Plutonium: Biomedical Research

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than about most other hazardous elements.

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Plutonium will figure prominently in
the production of power during the
next several decades because of its key
role in fueling breeder reactors and
because of its usefulness as a heat
source in various thermoelectric power
systems. This is a frightening prospect
to some, who would characterize plu-
tonium as "the most toxic substance
known to man." Plutonium, in certain
forms, is indeed a very toxic substance;
but its hazardousness is not easily com-
pared to that of other substances, pri-
marily because of lack of information
concerning these other substances with
which plutonium might be compared.
The toxicity of plutonium has been
of concern since milligram quantities
were first produced in the Oak Ridge
reactor, starting late in 1943. In Febru-
ary 1944, 11 milligrams were allocated
for studies in rats. Since that time, bio-
logical studies with plutonium have oc-
cupied the attention of increasing num-
bers of scientists in the United States
and abroad. Much has been learned
about the toxicology of plutonium—
more than is known about most other
hazardous elements (1).

Chemical and Physical Properties
of Biomedical Interest

The most common isotope of plu-
tonium, ^{239}Pu, has a 24,390-year half-
life and emits energetic alpha particles
(5.11 to 5.16 megaelectron volts). It
is used as a fissionable material in
explosive nuclear devices and as a fuel
in nuclear power reactors. Another iso-
tope, ^{238}Pu, is used as a heat source
in thermoelectric power devices, such

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as have been employed on lunar mis-
sions, on communications satellites, in
heart pace-makers, and proposed for
powering artificial hearts. Plutonium-
238 is also an alpha-emitter and has a
half-life of 86.4 years. The heavier iso-
topes of plutonium will become more
abundant as they are produced in
breeder reactors. Of these, ^{240}Pu and
^{242}Pu are long-lived alpha-emitters and
should not differ in any essential bio-
logical respect from ^{239}Pu. Plutonium-
241 is a relatively short-lived (13.2-
year half-life) beta-emitter and is of
primary interest as the parent of ameri-
cium-241, an alpha-emitter that accu-
mulates in tissues and constitutes a
hazard comparable to plutonium.

Plutonium is a chemically "difficult"
element. It will form compounds in
solution exhibiting valences of +3, +4,
+5, or +6. The +4 state is most com-
monly encountered under physiological
conditions, where it is always com-
plexed in some fashion. Weakly com-
plexed Pu(IV) will hydrolyze in near-
neutral solutions, forming a polymeric
hydrated oxide of variable composition.

Plutonium dioxide (PuO_2) is prob-
ably the most important compound of
plutonium, because of its desirable
properties for use as a nuclear fuel.
Plutonium metal oxidizes readily and
PuO_2 is the compound most likely to
be encountered following accidental re-
lease. The behavior of PuO_2 in the bio-
logical milieu may vary greatly de-
pending upon such factors as exact
chemical composition and particle size
and shape—factors determined by the
conditions under which the oxide par-
ticles are formed. The "biological vari-
ability" which toxicologists like to
blame for the lack of precision in their
animal toxicity data is often compli-
cated by "chemical variability" in stud-
ies with plutonium.

History of Biomedical
Research on Plutonium

The first biomedical studies with plu-
tonium were conducted in Joseph G.
Hamilton's laboratory at the University
of California, Berkeley, in February
1944. Shortly thereafter, studies were
begun at the University of Chicago and,
somewhat later, at Los Alamos Scien-
tific Laboratory and the University of
Rochester. These studies involved the
administration to laboratory animals of
several chemical forms of plutonium by
various routes. It was found that plu-
tonium injected into the blood was de-
posited principally in bone and liver,
that plutonium was not appreciably
absorbed from the gastrointestinal tract
when given orally, that it was not
quickly cleared from the lung when
introduced into the trachea, and that it
was not quickly lost from the body.
The acute toxicity of plutonium was
described in a number of animal spe-
cies and osteosarcoma was identified as
a possible long-term consequence of
plutonium deposition. By 1949 a co-
herent picture had emerged of the bio-
logical behavior of plutonium in the
rat (2).

These early studies were motivated
by concern for the safety of plutonium
workers. Some of these workers were
excreting small amounts of plutonium
in their urine. To know what this meant
required information on human excre-
tion of plutonium following injection of
known quantities. In 1945 and 1946
the Los Alamos Laboratory and the
Manhattan District Project Laboratory
at the University of Rochester injected
several seriously ill patients with very
small amounts of plutonium. A few
other patients were studied by the Chi-
cago and Berkeley groups. These are
the only experiments performed with
plutonium on human subjects; the plu-
tonium excretion data obtained provide
the principal basis upon which pluto-
nium burdens in human beings are esti-
mated from urinalysis data (3, 4).

