701337

Uranium · Plutonium Transplutonic Elements

Contributors

W. J. Bair · J. E. Ballou · B. Bleaney · G. W. Dolphin · P. W. Durbin
A. Ghiorso · J. E. Gindler · J. W. Healy · H. C. Hodge
D. A. Holaday · J. B. Hursh · W. H. Langham · A. de G. Low-Beer
J. F. Park · H. M. Parker · C. L. Sanders · L. M. Scott
G. T. Seaborg · N. L. Spoor · J. N. Stannard · D. M. Taylor
J. Vaughan · C. L. Yuile

Editors

H. C. Hodge · J. N. Stannard · J. B. Hursh

With 243 Figures

RECEIVED
LASL LIBRARIES
1974

Springer-Verlag New York · Heidelberg · Berlin 1973

LANL

0004838

rd Works at Richland,
ı and criticality potential
ɔlutonium being handled
oses of the U.S. Trans-
posal and environmental

f plutonium as an actual
he amounts on a weight
he high probability for
ıre have caused growing
medicine of plutonium.
ɔh extends back to the
behavior of plutonium
nuclides in the environ-
ɜ unclassified aspects of
ɜenland and Palomeres,
taken wherever possible.
ı this field which has in
lisciplines is emphasized
oth in industry and in
ɜicologic aspects at least
logist-toxicologist. Why
nue much longer to be

ɜs to the several chapter
ɜwaiting the completion
ıks are also expressed to
service in the course of

Chapter 8[1]

Biomedical Aspects of Plutonium (Discovery, Development, Projections)

J. N. STANNARD

I. Foreword

There is probably no single element in the periodic table with a comparable saga of discovery, development, manufacture and use covering a span of only one generation. Uranium and its isotopes along with its daughter products such as radium and radon, have been on the scene for decades. Uranium was known in nature and used in industry long before its possession of radioactivity was known or became of interest and importance. By contrast plutonium was only a theoretical possibility in the late thirties in the minds of MEITNER, BOHR, IRENE JOLIET-CURIE and workers at the Cavendish Laboratory at Cambridge University until SEABORG and his colleagues isolated a tracer quantity of element $^{238}94$ on the night of February 23, 1941, and 0.5 microgram of $^{239}94$ on March 28 of the same year. (The name "plutonium" was not assigned until the following year.) The fact that this element could undergo fission with thermal neutrons was found essentially simultaneously with its discovery and thus began the tremendous effort to produce it in quantity for military purposes. This story is so familiar that nothing further need be added here except to point out that kilogram quantities were available by the summer of 1946 and we are now talking of thousands of kilograms.

If military uses were the end of the saga of plutonium this section of the Handbook would be of much less interest and much shorter. But plutonium is central to the development of electrical power by nuclear fission and to a growing number of other uses in industry and medicine. SEABORG (1969) estimates that the United States will be using 20000 kilograms of ^{239}Pu by 1980, 60000 kilograms in the decade 1980–1990 and 80000 kilograms in decade 1990–2000. Meanwhile the use of the shorter-lived isotope ^{238}Pu for power in space vehicles and other uses is estimated at 10–20 kilograms in 1970–1980, 100 kilograms in 1980–1990, while medical uses will grow from essentially zero now to 5 kilograms in 1980–1990 to some thousands of kilograms in 1990–2000. Even if these estimates are in error there is no question that we already have and will continue to have very sizable amounts of plutonium on hand. An understanding of its biomedical effects, ways to handle it and to avoid its harmful effects in either man or his environment are essential. Such knowledge is clearly within the purview of the modern pharmacologist-toxicologist, to whom this volume is directed, as well as to the radiation biologist and health physicist.

1 Work supported in part by Contract #AT(11-1) 3490 between the U.S. Atomic Energy Commission and the University of Rochester and has been assigned Report #UR-3490-116.

LANL

0004839

II. General Toxicology of Plutonium

It has now become traditional to refer to plutonium as "the most toxic element known to man". In a general sense this may indeed be true. Some of the trans-plutonic elements discussed in Part 3 of this Handbook may exceed plutonium in toxicity on the basis of potential effects per unit of mass or even per unit of activity. Other radioactive elements at the bottom of the periodic table will go plutonium a close second or even exceed plutonium in some aspects of effects per amount deposited. But none of these other elements are expected to be around in the quantities approaching those described above for plutonium. Thus if the presence of potential sources is taken into consideration as part of the potential hazard, plutonium occupies a central position among the radioactive heavy elements whether or not it should turn out to be *the* most toxic element known to man.

The biological effects of the plutonium isotopes of primary interest in biology and medicine, ^{238}Pu and ^{239}Pu (see Chaps. 9 and 10 for discussion of other isotopes of plutonium as well as details concerning 238 and 239), are due internally almost if not entirely to the alpha particles released in their decay. The mass of 1 Curie of Plutonium-239 is 16.28 grams, that of 1 Curie of Plutonium-238 is 57.5 milligrams. Acute effects occur with body burdens measured in microcuries. Long-term effects, our primary concern with plutonium, may occur with nanocuries per gram of tissue. Thus chemical effects of the type familiar to the pharmacologist-toxicologist seem quite unlikely to occur. Chemical toxicity of a type and magnitude per unit of mass wholly new would have to be present for the effect to be significantly a chemical one. The contrast to natural uranium, the subject of Part 1 of this Handbook, is clear. Yet the chemical properties of plutonium, like those of the other elements described in this volume, play a critical role in determining distribution of the element to tissues and organs and its microdistribution within tissues and within cells. These distributions in turn determine the ultimate effects to a degree quite unexpected when biological studies with plutonium and other trans-uranic elements were begun. Thus although the effects are to be considered primarily radiation effects[2] variation in such chemical parameters as valence, polymerism, presence or absence of complexers, etc. are critically important. The study of the effects of plutonium and of the other trans-uranics is thus far from a routine reiteration of well-established radiation effects predictable from the study of external radiation sources or from radioisotopes with very different chemical properties.

