energy. It is not intended to be a detailed documentary record of the making of any inventions that happen to be mentioned in it. Therefore, the dates used in the Series should be regarded as a general temporal frame of reference, rather than as establishing dates of conception of inventions, of their reduction to practice, or of occasions of first use. While a reasonable effort has been made to assign credit fairly in the NNES volumes, this may, in many cases, be given to a group identified by the name of its leader rather than to an individual who was an actual inventor.

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UNIVERSITY OF ROCHESTER PROJECT FOREWORD

The University of Rochester Manhattan Project had its inception on April 5, 1943, with the appointment of Dr. Stafford L. Warren,* Professor of Radiology and Chairman of the Department of Radiology at the University of Rochester School of Medicine and Dentistry, as Consultant to the Manhattan Engineer District (later as Chief of the Medical Section). Under his guidance and direction the local project was established and its operational policies formulated. On November 2, 1943, Dr Warren was commissioned colonel in the Army Medical Corps, and the subsequent responsibility for the Project was assumed by the present Director on November 13, 1943.

In many respects the atmosphere of the work was in marked contrast to the academic freedom of a university environment. The research was frequently of applied rather than of fundamental nature, though the latter was by no means lacking. In addition to physical and spiritual isolation from our accustomed confreres, we found ourselves surrounded by a multitude of security, Army, governmental, and war-manpower regulations, but the majority of the personnel made the necessary mental adjustments without undue hardship and with commendable reasonableness and good grace. Not infrequently we found these apparent handicaps working to our mutual advantage.

The organization of the Project was likewise unusual and, to a certain extent, experimental. To accomplish the task in the specified time and to utilize effectively experienced personnel made scarce by the demands of the war, individuals were placed in positions where their capabilities could produce maximum benefit to the Project as a whole. To this end, ten autonomous but mutually interdependent divisions were established, whose coordination was effected through the Director's Office so that priorities on material, manpower, and concentration of effort could be channeled in the proper direction with the shifting phases of the various problems. Experiments were discussed and organized on a cooperative basis through a system of "planning sessions" in such a manner that the expert opinion of participating members of specialized divisions could make major contributions to the structure of many of the experiments. This procedure

*Now Dean of the Medical School, University of California at Los Angeles.

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also enabled the divisions of Pathology, Hematology, and Statistics to coordinate their activities with other divisions so that they could analyze properly the mass of experimental data which must, of necessity, pass through their respective laboratories.

It would be misleading to aver that this system of research procedure presented here was without fault and not beset by difficulties. It is not an easy matter for an investigator to reconcile his ideas and personal ambitions with those of a group for a common objective, especially when frequently his entire training and previous progress have been based upon individual achievement. Particularly is this true when he has not had the privilege of participating in the selection of his associates. The system, however, worked surprisingly well under somewhat unfavorable circumstances and is worthy of further exploration under peacetime conditions.

It is impossible to pay proper tribute to the many individuals—scientific, technical, and nontechnical—who participated in this endeavor. Neither can one, by reading the following pages, appreciate fully the mental and physical labor that went into the enterprise. Approximately two million man-hours were required to produce the research from which these volumes are derived.

The Administrative Office wishes to express its appreciation to the Project personnel for their confidence and loyalty; to the University as a whole for its support and cooperation; to the many Rochester industries and businesses for the materials supplied and the services rendered; to the Area Engineer's Office for its aid in facilitating the conduct of the program; to Dr. Ellice McDonald, Director of The Biochemical Research Foundation of the Franklin Institute, at Newark, Del., for his cooperation in coordinating the research under his contract with that of Rochester.

Andrew H. Dowdy, M.D.

Professor of Radiology and Director of the University of Rochester Project, 1943-1947; now Professor of Radiology, School of Medicine, University of California at Los Angeles

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VOLUME EDITOR'S PREFACE

This volume reports the experimental studies carried out by the Biological Chemistry Section of the Division of Radioactivity in the Manhattan Department of the University of Rochester. The excellent cooperation of other sections and divisions, as well as that of all the personnel of this section, in collecting the data and preparing the report is gratefully acknowledged.

The general problem undertaken was a comparison of the biological effects of three elements, polonium, plutonium, and radium, which had the common property of radioactive decay with emission of alpha particles. Since the biological distribution and excretion of plutonium were being studied exhaustively in other areas, the report on the work carried out here can be divided rather naturally into three main parts. Part I deals with the distribution and excretion of polonium; Part II discusses the distribution and excretion of radium; and Part III deals with the comparative toxicities of polonium, plutonium, and radium. The Manhattan Project reports on these subjects have been condensed and correlated, and, wherever feasible, pertinent data obtained subsequent to the writing of the original reports have been included in the body of the volume. In Part III, however, the difficulty of reanalyzing each group of data in the light of subsequent findings was too great; therefore the toxicity studies are included essentially as they appeared in the original Project reports. Subsequent data obtained in the toxicity experiments are recorded and discussed in Appendix 2 to Chap. 8.

The material presented in this volume is largely based on the following Manhattan Project reports:

Preliminary Report on the Metabolism of Polonium. Robert M. Fink and William F. Bale, M-1529, Aug. 2, 1944.

Progress Report on the Metabolism of Polonium. Robert M. Fink, M-1551, Sept. 21, 1944.

Progress Report on the Metabolism of Polonium. III. Tracer Studies in Two Human Subjects. Wallace L. Minto and Robert M. Fink, M-1579, Nov. 11, 1944.

Progress Report on the Metabolism of Polonium. IV. Further Intravenous and Oral Experiments with Rats. Wallace L. Minto, Robert M. Fink, Elizabeth K. Vittum, and Alice Taylor Gorham, M-1659, Apr. 16, 1945.

Polonium Literature Summary of Studies on the Physiological Behavior of Polonium. Hannah E. Silberstein, M-1519, June 23, 1944.

Inhalation of Volatilized Polonium by Rats. Charles P. Kimball and Robert M. Fink, M-1811, Dec. 20, 1945.

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Metabolism of Polonium. I. Tracer Studies in Three Human Subjects Following Intravenous or Oral Administration. Hannah E. Silberstein, William N. Valentine, John S. Lawrence, and Robert M. Fink. M-1837, Feb. 6, 1946.

Radium Poisoning: A Survey of the Literature Dealing with the Toxicity and Metabolism of Absorbed Radium. Hannah E. Silberstein. M-1695, May 26, 1945.

Metabolism of Radium. I. Tracer Studies on Rats after Intravenous Administration. Hannah E. Silberstein and Robert M. Fink. M-1739, Aug. 2, 1945.

Comparative Intravenous Lethal Dose Pilot Studies for Polonium, Radium and Plutonium in Rats. George A. Boyd, Robert M. Fink, George M. Suter, and Roger Metcalf. M-1878, June 1, 1946.

Comparative Intravenous Lethal Dosage Study of Radium, Plutonium, and Polonium in Rats with Clinical, Pathological, and Hematological Observations. George A. Boyd and Robert M. Fink. M-1902, July 22, 1946.

The three elements investigated proved to be very interesting ones for comparison studies in that they differ widely in their half-lives, distribution in the body, and rate of excretion. These differences appear to be reflected in their relative toxicities.

The problem of long-term human tolerance to a variety of radioactive materials is one that is likely to become of increasing importance. Even the most exhaustive studies of the type reported here may be insufficient to yield a completely satisfactory answer to that problem. Such studies are basic and necessary, however, and should be well worth while even if they assist only in clarifying the general problem of the toxicity of radioactive substances.

Robert M. Fink

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NATIONAL NUCLEAR ENERGY SERIES
Manhattan Project Technical Section

Division VI - Volume 3

BIOLOGICAL STUDIES WITH POLONIUM, RADIUM, AND PLUTONIUM

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Part I

DISTRIBUTION AND EXCRETION OF POLONIUM

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Chapter 3

STUDIES OF POLONIUM METABOLISM IN HUMAN SUBJECTS

It seemed desirable to have some data on the human excretion c polonium after the administration of known doses in order to obtain correlation with the more extensive data on rats. Inasmuch as it wa not possible to determine accurately the amount of polonium alread present in laboratory personnel or to rule out the possibility of sub sequent accidental exposure of persons working with polonium, suc personnel were not suitable subjects for excretion studies of thi type. Accordingly, the general problem was outlined to a number o hospital patients with no previous or probable future contact with po- lonium. Of the group who volunteered as subjects, four men and on woman were selected for the excretion studies outlined below.

The group ranged in age from the early thirties to the early forties. The polonium was administered intravenously to the first four sub- jects and orally to the fifth.

1. INTRAVENOUS STUDIES

By H. E. Silberstein, W. N. Valentine, W. L. Minto, J. S. Lawrence, and R. M. Fink

Case 1. A total of 22.6 microcuries (0.3 microcurie per kilogram of body weight) of polonium chloride was administered intravenously to subject 1, a male patient being treated for generalized lympho- sarcoma. The polonium was administered in 10 ml of sterilized isc tonic saline solution at pH 7.6. In order to determine as accurately as possible the amount actually administered, a second 10-ml sampl of the solution was immediately drawn into the syringe used for th injection and was expelled into an acid solution at approximately the rate used for the actual injection. The acid solution was set aside fo subsequent radioactivity measurement. This dummy-injection pro- cedure has been followed routinely and is quite necessary in huma

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studies, in which the loss of one-fourth to one-half the polonium occurs during the sterilization of the neutral solution in the autoclave.

In determining the amounts excreted in the daily urine collections the total daily volume was measured, and a convenient aliquot (about 5 per cent of the total) was taken, acidified to 0.5N H^+ with concentrated hydrochloric acid, and plated directly onto a silver-foil disk, which was read in an ionization chamber or alpha counter. The daily urinary excretion of polonium by the first subject and the concentration of polonium per milliliter of urine are given in Table 3.1 and

Table 3.1—Percentage of Theoretical Dose in Urine, Feces, and Blood of Subject 1 (Generalized Lymphosarcoma) after Intravenous Administration of 0.3 Microcurie of Polonium Chloride per Kilogram of Body Weight

Days after injection	% of theoretical dose excreted		% of theoretical dose per kilogram				
	Urine	Feces	Urine	Feces	Whole blood	Plasma	Blood cells
1	0.20	0.44	0.125	4.8	3.7	1.6	7.0
2	0.048	1.35	0.052	18.1			
3	0.056	1.37	0.038	24.0	4.7	1.4	9.0
4	0.038	1.92	0.024	19.4			
5	0.031	3.6	0.025	29.5	4.5	1.3	7.9
6	0.030	4.2	0.038	35.9			
7	0.021	0.92	0.019	14.4	3.5	0.7	7.3
8	0.033		0.024				
43	0.016		0.020		0.6	0.4	0.9

shown graphically in Fig. 3.1. Owing to an oversight the use of a glass urinal for these collections was not specified, so that it is possible that this ambulatory patient used a stainless-steel urinal and that the second, bedridden, patient used a metal vessel. A subsequent check indicated that use of the metal vessel would result in the loss of less than one-tenth of the polonium in the specimen.