During the late 1950's and 1960's the
support of biomedical research on plu-
tonium by the Atomic Energy Com-
mission (AEC) probably never fell
below the level of $1 million per year.
The AEC now spends more than $12
million annually for research on in-
ternally deposited radionuclides, ap-
proximately 50 percent of this research
being concerned with plutonium and
other transuranium elements. This in-
creased funding has resulted not only
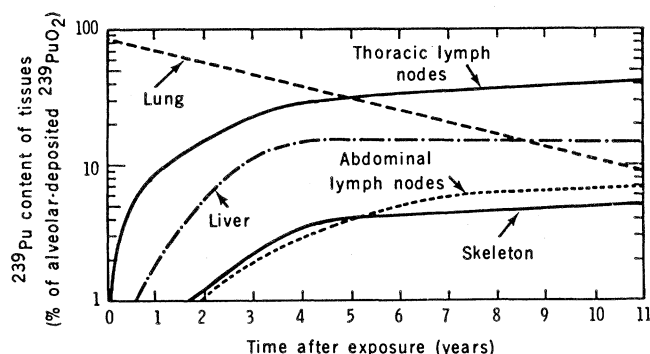
Fig. 1. The distribution of plutonium in beagles that have inhaled PuO₂. [Data from Park *et al.* (*6*)]

from concern for the future utilization of plutonium, but also from the realization that more numerous data are required from larger animals studied over longer periods of time. Current interest centers on these larger experimental efforts.

Studies with injected plutonium in beagle dogs, initiated at the University of Utah in 1952, were expanded in the 1960's to include more animals at lower exposure levels, and to include animals exposed to other transuranium elements (*5*). Studies at Battelle's Pacific Northwest Laboratories, Richland, Washington, on the long-term effects of inhaled plutonium dioxide, involving an initial 65 dogs exposed in the late 1950's, were expanded in 1970 and 1971 to include an additional 120 dogs exposed to lower doses of polydisperse aerosols of $^{239}PuO_2$, and 120 more dogs are currently being exposed to $^{238}PuO_2$ (*6*). Coordinated with this effort is a study of inhaled monodisperse plutonium aerosols in beagles at the Lovelace Foundation for Medical Education and Research in Albuquerque, New Mexico (*7*). A third part of this effort is under way at the Los Alamos Scientific Laboratory where different numbers of microspherical particles containing different amounts of ^{238}Pu and ^{239}Pu are deposited in the lung capillaries of hamsters (*8*). The practical occupational problem of plutonium-contaminated wounds is being studied in beagles at Colorado State University (*9*).

Of special interest is the continued surveillance of human beings who have been exposed occupationally to plutonium during the past nearly 30 years. This activity, under the title of the U.S. Transuranium Registry, is coordinated by the Hanford Environmental Health Foundation with the cooperation of Battelle's Pacific Northwest Laboratories and Los Alamos Scientific Laboratory and with data being supplied by other participating laboratories (*10*).

In this brief historical survey we have neglected many smaller projects as well as substantial contributions from other countries. Studies in the United Kingdom have been closely coordinated with efforts in the United States and have made significant contributions, particularly in regard to plutonium binding at the molecular level in blood and bone. French and Russian research efforts have been substantial and are becoming more widely known, as is also a growing effort by the Germans and Japanese (*1*).

Routes to Man

Plutonium has found its way to man, in readily measurable quantities, only through occupational exposure, where the route is usually direct—by ingestion, inhalation, or by way of a plutonium-contaminated wound. These direct routes of entry will be considered first; the possibilities for plutonium reaching man through a more general contamination of his environment will then be examined.

Alpha radiation from plutonium on the skin surface does not penetrate to the sensitive basal layer of the epithelium. Absorption of plutonium through the skin occurs only to a very slight degree, and probably only when the skin is damaged (*11*). Ingested plutonium is poorly absorbed from the gastrointestinal tract; only 0.002 percent of a 0.01*N* nitric acid solution of plutonium(IV) nitrate was absorbed when fed to rats and pigs (*12*). Infrequently encountered chemical forms may be absorbed to a greater extent. A few tenths of a percent of ingested plutonium citrate is absorbed; up to 2 percent of hexavalent plutonium compounds or chelate complexes may be absorbed (*13*). Very young rats show an enhanced gastrointestinal absorption of plutonium; 0.25 percent for

plutonium nitrate in 1-day-old rats (*14*). The human infant might be expected to show less enhancement of absorption, since his intestine is more fully developed at birth than is that of the rat.

Inhalation is a more probable route of significant plutonium deposition in man, as borne out by experience in the nuclear industry (*15*). The fraction of inhaled plutonium that will be deposited and retained in the lung will depend in a complex manner upon the physical and chemical properties of the specific material inhaled, and upon the respiratory characteristics of the person who inhales the plutonium. Plutonium aerodynamically capable of reaching the alveolar regions of the lung will be largely retained in the lung or systemically redistributed within the body.

Entry of plutonium through wounds has occurred in industry. Depending upon the nature and quantity of plutonium deposited and the location of the wound, the plutonium may be sloughed off with damaged tissue, accumulate in regional lymph nodes, be largely translocated to other tissues, or remain in situ.

Plutonium does not easily penetrate physiologic membranes. Its limited biological transportability makes plutonium a poor candidate for accumulation along environmental food chain pathways. The absorption of plutonium from soil through the root system of plants is very limited. Discrimination factors (concentration-in-plant/concentration-in-soil) are of the order of 10^{-4} to 10^{-6} (*16*). If the plant is eaten by man, less than 10^{-4} of the plutonium is absorbed from the intestine (*12*); or if first eaten by an animal, which is in turn consumed by man, two gastrointestinal absorption factors of 10^{-4} must be applied.

