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PHYSIOPATHOLOGY OF PLUTONIUM
CONTAMINATION: FUNDAMENTAL CONCEPTS

[Fisiopatología de la contaminación por plutonio: conceptos fundamentales]

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PHYSIOPATHOLOGY OF PLUTONIUM
CONTAMINATION: FUNDAMENTAL CONCEPTS

1. Introduction

Plutonium, a radioactive element whose value is becoming more and more evident because of its technological application, primarily in the atomic industry, is one of the most toxic nuclides, because of its biological behavior as well as its physical characteristics.

Produced for the first time in 1941 by Seaborg and others (Weast, 1966), it has been detected in nature in such small quantities that by itself it does not constitute any risk.

Of the radioactive Pu isotopes, Pu-239 is the one most used in the nuclear industry, where it is produced by irradiation of U-238 in nuclear reactors. Its high specific activity and long half-life determine its high radiological toxicity.

Risk of contamination is derived from both professional uses and applications of Pu in nuclear explosions and accidents which thus contaminate the biosphere.

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The increasing use of various isotopes of Pu in nuclear fuel and in other industrial, biomedical, and space applications, make it necessary to foresee future risks.

In order to evaluate the importance of some of them, we include a paragraph from Lovins' article (1973) on this subject.

"The Pu recovered from light water reactors will increase from slightly more than a ton at the present time, to 45 in 1980, 170 tons (metric) in 1985, and with the advent of the series of fast reactors, to several hundred tons by the first part of the next century. Even with current safeguards available to the AEC it is impossible to avoid the diversion of kg quantities of Pu to terrorist elements who have elementary means to fabricate arms appropriate to their goals. The most complex security systems in the world are incapable of stopping the series of hijackings, kidnappings, and thefts of important sums of money and materials."

The radiotoxicity of the various compounds of Pu is influenced by a series of factors dependent on the physicochemical state of its compounds, on the route of penetration into the organism, and on its interaction with organs and tissues.

This study is based on a bibliographical review and on an analysis of the different parameters of the physical, chemical and biological processes involved in internal contamination caused by Pu.

An attempt will be made to up-date knowledge concerning its toxicity and to facilitate, through a better understanding of the action mechanisms of this nuclide on fine cell structures, the work of persons and organizations involved with these risks.

Special attention is given to the process of inhalation of radioactive aerosols due to its probability of occurrence and because of the degree of irradiation derived from their entry through the respiratory tract. The study of the dynamics of distribution, movement, and incorporation into the various organs and tissues leads to a rational interpretation of internal contamination, evaluation of the degree of irradiation, biological effects, and therapy.

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2. General considerations

Although the existence of Pu in nature has been proven, its natural quantities are so low* (Levine and Seaborg, 1951; Hoffman et al., 1971) that the risk comes from its artificial state.

Fifteen isotopes of Pu are known (from Pu-232 to 246), all radioactive, essentially alpha emitters. Pu-241 and Pu-243 are beta emitters at 99.997% and 100% of their disintegration, respectively. The half-lives of the isotopes are from seconds to thousands of years.

Industrial producers neutron-bombard U-238 in nuclear reactors. The isotopic composition of the resulting Pu is a function of the time and conditions of bombardment (Schemata 1 and 2).

* Pu-239 in uranium minerals.....10⁻¹⁴-10⁻¹²
Pu-244 in bastnacite mineral (isolated in 1971)~10⁻¹⁷

The radiotoxicity of these alpha emitters, Pu-238, 239, 240 and 242, are comparable among themselves, as can be deduced from the values of the maximum permitted organic charges (Table I). Therefore, given the high toxicity of Pu, data come largely from animal experimentation, principally rodents (rats, mice, hamsters), dogs, and most recently pigs of a dwarf breed, developed in the Hanford labs, USA. These studies have been done with Pu-239 and to a lesser extent with Pu-238.

The existence of free Pu in the atmosphere and ground and sea deposits can lead to direct contamination by inhalation or through ecological cycles. Inhalation risks are greater than ingestion risks because of reduced gastro intestinal tract (GIT) absorption. Also, the ecological cycle on land involves great reduction factors (Romney et al, 1969). In the ocean, on the other hand, concentration factors are involved (Wong et al, 1970).

Since 1952, tests and nuclear accidents in space have liberated quantities of Pu in the biosphere approximately equal (according to the estimate of Cherdintsev et al., 1968 and 1970) to a layer 7.5 cm deep over the entire earth, with a concentration of Pu-239 of 10^{-12} g. The values of liberated Pu given by the Scientific Committee of the United Nations (Norwood, 1969), expressed for Pu-239, would assume an activity of 0.5 MCi, equal to approximately eight tons.

Data concerning global air activity (Bartoli et al., 1966) show values of 10^{-15} Ci/m³ of Pu-239 in the summer of 1963 and of 10^{-17} to 10^{-16} Ci/m³ in the USA in 1965 (Drobinski, 1966), values which coincide in order of magnitude with present maximums (Volchok et al., 1971).

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These values are still 10^1 to 10^5 times lower than the maximum permitted concentration (Harley, 1971). The current situation, therefore, is not dangerous. Nevertheless, even discounting the risk from nuclear tests, broad technological applications of Pu risk a growing concentration of Pu in the environment.