In the chapter immediately following this those chemical and physical properties of plutonium of direct bearing on biomedical effects are described in some detail. Those of particular pertinence to its deposition and retention in bone are considered further in Chap. 10.

It was found early on that plutonium injected intravenously deposited largely in and was retained avidly by bone. From this fact behavior analogous to that of radium in bone was anticipated. Grossly and in a qualitative sense this analogy has held. But as work progressed it became clear that the analogy was only a gross one and that plutonium, while a bone-seeker, represented a class of elements

2 This statement should not be taken to mean that *no* chemical effects occur beyond the role of chemistry in distribution and excretion. There is a growing number of facts which are leading investigators to consider that radiation dose alone may not be enough to explain all of the effects of deposited radionuclides. Nevertheless the statement made above that chemical effects if they do play a role would have to be of a type and magnitude not currently understood holds true. Also there are external radiation problems with large quantities of plutonium as detailed in Chap. 14.

LANL

0004840

which behaved very differently in bone than radium. While radium enters the mineral phase (hydroxyapatite) essentially in exchange for calcium, plutonium enters by a more complex route involving interaction with organic ligands and with essentially no simple exchange with calcium. The end result of deposit in bone for a long enough period is osteosarcoma just as occurs with radium. But the details of the process and the accompanying secondary phenomena are quite different and distinct. Because of this Chap. 10 deals extensively with plutonium "as a bone-seeker" both in terms of its behavior, i.e., metabolism, and its effects.

The contrast with uranium is also to be noted. Uranium exchanges for calcium in bone crystal as was made clear in the early work of NEUMAN and colleagues (NEUMAN and NEUMAN, 1948; NEUMAN et al., 1949a and b) and discussed in the first part of this Handbook. The exchange process may not be quite the same as for radium (FORMAN, 1971) but the contrast to plutonium is more marked.

It was also found quite early that plutonium is very poorly absorbed from the gastrointestinal tract. Accepted figures for the fraction going from the gastrointestinal tract to blood are 3×10^{-5} for plutonium isotopes, while a similar figure for radium is 0.3 (ICRP Publication II, 1959). Thus entry into the body by food or water ingestion is negligibly important, quite in contrast again to radium or uranium. Only puncture wounds and inhalation of plutonium in aerosol form are likely routes of occupational or environmental exposure with some exceptions to be noted in later sections.

Much effort has been expended on describing and understanding the metabolism of inhaled plutonium and its effects on lung, lymph nodes, bone and other tissues after inhalation. This work is summarized in Chap. 11 which concentrates on plutonium behavior and effects in soft tissue especially after inhalation.

It can be said with confidence that we have as yet recorded a case where clear-cut biological effects of plutonium deposited in the body have occurred in man. This reflects largely the foresight, engineering and fantastic effort in both resources and manpower devoted since its discovery to protecting workers and the environment from entry of plutonium into man or the biosphere. There have indeed been exposures, primarily from plutonium fires (it is quite pyrophoric), criticality accidents, "broken arrow" incidents (to be described subsequently), and the minute but inevitable introduction of this element into the environment of atomic energy workers and to a still lesser degree the biosphere itself particularly from atmospheric testing of nuclear explosives. But none of these exposures to date have produced body burdens of plutonium either acutely toxic or, by analogy to radium in man, expected to eventuate in detectable increases in the incidence of osteosarcoma.

It would be most unrealistic, however, to downgrade interest, research, and surveillance for plutonium because of these fortunate facts. The time needed to produce osteosarcoma and other forms of cancer in man is only now approaching. There is reason to believe that the body burdens are low enough not to produce cancer in the normal life span and we may escape seeing any cases at all from exposures to date. But even if we are so fortunate as to have no cases whatsoever appear from World War II exposures or those in the two decades since, the increase in quantities used and anticipated to be used, more non-military uses, and sheer probability tells us there will sooner or later be some demonstrated effects in man. Later chapters of this part summarize our experience to date and address the possibilities for the future (Chaps. 10, 11, 14).

Chap. 13 takes up ways to ascertain the body burden of plutonium in man ("Bioassay") while in Chap. 12 is described the fascinating story of how seemingly inadequate biological data, shrewd scientific intuition, and dedication to the

LANL

0004841

protection of workers, population and environment led to development and adoption of protection standards which are closely comparable to those derived today from a much larger body of information.

Before closing this general introduction to the toxicology of plutonium the matter of dosimetry requires attention. The radiobiologist and health physicist use standardized measures of radiation dose such as the rad (absorbed energy equivalent to 100 ergs/gm), the roentgen (a measure of exposure dose for X or gamma radiation, 2.58×10^{-4} coulomb per kilogram of dry air), the rem (rad or roentgen equivalent in man or mammal), and standard nomenclature for radioactivity such as the Curie which is 3.7×10^{10} dis/sec, and its multiples and subunits[3].

Of perhaps greater importance to mention here is the contrast in attitude toward doses and dosimetry between the field in which we are working and more conventional pharmacology and toxicology. Whereas in classical pharmacology and toxicology investigators, indeed all concerned, are usually satisfied to know what amount of drug or chemical was given and by what route, in radiation toxicology this is only the start. The radiation dose is calculated wherever possible *at the probable site of action*. Frequently this means the dose to a "critical organ" or a "target organ". Sometimes it even implies, as described in the section on dosimetry in Chap. 10, the dose to a particular cellular structure or even subcellular structure. Also where there is more than one potentially "critical" organ several such calculations may be done. Such "microdosimetry" is only just beginning in most other areas of toxicology e.g. where the concentration of drug at some critical interface may be considered rather than the amount injected or ingested. While obviously desirable, and made possible by the sensitivity and localization possibilities of radiation measurement instrumentation the lament seen in some of the following chapters that some of these quantities are known imperfectly should be viewed in perspective by the reader of this Handbook. We are fortunate indeed that relatively so much can be said about the dose to the target structure despite some limitations in detail. The classical toxicologist should find this phenomenon both interesting and stimulating as he peruses these chapters.