Fecal samples were obtained daily from this subject for seven days after injection. Each sample was weighed, a suitable known volume of 3N HCl was added, and the sample was homogenized with an electrically driven glass stirrer. Aliquots of each day's sample were digested and analyzed as described in Chap. 1. The total daily excretion through the feces and the concentrations of polonium therein are given in Table 3.1 and are shown graphically in Fig. 3.2. The concentrations of polonium in the blood of this first subject are also shown in Table 3.1.

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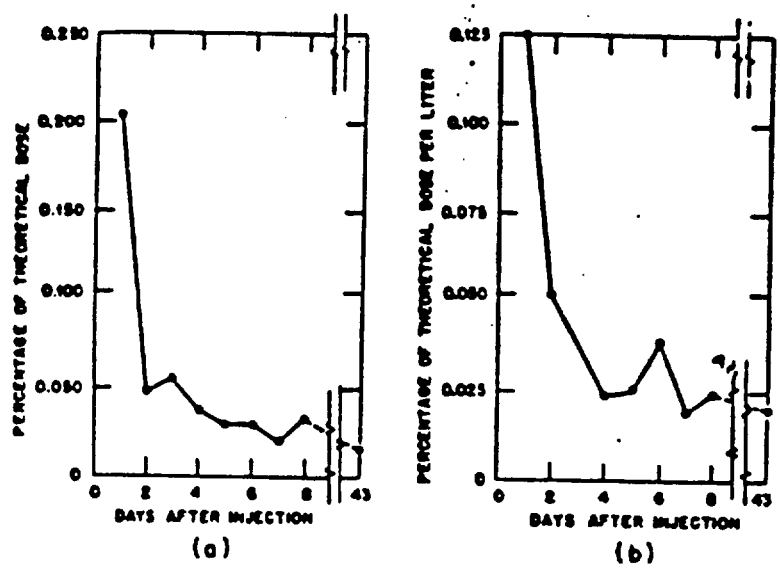

Fig. 3.1 — Urinary excretion of polonium by subject 1 (male, generalized lymphosarcoma) after intravenous administration of 0.3 microcurie of polonium chloride per kilogram of body weight. (a) Daily urinary excretion of polonium. (b) Daily concentrations of polonium in urine.

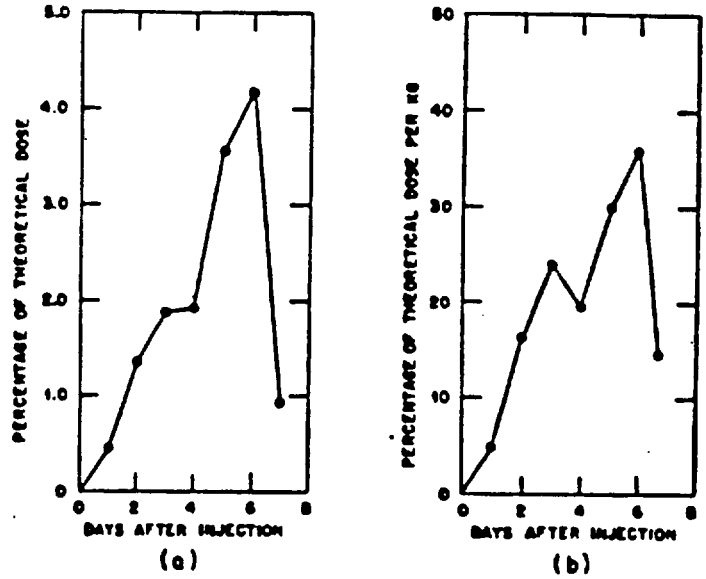

Fig. 3.2 — Fecal excretion of polonium by subject 1 (male, generalized lymphosarcoma) after intravenous administration of 0.3 microcurie of polonium chloride per kilogram of body weight. (a) Daily fecal excretion of polonium. (b) Concentrations of polonium in feces.

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Case 2. A total of 11.3 microcuries (0.17 microcurie per kilogram of body weight) of polonium chloride was administered by intravenous injection to the second male subject. This patient had acute lymphatic leukemia, which was the cause of his death six days after the injection of the material. As in the case of the first subject, the dose administered was determined by means of a dummy injection through the same needle immediately after the actual injection.

Table 3.2—Percentage of Theoretical Dose in Urine and Blood of Subject 2 (Acute Lymphatic Leukemia) after Intravenous Administration of 0.17 Microcurie of Polonium Chloride per Kilogram of Body Weight

Days after injection	% of theoretical dose excreted in urine	% of theoretical dose per liter			
		Urine	Whole blood	Plasma	Blood cells
1	0.84	0.58	2.3	1.6	5.5
2	0.137	0.156			
3	0.190	0.105	2.5	2.1	4.6
4	0.114	0.079			
5	0.107	0.066	1.7	1.2	
6	0.044	0.061	1.3	0.9	2.4

ie daily excretion and the concentration of polonium in the urine are shown in Table 3.2 and Fig. 3.3. On microscopic examination the urine samples showed some red blood cells, and the sample taken during the first day in particular was very dark colored. As both the red cells and the bile contained very much higher concentrations of polonium than did the urine, the presence of small amounts of either may well have raised the urine concentration beyond the range for normal subjects.

This patient passed very small amounts of feces, but a single sample obtained one day after the injection contained 8 per cent of the theoretical dose per kilogram of fecal matter, a value similar to that found for the corresponding sample from the first subject.

The concentration of polonium in the blood of subject 2 is also shown in Table 3.2. An autopsy was performed and tissue samples were taken about an hour after the death of this patient. The tissue samples were digested and plated out on silver foil, and their radioactivity was measured according to the methods described in Chap. 1. The concentrations of polonium found in the various tissues, expressed as percentages of the theoretical dose per kilogram of tissue, are tabulated in Table 3.3. The bile obtained from the gall bladder showed the highest concentration, being more than four times as high

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5	0.107	0.066	1.7	1.2	
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as the concentrations in the liver, spleen, and kidney, 70 times the concentration in the blood, and 1,500 times the concentration in the urine.

Table 3.4 gives the percentage of the theoretical dose found in various whole organs or tissues of the human subject six days after injection, as compared with the corresponding average values for five rats and a rabbit sacrificed 10 days after the intravenous injection of polonium.

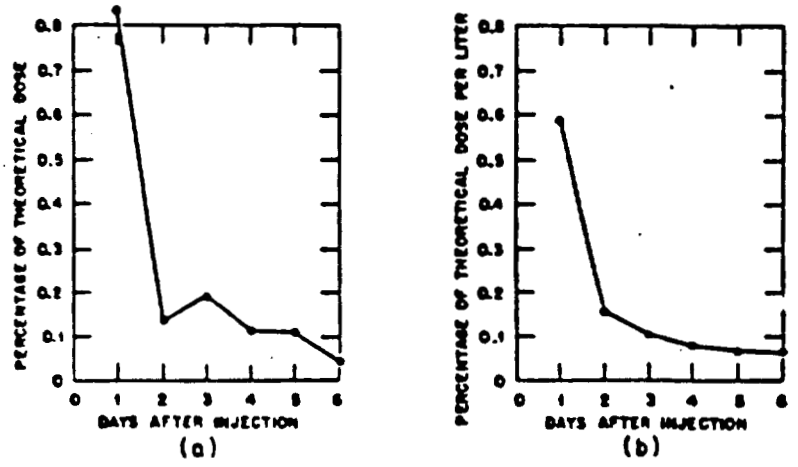

Fig. 3.3 — Urinary excretion of polonium by subject 2 (male, acute lymphatic leukemia) after intravenous administration of 0.17 microcurie of polonium chloride per kilogram of body weight. (a) Daily urinary excretion of polonium. (b) Daily concentrations of polonium in urine.

The values shown in Table 3.4 indicate a calculated recovery from the human tissues of about 60 per cent more polonium than was originally administered. T' inconsistency probably arose principally from the fact that adequate sampling procedures could not be carried out, and a single small tissue sample had to be taken as representative of a whole organ or tissue. Contamination of the tissue samples during their preparation for measurement is another possibility, and the exceptionally high value obtained for the heart muscle may have been due to this factor. In the rat the heart muscle ordinarily had a polonium concentration similar to that of skeletal muscle, provided that care was taken to remove excess blood from the heart. Accordingly, when a high value was obtained from the sample of human heart, a second aliquot from the heart digest was plated out and found to give

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a reading 30 per cent higher than the first sample. This increase of activity after standing indicated that, despite the seemingly adequate measures for the decontamination and segregation of glassware, the

Table 3.3 — Percentage of Theoretical Dose per Kilogram (Wet Weight) Found in Tissues of Subject 2 (Acute Lymphatic Leukemia) Six Days after Intravenous Administration of 0.17 Microcurie of Polonium Chloride per Kilogram of Body Weight

Tissue	% of theoretical dose per kilogram
Bile	91.0
Liver	21.0
Heart*	20.0
Spleen	17.0
Kidney	13.6
Testes	4.3
Lungs	4.1
Skin (from chest)	3.9
Omental nodes	3.8
Sternal marrow	3.1
Vertebral marrow	2.8
Pancreas	2.7
Cervical nodes	2.6
Submaxillary glands	2.6
Blood cells	2.4
Muscle (from chest)	1.7
Bone (rib)	1.7
Thymus	1.5
Duodenum	1.5
Whole blood	1.3
Epididymis	1.1
Stomach	0.9
Blood plasma	0.8
Seminal vesicles	0.9
Thyroid	0.8
Aorta	0.8
Prostate	0.7
Rectum	0.1

*Probably contaminated.

heart digest had probably been stored in a contaminated bottle. More stringent measures were instituted thereafter in order to avoid further occurrences of this sort. In any event, it seemed that in this human study, in contrast to the rat and rabbit experiments, the theoretical dose as determined by the dummy injection was probably a more accurate measure of the polonium injected than was the amount

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recovered, as estimated from excreta and tissue analyses. For this reason, and particularly because the inconsistency between the theoretical dose and the estimated recovery may have been due largely to

Table 3.4 — Amount of Polonium in Whole Tissues Expressed as Percentage of Theoretical Dose for Subject 2 and as Percentage of Dose for 10-day Experiments with Five Rats and a Rabbit

Tissue	Subject 2, % of theoretical dose*	Rats, % of dose	Rabbit, % of dose
Muscle†	45	13.4	3.8
Liver	43	10.8	5.0
Skin‡	35	10.8	6.6
Skeleton§	17.0	8.5	3.6
Heart	7.0¶	0.27	0.097
Kidneys	5.0	7.0	6.0
Spleen	4.1	4.5	0.050
Blood cells**	3.9	5.0	3.2
Lungs	3.5	0.94	0.24
Pancreas	0.43	0.71	0.005
Blood plasma**	0.34	0.34	0.61
Rectum	0.180		
Stomach	0.174	0.38	0.24
Testes	0.128	0.47	0.149
Duodenum	0.076		0.41
Prostate	0.034	0.060	
Thyroid	0.031	0.090	0.004
Seminal vesicles	0.020	0.150	0.025
Thymus	0.003	0.180	0.043

* High calculated recovery value (approximately 160 per cent) in subject 2 probably due mostly to assumption that small samples of skin, liver, muscle, bone, etc., were representative of whole tissue.