If plutonium is to reach man via environmental routes, physical transport seems more likely than biological transport. Thus, plutonium in the soil might be resuspended and either deposited on food or directly inhaled by man. Grazing animals, inhaling near soil level, might be particularly prone to such uptake of resuspended plutonium. The many complex variables involved in such physical redistribution of environmental plutonium would seem to defy parametric evaluation. Some information has been obtained, however, from the observation of actual exposure situations following field tests or accidents involving plutonium. Jackrabbits in-

habiting the Nevada Test Site have accumulated plutonium in their bones equivalent to 0.05 to 5.0 times the amount of plutonium present in a gram of the soil on which they live (17). On the other hand, of 100 residents studied from the Palomares, Spain, area where plutonium was accidentally dispersed following the crash of a U.S. bomber carrying nuclear weapons, none showed detectable lung burdens or statistically significant amounts of plutonium in urine, even though the ground was highly contaminated (18).

The total earth may also be considered a "test site" in which an estimated 0.3 to 0.5 million curies of plutonium has been uniformly distributed as a result of weapons being tested in the atmosphere (19). In the world's oceans, there is evidence for the accumulation of plutonium in sediment-feeding organisms (20). The concentrations attained are similar to those measured in man. Average quantities of about 0.4 picocurie (10^{-12} curie) in lung, 1.3 picocuries in liver, and 0.4 picocurie in skeleton, or a total of about 2 picocuries in the total man, were measured in tissue samples from autopsies in the Boston area in 1965 to 1966 (21). Similar amounts have been measured in human beings in other regions of the world. These data suggest that each person might accumulate about 10^{-17} of the total amount of plutonium in the environment.

One must acknowledge, however, that the information available on environmental distribution and redistribution of plutonium is inadequate for predicting the probable accumulation of plutonium in man, particularly because of the possibilities of very long term changes occurring in the biological availability of the element.

Distribution, Retention, and Dosimetry

It is convenient to distinguish between what has been termed "systemic" plutonium and the plutonium deposited directly in a tissue by virtue of a particular route of entry. Thus, plutonium in bone, liver, or other organs, deposited from the blood, is termed systemic, and might be expected to show a similar pattern of distribution and retention whether initially absorbed from the lung, the intestine, or from a wound. On the other hand, plutonium deposited in the lung by inhalation or in a wound by injection will be directly influenced
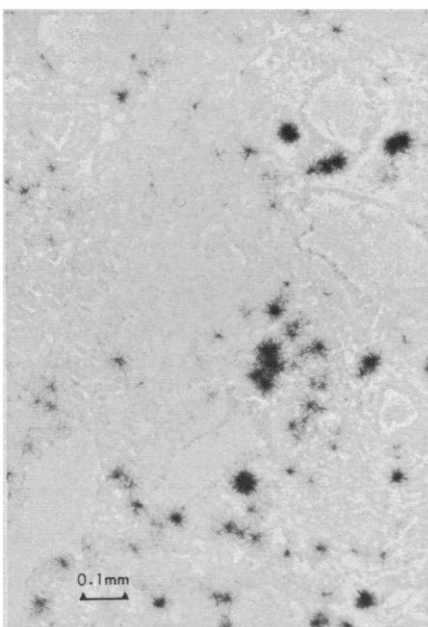
Fig. 2. Autoradiograph showing nonuniform distribution of inhaled plutonium nitrate in the periphery of the lung of a beagle. [Courtesy of J. F. Park]

in its subsequent behavior by the physical and chemical nature of the material deposited. Because plutonium is most likely to gain entry by inhalation or through a wound, we will first consider such deposition and follow with a consideration of systemically distributed plutonium.

Lung and pulmonary lymph nodes. The initial deposition and early clearance of inhaled plutonium from the lung is determined by aerodynamic and physiologic factors common to the inhalation of any particulate material. These factors have been described by the Task Group on Lung Dynamics of the International Commission on Radiological Protection (ICRP) (22). An initial rapid clearance phase is largely completed within the first few days after exposure and involves, primarily, the larger particles deposited on ciliated epithelium in the upper regions of the respiratory tract. These particles are propelled along the respiratory passages by ciliary action, swallowed, and, in the case of plutonium, almost totally excreted in the feces. Particles deposited on the nonciliated epithelium below the terminal bronchioles and in the alveoli are rapidly phagocytized by alveolar macrophages which may transport the particles to the ciliated epithelium of the bronchioles (23). Plutonium is less efficiently removed by this mechanism than are most other particles. Plutonium immobilized in the alveoli

may be engulfed by alveolar epithelial cells, transported to pulmonary lymph nodes, or incorporated in fibrotic regions of pulmonary tissue; whatever the mechanism, plutonium is retained in lung for a long time (23).

The loss of deposited plutonium from the alveolar regions of the lung is usually described as an exponential process and characterized by a retention half-time, although this is a somewhat arbitrary procedure and half-times tend to become longer as retention is measured over longer time periods. In rats these half-times vary from about 100 to 400 days. In the beagle, half-times vary from 200 days for the more soluble compounds to 500 to 1000 days for $^{239}PuO_2$ (23, 24).