III. Development of Biomedical Information on Plutonium

The several chapters to follow in this part of the Handbook will concern largely the *present status* of information and concepts regarding the metabolism and effects of this element. In many respects the history of the development of this information is unique (along with that for uranium in quantity and the other transuranics). It clearly is pertinent to the understanding of current work. Also the presentations in other chapters deal primarily with the findings and not the organization of the studies or their background. For these reasons a short summary of the development of biomedical information on plutonium is considered pertinent.

A. Early Beginnings

The recognition of potential biomedical hazards from the new radioactive materials brought into being by the atomic bomb project was essentially simultaneous with the decision to proceed with the project. But the accomplishment

3 The uninitiated pharmacologist-toxicologist can find these units defined in more detail in several places such as the LAPP and ANDREWS text (1971) or introductory radiology treatises.

LANL

0004842

of the first self-sustanining chain reaction on December 2, 1942 made the need for biomedical information urgent. Many details with dates are contained in the chapter herein by LANGHAM and HEALY (Chap. 12) on Maximum Allowable Concentrations and Maximum Permissible Body Burdens of Plutonium.

Much of the early work concerned primarily biological effects of *external* radiation sources. Particular emphasis was placed on those features which were "new" e.g. pile radiations (slow and fast neutrons plus gamma radiation), irradiation from beta particles, and the effects of doses of these in the "tolerance" range. This work had to be done to understand the effects of deposited radionuclides, particularly fission products, as well as in its own right. No attempt is made in this volume to summarize any of these studies since the literature is replete with reviews. (A good overview can be seen in the summary papers contained in a special issue of Radiology entitled "The Plutonium Project", issued in September 1947, and detailed in the bibliography.)

Because of the extremely small quantities of plutonium available in the early phases of the project and the high security classification of all such work the early information perforce involved only small animals and a small group of investigators. The first biological studies were carried out at the Radiation Laboratory of the University of California, Berkeley under the direction of Dr. JOSEPH HAMILTON and his associates. Early reports were "in-house" documents or letters, but the data can be seen in now declassified documents such as those by HAMILTON (1944), SCOTT et al. (1945), CROWLEY, LANZ, SCOTT, and HAMILTON (1946) and later in published papers from the same group (e.g. SCOTT et al., 1948, 1949; COPP, AXELROD and HAMILTON, 1947; and HAMILTON, 1947, 1948).

This work was carried out under the aegis of the Plutonium Project's Health Division which was in turn a part of the Metallurgical Laboratory Organization based at the University of Chicago. These early experiments showed quickly that intravenously injected plutonium went largely to bone, at least in the rat, and announced its potential similarity to radium.

B. The "Plutonium Project" Years

As larger quantities of plutonium became available, other laboratories began biomedical studies of its metabolism and effects. Various studies were undertaken at Chicago, Los Alamos, Rochester, and the Clinton Laboratories at Oak Ridge[4]. The fact that plutonium was indeed a "bone-seeker" was early and easily confirmed (LANGHAM, 1946; VAN MIDDLESWORTH, 1947; R. D. FINKLE, 1946). Details are contained in Chap. 10 and those especially pertinent to radiation protection in Chap. 12. Extension to many species and routes of administration more pertinent to potential exposure of man soon followed as described in some detail in Chap. 10. Comparison to other radionuclides particularly radium and strontium was contained in the Chicago reports (BRUES et al., 1946; LISCO et al., 1947) and to radium and polonium, an alpha emitter which does not seek bone, in the Rochester reports (BOYD et al., 1950a and b; FINK, 1950).

Considerations of relative energy and half-life predicted that plutonium would be less toxic on an energy basis than radium. A factor as high as 50 was proposed

4 The "Plutonium Project" officially encompassed work at the University of Chicago (Metallurgical Laboratory), University of California, Clinton Laboratory near Oak Ridge, Tennessee and the National Cancer Institute in Bethesda, Maryland. Work at other sites such as Rochester, Columbia, Los Alamos, etc. was under other divisions of the Manhattan District, but for the present discussion no distinction is made since we are considering the developments during the *years of* the Plutonium Project.

LANL

0004843

(see LANGHAM and HEALY, Chap. 12 herein for calculation). But the facts were very different. As a carcinogen for the production of osteosarcomas (as well as for many other end-points) plutonium turned out to be considerably *more* toxic than radium. The importance of this for understanding of mechanism is taken up in detail in the chapter on "Plutonium as a bone seeker" (Chap. 10) and its significance to radiation protection decisions in Chap. 12.

C. The Utah Project

Most of the more pertinent information on plutonium effects in the above reports involved small rodents, although a few dogs were used in some acute studies. Also the work naturally had some of the characteristics of the war-time pressures. For this reason, and because the need for work specifically focused on long-term effects was made especially evident by the Plutonium Project studies, a new approach was begun in the early 1950's under the sponsorship of the then new U.S. Atomic Commission. This was to organize a full-scale comparison of several bone-seeking radionuclides in a long-lived animal covering a wide range of doses. The project was domiciled in the Department of Anatomy at the University of Utah, Salt Lake City. The beagle dog was chosen as the test subject and the dosage a single intravenous injection. Because of the cost and organizational continuity required for such an experiment only the specific interest and financial commitment of a governmental agency could bring off such a program successfully. Yet the large national laboratories were off on other tacks, in part at least. Thus was born a new concept in the peace-time support of biomedical research. The proposal was to do the work entirely by contract to a University. This, I believe, was the first such contract for a *specific* long-term study using specific substances[5].