Prospective Pu-239 (industrial) and Pu-238 (medical and aeronautic) applications will use 60 to 80 tons of Pu-239 in the next decades and up to 6 tons of Pu-238 by the end of the century

(Seaborg, 1970, and Langham, 1971). Contamination from these astounding quantities is assumed to be effectively controlled in their production and use. Nevertheless, they potentially contain considerable risk.

3. Plutonium--its physical and chemical aspects

Plutonium-239, by its nature an alpha emitter of long half-life (2.4×10^4 years), high specific activity (6.2×10^{-2} Ci/g), and metabolic characteristics--bone seeking, slowly eliminated--is a very radiotoxic nuclide.

Table II specifies the disintegration characteristics of some of the more interesting isotopes of Pu from the biological point of view. Of the ten identified particles which Pu-239 emits during disintegration, only three contribute more significantly to the "dose" of radiation. During its disintegration (to U-235) the characteristic X-rays, LX, emitted form only 4% of the total. Low-energy gamma radiation is a slight proportion ($1.4 \times 10^{-2}\%$) of the total alpha energy. These X and gamma emission do not represent a radiation risk in cases of internal contamination, due to their small contribution to the "dose". Interestingly, internal contamination is evaluated with the possibility of direct detection (body radio-activity counter) (Santos, 1968).

The low thermal conductivity of Pu-238, even lower than uranium (Vol'skii, 1970), makes it a useful heat source in thermoelectric generators with various purposes.

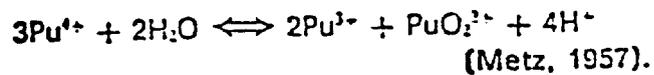
The most important biological aspects of the chemistry of Pu concerns its states of oxidation, its tendency to hydrolyze, and its capacity to form complexes.

States of oxidation

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The polyvalence shown by Pu, from Pu III to Pu VI, and the proximity of its oxidation potentials permit equilibrium states in solution among its ions of different valences. This coexistence explains the chemical complexity of this nuclide in its biologic behavior.

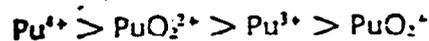
Pu dismutates as follows, referring to tetrapositive Pu, the most frequent on the physiological level:



The formation of oxygenated bonds based on Pu^{4+} produces equilibrium. The degree of dismutation is a function of the acidity of the solution and the presence of complexing ions.

Hydrolysis

The hydrolytic tendency of the different degrees of oxidation decreases in this order:



influenced by the Pu concentration and hydrogen ions.

Pu can hydrolyze to insoluble hydroxide, passing through intermediate states of polymerization with formation of colloidal aggregates. This phenomenon can occur at physiological pH, influencing, qualitatively and quantitatively, its distribution and deposit in the various systems, organs, and tissues.

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Complexes: Stability

Pu complexes with anions of mineral acids (nitrates, carbonates.. and of organic acids (citrate, proteinate). Stability depends on the complexing bonders. Bonders of great chemical stability can form complexes which dissociate at physiological pH. Other non-biodegradable bonders form biologically stable complexes. Thus, the interaction of Pu with the broad variety of biological bonders produces simultaneous mechanisms of dissociation and formation of new complexes which favorably or unfavorably influence retention, excretion, and elimination therapy.

4. Internal contamination

Routes of penetration: Relative importance

The risks of internal radiation derived from the different types of exposure are conditional upon the physical and chemical characteristics of Pu and its route of entry, since its distribution and deposit in the organism varies qualitatively and quantitatively with the route of penetration and the transportability of the compound.

Internal contamination can be directly into the blood, through wounds or lesions on the skin, and indirectly through the respiratory tract (R.T.) by inhalation and G.I.T. by ingestion.

Inhalation represents the greatest indirect danger, since absorption into the blood from the R.T. is 10^2 to 10^3 that of the G.I.T.

4.1. Inhalation

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Radioactive aerosols. Different aspects of handling Pu (industrial processes, transport, storage, etc.) and accidents (fire or explosion) produce radioactive aerosols. Its fusion point (640°C), pyrophoric properties, and ease of oxidation, already mentioned, favor aerosol formation. Oxidation can be spontaneous (self-oxidation) or caused by fire or explosion. In both cases Pu oxide particles form, their size and solubility dependent on the temperature of oxidation or ignition. The aerosol can come from solid substances (metal oxides, precipitates of Pu compounds) or from the solutions being handled (pouring, agitation, filtration, etc.) (Vol'skii et al., 1970).

For the purpose of protection and due to the fact that humidity favors oxidation, all industrial and laboratory operations should be carried out in an inert atmosphere and in calm installations.

Physicochemical and biological factors, such as particle size, anatomy and physiology of respiratory system, solubility, etc., influence the behavior of these particles in the R.T., which are dealt with in the corresponding sections of this article.

Before considering the influence of the remaining factors, and in relation to the solubility of the compounds of Pu, we feel it helpful to mention the concept of transportability introduced by the ICRP (1968). Transportability includes the physicochemical phenomena which occur during the interaction of the Pu compounds with organic fluids (formation of complexes, reaction with cells, etc.), conversion to a greater or lesser mobility and displacement of these compounds.