The most extensive data on the fate of inhaled plutonium are those for PuO_2 in the beagle (6). Nearly 100 dogs were exposed to $^{239}PuO_2$ aerosols with depositions varying from less than 1 microcurie to about 50 microcuries. About 80 percent of the plutonium initially deposited in the alveolar regions of the lung was retained in the dogs 10 years after exposure; 10 percent remained in the lungs, 40 percent was accumulated in thoracic lymph nodes, 15 percent was translocated to liver, and about 5 percent each to abdominal lymph nodes and skeleton (Fig. 1).

The mean concentration of plutonium per gram of tissue (and therefore the mean radiation dose) was highest for the thoracic lymph nodes and next highest for the abdominal lymph nodes; concentrations in lung and liver were about a thousandfold lower; and in skeleton and spleen, about one-tenth those in lung and liver. The mean dose to a tissue may be less important, however, than the dose to localized regions within the tissue. Autoradiographs show plutonium particles concentrated within certain regions of the lung as illustrated in Fig. 2. In lymph nodes, plutonium is also concentrated within the medullary sinus and around, but generally not in, germinal centers. In the same animal, some thoracic and abdominal lymph nodes may contain little if any plutonium, while other nodes may contain relatively high concentrations. A recent autopsy report provides striking evidence of the nonuniformity of plutonium distribution in man (25) (Table 1).

In summary, as deduced principally from studies in the beagle, inhaled "soluble" plutonium may be largely cleared from the lung within a year or

two and will be translocated principally to bone and liver. Inhaled "insoluble" plutonium will be retained much longer in the lung and will be translocated principally to lymph nodes draining the pulmonary region. Plutonium is heterogeneously distributed in the lung and in lymph nodes, with a correspondingly nonuniform distribution of radiation dose.

Wound-sites and regional lymph nodes. "Soluble" plutonium compounds, injected intramuscularly in rats, may move quite slowly but are eventually translocated to bone and liver (24, 26). However, plutonium metal implanted subcutaneously in rats and rabbits was absorbed only to a maximum of 1.2 percent during the subsequent life-span of the animals (27). Seven days after intradermal injection of miniature swine with plutonium nitrate in 0.2N nitric acid, 12 percent of the dose was present in regional lymph nodes, 7 percent in liver, and 5 percent in bone (28). In beagles with air-oxidized plutonium implanted subcutaneously in a paw, 17 percent of the activity had moved within a year to the proximal lymph node; during this same period, only about 0.1 percent had translocated to skeleton and about the same amount to liver (9). Because of the uncertain but potentially hazardous consequences of plutonium-contaminated wounds, such wounds, when they occur in human beings, are very thoroughly cleansed and the tissue surrounding the wound may be excised.

Systemic distribution of plutonium via the blood. Plutonium will reach the blood by absorption from the lung, the gastrointestinal tract, or a puncture wound. Much of the data on the behavior of plutonium in animals has come from studies in which plutonium was injected directly into the bloodstream. This difference must be kept in mind. As previously noted, plutonium is prone to hydrolyze at physiological pH. Such "polymeric plutonium," when injected, is rapidly lost from the blood and deposited primarily in liver; monomeric plutonium (complexed by citrate or some physiologic agent) is more slowly lost from blood and is more readily deposited in bone (29).

The retention of plutonium citrate in the circulating blood of several species, including man, is shown in Fig. 3. Plutonium in blood is associated with the iron-binding protein, transferrin (30); the stability of this complex ex-

Table 1. Concentration of plutonium in tissues taken at autopsy from a human being exposed occupationally to the element. [Data from Nelson *et al.* (25)]

Tissue	Plutonium (picocurie/ gram)
Lymph nodes	
Carina	61
Intrapulmonary	20
Hilar	12
Hepatic	0.18
Lung	
Pleura and subpleura	0.52
Parenchyma	0.009
Other	
Lumbar vertebrae	0.34
Rib	0.10
Liver	0.04

plains the long time that plutonium remains in blood.

Liver. About one-third of intravenously injected plutonium citrate is deposited in the liver of beagles (31). This plutonium is initially deposited quite uniformly in the hepatic cells (32). Within these cells it is associated with the iron-binding protein, ferritin, and is accumulated in lysosomes. Over a period of years there is a tendency for aggregation of plutonium within reticuloendothelial cells and for compression of the older, plutonium-laden cells by regenerating areas of the liver (32). During the first 1000 days after injection, any loss of plutonium from the liver seems to be balanced by an input of plutonium translocated from bone. Beyond 1000 days, the amount of plutonium in the liver decreases with a

Fig. 3. Retention of plutonium in the blood after intravenous injection of plutonium-(IV) citrate. [Modified from Durbin (4)]

half-time of about 8 years (31). Based on extrapolation of data from several animal species, a half-time of 40 years has been estimated for the retention of plutonium in the liver of man (24).