† Total weight of muscle tissues estimated as 41.7 per cent of body weight in man and 45.4 per cent of body weight in rat. Muscle taken from chest in man, from leg and/or abdomen in rats.

‡ Total weight of skin estimated as 18 per cent of body weight in man and in rats. Skin taken from chest in man, from abdomen in rats (with fur included).

§ Weight of total skeleton estimated as 15.9 per cent of body weight in man and 10.9 per cent in rats. Bone sample taken from rib in man, from femur or tibia in rats.

¶ Heart digest probably contaminated in laboratory.

** Total weight of blood estimated as 4.9 per cent of body weight in man and 5.5 per cent in rats. Total weight of plasma derived from application of hematocrit values to estimated total blood weight. Blood-cell value derived by difference between plasma and whole blood.

errors in a very few tissues, the human data are left in terms of percentages of theoretical (dummy) dose without attempting to correct for retention or recovery.

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The relative concentrations of polonium in the tissues of man, rat, and rabbit expressed on an approximately comparable basis are shown in Table 3.5. The data on percentage of theoretical dose per gram for subject 2 have been adjusted for the factor of body weight by multiplying by 1/100 of the body weight in grams for comparison with the

Table 3.5 — Relative Polonium Concentrations* in Various Tissues of Man, Rats, and Rabbit

Tissue	Subject 2	Rats	Rabbit
Bile	88	0.30†	1.72
Liver	13.7	3.8	5.4
Heart	13.1‡	0.76	0.91
Spleen	11.0	27	6.6
Kidney	8.7	11.9	33
Testes	2.7	0.61	2.5
Lungs	2.6	2.3	1.72
Skin	2.5	0.80	1.54
Omental nodes	2.4	17.5	
Bone marrow	1.92	6.2	8.3
Pancreas	1.71	5.7	1.66
Cervical nodes	1.67	8.4	4.1
Submaxillary glands	1.64	1.30	5.7
Blood cells	1.54	3.6	4.3
Muscle	1.09	0.39	0.23
Bone	1.09	1.16	0.89
Thymus	0.89	8.3	1.46
Duodenum	0.87		1.80
Stomach	0.58	0.34	1.09
Seminal vesicles	0.57	0.59	3.0
Blood plasma	0.57	0.14	0.43
Thyroid	0.52	3.5	1.63
Prostate	0.45	1.11	

*Concentrations adjusted for body weight in subject 2 (relative concentration = percentage of theoretical dose per gram × one-hundredth of body weight in grams) and for body weight and retention in 10-day intravenous experiments with five rats and a rabbit (relative concentration = percentage of dose per gram × percentage retained of body weight in grams).

†Rat bile value taken from duct ligation experiment 28.

‡Heart digest probably contaminated in laboratory.

rat and rabbit data of Table 2.29, but, as stated previously, no corrections have been made for the estimated recovery or retention figures. The relative concentrations of polonium in the various tissues of subject 2 (Table 3.5) in general agree fairly well with the comparable values for either the rat or the rabbit, perhaps agreeing some-

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what more frequently with the rabbit. The human bile, liver, and muscle values are higher, and the bone-marrow, lymph-node, blood-cell, and thyroid values are lower than those for either the rat or the rabbit. Data on the amount of polonium in entire organs and tissues (Table 3.4) show more differences because they involve the added variations due to differences in excretion and the differing sizes of the organs in the three species.

It is obviously impossible to evaluate accurately the effect of the pathological state of the human subject upon the distribution of polonium in his body, but some points seem worth mentioning. The possible effect of the kidney damage on the values of urinary excretion has already been discussed. The principal autopsy findings were numerous petechial hemorrhages, cramming of the spleen and bone marrow with round cells, hyperplasia of the young lymphocytes in the lymph nodes, and confirmation of the jaundice and anemia noted above. It seems possible that the infiltration of round cells might have lowered the spleen and bone marrow values from those found in a normal subject, although cause and effect might be reversed, as with the hyperplasia in the lymph nodes. Anemia would be expected to reduce the polonium concentration in blood because of the relatively high concentration ordinarily found in red blood cells. The jaundice, although not especially interesting to the pathologists in this case, is perhaps of more interest in this tracer experiment on account of the very high concentration of polonium found in the bile. During jaundice the concentration of bile is reported to be particularly high in the liver, skin, muscle, and plasma. Inasmuch as in these tissues the human subject had relative polonium concentrations considerably higher than did the rats, it seems possible that the jaundice contributed in some measure to the high values.

Thus as they stand, the tissue data indicate a fairly close similarity between the human, the rabbit, and the rat with respect to the distribution of polonium administered intravenously, and it seems probable that a man in good general health would show an even closer similarity. If, however, the data on subject 2 show an essentially normal distribution of polonium in humans, then that distribution is quite favorable as compared with that in the rat, for the human put a higher concentration of polonium into such relatively insensitive tissues as liver, skin, and muscle and a lower concentration into bone marrow, lymph nodes, pancreas, thymus, and thyroid.

Case 3. Subject 3, a male patient with chronic myeloid leukemia, was injected intravenously with 10 ml of sterile physiological saline, pH 7.4, containing 12.0 microcuries of polonium chloride. The dose was equivalent to 0.18 microcurie per kilogram of body weight. The

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patient had a moderately elevated blood NPN, 53 mg % prior to injection and 60 mg % on the sixth day after injection, possibly indicating a mild disturbance in renal function.

The excretion data from this case are shown in Table 3.6 and in Figs. 3.4 and 3.5. The total daily polonium in the urine was fairly

Table 3.6 — Percentage of Theoretical Dose in Urine and Feces of Subject 3 (Chronic Myeloid Leukemia) after Intravenous Administration of 0.18 Microcurie of Polonium Chloride per Kilogram of Body Weight

Time after injection	% of theoretical dose excreted		% of dose per liter in urine	% of theoretical dose per kg in feces
	Urine	Feces		
Hr				
0–1	0.009		0.067	
1–3	0.010		0.075	
3–5	0.006		0.042	
5–24	0.065		0.046	
Days				
1	0.090	0.21		9.6
2	0.125		0.067	
3	0.153	1.52 (48 hr)	0.077	5.5
4	0.146	0.25	0.075	8.0
6	0.059	0.38	0.052	6.6
7	0.157	1.00	0.072	7.3
8	0.086	0.17	0.055	6.1
9	0.080	1.15	0.050	5.0
10	0.103	0.55	0.048	6.2
11	0.077	1.70	0.043	5.7
13	0.059	0.73	0.046	7.0
14	0.080		0.046	
15	0.070	0.82 (48 hr)	0.040	7.3
16	0.069		0.037	
17	0.140	2.1 (48 hr)	0.093	7.8
18	0.058		0.047	
30	0.043	0.58	0.023	3.8
70	0.021	0.254	0.013	1.3

constant for several days after injection. It averaged 0.097 per cent of the theoretical dose per day for the first 18 days and fell to 0.02 per cent at 70 days. The polonium appeared in the urine as soon as 1 hr after injection at a concentration as high as that seen two or three days later. From the 1st to the 18th day urinary concentrations varied between 0.04 and 0.09 per cent of the theoretical dose

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per liter. The average daily fecal output during the first 17 days was 0.71 per cent of the theoretical dose, nearly 10 times the urine content. Although the 24-hr fecal excretion values show marked fluctuations, the concentration of polonium in the feces remained at a fairly

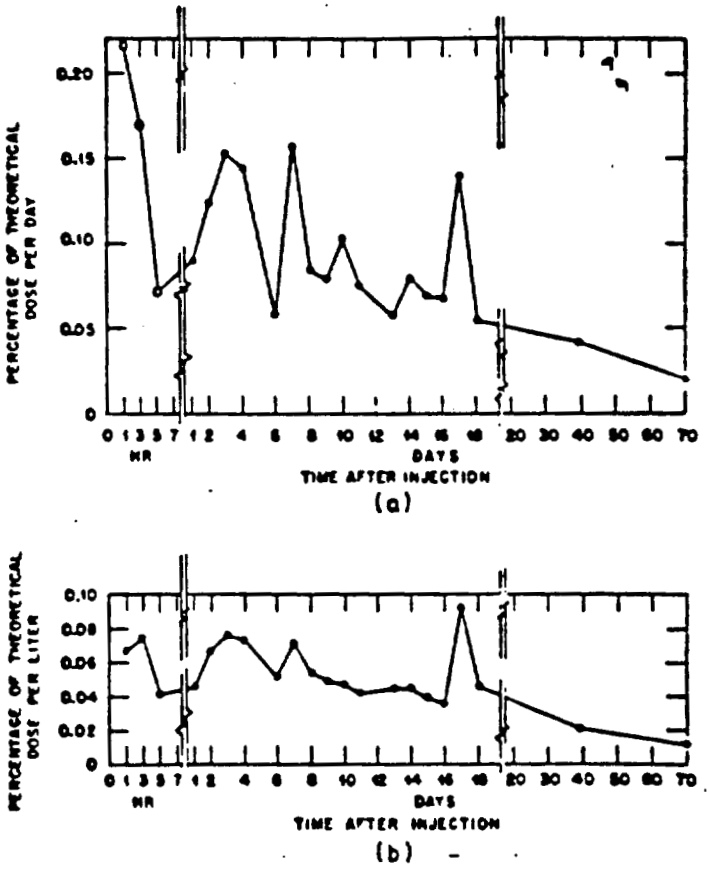

Fig. 3.4—Urinary excretion of polonium by subject 3 (chronic myeloid leukemia) after intravenous administration of 0.18 microcurie of polonium chloride per kilogram of body weight. (a) Daily total urine. Dot, observed 24-hr rate; circle, 24-hr rate estimated from short periods. (b) Concentration in urine.

constant level—between 5 and 10 per cent of the theoretical dose per kilogram for as long as 17 days after injection. By 70 days it had dropped to about one-third the earlier values.