Deposit in relation to particle size

The size of the particles determines depositing of the first order. In this respect, the percentages of deposit in the different parts of the R.T. are valid for Pu in relation to the aerodynamic diameter of the particles* according to the curves shown in Figure 1, for a given respiratory volume; for greater volumes, maintaining the same respiratory rhythm, the proportion of large particles which pass to the lower tracts declines, which is equivalent to a shortening of the curves by a displacement of the zero of deposit (100% of NP deposit)** to values of particle diameter, given by the inverse of the square root of the relation of the respiratory volumes (Lara, 1969).

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4.1.1. Deposit and mobilization of particles in the respiratory tract

In differentiation of the processes of deposit and mobilization in the R.T. we follow the Study Group on Pulmonary Dynamics (S.G.P.D.) of ICRP (1964), dividing the R.T. in three parts: nasal-pharyngeal (NP), tracheo-bronchial (TB) and pulmonary (P).

The NP includes the upper respiratory channels: nasal cavities, pharynx and larynx.

The TB includes the trachea, the bronchial tubes and end bronchii.

The P is made up of the respiratory bronchioles, alveolar passage, and alveoli. In Fig. 2, the deposit and movement of Pu

*Diameter of a sphere of density 1, which has the same sedimentation rate as the particle.

**NP = Nasal-pharyngeal.

particles in the R.T. is represented along with transportation to other parts and eliminatory channels. The transportable compounds inhaled are diffused in the blood and organic fluids, and are transported to be deposited in organs or tissues or excreted in the urine.

Of the non-transportable ones, a fraction of the NP deposit is exhaled, another part is moved by ciliary action toward the esophagus and G.I.T.; the remaining fraction which is deposited in the lungs (lower parts) is slowly moved either toward the G.I.T. and eliminated in the feces, or toward the blood and lymph by solubilization of the particles or by transport through the pulmonary epithelium.

4.1.2. Kinetics of movement

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The process of elimination of radioactive particles from the R.T. is of great importance because of the influence that the time of exposure has on the dose of radiation to the lung. The mechanics of this process are basically ciliary action, phagocytosis* and transport to the circulatory system: blood and lymph.

The anatomical and physiological characteristics of the respiratory system listed below influence ciliary action:

Nasal passages, trachea and bronchii are coated with a mucous membrane whose cells are provided with mucus-secreting glands as well as with an epithelium with vibratory cilia which move the mucus toward the pharynx, where it is expectorated or swallowed.

In the lower tracts (bronchioles) there are no secreting glands nor vibratory cilia, and mobilization is left to cells of the alveolar epithelium which are phagocytic in nature engulf the particles which arrive at the alveoli (Fering, et al, 1965).

Transport by phagocytosis, in the case of inert particles, is intracellular and is conditioned by the life cycle of the phagocyte; in the case of radioactive particles, transport can be extracellular as well, since due to the high radiotoxicity of Pu, cell death and subsequent lysis of the cell can occur with the inevitable freeing

*Trapping and engulfing foreign particles.

of the particles into extracellular spaces. The frequency of this extracellular phase depends, therefore, on the cytotoxicity of the inhaled compound (Gross, 1964; Sanders, et al., 1970, Lutz, 1970).

The degree of phagocytosis is also conditional on a series of physicochemical factors such as: particle size, affinity of particles for serum proteins, and physiological and pathological factors such as congenital defects or defects acquired from respiratory disease, which must be considered in order to interpret a contamination by inhalation.

4.1.3. Retention of particles in the respiratory tract

In this process the response of the cell to the presence of particles of Pu plays a great role. Cassaret (1964), at the University of Rochester, and later Sanders (1969) studied the cellular process in its qualitative and quantitative aspects in macrophages of rat lungs, determining the phagocytic degree and index (P.D. and P.I.).*

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Experiments were carried out with six groups of rats exposed to aerosols with particles of medium diameter, between 0.1 and 0.2 μ , isolating the cells by means of washing the lung with saline solution at intervals of time from fifteen minutes to twenty-five days after exposure. In the graph (Figure 3) is represented the degree of phagocytosis of the particles in relation to the time, independently of the dose. It is generally observed that the alveolar macrophages are capable of accumulating a great number of particles, reaching as high as 80% to 90% of the particles phagocytized the first day.

These values of phagocytic degree justify the use of pulmonary washing as a therapy to eliminate particles from the R.T.

With respect to the P.I. they observed a rapid increase following inhalation, remaining constant for some weeks, and diminishing later, these changes being related to the quantity of

*P.D. = % of phagocytized particles.

P.I. = % of macrophages which phagocytize particles.

Pu initially deposited in the alveoli.

In the experimental study to which we refer, and by means of a statistical analysis, a correlation index of 0.91% was obtained between the phagocytic index in % and the logarithm of the quantity of Pu present in the lung, expressed in μCi . These experimental values are graphically represented in Figure 4, in which the different types of points correspond to the different groups of animals used. The center line (1) is the line of statistic regression delimited by lines (2) and (3), which represent the intervals of 95% degree of confidence of the total, while the broken lines correspond to the same degree of confidence for individual samples.

