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.

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.

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

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.

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 [redacted] demands of the war, individuals were placed in positions [redacted] r capabilities could produce maximum benefit to the Project [redacted] 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

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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

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-1658, 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.

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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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 subjects 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 lymphosarcoma. The polonium was administered in 10 ml of sterilized isotonic saline solution at pH 7.6. In order to determine as accurately as possible the amount actually administered, a second 10-ml sample of the solution was immediately drawn into the syringe used for the injection and was expelled into an acid solution at approximately the rate used for the actual injection. The acid solution was set aside for subsequent radioactivity measurement. This dummy-injection procedure has been followed routinely and is quite necessary in huma.

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

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 ed in cells than in plasma, between three and five days after in- ion, 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 $2^1/_2$ 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 pe between 10 and 30 days, and finally fell to 3×10^{-3} per cent at days. By this time probably less than 0.6 microcurie remained in the body, giving 10^{-4} microcurie per day in feces and 10^{-5} 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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