Blood sampling for analysis was begun 15 min after injection. Because of this patient's high white count it was possible to follow the

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polonium content not only in plasma and red cells but also in the white blood cells for more than two weeks after the beginning of the experiment. For this separation the 5-ml blood sample was poured into a conical 12-ml centrifuge tube and allowed to stand until the red cells settled to the bottom. Sedimentation was complete after 2½ to 3 hr in

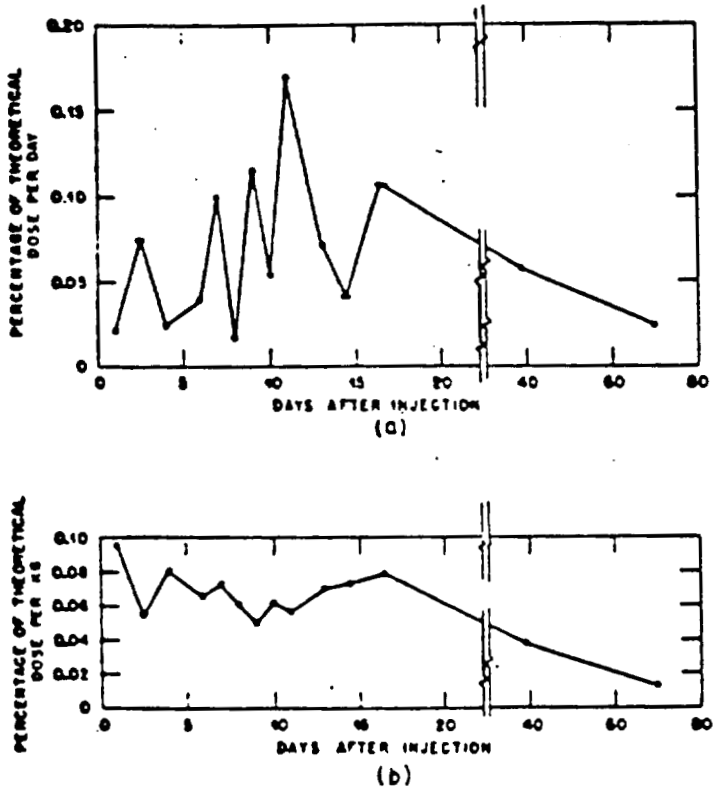

Fig. 3.5—Fecal excretion of polonium by subject 3 (chronic myeloid leukemia) after intravenous administration of 0.18 microcurie of polonium chloride per kilogram of body weight. (a) Daily total feces. Readings marked by a dash are daily averages taken from 48-hr collections. Dots are individual readings. (b) Concentration in feces.

the first few samples, but later samples required 4 to 5 hr. The white cells, together with most of the plasma, were then carefully pipetted into a second centrifuge tube, and the two fractions were centrifuged for 40 min. Both hematocrits were then recorded, and the plasma was removed from both tubes and combined for analysis. The samples taken at 3 and 5 hr after injection were left standing overnight

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before the white cells were drawn off for centrifuging. The analytical results are given in Table 3.7 and Fig. 3.6.

The injected material disappeared rapidly from the blood stream. On the basis of an estimated total blood volume of 4.9 liters (7 per cent of the body weight) and the observed concentrations in blood and

Table 3.7 — Percentage of Theoretical Dose per Liter in Whole Blood and Blood Fractions of Subject 3 (Chronic Myeloid Leukemia) after Intravenous Administration of 0.18 Microcurie of Polonium Chloride per Kilogram

Time after injection	Percentage of theoretical dose per liter			
	Whole blood	Plasma	Red cells	White cells
Hr				
0.25	0.52	0.58	0.25	0.79
1	0.47	0.37	0.43	0.72
3	0.35	0.11	0.64	0.63
5	0.95	0.40	0.84	1.30
24	0.95	0.67	1.15	1.40
Days				
2	1.1	1.02	0.67	1.85
3	1.3	0.95	1.50	2.3
4	1.5	1.14	1.85	2.1
6	1.3	0.81	2.1	3.5
7	1.2	0.80	1.83	3.1
8	1.2	0.73	2.1	2.2
9	1.0	0.44	2.1	2.3
10	1.3	0.75	2.1	2.9
11	1.2	0.51	1.93	2.9
13	1.2	0.66	2.3	2.1
14	0.7	0.68	0.55	1.87
15			1.80	2.4
16	1.0	0.69	1.77	1.85
17	0.95	0.69	1.71*	
18	1.0	0.57	1.64*	
40	0.44	0.41	0.72*	
71	0.26	0.20	0.32*	

*Values include white cells.

plasma, it was calculated that only 2.3 per cent of the theoretical dose was present in the whole circulation, and 1.3 per cent in the circulating plasma, at the end of 15 min. The lowest blood value was found at 3 hr, but this condition was largely accounted for by the drop in plasma content to less than 0.3 per cent of the theoretical dose in

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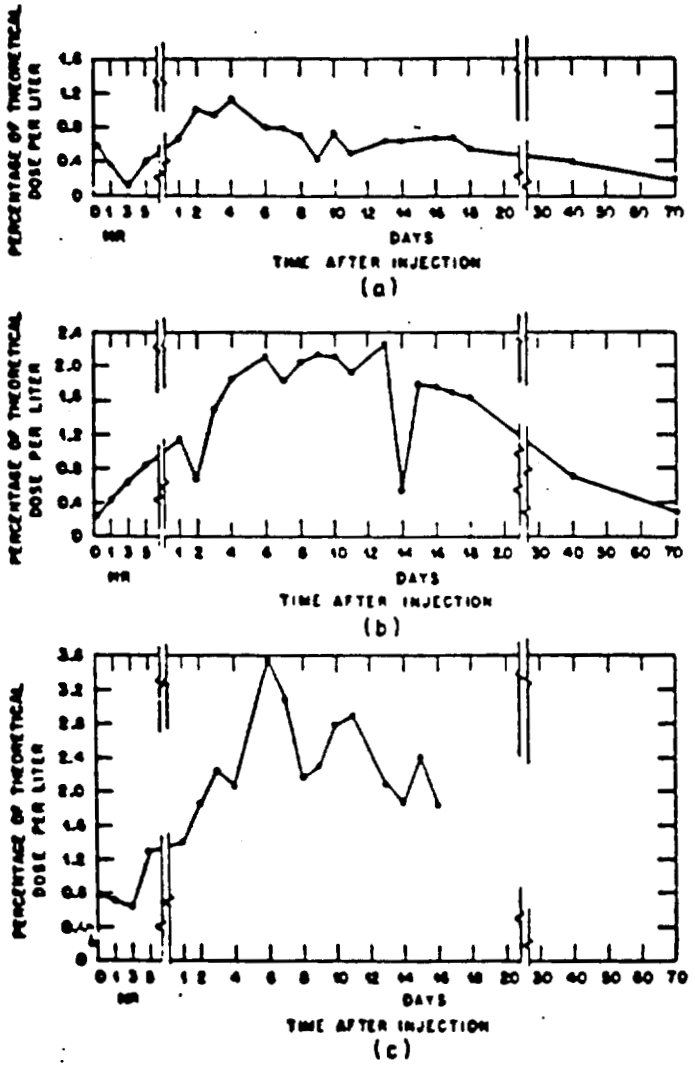

Fig. 3.6—Percentage of theoretical dose of polonium per liter in plasma, red cells, and white cells of subject 3 (chronic myeloid leukemia) after intravenous administration of 0.18 microcurie of polonium chloride per kilogram of body weight. (a) Plasma. (b) Red cells. (c) White cells.

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total circulating plasma, and the red cells already showed a marked uptake of polonium. (See the discussion in Sec. 5 concerning the in vitro increase of the proportion of the polonium in the red blood cell fraction.) A portion of the cell uptake observed in the early blood samples probably took place in vitro while these samples stood in the test tubes for 3 to 18 hr. The plasma content rose by the fourth

Table 3.8 — Percentage of Theoretical Dose in Blood and Urine of Subject 4 (Chronic Myeloid Leukemia) after Intravenous Administration of 0.18 Microcurie of Polonium Chloride per Kilogram of Body Weight

Time after injection	% of theoretical dose excreted in urine	% of theoretical dose per liter in urine	Time after injection	% of theoretical dose per liter: Whole blood	Plasma	Cells
			25 min	1.7	2.4	0.75
Hr			Hr			
0–1.7	0.018	0.33	1	1.5	1.95	0.75
			2.5	2.3	2.6	1.50
1.7–3.5	0.009	0.025	4.5	2.2	1.92	2.6
3.5–24	0.042	0.057	23	1.10	0.99	1.20
Days			Days			
1	0.069					
2	0.063	0.060	2	1.7	1.34	2.3
4	0.056	0.045	4	2.3	2.1	2.8
5	0.064	0.046	5	2.3	1.92	2.8
6	0.060	0.046	6	2.2	1.80	2.8
7	0.052	0.060	7	1.7	1.45	2.0
8	0.053	0.027	8	2.0	1.99	2.1
9	0.044	0.047	9	1.8	1.29	2.7
11	0.044	0.028	11	1.6	1.14	2.3
12	0.040	0.029	12	1.7	1.44	2.3
13	0.034	0.027	13	1.7	1.26	2.4

day to about 10 times the level at 3 hr and then gradually fell, so that by 70 days it was again similar to the 3-hr value. Red cells, with a concentration generally two to four times that of the plasma, contained about 2 per cent of the theoretical dose per liter during the second week after injection, but the content decreased to about one-tenth of that level at 70 days. White cells showed a somewhat greater uptake than red cells as soon as 15 min and 1 hr after injection. No data are available concerning the in vitro uptake of polonium by white cells, but such an uptake might well affect the results in the early white cell samples. After the sixth day, when the white-cell content reached 3.6 per cent of the theoretical dose per liter, it decreased to a value close to that of the red cells on the 16th day.