Another new feature was the introduction of a guiding group of experts from nearly all interested laboratories to *plan* the experiments. Known affectionately as "The Founding Fathers", this group planned every phase of the experiments to be done in collaboration with the responsible investigators at Utah. They have kept and been kept in close touch with the work, as exemplified by the proceedings of the 20th Anniversary symposium (STOVER and JEE, 1972) where the "Founding Fathers" took an active part. The success of this particular mode of attack can be seen from the several key symposia sponsored by this group (e.g. MAYS, JEE, and LLOYD, 1969; STOVER and JEE, 1972) and the ubiquitous referencing of their work in the chapters to follow. The patience and dedication of all concerned deserve special mention since this type of research is expensive per unit of new information gained, is likely to lose "glamor" as the years go by, and is fraught with apprehension for the unexpected epidemic or mistake in planning. Yet there seems to be no substitute for the passage of time in unfolding the biological effects of low level exposures to radiation or other agents.

D. Inhalation Studies

While these animal studies at Utah using the intravenous route of entry gave and continue to provide a large body of information on mechanisms of effect and metabolism of plutonium once it had entered the blood stream it was clearly recognized as outlined in Sec. II, that inhalation was the most likely exposure

5 Parallels are seen in the long term inhalation study on uranium dioxide at Rochester described in Part 1, the external radiation and fission product study at Davis, California and several others begun more recently. However, the Utah project was the first one newly organized around so large and specific a task.

LANL

0004844

route of entry to man. In some of the Plutonium Project work (Berkeley and Chicago) small rodents received plutonium by inhalation or intratracheal injection and a very limited amount of information was obtained in man. The earliest report was that of SCOTT et al. (1945) followed by those of ABRAMS et al. (1946, 1947). Some of these were later published in the open literature as cited.

The work indicated long retention times in the lung of the dioxide and considerable dependence on valence state, compound, etc. as described in Chaps. 9 and 10 herein. But the inhalation route was clearly in need of much more thorough investigation, particularly since incidence of pulmonary cancer was reported from placement of radionuclides in the lung at about this time (WAGER et al., 1956). Just at the end of the Manhattan Project days a formal study of the fate and effects of inhaled plutonium was begun at Hanford using larger and longer-lived animals. This developed through the 1950's and 60's at Hanford (now Batelle-Northwest Laboratories) into an effort comparable in scope to that at Utah and it so continues (THOMPSON, 1967; TOTTER, 1972).

The inhalation work was not organized in the same way as the Utah project since much more range-finding work needed to be done before a long-term experiment at low doses could be mounted. Data of pertinence to this central problem are now ready and are reviewed and summarized for the first time in so complete a form in Chap. 11 of this volume.

The University of Rochester Atomic Energy Project was involved through the war years and thereafter in a major experiment with inhaled uranium as well as several on-going programs in other aspects of inhalation problems and had developed a strong group in fundamental aerosol physics. In the early 1950's they built a special facility for experiments with alpha emitters, particularly inhalation experiments. While a considerable fraction of their effort was devoted to ^{210}Po partly as a model for the effects of radon daughters, to long-term and short-term experiments with radon in mice and dogs, and to basic pulmonary mechanism and aerosol studies, a reasonably extensive plutonium inhalation experiment was completed. Dogs were exposed to both ^{239}Pu and ^{238}Pu. These results were described by YUILE, GIBB, and MORROW (1970), and are compared to other work in Chaps. 10 and 11.

These inhalation studies have proven beyond doubt that the metabolism of inhaled plutonium can be and usually is quite different from that of the systemically administered isotope and that the results could not have been predicted from studies using the parenteral route. The importance of the lymphatic system, particularly pulmonary lymph nodes, has been emphasized even though its role in effects is not yet entirely clear. Recently, strong evidence has been presented that plutonium deposited by inhalation can produce pulmonary cancer, in the dog at least, although there are differences between the major studies which need resolution. Thus bone may frequently *not* be the critical organ when certain poorly transportable (i.e. insoluble) compounds of plutonium are inhaled. The bearing of this on determination of maximum permissible air concentrations is obvious as discussed by LANGHAM and HEALY in Chap. 12.

E. Information from Experience with Man

In parallel with these experimental studies every effort was made to gather information on man. As described in Sec. II there is, to date, no documented case of plutonium *effects* in man. However, the efforts in control, bioassay, and tissue analyses of hospital patients and nuclear energy workers who received small amounts of plutonium has resulted in a modicum of metabolic data for man. The

LANL

0004845

primary sources of information are Los Alamos and Hanford, although others contributed, particularly to the hospital patient studies. These show some evident differences between man and experimental animals, particularly in retention times in different organs and in excretion kinetics. The metabolic contrasts are summarized in Chap. 10 and from the point of view of occupational exposure in Chaps. 13 and 14 which take up respectively, bioassay (i.e. radiobioassay) and a detailed consideration of experience with plutonium under conditions of occupational exposure.

A review of the metabolic information obtained from man over the last twenty five years has been published recently by DURBIN both as a UCRL report with very full documentation (DURBIN, 1971) and as a chapter in the Utah anniversary volume cited earlier (STOVER and JEE, 1972). This reexamination and reconsideration of the accumulated information negates some of the older concepts of plutonium metabolism and emphasizes the role, in man, of complex formation with iron analogues such as transferrin.

It also reiterates and strengthens the views gained from animal work that not only is plutonium quite different from those nuclides which exchange for calcium in the way it deposits in bone but that it, along with the other actinides, has a component of concentration and effect in soft tissue of considerably greater importance in understanding its metabolism and effects than is the case with the "volume-seekers".