Bone. Plutonium circulating in blood as a transferrin complex is preferentially deposited on the endosteal surfaces of bone where it is in a good position to irradiate the cells which are the presumed sites of cancer induction (33). Depending upon the rate of growth and remodeling of the particular bone, plutonium may remain on the bone surface, it may be buried by apposition of new bone, or it may be concentrated in osteoclasts involved in bone resorption. Plutonium freed from the bone surface is collected in macrophages which migrate through the bone marrow (34). Because of its migration to less sensitive sites, the critical period for exposure to bone-deposited plutonium may be a limited one and may be much shorter in the young, growing animal than in the adult. An autoradiogram illustrating the deposition of plutonium in bone is shown in Fig. 4.

Measured half-times for gross retention of plutonium in bone have ranged from about a year in mice, to several years in rats and rabbits, and to more than 10 years in dogs (24, 26). A half-time of 100 years has been estimated for retention of plutonium in the skeleton of man (24).

Other tissues. Tissues other than liver and bone account for about 10 percent of the total plutonium in man 1 year after intravenous injection of plutonium citrate, according to the rather meager data obtained from human beings (4). Studies in several animal species have given no indication, however, that tissues other than liver, bone, and lung accumulate sufficient plutonium to be of critical concern (26).

Excretion. Probably the most extensive biological data on plutonium are those related to its excretion in urine and feces. This is because analysis of excreta is the most sensitive indicator, and in many cases the only indicator, of the presence of plutonium in the body. In the evaluation of human systemic deposition of plutonium, the following equation has usually been employed:

$$\text{Initial intake} = \text{daily urinary excretion}/0.002 \, t^{-0.74}$$

where *t* is the time in days since intake (3). Total excretion is estimated to be about 5 percent during the first 20 days
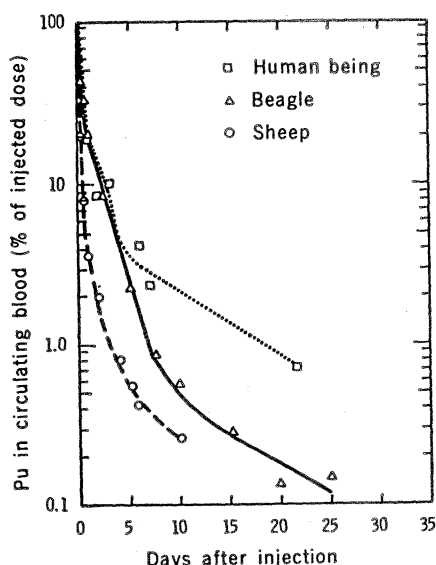
after injection, about 10 percent by 2 years after injection, about 19 percent by 20 years after injection, and 22 percent after 40 years (4). Plutonium body burdens estimated from urinary excretion data cannot be considered to be very precise.

Biological Effects

No specific physical injury to man has been shown to be caused by plutonium exposure. Many workers exposed to plutonium have been greatly inconvenienced—even pained—by the countermeasures taken to avoid possible effects, and a certain amount of psychological trauma has undoubtedly occurred. It must also be acknowledged that the earliest exposures of human beings to plutonium occurred less than 30 years ago and the latent period for manifestation of possible carcinogenic effects is expected to be long. The U.S. Transuranium Registry was established in 1968 to maximize the biological and medical information obtainable from exposed workers (10). Some 3000 present or former employees of the major AEC laboratories have given permission for release of their medical and health physics records and nearly one-fourth of these have authorized autopsy. The accumulation of data in this program will be slow and costly, but these data are our only source of information on the possible effects of plutonium in human beings.

We must currently rely on animal studies for all information on the biological effects of plutonium. The acute toxicity of injected plutonium is due primarily to destructive effects on the hematopoietic system resulting from irradiation of the bone marrow by plutonium deposited on bone surfaces, or released from bone into the marrow. At lower doses of plutonium, effects on blood cells are noted but these are not responsible for the death of the animal. Thus, beagles injected with 0.1 microcurie of plutonium per kilogram show only a marginal leukopenia, and no hematopoietic effects are observed with injections of 0.016 microcurie per kilogram. With this latter dose, one-third of the animals that died had plutonium-induced osteosarcoma (35). Leukemia or other hematopoietic neoplasia do not seem to be induced by plutonium.

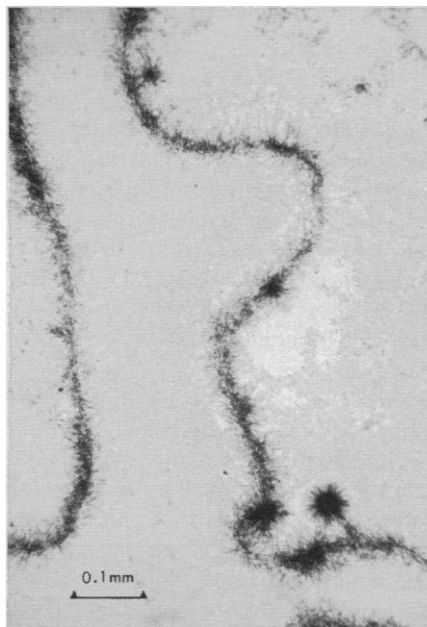The most sensitive index of plutonium toxicity in bone is the induction

Fig. 4. Autoradiograph showing deposition of plutonium on the surface of a bone spicule of a beagle, 1 day after injection of plutonium(IV) citrate. [Courtesy of W. S. S. Jee]

of osteosarcoma. In Table 2 are shown the data on bone tumor incidence in the beagles studied at the University of Utah (36). The incidence of bone sarcoma is high in all groups of dogs for whom complete data are available. With decreasing dose the time to tumor appearance increases. Great interest centers on the dogs in the lower dose groups, injected in the later part of the experiment, and only now approaching the point when they might be expected to develop tumors.