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Case 4. The fourth subject for intravenous administration was a female patient receiving palliative radiotherapy for chronic myeloid leukemia. She was given an intravenous injection of 8.6 microcuries

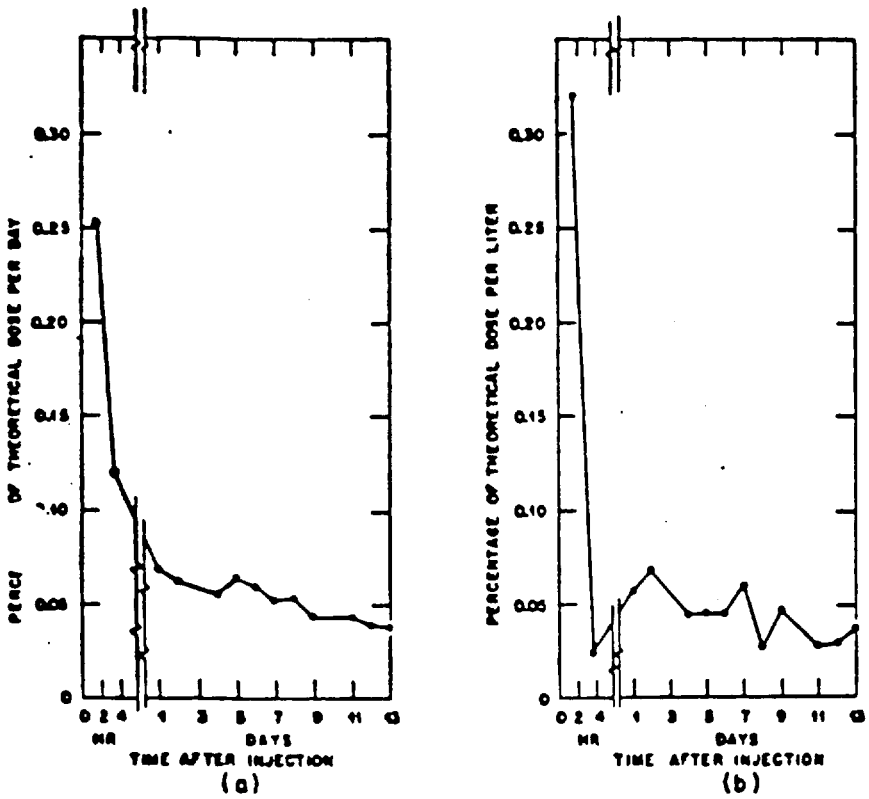

Fig. 3.7—Urinary excretion of polonium by subject 4 (chronic myeloid leukemia) after intravenous administration of 0.18 microcurie of polonium chloride per kilogram of body weight. (a) Daily total urine. Dot, observed 24-hr rate; circle, 24-hr rate estimated from short periods. (b) Concentration in urine.

of polonium chloride (0.18 microcurie per kilogram) in 10 ml of sterile physiological saline adjusted to pH 7.0. No fecal collections were made in this case, but the urine and blood were followed for 13 days after injection. The data are given in Table 3.8 and Figs. 3.7 and 3.8.

The immediate urinary output, that is to say, during the first 100 min, was relatively high (0.3 per cent of the theoretical dose per liter) in comparison with subject 3, yet the total first 24-hr excretion

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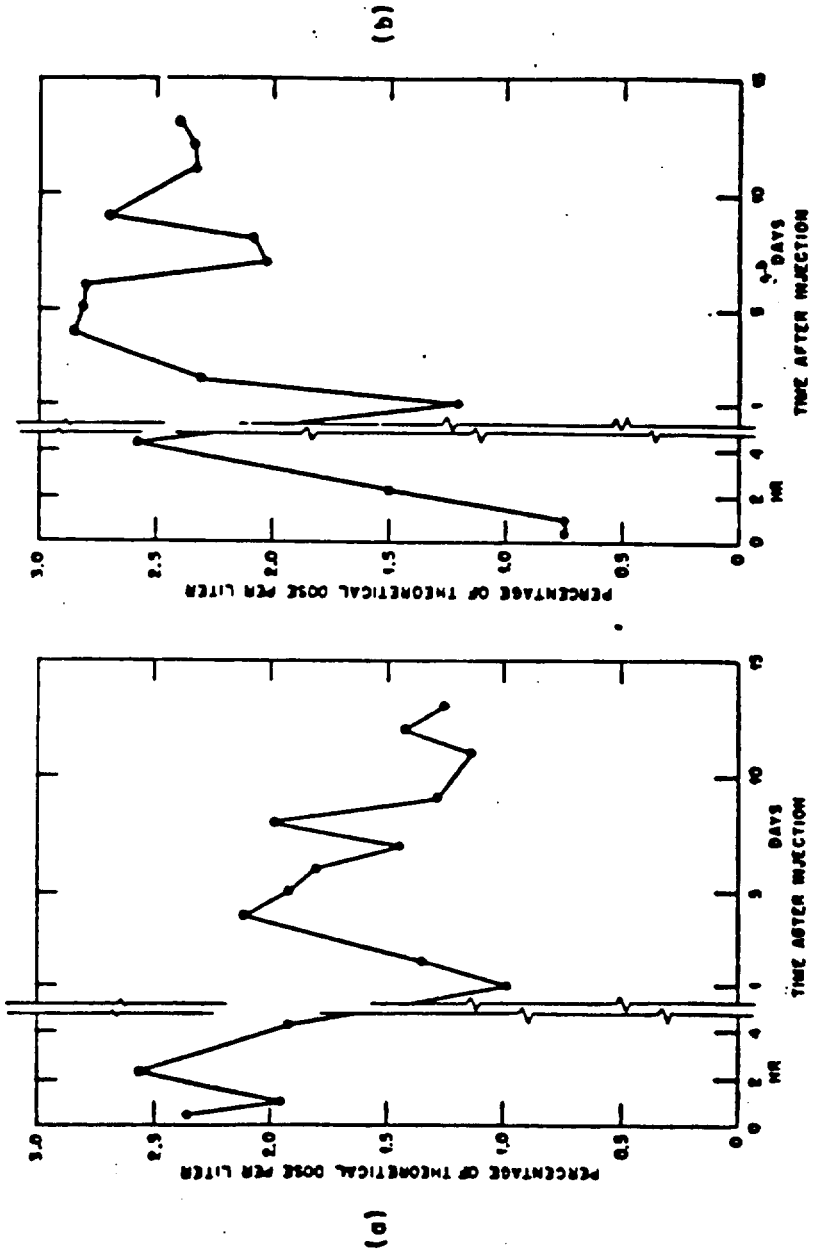

Fig. 3.8—Percentage of the theoretical dose of polonium per liter in plasma and blood cells of subject 4 (chronic myeloid leukemia) after intravenous administration of 0.18 microcurie of polonium chloride per kilogram of body weight. (a) Plasma. (b) Cells.

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was lower than in the previous cases. The daily excretion showed a very gradual decrease during the next 12 days, with an average daily value of 0.05 per cent of the theoretical dose. Concentrations remained fairly constant at a level about one-tenth of that found in the first sample.

The loss from the blood stream was not quite so rapid as in subject 3. An estimated 5.2 per cent of the theoretical dose was in the total circulation 25 min after injection. The lowest observed blood value was at 23 hr, when the total blood content was about 3.4 per cent and the total plasma content was about 1.8 per cent of the theoretical dose. The concentration in both cells and plasma rose again (in cells more than in plasma), so that the highest whole-blood value, 2.3 per cent of the theoretical dose per liter, was seen at four and five days. Separate red and white cell analyses, performed on two occasions, showed a higher concentration in white cells. At 23 hr 1.1 per cent of the theoretical dose per liter was in red cells and 1.5 per cent in white cells; at four days red cells contained 2.7 per cent, and white cells 4.1 per cent. The table and figures show the calculated combined cell values for these periods in order to be consistent with other data on total cells.

2. COMPARISON OF INTRAVENOUS STUDIES

By H. E. Silberstein, W. N. Valentine, W. L. Minto, J. S. Lawrence, and R. M. Fink

The combined data on the urinary and fecal excretion of polonium by the four human subjects, as compared with the average data from our intravenous experiments with rats, are given in Table 3.9. Human urinary excretion appears very similar to the rat's and much lower than that found in our single rabbit experiment. The average human values shown are somewhat higher than the rat values during the first four days, but the difference is contributed by the moribund, jaundiced subject 2 and by subject 3, who showed some clinical evidence of renal malfunction. Evidence is found, at least in the case of subject 1, of a somewhat more rapid decrease in the human urinary excretion rate than was found for the rats. The scanty data on human fecal excretion fall below the average rat data for the first week, showing a more prolonged lag in reaching the maximum daily rate. Yet they are generally within the range of results obtained in the individual rat experiments. In general, then, human and rat excretion data, as well

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as human, rat, and rabbit tissue data as discussed under case 2, appear to be quite similar in most respects when polonium has been administered intravenously.

Table 3.9—Summary of Data on Daily Urinary and Fecal Excretion after Intravenous Injection of Polonium Chloride in Human Subjects and Rats

Days after injection	Urinary excretion, % of dose* per day						Fecal excretion, % of dose* per day			
	Subject No.				Human average	Rat average	Subject No.		Human average	Rat average
	1	2	3	4			1	3		
1	0.20	0.84	0.081	0.069	0.300	0.190	0.44	0.21	0.32	1.74
2	0.048	0.137	0.125	0.083	0.094	0.063	1.35	0.76	1.05	3.2
3	0.056	0.190	0.153		0.133	0.065	1.37	0.76	1.06	3.9
4	0.038	0.114	0.146	0.056	0.113	0.088	1.92	0.25	1.09	3.5
5	0.031	0.107		0.064	0.067	0.078	3.55		3.55	3.0
6	0.030	0.044	0.059	0.060	0.048	0.079	4.16	0.39	2.27	2.4
7	0.021		0.157	0.052	0.077	0.056	0.82	1.00	0.96	1.89
8	0.033		0.088	0.053	0.057	0.060		0.17		1.71
9			0.080	0.044	0.062	0.062		1.15		1.63
10			0.103		0.103	0.077		0.85		1.57
11			0.077	0.044	0.060	0.040		1.70		1.45
12				0.040		0.049				1.49
13			0.059	0.038	0.048	0.057		0.72		1.09
14			0.080		0.080	0.089		0.41†		0.97
15			0.070		0.070	0.048		0.41†		0.98
16			0.069		0.069	0.051		1.06†		1.06
17			0.140		0.140	0.052		1.06†		0.95
18			0.056		0.056	0.053				
39 or 43	0.016		0.043		0.030	0.058		0.59		0.44
70			0.021		0.021	0.036		0.25		0.25

*Dose taken as total amount recovered in the rat, and as the amount in the dummy-injection solutions in the human studies.