It is possible to predict, within certain limits of confidence, the quantity of Pu present in the lung during the first weeks following an explosion, determining the P.I. by means of the procedure of saline washing of the lung.*

Intra- and extracellular localization of Pu particles

The presence of Pu particles in the alveolar (macrophages), which is the most frequent location, and in limited cases, in the pulmonary alveoli, is confirmed by autoradiographic studies (Figures 5 and 6) (Sanders, 1970).

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4.2. Ingestion: Gastro intestinal tract (G.I.T.)

The risk of penetration by direct ingestion is improbable in industrial exposure due to the rigorous measures of protection taken, and could only be conceived in accidental cases. The G.I.T. is more properly a transport route for the Pu inhaled and deposited in the R.T. where it passes to the G.I.T. (by means of the mechanisms of mobilization previously mentioned) in different proportions and at different times (ICRP, 1964) according to the region

*Lung washing is an infrequent practice in medicine today. Years ago it was used a great deal due to its innocuousness and simplicity. Current use of antibiotics has relegated it practically to oblivion. García Vicente (1929).

of the R.T. where the deposit occurred.

The fraction which reaches the blood by ingestion is extremely small, $3 \times 10^{-3}\%$ of the amount ingested (ICRP, 1959), which places it, for the purposes of dosimetry, in the third order of importance, greatly different than the values of absorption caused by inhalation and absorption through wounds.

With rats and adult pigs (Katz, et al., 1955) and (Weeks, et al., 1950), for different compounds of Pu, administered orally, a maximum absorption of 0.007% was obtained, with intermediate values of 0.003 in rats and 0.002% in pigs, coincident in order of magnitude with the value of ICRP. These low values of absorption are explained by the reactions which can take place in the G.I.T. with the abrupt changes of acidity in the stomach and increases in the pH in the intestine below the duodenum. Thus, the soluble transportable compounds of Pu can be totally or partially destroyed at gastric pH, and hydrolyzed in the alkalinity of the intestinal juice with the formation of non-transportable-ratio-colloids (Nenot, 1967).

The degree of absorption seems to be associated also with age, as shown with young pigs (Buldakow, 1968), in which an increase of absorption was observed.

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4.3. Transcutaneous absorption

Data concerning absorption through the skin is insufficient and often contradictory, and a distinction must be made between unbroken and broken skin. In the case of the former, absorption can take place by diffusion through the epidermis or by penetration in hair follicles or in secretory ducts of the sweat and oil glands.

In the case of lesions, absorption is more direct, the amount depending on the type of lesion (incision, contusion, burns, etc.) and the depth and anatomical location. Therefore, in wounds, a direct entry into the blood may exist (as if an intravenous injection were performed), or the simultaneous entry into the blood and retention in the tissues of the wound, where the Pu is absorbed slowly.

Experiments on animals with short exposures (up to one hour) gave absorption values of $10^{-4}\%$ and $10^{-3}\%$ of the quantity applied to unbroken skin, increasing to approximately 2% with greater acidity of the solution and greater exposure time (Weecks, et al., 1953 and Ballow, et al., 1957). Nevertheless, under these conditions chemical burns can be produced, and the skin can no longer be considered unbroken.

In man, transcutaneous absorption is less than in animals (Langham, 1959), on the order of $10^{-4}\%$ /hour, after remaining eight hours on the palm of the hand, although the difference of skin according to the region being considered must be taken into account.

In general, penetration through the skin is influenced by the extent of the affected surface, characteristics of the contaminating compounds, and by the pathological effects on the skin of the solvents used.

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5. Diffusion in the blood: Interaction with plasma proteins

Whatever its origin, the Pu which reaches the blood can: a) be absorbed and excreted in the urine without change, if the compound is very stable; b) disappear in a few minutes to be mobilized by the liver, if strongly hydrolyzed; and c) form complexes with the proteins if the compound is unstable, in which case, approximately 90% joins a beta globulin (transferrin) to form a very stable complex.

The interaction with the proteins, therefore, is influenced by the physicochemical characteristics of the Pu compound which reaches the blood. Studies "*in vivo*" of Pu distribution in serum proteins of different types (Boocock, et al, 1965), in rats and (Muntz, et al, 1947) in dogs, and "*in vitro*" with compounds of Pu and human serum (Bruenger, et al, 1970), show the interaction mentioned.

The affinity of Pu for transferrin (Massey, 1967) is analogous to the affinity of iron for this same protein, and transport from the blood to organs and tissues is common to both in the first phase, until deposit in the tissues, which is done by different

mechanisms. Iron is incorporated into the cells because specific receptors of transferrin exist in them (Fletcher, 1968) this protein, then, is what determines the destruction of the iron. Excess iron is stored in the liver, spleen and other tissues in the form of ferretin and hemosiderin. Specific Pu receptors do not exist in the cells and it is supposed that depositing takes place due to different mechanisms, among which other proteins which carry iron seem to be involved (ferritin and hemosiderin) in some cases and glycoproteins in others.

6. Distribution from the blood

For the study of the distribution of absorbed Pu, an "experimental model" is used, obtained by intravenous injection of complexed Pu compounds, which can be representative of the compounds which later pass to the blood following penetration through the different routes of internal contamination.