Studies in rodents have also indicated osteosarcoma as the most sensitive effect of plutonium injection (37, 38). In studies of many hundreds of rats, Russian workers have reported osteosarcoma induction after inhalation, intratracheal, subcutaneous, intracutaneous, intraperitoneal, or oral administration (39). By all of these routes, bone sarcomas were induced when the average radiation doses in bone were as low as 30 to 70 rads (40). From these data, and assuming a time independent linear dose-response relationship, Mays and Lloyd (38) have calculated an increased osteosarcoma incidence of 0.38 percent per rad for beagles, 0.10 percent per rad for mice, and 0.06 percent per rad for rats. These numbers, it should be emphasized, relate to the average rad dose to the total bone; tumor-sensitive bone surfaces may receive a dose 20 times higher than this average dose (5).

Of more interest than absolute incidence figures is the finding in the Utah studies that plutonium-239 is five to ten times more toxic than radium-226 on the basis of the same total energy delivered to bone (5). This difference is attributable to the more hazardous localization of plutonium on bone surfaces. The surface-to-volume ratio in trabecular bone of man is about half that in the beagle. Since plutonium is deposited initially on bone surfaces, its concentration at these surfaces in man, relative to the average concentration in total bone, should be twice that in the dog. The rate at which surface deposits became buried by apposition of new bone in the 1.5-year-old dogs of the Utah study was probably ten times that to be expected in adult man. Both of these factors would suggest a greater toxicity of plutonium—relative to radium—in man than in the dog (41).

The comparison with radium is important because of the abundance of data on the toxicity of radium in human beings. These data serve as the basis for all evaluations of the hazards of internally deposited bone-seeking radioactive elements in human beings. The greater hazard of plutonium is

Table 2. Induction of bone sarcomas in beagles injected with ^{239}Pu. [Data from Jee (36)]

Amount injected (microcurie/ kilogram)	Dogs (No.)	Sarcomas/ deaths	Dogs with sarcomas	
			Mean time from exposure to death (years)	Rads to skeleton*
2.9	9	7/9	4.1	4900
0.91	12	12/12	3.6	1300
0.30	12	12/12	4.5	600
0.095	12	10/12	7.2	310
0.048	13	9/13	8.5	190
0.016†	13	4/12	9.9	78
Controls‡	12	0/12	11.5	0

* Calculated cumulative radiation dose to skeleton at 1 year before death.   † Additional studies at dose levels of 0.016. 0.006, 0.002, and 0.0006 microcurie per kilogram are still in progress.   ‡ The mean time from exposure to death applies to all control dogs, none of whom developed bone sarcomas. Natural incidence of bone sarcoma in the beagle has been estimated at 1/10,000.

recognized in ICRP calculations by a "nonuniform distribution factor" of 5, a number which is apparently not over-conservative.

The acute and chronic toxic syndromes for inhaled plutonium have been well defined in rodents and dogs (1, 6, 23, 26). Lymphopenia is the earliest response seen in animals after inhalation of PuO_2 and occurs in dogs with total lung depositions as low as 0.2 to 1 microcurie (6). Figure 5 shows data from the study of inhaled $^{239}PuO_2$ in beagles, conducted at Pacific Northwest Laboratories (6). Forty of the dogs died between 55 and 200 days after exposure because of plutonium-induced pulmonary insufficiency. Twenty-two dogs that survived more than 1600 days had malignant lung tumors. The estimated initial alveolar deposition in the dogs with lung tumors was 0.2 to 3.3 microcuries or 0.003 to 0.05 microcurie per gram of bloodless lung. Metastasis occurred to thoracic lymph nodes and to many systemic organs, but no primary tumors were seen in lymphatic tissue.

The data in Fig. 5 are difficult to interpret because the incidence of lung tumors was essentially 100 percent at the lowest dose of inhaled PuO_2 tested. There is, however, a gradation of hazard with dose in terms of survival time. If we extrapolate the curve in Fig. 5 to the life expectancy of the beagle, we might conclude that a dose of more than 1 nanocurie per gram could cause premature death due to a lung tumor. The extrapolation is very uncertain, however.

Data from a number of studies in rats also point to lung cancer as the most sensitive manifestation of inhaled PuO_2 (6). In rats exposed by inhalation to more soluble forms of plutonium, osteosarcomas were seen, as well as lung tumors (39).

The tissue affected by the neoplastic process will depend on the route of entry and the form of plutonium involved. Inhaled insoluble plutonium will most probably result in lung tumors; inhaled soluble plutonium may produce both lung and bone tumors; systemically deposited plutonium will most probably produce bone tumors

Countermeasures for Internally Deposited Plutonium

Because human beings can be contaminated with plutonium, and because of its toxicity in experimental animals,

there has been a continuing effort to develop countermeasures for treatment of contaminated individuals. By far the most effective of these procedures has been the surgical removal of tissues adjacent to contaminated wounds. For the removal of systemically distributed plutonium, the only clinically approved procedure is that involving administration of the chelating agent, diethylene-triaminepentaacetic acid (DTPA). The DTPA forms a very stable chelate complex with plutonium which is then excreted in urine (42).