†Value represents half a 48-hr collection.

An apparently real difference between man and rat with respect to polonium metabolism is seen in the blood data (see Table 3.10). The concentration of polonium fell more slowly in the human plasma and more rapidly in the human cells and whole blood than was the case in the rat experiments.

3. ORAL ADMINISTRATION

By H. E. Silberstein, W. N. Valentine, W. L. Minto, J. S. Lawrence, and R. M. Fink

Case 5. Subject 5, a male patient hospitalized for x-ray treatment of chronic myeloid leukemia, was given 18.5 microcuries of polonium chloride in 2 ml of 0.3N acid, diluted in a glassful of tap water just

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before drinking. This oral dose was equivalent to 0.19 microcurie per kilogram of body weight. Starting 1 hr after the ingestion, four blood samples of 5 ml each were drawn at 2-hr intervals during the first day. Thereafter the samples were taken at the end of each 24-hr

Table 3.10 — Relative Concentrations* of Polonium in Plasma, Blood Cells, and Whole Blood of Human Subjects and Rats

	Days after injection	Subject No. 1	2	3	4	Human average	Rat average	No. of rats	Rat range
Blood plasma	1	1.2	1.0	0.45	0.48	0.78	0.03	1	
	2 or 3	1.1	1.3	0.83	0.64	0.92			
	5 or 6	1.0	0.7	0.54	0.92	0.79			
	9,10, or 11			0.50	0.62	0.56	0.10	4	0.04–0.16
	18			0.38		0.38			
	40 or 43	0.30		0.27		0.28			
	50						0.01	4	0.03–0.11
	71			0.13		0.13			
Blood cells	1	5.3	3.4	0.76	0.58	2.5	5.5	1	
	2 or 3	6.7	2.6	0.93	1.15	2.9			
	5 or 6	5.9	1.5	1.40	1.36	2.5			
	9,10, or 11			1.40	1.13	1.3	2.4	3	2.1–2.6
	18			1.09		1.1			
	40 or 43	0.7		0.48		0.59			
	50						3.9	4	3.0–4.7
	71			0.21		0.21			
Whole blood	1	2.8	1.4	0.63	0.53	1.3	2.6	1	
	2 or 3	3.5	1.5	0.86	0.82	1.7			
	5 or 6	3.4	1.0	1.0	1.1	1.6			
	9,10, or 11			0.86	0.86	0.86	0.94	3	0.87–1.06
	18			0.64		0.64			
	40 or 43	0.4		0.29		0.35			
	50						1.7	4	1.1–2.0
	71			0.17		0.17			

*Data adjusted for differences in body weight by multiplying the concentration expressed as percentage of dose per gram by ⅙ of the body weight in grams.

period. The urine samples of the first few hours were also kept separate for analysis, but after the first day they were pooled in 24-hr collections. All stool specimens represented 24-hr collections, except on two occasions when 48-hr stools were passed. After the patient's discharge from the hospital, he continued to bring specimens when he came in for checkups. The data are shown in Tables 3.11 and 3.12 and in Figs. 3.9 to 3.11.

A small amount of the ingested material was found in the first urine sample, collected at 2½ hr. Although about 20 per cent of the first day's urinary output was excreted during the first 7 hr, it is clear from the urine-concentration figures that the excretion rate lagged until some time after 7 hr. On the fourth day the urine content showed

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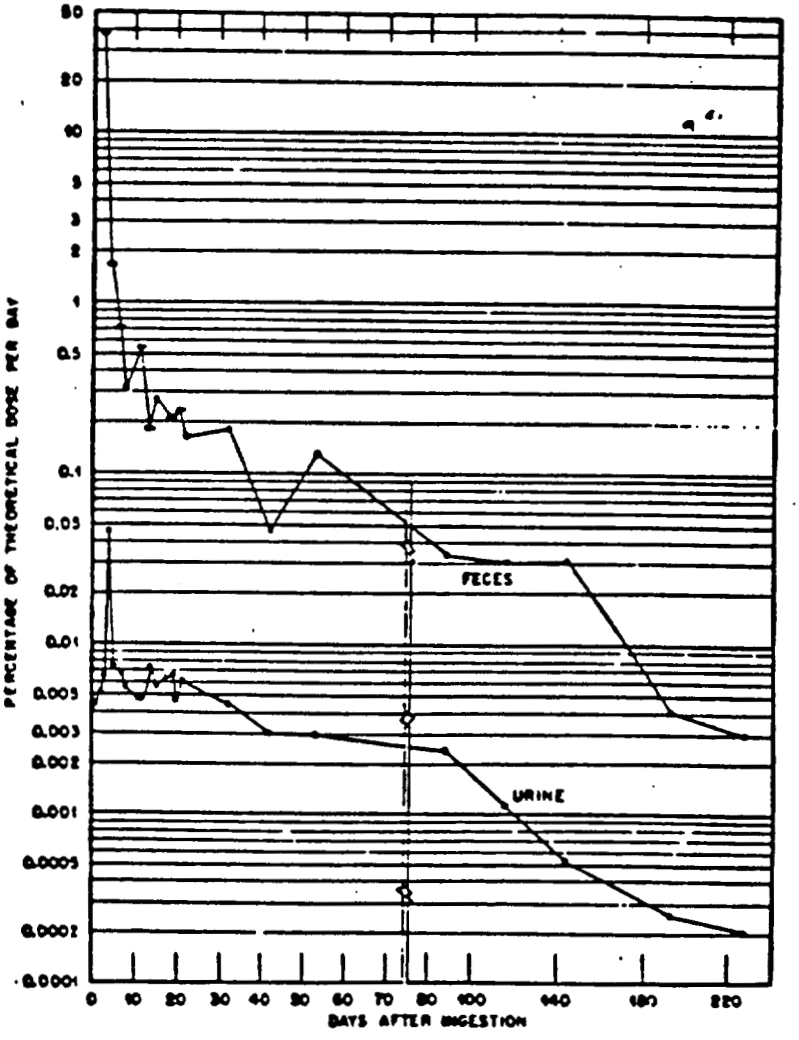

Fig. 3.9—Urinary and fecal excretion of polonium by subject 5 (chronic myeloid leukemia) after oral administration of 0.19 microcurie of polonium chloride per kilogram of body weight. Dots and circles represent single 24-hr collections. Dashes represent daily averages taken from 48-hr collections.

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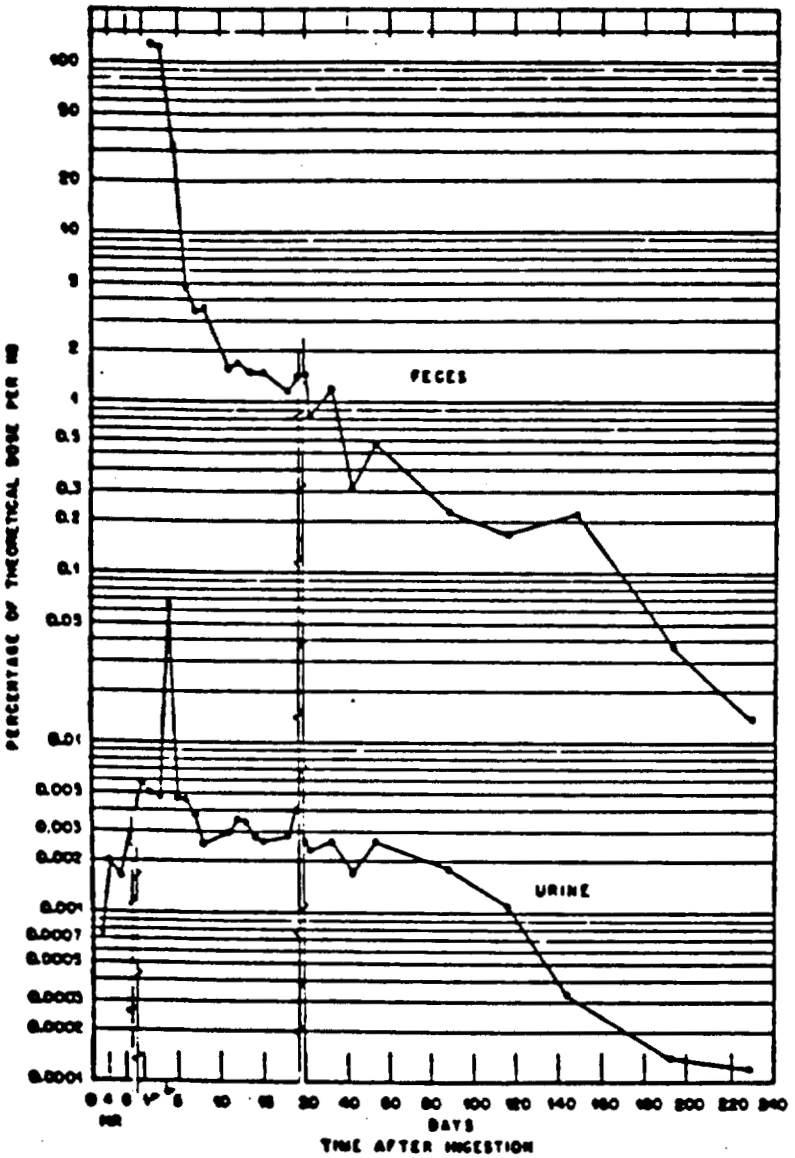

Fig. 3.10 — Percentage of the theoretical dose of polonium per kilogram in urine and feces of subject 5 (chronic myeloid leukemia) after oral administration of 0.19 microcurie of polonium chloride per kilogram of body weight.