Of special interest is the work on excretion of plutonium by man. With minute body burdens and a substance with a very long half-life the measurements of amounts of plutonium in urine and feces require the ultimate in painstaking technique and sensitive instrumentation. The fact that excretion kinetics seem to follow a power function of time over a measurement period of five years was clear from the data summarized by LANGHAM (1959). Such information is most useful in attempting to estimate body burden from excreta contents even though it is subject to many restraints. But perhaps most notable is the magnitude of the effort in manpower, resources, and patience necessary and expended to produce this information.

F. Therapeutic Removal

Even though the number of exposures of man has been small the long term toxicity of plutonium is so great relative to many materials that considerable effort has been expended on possible means for therapeutic removal. Most of this work has been published since the middle 1950's and has emanated largely from laboratories with potential exposure situations or ongoing experimental programs. Although the first publications on therapeutic removal came from SCHUBERT (1947, 1955) then at Chicago, the Hanford group has probably been the most active among American laboratories in this area. A fairly considerable effort in this area has also occurred in the United Kingdom.

Although animal experimentation has progressed steadily, as reviewed in Chap. 10, the chances for *bona fide* trial of therapeutic removal methods in man have, fortunately, been scarce. Therefore the field has not been a rapidly progressing one although present practices are clearly based on firmer understanding and the wisdom of experience compared to a decade ago (Chap. 14).

Of the several approaches tried, only the chelating agents and such procedures as pulmonary lavage (MCCLELLAND, 1971) now remain under serious study for possible use in accidental exposure cases in man. The present status of chelation therapy is summarized in this volume as much for its inherent interest to the

LANL

0004846

pharmacologist-toxicologist as for demonstrated effectiveness in therapy. However, there are recent cases which indicate that a considerable fraction of the body burden may be removed if chelation therapy is begun early and handled correctly, particularly if combined with other measures.

G. Work Abroad

The above paragraphs have dealt entirely with work in the United States. Since the production of plutonium during the war years was entirely within the United States this is understandable. Unlike some other aspects of the development of nuclear energy for military purposes, it appears that no work was done with plutonium outside the United States until after World War II. However, every country with a reactor program now has an interest in the field, primarily for monitoring workers and the environment. Several quite extensive programs have developed over the last decade and a half.

The United Kingdom has developed a fluorishing bioassay program for plutonium, and interest in potential environmental contamination and, of course, a considerable research interest and capability in various fundamental aspects as evidenced by the authorship of two major chapters in this part of this Handbook by U. K. scientists.

Work in the Soviet Union on biomedical aspects of plutonium has been and is of considerable magnitude. Much of the Russian work is cited in Chaps. 10 and 11. A fine translation of the book "Problems of Plutonium Toxicology" by BULDAKOV, LYUBCHANSKI, MOSKALEV, and NIFATOV (1969) has been prepared by the Lovelace Foundation (translated by HORVATH, edited by THOMAS, 1970) and is recommended. Although the approach is somewhat different in the U.S.S.R. work, there is general agreement between the Soviet and U.S. work except for matters of detail. As seen in other aspects of radiobiology the Soviet work tends to stress physiological and biochemical, i.e. functional alterations, brought about by the agent rather more than does U.S. work. Also the Soviet work goes much further into detail concerning environmental contamination by plutonium especially from weapons tests, than does that from the U.S.A. at comparable times.

In continental Europe the "Euratom" group (European Atomic Energy Community) has issued regular reports on "the movement of certain isotopes in animals and in man" from the Centre d'Etudes Nucleaires de Fonteray-au-Roses, France (EUR 3918f, 1968; EUR 4527, 1971) and the installation at Saclay, France has an ongoing program with plutonium including an aerosol inhalation facility (LUTZ and ROUVROY, 1966). The Italian counterpart at Casaccia has a well developed laboratory for radiotoxicology (TESTA, 1969, 1970a) and special techniques for the determination of plutonium in biological materials (TESTA et al., 1970b). The primary thrust of many of these programs is not so much the Pharmacology and Toxiology of the element as its determination and control in and around installations where it is in use. However the development of well-equipped laboratories for inhalation studies presages interest and capabilities in these laboratories of importance to the subject of this volume.

Relatively recently Japan has developed a laboratory at the National Institute of Radiological Sciences in Chiba-City specifically for studies of the metabolism and effects of inhaled plutonium (SUZUKI et al., 1971; WATANABE et al., 1971).

The European Institute for Transuranium Elements was set up in 1960 at Karlsruhe, West Germany as part of a major nuclear research center already in operation. Centered around nuclear fuel fabrication and the physical and chemical properties of the various transuranium elements this Institute has 25 alpha

LANL

0004847

laboratories, hot cells for various levels of activity, etc. VAANE (1969) working in this Institute presents a general summary of hazards connected with handling of transuranium elements and methods for personnel protection primarily, it appears, using this laboratory as a model. Again the thrust is primarily hazard control, measurements, and interpretation of the data from the working environment as they bear on good industrial medicine.

Recently a seminar on radiation protection problems relating to the transuranium elements was held under the auspices of the Commission of the European Communities and the European Nuclear Energy Agency. The proceedings (Commission of the European Communities, 1971) provide a good overview of work and views in the European laboratories and the relations between their work and that in other parts of the world. While titled "transuranics" the bulk of the discussions concern plutonium.

Thus capability for study and understanding and interest in the general radiotoxicology of plutonium are quite widespread. But the Centers for broad biomedical studies, particularly long-term effects, are not numerous abroad. This is not surprising in view of the cost in both time and patience of this type of research. Indeed we can feel fortunate that as many groups have entered this field as have been involved. The subsequent chapters will be drawing on nearly all of the major programs described.