The distribution and deposit in the various organs and tissues are conditioned by the stability of the compounds which have passed to the blood or which have been formed by hydrolysis at physiological pH. In the case of heavily complexed compounds, deposit takes place preferentially in the bone at a proportion of about 80%. If the compound has been hydrolyzed, the deposit takes place preferentially in the liver, at a proportion of 70 to 80%.

6.1. Distribution in the skeleton and bone marrow

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Deposit of Pu takes place on the surface of the bone (Stover, 1970), mainly in the cells of the endostium, and to a lesser degree on the periostium. This surface location (Marshall, 1969) is also characteristic of other radioactive nuclides, such as thorium, americium, different from the rare earth group, which, like radium, is diffused more in the mineral part of the bone (distribution in volume).

The selectivity for the cells of the endostium is associated with the presence in those cells of a glycoprotein, sialoprotein, to whose carboxylic groups Pu is joined to form a very stable

complex (Chipperfield, 1970, and Herring, 1962). This incorporation includes mechanisms for the dissociation of the Pu-transferrin complex at the level of the bone surface and diffusion of the Pu from the blood, with the changes of pH derived from the presence of specific organic acids of the bone (lactic, citric) mainly influencing this.

Experiments with different species of animals and in different parts of the skeleton show the non-homogeneity in the distribution in the bone in medullary spaces, and later, according to Jee (1972) at the base of the cranium.

Pu can be localized in the bone marrow* before being deposited in the bone in medullary spaces, and later, according to Jee (1972) and Erleksova (1970), the Pu mobilized from the bone deposits can be found:

- a) recirculating in the blood,
- b) in spaces in the bone marrow,
- c) retained in cells of the reticulo endothelial system.

The accumulation and retention in the medullary macrophages seem to be associated with processes of phagocytosis and existence of the iron storage protein, hemosiderin.

In this respect (Vaughan, et al, 1967) found Pu and hemosiderin simultaneously in macrophages of bone marrow, and (Taylor, et al, 1967) in histological studies higher concentration of Pu in tissues rich in hemosiderin.

6.2. Distribution in the liver

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The fractions which are deposited in the liver and the characteristics of their distribution are a function of the physicochemical state of the compound and of the route of penetration. In general, low relations of liver/bone deposits indicate the entrance in blood of complexed transportable compounds, just as high values suggest the existence of hydrolyzed Pu.

*Referring to red bone marrow, hematopoietic organ, and not to the yellow bone marrow, inactive from the hematopoietic point of view.

By intravenous injection of complexed compounds in dogs and rabbits a diffuse initial distribution in all liver structures was observed (Cochran et al., 1962), and later, an irregular redistribution and accumulation in cells of the endothelial network according to the degree of polymerization reached in their interaction with organic fluids.

With easily hydrolyzable compounds, the initial distribution is not homogeneous, and the Pu aggregates are localized in macrophages mainly in peripheral zones of the hepatic lobes (Lindenbaum et al., 1967).

Mechanisms of interchange between Pu and proteins seem to be involved in incorporation into the liver, especially processes of phagocytosis in redistribution.

In this respect, histological studies of dog livers *in vivo* (Stover, 1970a) and *in vitro* (Bruenger, 1968) show the existence of Pu associated with ferritin in the liver. This leads to the supposition that the incorporation takes place according to the following reaction:



The processes of phagocytosis, on the other hand, facilitate the mobilization and interchange of Pu between the hepatic compartment and the Kupffer cells

Other tissues

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The retention of Pu in the spleen, kidney, etc., is considerably less than in the lung, skeleton and liver, which are considered to be critically susceptible to effects of induced radiation.

7. Toxicity

In addition to the previously mentioned factors in distribution and deposit, other parameters related to the doses of radiation influence the toxic effects. We shall analyse these parameters below.

Dose as a function of distribution

Doses originating from the same organic charge can be different according to the organ being considered, not only for the purpose of annual doses, but for an accumulated dose over fifty years of professional exposure (compromised dose). Thus, on the basis of distribution of a maximum permitted organic charge of 0.04 μCi at 50% in bone and liver, the accumulated doses would be 57 rad for the former and 14 rad for the latter (Mays *et al.*, 1970). If, in addition, the influence of age is considered, the distribution coefficient can be different, with a greater percentage in the liver of young persons due to the greater affinity for iron and more active bone replacement.

In the bone marrow, the distribution of Pu is also related to irradiation of hematopoietic and osteogenic cells.

In the R. T., the doses which correspond to the same charge vary considerably, according to whether the lungs or the mediastinal lymphatic ganglia are considered the critical organ (Myers, *et al.*, 1972). Thus, the same annual permitted dose in the lung or lymphatic ganglia is equivalent to values of charges which differ by a factor of approximately 100 (16 and 0.21 nCi).

The risk of induced radiation of a particular tissue and charge also varies with the characteristics of the deposit. The same charge of Pu in the mediastinal lymphatic ganglia represents less risk if it is encapsulated than if it is a temporary movable deposit (Morgan, 1970).