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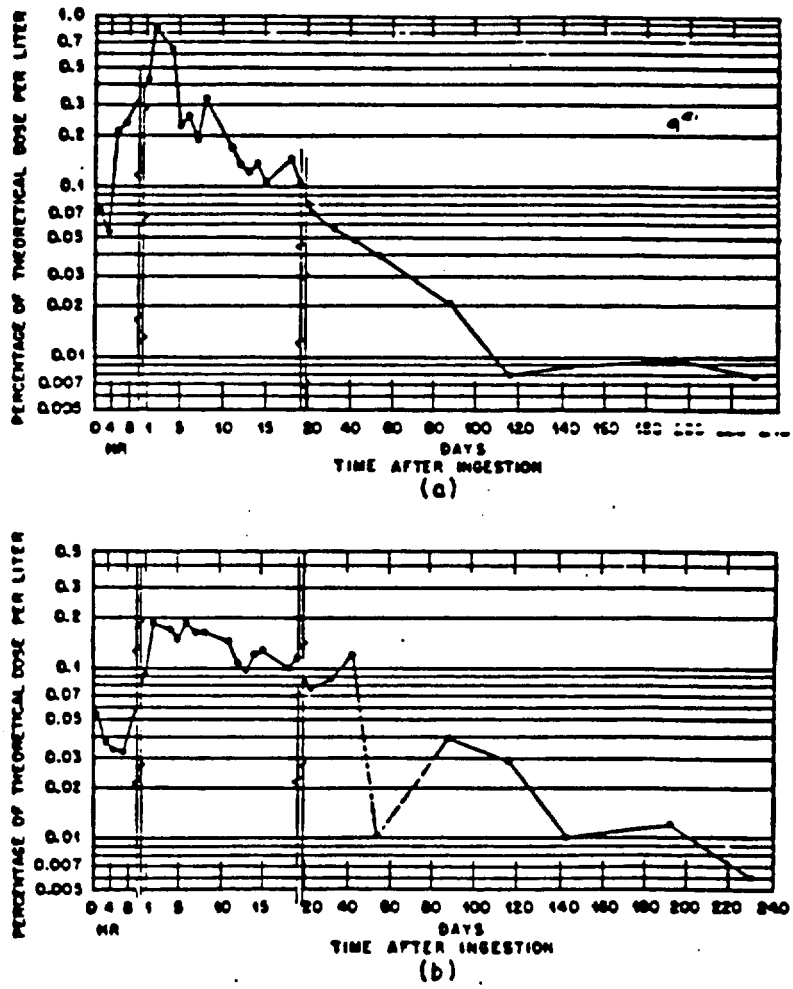

Fig. 3.11 — Percentage of the theoretical dose of polonium per liter in plasma and blood cells of subject 5 (chronic myeloid leukemia) after oral administration of 0.19 microcurie of polonium chloride per kilogram of body weight. (a) Plasma. (b) Cells.

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Table 3.11 — Percentage of Theoretical Dose in Urine and Feces of Subject 5 (Chronic Myeloid Leukemia) after Oral Administration of 0.19 Microcurie of Polonium Chloride per Kilogram

Time after ingestion	% of theoretical dose excreted		% of theoretical dose per liter in urine	% of theoretical dose per kilogram in feces
	Urine	Feces		
Hr				
0–2.5	0.00020		0.00075	
2.5–4.5	0.00032		0.0020	
4.5–7	0.00035		0.0018	
7–24	0.0037		0.0058	
Days				
1	0.0045	0.00065		0.0036
2	0.0052	40	0.0050	126
3	0.0066	36	0.0047	122
4	0.046		0.064	
5	0.0074	3.3*	0.0047	33
6	0.0073	1.33	0.0048	4.7
7	0.0067	0.118	0.0037	3.4
8	0.0056	0.32	0.0025	3.6
11	0.0048	0.90	0.0029	1.6
12	0.0047	0.171	0.0035	1.7
13	0.0053		0.0034	
14	0.0071	0.37*	0.0028	1.5
15	0.0057	0.27	0.0026	1.5
18	0.0064	0.135	0.0028	1.15
19	0.0065	0.28	0.0040	1.41
20	0.0047	0.26	0.0026	1.48
21	0.0059	0.21	0.0024	1.32
22	0.0058	0.162	0.0023	0.83
32	0.0044	0.181	0.0026	1.20
42	0.0030	0.046	0.0017	0.31
53	0.0029	0.129	0.0026	0.86
88	0.0023	0.037	0.0018	0.23
116	0.00113	0.031	0.0011	0.17
144	0.00052	0.032	0.0003	0.22
183	0.00025	0.004	0.0001	0.04
227	0.00020	0.003	0.0001	0.01

*Collection for 48 hr.

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a sudden tenfold increase to nearly 0.05 per cent of the theoretical dose, an amount comparable to the early excretions following the intravenous administration of similar doses. If not due simply to con-

Table 3.12 — Percentage of Theoretical Dose per Liter in Blood, Plasma, and Cells of Subject 5 (Chronic Myeloid Leukemia) after Oral Administration of 0.19 Microcurie of Polonium Chloride per Kilogram of Body Weight

Time after ingestion	Percentage of theoretical dose per liter		
	Whole blood	Plasma	Blood cells
Hr			
1	0.06	0.072	0.054
3	0.05	0.054	0.038
5	0.13	0.21	0.034
7		0.24	0.033
26	0.26	0.42	0.092
Days			
2	0.53	0.85	0.184
4	0.42	0.83	0.172
5	0.19	0.23	0.150
6	0.22	0.26	0.184
7	0.18	0.188	0.162
8	0.26	0.33	0.166
11	0.16	0.168	0.146
12	0.12	0.134	0.110
13	0.11	0.121	0.100
14	0.13	0.133	0.122
15	0.11	0.105	0.127
18	0.13	0.145	0.102
19	0.11	0.103	0.115
20	0.080	0.078	0.084
21	0.084	0.084	0.085
22	0.075	0.071	0.079
32	0.071	0.057	0.089
42	0.083	0.049	0.122
54	0.026	0.040	0.010
88		0.021	0.039
118	0.014	0.008	0.019
144	0.009	0.009	0.009
193	0.011	0.010	0.012
228	0.007	0.008	0.006

tamination, this phenomenon might conceivably be related to the retention of feces during the same day, possibly causing a somewhat higher absorption rate in that period. Except for the fourth day, the daily urine values remained fairly constant for 30 days, fluctuating

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between 4.5 and 7.4×10^{-3} per cent of the theoretical dose, and then gradually declined to 2×10^{-4} per cent at 227 days after the beginning of the experiment.

The fecal elimination of the ingested polonium was negligible during the first 24 hr, but by the end of the third day 76.5 per cent of the theoretical dose had been eliminated by this route. This elimination rate then fell sharply to less than 1 per cent of the dose per day by seven days. Between 11 and 32 days it remained at about the level of 1 per cent of the theoretical dose per kilogram of feces, thereafter decreasing gradually to a concentration of 10^{-5} per cent per kilogram or about 3×10^{-3} per cent per day, 227 days after ingestion. In plotting the daily fecal excretion data in Fig. 3.9 the average of two consecutive days was used, wherever possible, in order to equalize the misleading irregularities in defecation. Daily total urinary excretions are also shown in Fig. 3.9, and the concentrations in terms of percentages of the theoretical dose per kilogram of feces or per liter of urine are plotted in Fig. 3.10.

As shown in Table 3.12, the polonium had already appeared in the od stream within 1 hr after ingestion. The highest observed blood lue was 0.5 per cent of the theoretical dose per liter of whole blood at 48 hr. No blood sample was obtained on the third day, when the peak concentration most likely occurred. After the fourth day the whole-blood content decreased steadily to about 0.01 per cent of the theoretical dose per liter by the 116th day. The uptake in cells was approximately one-fifth of that in the plasma during the first four days. Thereafter plasma and cell concentrations remained essentially the same. This situation is in sharp contrast with rat ingestion experiments, in which, at 10 days, the cell concentration was found to be about 100 times that of the plasma. Plasma and cell values are shown graphically in Fig. 3.11. The broken lines to and from the 54-day cell value are used to indicate an obvious question concerning the accuracy of that particular determination. At 228 days the blood activity was barely detectable, registering only 0.007 per cent of the theoretical dose per liter.

Any attempt to estimate the absorption of polonium from the gastrointestinal tract on the basis of the data available in this case would be largely conjectural. The values for both blood and urine are approximately one-tenth of the corresponding values found following the intravenous administration of similar doses. This fact indicates that possibly 10 per cent of the theoretical dose may have been absorbed. The absorbed material may, however, be deposited in such organs or in such a chemical form as to allow it to be more readily mobilized into the blood stream and excreted through the kidneys than after in-ction. Some such process seems to have taken place in the rat

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ingestion experiments, in which the urinary output and the blood concentration, in relation to the amount found in the body after sacrifice, was much higher than in injected animals. If the human shows a similar tendency, the data for subject 5 would indicate that considerably less than 10 per cent of the ingested polonium had been absorbed.

4. RENAL EFFICIENCY IN POLONIUM REMOVAL

By H. E. Silberstein

With a considerable collection of data available from these studies, it seemed that some expression of the effectiveness of the kidneys in removing polonium from the blood stream would be useful. Aub et al.[1] have shown, for one human radium-poisoning case, that only about 1 per cent of the radium present in the blood stream at any one time was excreted per day in the urine, that is, less than 0.01 per cent of the amount that passed through the kidney circulation. Similar estimates on the basis of whole-blood content in our five human subjects, as well as in several rat experiments, gave about the same value for polonium removal as for radium.

Removal of plasma constituents is, however, usually considered the better expression of kidney efficiency inasmuch as that fraction is presumably more available for excretion. Total polonium in the circulating plasma at the end of each 24-hr period was calculated from estimated individual blood volumes and from hematocrit and polonium concentration values of each sample. The polonium in each day's urine was then expressed in terms of percentage of the total polonium in plasma at the end of the corresponding period. This value remained essentially the same in each case throughout the period of observation in spite of daily fluctuations. Both subject 4, an intravenous subject with apparently normal kidney function, and subject 5, the oral-administration case, excreted on the average 1.5 per cent of their plasma polonium every 24 hr. The assumption, made by Aub et al., of 100 passages of the blood through the kidneys per day would indicate that less than 0.02 per cent was continuously removed. Subject 3, an intravenous case with slight evidence of renal malfunction, showed a somewhat higher average rate of 0.05 per cent continuously removed from the circulating plasma.

Calculation of standard clearances for polonium in these experiments, as well as from single sets of blood and urine data on a few laboratory workers who had assimilated detectable amounts of polonium, yielded extremely low values ranging from 0.01 to 0.08 ml of whole blood cleared per minute. The average concentration of polonium for each of the last three experimental subjects fell close to an

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over-all average of 0.04 ml. Clearance values during the first few hours after injection were somewhat higher than the individual average, whereas in the early period after oral administration they were lower than the average. A very cursory glance at the literature reveals that these values for polonium clearance by the kidneys are considerably lower than for some similar metals. Arsenic, for example, may be cleared 100 to 200 times faster, and selenium at least 50 times faster, than polonium. Whether this is due to extremely slow glomerular filtration or to a high tendency for reabsorption of the material is impossible to say at present.