IV. Newer Uses of Plutonium

Plutonium-239 as a fissile material of very long half-life will probably continue to be the most abundantly used isotope of this element on a mass basis. The increase in number and size of power reactors and particularly the almost certain addition of the breeder reactor to the nuclear power program brings plutonium from an element whose employment was limited to the military and its control primarily a problem for large governmental projects to an item of commerce. Thus a large increase is to be expected in amounts of this isotope available and in use. SEABORG (1969) predicts that power reactors alone will be producing approximately 10000 kilograms per year of plutonium and heavier isotopes by the year 1975 and that this may rise by a factor of three by 1980. Despite the increase in amounts, however, these developments do not presage any qualitatively new biomedical problems except that the Pharmacologist-Toxicologist is more likely to need some knowledge of the field.

Plutonium-238 with a half-life of about 90 years is now becoming an important isotope. With a significantly long but not too long half-life, alpha particle emission at 5.4 MeV with relatively little contaminating gamma or other "external" radiations the isotope is very useful in heat sources for specialized uses[6]. For example 1 gram of ^{238}Pu will liberate about 42000 watt-hours of energy in ten years while decaying by only 7 per cent in that time (SEABORG, 1969). Such sources are very useful in thermoelectric generators for use in the space program or in other situations of isolation. Many such devices (called SNAP devices for "Systems Nuclear Auxiliary Power") are powering satellites (weather and navigational) and also some components of the manned space program such as sources left on the moon to power long-term scientific experiments. The usefulness of such sources in vehicles for planetary exploration, or indeed for terrestrial power sources in isolated locations is obvious. Despite some problems with purity of isotope these sources are almost unique in requiring relatively little radiation

6 For details of external radiation hazards with plutonium in large quantities see Chap. 14.

LANL

0004848

shielding, e.g. when carried in or on a manned vehicle, because of the almost pure alpha particle emission produced.

Further Plutonium-238 is being considered seriously for new biomedical applications. It is a prime candidate for a radioisotope-powered artificial heart and as a miniaturized power supply for cardiac pacemakers thus eliminating the need for periodic replacement of batteries in such devices. Problems remain before such applications can be very general but projections for amounts of this isotope needed by the late twentieth century presume these problems will be overcome in another two decades at the most. The principal problem is the need for shielding against the small but inevitable amount of neutron and gamma radiation produced in the normal decay of ^{238}Pu and the presence as impurities of other radioisotopes with much larger contributions of external radiation. Thus development of sources of very high degrees of purity is important. The technology is essentially available to do this but the added cost of such purification is an obstacle to general use of such devices in medical practice or research outside of special governmental projects.

There are some potential uses of ^{238}Pu as a pure heat source in medical applications (i.e. not involving conversion to electrical power) but these are not very far along.

The development of these sources brings closer to the pharmacologist-toxicologist in a major medical center a need to know something of the radiobiological phenomena which are described in the subsequent chapters.

Since the specific activity of ^{238}Pu is much higher than that of the more commonly encountered ^{239}Pu the toxicity per unit of mass would be excepted to be higher. This is taken up in Chap. 10 and includes an indication that the 238 isotope may be metabolized somewhat differently from ^{239}Pu. This should be kept in mind in the unlikely but finite possibility of release of ^{238}Pu from a sealed source or environmental contamination with it.

At the present time none of the other isotopes of plutonium show sufficient potential for general use outside of very specialized installations to be considered here.

V. Summary[7]

The chapter is designed primarily to introduce the pharmacologist-toxicologist from another area to the primary features of plutonium toxicology, to guide the reader to the detailed discussions in other chapters, and to provide an historical and prospective overview. While many details are remanded to later chapters and other reviews, the chapter is intended to provide a condensed survey of the principal problems.

The development of biomedical knowledge regarding plutonium is very different from that of uranium, radium, and other naturally occurring radionuclides of long half-life. First produced in 1941 in less than microgram quantity, grams were available in a remarkably short time and this was followed within months by kilogram quantities. As for the future, about 20000 kilograms of the

7 Reference is made herein to many "in-house" documents important to historical perspective; most or all of these can be obtained through the Division of Technical Information Extension, U.S. Atomic Energy Commission by ordering photocopy from Microsurance, Inc., Oak Ridge Microreproduction Center, P.O. Box 3522, Oak Ridge, Tennessee 37830, or the National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia, 22151. If difficulty is experienced the editors will attempt to aid interested readers in obtaining such documents for review or personal use.

LANL

0004849

isotope ^{239}Pu are expected to be needed by 1980, 60000 kilograms in the decade 1980–1990, and 80000 kilograms in the 1990–2000 decade. Amounts needed of the shorter half-life ^{238}Pu will be smaller by weight but very substantial if its shorter half-life and higher specific activity are taken into account. Further, instead of being largely limited to large governmental installations plutonium will almost certainly become in the future more an article of general commerce. Because of the increased quantities and this latter fact more general knowledge of its behavior and potential biological effects is needed among toxicologists and pharmacologists.

Plutonium has often been called "the most toxic element known to man". While not quite true it is indeed a most effective agent in producing long-term effects in the body. Its general toxicology is that of a "bone-seeker" superficially like radium, uranium, or strontium but with many significant differences. Because of its tendency to be a "surface seeker" rather than a "volume seeker" it is markedly more effective than radium on an activity basis in producing damage such as the induction of osteogenic sarcoma. Also the contrast in behavior between inhaled plutonium and that entering by other routes is so large that bone may not be a "critical organ" under conditions of inhalation exposure, and the component of deposition in and damage to soft tissue is much larger than with radium no matter what the route of administration.