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Effects as a function of the dose:

The relation of dose to effect is in direct proportion in the bone and in indirect proportion in the liver for high doses (Stover, 1972). These opposite effects are explained by the fact that in the skeleton high doses inhibit normal replacement, thus impeding the mobilization of the Pu, which is retained as "frozen", while in the liver high doses, on the contrary, cause the death of the hepatic cells, thus accelerating the normal mobilization away from the liver.

For the lung, the dose/effect relation is influenced, as is its deposit, by the characteristics of the particles inhaled, particularly by the surface, and by the activity per particle, due to the relation which, for the purpose of mobilization, the area has with distribution and transport (Thomas, 1971), with differences in activity for particles the same size with different isotopes of Pu.

Considering the relation among size, number, and extent of deposit of particles of a certain activity, the effects are different according to whether the activity is concentrated in a small number of particles (hot spots) or extended.

Sensitivity to radiation:

The nonuniform distribution of the Pu and the radio-sensitivity of the zone where it is concentrated can lead to the freeing of a greater dose where these factors coincide.

Age at the time of contamination is a factor which influences the total radiation dose, just as does the temporal distribution of that dose (Sikov, 1972). Thus, equal doses can cause different effects in the function of cells, due to the differences in radio-sensitivity with age. This difference is to be expected in man, who due to his life-span has a proportionately longer period of youth than the animals.

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7.1. Acute and chronic toxicity, lethal and tumor-causing doses

Until now, there are no proofs of cancer induced by Pu in man, which does not guarantee that it will not happen in the future, since it seems that not enough time has passed since the beginning of professional exposure to Pu for the organic changes to be significant in relation to fifty years of exposure. Nevertheless, there is evidence of the carcinogenic risk of other radioactive nuclides inhaled and retained in the lungs, deduced from studies of miners and exposed populations (Hiroshima and Nagasaki) (Lorenz, 1969).

This possibility has been repeatedly demonstrated in animals: nevertheless, in order to extrapolate these results of animal experimentation to man, even in the qualitative aspect alone, there are many limitations derived from the differences of tissue sensitivity, life-span, and other genetic, environmental and habit factors between experimental animals and man. An example is man's smoking habit.

There are, therefore, no conclusive data until now, which allow the establishment of absolute figures for the dose/response relation, above all for chronic exposures and low levels of activity.

In animal experimentation, the acute forms of toxicity are manifested by an irradiation syndrome comparable to that produced by a total irradiation with X-rays, and forms of a chronic nature can produce broncho-alveolar tumors in the lung, bone cancers and bone fractures in the skeleton, and, with less frequency, liver tumors.

Some lethal and tumor-causing dose values are expressed in Table 3, for experimental animals.

Lethal doses for dogs via I. V. and inhalation would be equal in man approximately to 1.3 nCi for the entire body, and approximately 100 μ Ci for the entire lung. On the other hand, the values in μ Ci which produced osteosarcomas by I.V. injection and those which led to neoplasm in the lung would be equivalent to approximately 25 times the total charge and 1,000 times the maximum permitted pulmonary charge for man. Langham (1969) calculated as dose limit for lungs, bone and liver in man, median accumulated doses of 100, 50 and 100 rad respectively, considering these values as extremes which would not cause biological consequences for the population in general.

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7.2. Effects on the lung

The pathological effects on the lung caused by the alpha radiation of Pu can lead to sclerosis due to destruction of the pulmonary parenchyma (Koshnrnikova, et al., 1972). The anatomical pathological lesions have been qualitatively the same with various

Pu compounds, with the severity of lesion and its characteristics depending on the dose of radiation and time. The progress of pulmonary sclerosis is accompanied by inflammatory processes and nonspecific biochemical changes in the cells. Recently, (Nettlesheim, 1972)* different chemical, viral and bacterial agents have been confirmed as causes of cancer. The infections or inflammations produced by these agents cause synergistic or antagonistic effects as a consequence of the fact that the deposits of radioactive nuclides can be prolonged in the affected areas or because they impede defense mechanisms (expectoration...).

The cells most affected in the pulmonary tissues can be those of the alveolar epithelium or of the end bronchii, and of the former those of type II are considered forerunners of neoplasms in acute cases.

In chronic exposure, due to mobilization, the mediastinal lymphatic vessels and ganglia are also potentially exposed as a consequence of the fact that deposit in them can be up to 100 times that in the lung (Swint, 1972). The histological type of lung tumor is principally broncheo-alveolar adenocarcinoma (Howard, 1970).

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7.3. Effects on the skeleton

The severity of lesion depends on the dose of radiation to the bone surface, the volume of cells exposed and the activity of bone tissue proliferation.

The influence of proliferation activity is emphasized by the greater sensitivity to radiation of the young skeleton, and as a result the incidence of cancer can be greater in the young than in adults.

With relation to the radiation dose, an analysis of the frequency of bone cancer induced with Pu suggests a linear dose/response ratio (Erokhin, 1970) in chronic exposures of long duration, with this ratio diminishing to a median dose which does not produce cancerous effects.

*And Creasia, et al. (1973).

Nevertheless, in animal experimentation it has not been possible to set minimum doses in many species which do not cause bone cancer. For man the dose/response ratio for Pu is not known, and the values for tumor-causing doses have been established by comparison with Ra²²⁶, always keeping in mind the differences in distribution and radiotoxicity which exist between them.