5. RED CELL UPTAKE OF POLONIUM IN VITRO

By A. T. Gorham

A short experiment to determine the in vitro uptake of polonium by red cells was undertaken for several reasons: (1) to ascertain whether the relative distribution of polonium between the cells and plasma in the early samples drawn from human subjects was actually the distribution obtained at the time the samples were drawn, or whether distribution could change while the blood samples were being handled in the laboratory, (2) to determine whether any detectable in vitro differences existed between rat and human red cells with respect to their in vitro uptake of polonium similar to the apparent differences noted in the in vivo experiments, and (3) to check literature reports of direct hemolytic action of alpha particles.[8]

Results obtained with three human and two rat blood samples are shown in Fig. 3.12. The human blood was drawn, heparinized, and kept under sterile conditions in paraffined tubes. The rat blood samples consisted of pooled collections from three rats, from which blood from the femoral vein was allowed to drip into heparin in paraffined tubes under semisterile conditions, i.e., after treatment of the instruments and the skin around the incision with 70 per cent alcohol. The polonium was added in a very small volume of neutral isotonic saline. The data show that as blood containing polonium stood in the laboratory at room temperature for increasing periods of time, progressively higher proportions of the polonium could be centrifuged with the red cell fraction; the data also indicate that the proportion in the cell fraction increased more rapidly in rat blood than in human blood.

The ratio of red cell concentration to plasma concentration in the first few hours after the intravenous injection of polonium into human subjects rose much more rapidly than in the tests in vitro. Accordingly, it seems improbable that an increase in the cell concentration

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in vitro during the time between the taking of the blood sample and the final separation of cells and plasma (generally 30 to 90 min) had an important effect on the results obtained.

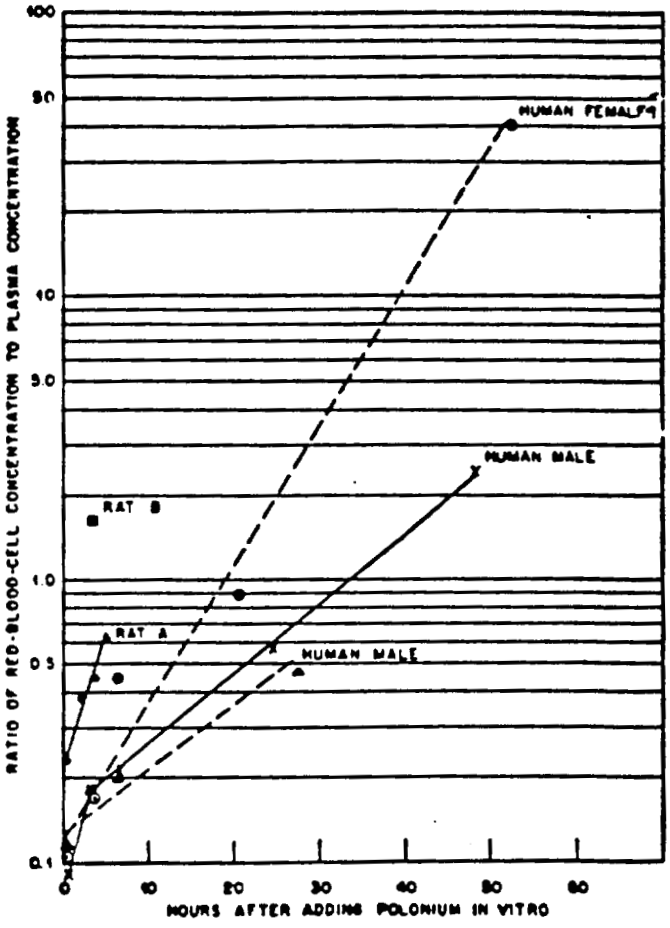

Fig. 3.12—In vitro uptake of polonium by blood cells of human subjects and rats.

Human blood to which had been added 0.5 microcurie of polonium per milliliter showed no hemolysis after standing 24 hr and only a slight hemolysis, similar to that shown by a control sample, after 52 hr. Such a concentration of polonium would be expected in the blood only after the intravenous administration of about 1,000 microcuries per kilogram. Since 200 microcuries per kilogram was fatal to rats

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within a week, it may be concluded that the possible direct destruction of red cells by alpha particles is of no clinical significance in polonium poisoning. The pooled rat blood samples hemolyzed quickly, either with or without the addition of polonium, and attempts to detect cell damage due to polonium were unsuccessful.

No convincing evidence has yet been obtained as to whether the polonium actually becomes attached to the red blood cells or merely goes into a colloidal form that can be swept down with the cells during centrifugation. The point might be settled by an auotradiograph of a very dilute blood smear, but preliminary attempts along this line have not been successful.

6. ABSORPTION OF POLONIUM THROUGH HUMAN SKIN

By R. M. Fink

An experiment was carried out to determine the possibility of detecting absorption through the skin by a direct measurement of the amount of activity remaining on the skin. A 0.01-ml drop of an isotonic saline solution of polonium chloride containing 2,000 counts per minute was placed on a finger tip and allowed to dry. The activity was measured by clamping the finger in an accurately reproducible ition in front of a portable ionization chamber, and the meter sen- rity was checked by means of a similar droplet of solution dried on a metal rod, which could substitute for the finger in the clamping arrangement. A plastic guard kept the finger from contacting any objects except during actual measurement. Immediately after the drop had dried, the activity on the finger measured 9 per cent less than the activity on the metal rod, owing probably to the poorer geometry in the case of the finger. A rather bumpy curve of loss of activity from the finger was obtained, the reading being down to 94 per cent of the original value in 4 hr, 89 per cent at 10 hr, 85 per cent at 15 hr, 84 per cent at 24 hr, 80 per cent at 30 hr, 80 per cent at 48 hr, and 70 per cent at 96 hr. Unfortunately, from the minute the ventilated finger guard was put on, the finger started to collect dust, dirt, lint, and dried perspiration, most of which refused to blow off in a gentle air stream. Accordingly, at the end of the 96-hr test period a portion of the fuzz on the finger was removed gently with a camel's hair brush, whereupon the activity reading rose from 70 to 76 per cent of the original activity. Since the finger was still quite dirty, it was then rinsed in distilled water, and the activity rose still higher, going back to 90 per cent of the original reading. Measurement of the activity in the distilled-water rinse showed it to contain 13.5 per cent of the active material originally placed on the finger, or 3.5 per

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cent more than the difference between the original and final readings of the finger. The finger was then rinsed in Clorox (sodium hypochlorite), and the activity dropped to less than 100 counts per minute. Unfortunately the sodium hypochlorite interfered with the plating out of polonium on silver, and the amount of solids in the solution prevented the accurate reading of an evaporated sample, so that no check of the amount of activity in the second rinse solution was obtained except for proof that it contained more than 50 per cent of the original activity. It was not expected that anything less than complete absorption of the activity would give readable quantities in the urine unless the urinary excretion were superefficient, as was apparently the case in the stomach-tube experiments with rats. Urine counts that had been running from 1 to 3 counts per minute per 24-hr collection before the experiment started dropped to 0.3 count per minute on the first day of the experiment and were therefore discontinued. At one point during the experiment a drop of kerosene was accidentally spilled on the test finger, and the activity after the kerosene dried measured the same as before. As was expected, the principal conclusion from the experiment is that absorption of polonium through the human skin is too slow to be accurately measurable by methods involving the measurement of the amount remaining on the skin. If, as seems probable, the method used is accurate to ± 10 per cent, it may be concluded that the polonium chloride present on the hands was absorbed at a rate not exceeding 2 per cent per day.

7. SUMMARY

The rates of excretion of polonium by four human subjects, injected intravenously with 0.17 to 0.3 microcurie of polonium per kilogram of body weight, were of the same order of magnitude as those observed in experiments with rats. During the first week after injection their average daily urine content was 0.1 per cent of the theoretical dose. In two cases, followed for longer periods, this daily average fell to about 0.06 per cent during the second week and to 0.03 per cent at 40 days. On a single observation the urine collected on the seventieth day after injection contained 0.02 per cent of the theoretical dose. Polonium was eliminated in the feces at a level 10 to 20 times higher than in the urine. Fecal analyses on two of the subjects showed an average daily output of 1.5 per cent of the theoretical dose during the first week. The subject whose early fecal contents had been the lower of these two continued to excrete amounts fluctuating around 0.8 per cent of the theoretical dose per day for another two weeks and then dropped to 0.6 per cent at 40 days and 0.25 per cent at 70 days.

Evidence of the rapid disappearance of injected polonium from the blood stream was found by early sampling in two cases. Within the

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first half hour the average total circulating polonium was less than 5 per cent of the theoretical dose. The whole-blood concentration at the end of 24 hr in the four cases averaged 2 per cent of the theoretical dose per liter. Each case showed a moderate rise, more marked in cells than in plasma, between three and five days after injection, the average at three days being 2.7 per cent of the theoretical dose per liter of blood. The values then fell gradually to about one-tenth of this level at 70 days. The concentration in cells was generally two or three times greater than in plasma, and somewhat greater in white blood cells than in red blood cells. The uptake by cells was found to be more rapid in the animal body than in experiments in vitro at room temperature.

Following the ingestion of polonium in the one case studied, traces of the material appeared rather soon in the blood and urine, but the total absorption was probably less than 10 per cent of the theoretical dose. The first blood sample, taken 1 hr after administration, contained 0.06 per cent of the theoretical dose per liter. After 48 hr the whole-blood concentration was 0.5 per cent per liter, and this very gradually fell to a barely detectable amount, less than 0.01 per cent of the theoretical dose per liter, 225 days later. Plasma concentration rose more rapidly in the early period, but after the first week plasma and cell concentrations were similar. By the end of the first 2½ hr the urine contained 2×10^{-4} per cent of the theoretical dose, but the most rapid early excretion rate, 0.006 per cent per liter, occurred during the latter two-thirds of the first day. Daily urinary excretions were 5 to 7×10^{-3} per cent of the theoretical dose for 30 days after ingestion and then gradually fell to 2×10^{-4} per cent at 230 days. Fecal elimination was 77 per cent of the theoretical dose by the end of three days, averaged 0.26 per cent of the theoretical dose per day between 10 and 30 days, and finally fell to 3×10^{-3} per cent at 230 days. By this time probably less than 0.6 microcurie remained in the body, giving 10^{-4} microcurie per day in feces and 10^{-8} microcurie per day in urine.

A brief experiment to test the absorption of polonium through the human skin indicated that it was absorbed at a rate not exceeding 2 per cent of the dose per day.

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