Several hundred people have been treated with DTPA following incidents of plutonium contamination; the DTPA is usually administered by a series of intravenous injections or by inhalation. Removal of about 50 percent of the plutonium that would otherwise be retained is probably an exceptionally good result (43). Much better results are obtained in animal experiments, where larger DTPA doses can be employed and the timing of treatment optimized (44).

Inhaled, insoluble plutonium is not effectively mobilized by DTPA treatment, nor by a wide variety of physiologically active materials that have been tested (42). Pulmonary lavage—irrigation of the lung with physiological saline solution—has removed as much as 50 percent of the plutonium deposited in lungs of rats, dogs, and baboons (42); when used in one human being with lung-deposited plutonium, there was evidence of some plutonium removal (7).

Evaluation of Hazards and Exposure Limits

The first attempt to evaluate the hazardous effects of plutonium in man and to establish exposure limits was made in 1944. On the basis of the accepted permissible body burden of 100 nanocuries for radium, and with the assumption of equivalent toxicity for equal energy deposition by radium and plutonium, a value of 300 nanocuries was derived as a permissible body burden of plutonium. As experimental evidence on plutonium toxicity was accumulated, this early limit was revised downward until, in 1949, a conference between British, Canadian, and American representatives at Chalk River, Ontario, initiated discussions that led to an internationally accepted permissible body burden of 40 nanocuries. This value for *occupational exposure* was

subsequently adopted by both the ICRP and the National Council on Radiation Protection (NCRP) and has persisted to the present day (8).

The 40-nanocurie limit for plutonium, as originally derived, was based upon three major assumptions: (i) that comparison with the limit of 100 nanocuries for radium is acceptable as a standard; (ii) that bone, which is the critical organ for radium, may also be considered the critical organ for plutonium; and (iii) that comparative effects of radium and plutonium on the bone of animals can be meaningfully extrapolated to man. An evaluation of the 100-nanocurie limit for ^{226}Ra would be beyond the scope of this article. Suffice it to say that no radiation exposure limit is better supported by human data on dose-effect relationships than the limit of 100 nanocuries for radium (45).

With regard to the second assumption, it is clear from animal studies that bone cannot be always considered the critical organ for plutonium. The exposure of liver, lung, and lymph nodes must also be considered.

In the case of bone, where comparison with radium is legitimate, can the comparative effects measured in animals be extrapolated to man? The ICRP and NCRP assume that plutonium is five times more hazardous than radium, because of its more hazardous localization in bone. Results from dog studies at the University of Utah indicate that this factor falls in the range of 5 to 10. There is reason to believe that the factor would be higher in man, because of man's lower bone surface area relative to total bone volume, and because of man's slower turnover of plutonium from bone surfaces. From this line of reasoning one would conclude that the 40-nanocurie limit for plutonium is severalfold "less safe" for bone than the 100-nanocurie limit for radium.

Comparison with radium is not appropriate when the critical organ is other than bone. In the case of lung, if one follows the customary approach of limiting occupationally incurred radiation doses to 15 rems (40) per year, the maximum permissible lung deposit becomes 16 nanocuries, or 0.016 nanocurie per gram of lung. This concentration may be compared with a level of 1 nanocurie per gram of lung, which seems not to shorten the survival time of a beagle dog (Fig. 5). The margin of safety is less than totally reassuring because of the absence of data for

exposure to smaller amounts of plutonium.

If one were to limit the lymph node dose to 15 rem per year, a much more restrictive limit would be derived than that based on dose to lung. Such a limit has not been applied, on the grounds that animal experiments do not indicate that lymph nodes are the critical tissue.

If one were to limit the dose to 1700 grams of liver to 15 rem per year, the permissible liver burden would be 27 nanocuries, which, depending upon the route by which plutonium reached the liver, might correspond to a total body burden of 50 to 200 nanocuries, a limit less restrictive than the present limit based on bone.

These speculations only hint at the complexity of the problem. We have not considered the necessity to limit daily, weekly, or annual intake so that the accumulation of plutonium over a lifetime is kept within acceptable limits; nor the distinction to be made between occupational exposure and exposure of the general population. A major problem is the basic contradiction of a system that evaluates hazard in terms of average radiation dose to an organ, when we know that this dose is very nonuniformly distributed within the organ. Unfortunately, we do not yet know enough about the precise distribution of dose, or the effect of very high doses to very small volumes of tissue, to handle the problem in any other way.

It should be noted that committees of the ICRP and NCRP are continually reviewing permissible exposure limits for plutonium and other radionuclides. We are members of both these committees; it is our personal view that plutonium exposure limits will be changed within the next few years, in the direction of tightened control—that is, lowered permissible exposures; but that the change probably will not be large.