7.4. Effects on the liver

In the liver, effects vary within broad limits with time, physico-chemical form, and characteristics of the deposit. Thus, one hundred days were needed to accumulate a critical dose* (1500 rad) with monomeric Pu (Lindenbaum, 1972). On the other hand, with polymeric Pu a critical dose (100 rad) was reached in the dog liver only a few days after a single injection.

It is estimated from animal experimentation that the minimum time for the appearance of tumors after contamination is about seven years, greater in many cases than the average life of most experimental animals.

In man, the average life and environmental factors related to work, habits and food can favor the induction and frequency of tumors (inhalation of toxic solvents in the Pu industry, alcohol ingestion (Cole, 1965), and the possible influence of chemical additives in foods).

The most frequent type of tumor is that located in the bile ducts.

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8. Elimination by excretion

From very abundant animal experimentation, and from a few human cases, it has been deduced that the elimination of Pu in the urine and feces varies among species, and that in man it is slightly less than in some animals.

Mechanisms in this elimination involve plasma proteins and the metabolism of iron (Durbin, 1971). According to that,

* Dose above which there are losses of liver Pu to the circulation and transport to the bone.

filtration by the kidneys and subsequent excretion in the urine would be conditioned by the proportion of Pu united with plasma proteins, and the degree of this elimination would be in an inverse ratio to the union of the mentioned proteins.

In addition, physiological and pathological processes which lead to reduction of urine excretion in some cases (iron-poor anemics) and to its increase in others (renal dysfunction) are involved in the mechanism of excretion.

G. I. elimination and excretion in the feces, which includes the elimination of Pu in bile and other digestive juices, is partly influenced by the state of the liver and by digestive functions, as well as by the union of Pu with ferritin or hemosiderin. In the first case, elimination is through the hepatocyte, and in the second case the cells of the endothelial system are involved.

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Following this hypothesis, the differences of excretion among the different species and man would be explained by the differences in iron content in the diet (of dog and pig) and by the influence which the state of the digestive function has on the absorption of iron, which shows up as a greater elimination of Pu in dogs (differences in pH between G. I. T. of man and dog).

The elimination of Pu via kidneys or intestine is relatively slow and the degree of excretion low, as shown by calculations (Langham, 1959) on accumulated excretions (urine and feces) for Pu and Ra, based on human experiments. Even in the first twenty-four hours, the degree of elimination of Pu is less than 1% of the dose administered, and the total accumulated excretion over 50 years suggests that it would be on the order of 17%, while corresponding values for Ra, initial and final, are 40 and 97% respectively.

These elimination characteristics allow the detection of contents of Pu in the organism by analysis of excretions, months and even years after internal contamination, but analytic procedures of high sensitivity are needed to be able to determine Pu activities corresponding to fractions of total and pulmonary MPOC * (Table 1).

*Maximum permitted organic charge.

In the radiotoxicology laboratory* directed by one of us, Pu-239 in urine is determined by alpha spectroscopy following separation and purification by electro-deposit, and the sensitivity reaches detection limits on the order of 10^{-6} μCi /twenty-four hour urine and one thousand minutes of count.

9. Evaluation of internal contamination

In order to evaluate internal contamination from professional or accidental exposure to inhalation of radioactive aerosols, direct and indirect methods and combinations of both are used, according to the case. By direct measurements (techniques of *in vivo* counting), determination can be made of the Pu content in the lung. This method is based on the measurement of LX radiations**, an emission which takes place is 4% of the alpha disintegrations of Pu. Other direct measurement techniques use the gamma emission of Am-241. Precision in these cases is greater when the ratio of Pu/Am of the inhaled compound is known.

By indirect measurements (analysis of excretions), Pu content can be determined (circulating and pulmonary charges) when the physico-chemical characteristics of the compound inhaled, particle size distribution and time since contamination are known.

The interpretation of these measurements is subject to limitations and specific problems, derived from the complexity shown by Pu in its distribution and elimination from the organism; on the other hand, human experimental data which served as a basis are therefore still insufficient if a precise estimate is desired. "Approximate estimates can be made based on available "excretion models". Because more data are available concerning the kinetics of elimination in urine, we refer mainly to estimates of organic charges based on data of excretion by this route.

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* Division of Protection and Safety of the C.N.E.N., "Juan Vigon".

** 13.6, 17.2 and 202.2 KeV.

Circulating charge and initial pulmonary charge:

In order to estimate the circulating charges (C.C.) and initial pulmonary charge (I.P.C.), we follow the excretion model of Nelson (1967) based on the new pulmonary model (I.C.R.P., 1964) and human experiments (Langham, 1950), and the model of Healy (1957) concerning values of Pu excretion in urine as a function of inhalation of an aerosol of Pu oxide and nitrate. In this model it is considered that the fractions deposited in the different compartments depend on the aerodynamic diameter of the aerosol, and that the Pu which passes into the blood follows the same mobilization and excretion mechanism as the citrate of Pu in the experiments of Langham, independently of the chemical characteristics of the inhaled compound.