The fact that the plutonium isotopes of most interest in biology and medicine are almost exclusively alpha emitters (in terms of internal contamination problems) puts them in a class with many other radionuclides in that effects occur at concentrations far below those associated with conventional "chemical" toxicity. Thus it is commonly assumed that the radiation dose is the prime if not the only cause of biological effect and that this is the more likely because of the high relative effectiveness (RBE) of alpha particles. Chemical properties affect primarily metabolism of the isotopes (absorption, distribution and excretion). Such properties include not only basic chemistry of the element but valence state, compound, complexes, etc. However, it cannot be proven beyond doubt that there is absolutely no chemical toxicity since there is no stable isotope for comparison and actually many inconsistencies persist.

The chapter considers primarily laboratory groups working in the United States both now and in the past. This occurs in part because plutonium was available only in the U.S.A. until the late 1940's and early 1950's. However, an abbreviated and undoubtedly incomplete survey of work and organizations in other countries is included in this chapter so that the technical reader not in the field of radiation toxicology can know where to look in his geographical area.

The chapter concludes with short review of prospective newer uses of plutonium isotopes in the space program and in medicine.

References

ABRAMS, R., SEIBERT, H. C., FORKER, L., GREENBERG, D., LISCO, H., JACOBSON, L. O., SIMMONS, E. L.: Acute toxicity of intubated plutonium. USAEC Report, CH-3875, Metallurgical Lab. Univ. of Chicago (1946).

ABRAMS, R., SEIBERT, H. C., POTTS, A. M., FORKER, L. L., GREENBERG, D., POSTEL, S., LOHR, W.: Metabolism and distribution of inhaled plutonium in rats. USAEC Report MDDC-677, Metallurgical Lab. Univ. of Chicago (1947).

BOYD, C. A., SILBERSTEIN, H. E., FINK, R. M., FRENKEL, A., MINTO, W. L., METCALF, R. G., CASARETT, G., SUTER, C. M.: Pilot studies of the intravenous lethal dosage of polonium, plutonium and radium in rats. Chap. 7 in Biological studies with polonium, radium and plutonium, Ed. R. M. FINK, NNES, Div. VI, vol. 3, p. 211–294 (1950a) [also Report M-1878 (1946)].

LANL

0004850

Boyd, C. A., Williams, A., Minto, W. L., Tiedeman, D. V., Fink, R. M., Casarett, G., Metcalf, R. G.: Simultaneous studies on the intravenous lethal dosage of polonium, plutonium and radium in rats. Chap. 8 in Biological studies with polonium, radium and plutonium, Ed. R. M. Fink, NNES, Div. VI, vol. 3, p. 295–404 (1950b) [also Report M-1902 (1946)].

Brues, A. M., Lisco, H., Finkel, M.: Carcinogenic action of some substances which may be a problem in future industries. USAEC Report No. MDDC-145, July (1946).

Buldakov, L. A., Lyubchanskii, E. R., Moskalev, Y. I., Nifatov, A. P.: Problems of plutonium toxicology. Moscow: Atom Publications 1969. Translation by A. A. Horvath, Edit. by R. G. Thomas, LF-tr-41, UC-48 (1970).

Commission of the European Communities: Radiation protection problems relating to transuranium elements. Proceedings of a seminar sponsored by the Commission and the European Nuclear Energy Agency at Karlsruhe, West Germany, Sept. 1970. Published by Directorate General for Dissemination of Information — C.I.D. as report EUR-4612 d-j-3. Luxembourg, 1971.

Copp, D. H., Axelrod, D. J., Hamilton, J. G.: The deposition of radioactive metals in bone as a potential health hazard. Amer. J. Roentgenol. 58, 10–16 (1947).

Crowley, J., Lanz, H., Scott, K., Hamilton, J. G.: A comparison of the metabolism of plutonium in man and the rat. U.S.A.C.C. Report CH-3589 (1946).

Durbin, P. W.: Plutonium in man: a Twenty-five year review. USAEC Report, UCRL-20850 (UC-41, TID-4500) June 1971, see also chap. VII.2 in Stover and Jee, 1972, op. cit.

EURATOM: Movement de certains isotopes chez les animaux et chez l'homme. Annual Report of European Atomic Energy Community and Commissariat à l'Energie Atomique. Report EUR 3918f, Association No 049-64-3 B1AF, May (1968). Also Annual Report (1969), EUR 4527f (1971).

Fink, R. M. (Ed.): Biological studies with polonium, radium and plutonium. NNES Div. IV — vol. 3. New York: McGraw-Hill 1950.

Finkle, R. D.: The toxicity and metabolism of plutonium in laboratory animals. USAEC, Report No CH-3783, August (1946).

Forman, H.: Translocation of drugs into bone. Handbook of experimental pharmacology, vol. XXVIII/I, Ed. by B. B. Brodie and J. R. Gillette, chap. 13, p. 249–257 (1971).

Hamilton, J. G.: Metabolism of product. Metallurgical Laboratory Report, No CN-2383, Nov. (1944) (see also MDDC-1018).

Hamilton, J. G.: The metabolism of the fission products and the heaviest elements. Radiology 49, 325–343 (1947).

Hamilton, J. G.: The metabolic properties of the fission products and the actinide elements. Rev. Mod. Physics 20, 718–728 (1948).

International Commission on Radiological Protection: Report of Committee II on permissible dose for internal radiation (1959). ICRP Publication 2, New York-London: Pergamon Press 1959. Also Hlth Phys. 3, 1–380 (1960).

Langham, W. H.: Metabolism of plutonium in the rat. USAEC Report AECD-1914 (Los Alamos Report LADC-472), dated May (1946), declassified April (1948).

Langham, W. H.: Physiology and toxicology of plutonium-239 and its industrial medical control. Hlth Phys. 2, 172 (1959).