The Future of Biomedical Research on Plutonium

Having noted in the introduction to this article that probably more is now known about the toxicology of plutonium than about most other elements, it might be logical for us to conclude that future efforts should be devoted to less well understood elements. Such a conclusion would, indeed, be justified if plutonium were a problem for a few
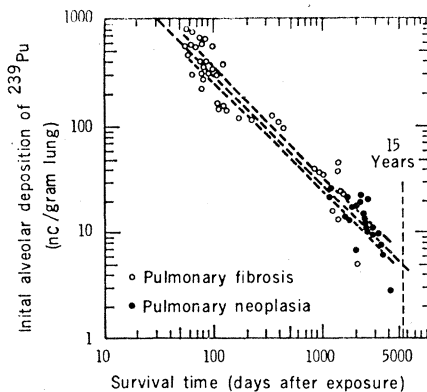
Fig. 5. Survival time of beagles as a function of PuO₂ deposition in the lung. [Data from Park *et al.* (*6*)]

thousand workers employed in a carefully controlled nuclear industry—the situation which has prevailed for the past 25 years. This is not, however, the prospect for the future, which has been touted as the "Plutonium Age"—an age when most of our energy will be derived from plutonium, an age when tens of thousands of people may be walking our streets with cardiac assist devices powered by ^{238}Pu, an age when millions of curies of plutonium wastes will have to be kept from contact with man for future hundreds of thousands of years (*8*). If these are the prospects, it behooves us to spare no efforts in our pursuit of information on the behavior of plutonium in man and his environment.

Priority must be given to the intensive follow-up of persons known to have been exposed to significant amounts of plutonium. Only from these persons can we obtain direct information on possible effects of plutonium in man. We should also take advantage of accidentally exposed environments to learn all we can, in a real-life situation, about the movement of plutonium in the biosphere.

More data on toxicity are required from studies of animals exposed to the lower amounts of plutonium that approach those now considered safe for man; such data are needed for a wider variety of plutonium isotopes and compounds. We are too dependent upon data from rodents and beagles which may—and in all likelihood do—possess pecularities in their handling of plutonium that are not shared by man; comparative studies in other species should be undertaken. It must be recognized, however, that we can never collect enough data on observed effects in man or animals to be confident that significant effects will not occur in an

exposed population numbered in billions. Such confidence can come only from an understanding of the mechanisms involved in tumor induction, which could allow us to predict the relationship between cancer incidence and dose, and whether there is, indeed, a threshold dose below which no effects will occur.

The entirely proper concern now expressed in many quarters for the toxicity of plutonium, and of other potential radioactive contaminants of our future environment, is no doubt magnified by the unusual properties of these materials that are present in such small quantities, so invisible and mysterious in their action, while at the same time so readily detectable. This same combination of widespread concern, scientific accessibility, and small bulk, should prove uniquely advantageous for their future control. The key to this control is greater knowledge—knowledge that must be acquired before its application becomes critical.

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Institutions in Modern Society: Caretakers and Subjects

The training, retraining, and rehabilitation of people in urban, industrial California—a view of the future?

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Only some 30 years ago California was known as a haven for elderly, retired persons, as a sunny and pleasant locale in which to vacation, and as an agricultural region abounding with broad expanses of colorful orange groves. It was known, of course, for Hollywood. In 1940, the population of the state was estimated at 6,907,387 (*1*, table BK-1, p. 9).

In 1969 California was on the verge of becoming the nation's most populous state, with an estimated 19,834,000 persons. During this same year, overall urbanization in California was 86.4 percent, second only to New Jersey (99.6 percent); and within its boundaries there had developed the nation's second largest manufacturing complex (*1*, p. vii), the largest being that of New York.

The three interrelated processes of population growth, urbanization, and industrialization have tended to bring about changes in the overall organization of the institutions of the state, including those that deal with education, social welfare, mental and physical health, and incarceration. As in other states, subsystems have evolved out of California's institutions. Through these subsystems, the state has become involved in the training of youth, the problems of unemployment, and the care of dependents, the blind, the disabled, the ill, and the incarcerated. The formal institutions involved in these activities represent efforts to achieve certain ends that have been designated as either desirable or necessary by the legislature and the courts. Within their respective institutional structures, all of these functions are claimed to be generally oriented toward the philosophy, if not the practice, of rehabilitation, in the broadest sense of the term. In short the major purpose of these institutions is to engage in processes and programs that lead toward the entry or the reentry of citizens into the "productive sector" of society.

In an urbanized, industrialized, and still-growing state such as California, how extensive are these efforts on the part of the aforementioned institutions? During a defined period of time, how many people are under institutional care or control in one form or another? What questions arise with respect to current trends? And what are the implications for the future of our society and for the assignment of priorities?

Institutional Reports

The most complete data available on the number of citizens involved in the state's institutions of education, social welfare, health, and penology (either in the capacity of employee or recipient of services) are the annual reports issued by the institutions concerned. However, such reports do not contain information on overlap of functions and rates of recidivism. Thus, the most sensible approach to assessing the total number of people involved in such state activities is to form an estimate for any given day, thereby minimizing overlap and recidivism. With this in mind, one may ask how many people are either employed by these institutions or in their care during any given day in 1969, the most recent year for which data are available.