Lapp, R. E., Andrews, H. L.: Nuclear radiation physics, fourth ed. Englewood Cliffs, New Jersey: Prentice-Hall 1972.

Lisco, H., Finkel, M., Brues, A.: Carcinogenic properties of radioactive fission products and plutonium. Radiology 49, 361–363 (1947).

Lutz, M., Rouvroy, H.: Description d'un dispositif permet tant la contamination d'animaux de laboratoire par inhalation d'aérosols radioactifs. Report CEA-R 3086 Commissariat a l'Energie Atomique, Centre d'études nucléaires de Saclay, France (1966).

Mays, C. M., Jee, W., Lloyd, R. D. (Eds.): Delayed effects of bone-seeking radionuclides. Proceedings of a symposium held at Sun Valley, Idaho. Salt Lake City: Univ. of Utah Press 1969.

McClelland, R.: Paper presented at Eleventh Hanford Biology Symposium, Richland, Washington, Sept. 1971 (to be published).

Middlesworth, L. van: Study of plutonium metabolism in bone. USAEC Report MDDC-1022, June (1947).

Neuman, W. F., Neuman, M. W.: The deposition of uranium in bone. II. Radioautographic studies. J. biol. Chem. 175, 711–714 (1948).

Neuman, W. F., Neuman, M. W., Main, E. R., Mulryan, B. J.: The deposition of uranium in bone. IV. adsorption studies *in vitro*. J. biol. Chem. 179, 335–340 (1949a).

Neuman, W. F., Neuman, M. W., Main, E. R., Mulryan, B. J.: VI. Ion competition studies. J. biol. Chem. 341 (1949b).

LANL

0004851

The Plutonium Project. Ten papers collected under this title in Radiology 49, 269–365, Sept. (1947)[8].

SCHUBERT, J.: Treatment of plutonium poisoning by metal displacement. Science 105, 389–390 (1947).

SCHUBERT, J.: Removal of radioelements from the mammalian body. Ann. Rev. Nuclear Sci. 5, 369–412 (1955).

SCOTT, K. G., AXELROD, D. J., CROWLEY, J., HAMILTON, J. G.: Deposition and fate of plutonium, uranium and their fission products inhaled as aerosols by rats and man. Arch. Path. 48, 31–54 (1949). Report No CH-3590, Dec. 1945, and MDDC-1276.

SCOTT, K. G., AXELROD, D. J., FISHER, H., CROWLEY, J., HAMILTON, J. G.: The metabolism of plutonium in rats following intramuscular injection. J. biol. Chem. 176, 283–293 (1948).

SEABORG, G. T.: The synthetic actinides — from discovery to manufacture. Amer. Nuclear Soc., San Francisco, Calif., Dec. 2, 1969 (see also chapt 1.1 "Plutonium revisited" in STOVER and JEE, 1972, op. cit.).

STOVER, B. J., JEE, W.: Radiobiology of plutonium, p. 1–552. Salt Lake City: The J.W. Press, Univ. of Utah 1972.

SUZUKI, M., OKABAYASHI, O., WATANABE, S., HONGO, S., OHNO, S.: Studies on the inhalation of submicron plutonium nitrate aerosols in Wistar adult rats. Natl. Inst. Radiol. Sciences (Japan), Pub. 8, "Report of Project on Plutonium" (1971).

TESTA, C.: New radiotoxicological methods used at the Italian Nuclear Center of Casaccia. Comitato Naziconale Energia Nucleare (CNEN), Report CNEN-RT/PROT (69) 44 (1969).

TESTA, C.: Column reversed-phase partition chromatography for the isolation of some radionuclides from biological materials. Analyt. chim. Acta 50, 447–455 (1970).

TESTA, C., MASI, G., MARCHIONNI, V.: Allestimento di un laboratorio per las determinazione di plutonio in campioni biologici: Messa a punta e confronto di vari methodi di analisi. Report CNEN-RT/PROT (7) 14, (1970).

THOMPSON, R.: Biological factors. Chap. 23 in Plutonium handbook. Edit. by O. J. WICK. New York: Gordon and Breach 1967.

TOTTER, J. R.: Biological research with plutonium, 1944–1984, chapt. I.2 in STOVER and JEE, 1972 (op. cit.).

VAANE, J. P.: Hazards connected with the handling of transuranium elements and methods used for the protection of personnel. Actinides Reviews 1, 337–370 (1970).

WAGER, R. W., DOCKUM, N. L., TEMPLE, L. A., WILLARD, D. H.: Toxicity of radioactive particles IA. Intratracheal injection of radioactive suspensions. Hanfords Works Report HW-41500, pp. 61–72 (1956).

WATANABE, S., SUZUKI, M., HONGO, S., OHATA, T.: A study on the apparatus and method for inhalation experiment of plutonium aerosol. National Institute of Radiological Sciences (Japan). Pub. 8, Report of Project on Plutonium (1971).

YUILE, C. L., GIBB, F. R., MORROW, P. E.: Dose-related local and systemic effects of inhaled plutonium-238 and plutonium-239 dioxide in dogs. Radiation Res. 44, 821–834 (1970).

8 Titles and authors are as follows: ZIRKLE: Introduction; Comments on the acute lethal action of slow neutrons; LORENZ et al: Biological studies in the tolerance range: JACOBSEN and MARKS: The hematological effects of ionizing radiation in the tolerance range; PROSSER et al.: The clinical sequence of physiological effects of ionizing radiation; RAPER: Effects of total surface beta irradiation; HAMILTON: The metabolism of the fission products and the heaviest elements; BLOOM: Histological changes following radiation exposures; HENSHAW et al.: The biologic effects of pile radiations; LISCO et al.: Carcinogenic properties of radioactive fission products and of plutonium; STONE: Editorial: The plutonium project.

LANL

0004852