Circulating charge (C.C.):

The C.C. resulting from inhalation of an aerosol consists of the sum of the contributions of Pu to the blood proceeding from the compartments of the R.T. (NP and TB). Figure 7 presents the C.C. resulting from the inhalation of Pu oxide and nitrate as fractions of the aerosol inhaled, as a function of the aerodynamic diameter. According to the graph, the percent of the inhaled dose which reaches the blood varies with the size of the particles; for oxide, the percent is between 1 and 6, and for nitrate, between 9 and 20%. According to that, for particle sizes of 0.2μ , the C.C. values for oxide and nitrate are approximately 3 and 10%, respectively.

DOE ARCHIVESInitial Pulmonary Charge (I.P.C.):

The quantity of Pu which remains in the pulmonary compartment following a rapid initial elimination of Pu from the R.T. constitutes the I.P.C. In Figure 8 the I.P.C. is represented as a function of the diameter of the particles; comparing the curves of the C.C. and I.P.C. In the case of oxide, the slope of the I.P.C. increases with the size of the particles in a proportion analogous to that of the C.C., so that up to sizes the order of 1μ , the relation

C.C./I.P.C. remains practically constant, which allows the calculation of one as a function of the other.

For larger particle sizes, the slope of the C.C. diminishes, while that of I.P.C. increases; so does the quotient C.C./I.P.C., which corresponds to the fact that particles of larger size are mobilized into the blood more rapidly from the NP deposit than those of smaller size deposited in the lower areas of the R.T.

In Figure 9 the excretion of Pu is represented in DPM* as a function of the time and particle size, corresponding to inhalation of oxide and nitrate, including that proceeding from intravenous injection (Langham, 1950), of interest for the purpose of comparison. These excretion values correspond to a C.C. of 1 nCi.

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In this figure (for oxide) it can be observed that for small particle sizes, the excretion is small, and for larger sizes, on the order of 10 μ , the initial excretion values are greater and from the beginning follow a rhythm analogous to that obtained with an intravenous injection. In any case, after a year, the rhythm is independent of the size. This process is analogous in the case of nitrate, but the time from which the rhythm is independent of particle size is notably reduced.

In Figure 10 (excretion originating from an I.P.C. of 1 nCi) it is observed that excretion decreases with the decrease in particle size, as in Figure 9, but the dispersion is greater when dealing with C.C. It is also observed that, for particles up to 1 μ , the degrees of excretion coincide (with those of C.C.) in their independence of particle size and times; nevertheless, for larger sizes, excretions are greater by a factor which could be estimated on the order of 4 for nitrate and 2 for oxide.

These excretion models could also be used to estimate these charges when complete information is not available concerning the nature of exposure and contamination.

For the purpose of orientation, in Table 4 some estimates as a function of existing exposure data are indicated.

* Disintegrations per minute.

Following the graph of Figure 10, and based on the inhalation of 1 nCi and a urine detection limit of 10^{-2} DMP/sample, Pu content can be evaluated with a certain approximation even years after contamination.

Estimation from fecal excretions presents difficulties related to obtaining samples and precise data of exposure, since quantitative interpretation requires immediate and continuing (in the first week) determinations and exact knowledge of the granulometry of the aerosol.

Evaluation of Pu content in wounds

Plutonium in wounds is determined by direct measurement* using INa(Tl) fine-layer detectors.

The detection limit varies as a function of the depth of the Pu in the wound.

An example is presented in Figure 11, the system available in the Medical Service of C.N.E.N. "Juan Vigon".

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10. Elimination therapy

The therapy for internal contamination by radioactive nuclides is based on accelerating the processes of mobilization, in order to impede deposit or to achieve more rapid elimination of the incorporated radioactive nuclide. Procedures used include chemical, physical or biological means, applicable according to the radioactive nuclides and circumstances during contamination. Although procedures common to other radioactive nuclides can be applied to Pu, its specific characteristics within the group of actinides influence differences of effectiveness with combined therapy, which justifies the separate study of this radioactive nuclide.

In its interaction with the organism, the chemical complexity of Pu facilitates the co-existence of different physicochemical states of its compounds, which, combined with the physical

*Of LX rays of Pu-239 or Gamma of Am-241.

characteristics (specific activity, half-life, etc.), explains the differences of its metabolic response and therapy with respect to other transuraniums.

In animal experimentation and in some human cases, physical procedures ("dragging"), electro-aerosols, physicochemical procedures, procedures of natural mobilization stimuli, and chemical procedures based on complexes with chelates are used.

"Dragging" with citrate of Zr, as in other immunological procedures, with antiserum and in anaphylactic shock, has been tested only on animals, with little success.

Other physical and biological means include pulmonary washings, use of bronchodilating medication, and expectorants, adding to the effectiveness of the therapy due to previous preparation or by synergic effect in combined therapies; in these last a polysaccharide, "Glucan", which provokes a dispersion of the colloidal aggregates, has been used with success in animals (Lindenbaum, et al., 1968), facilitating the mobilization of polymeric Pu by DTPA*.

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The elimination of Pu by means of chelates has been the most used, either alone or in combined therapy with physical or biological means. The chelate compounds tested have been mainly those of the polyaminocarboxylic acid series and others, like sodium citrate, which form transportable complexes with Pu that are rapidly and almost totally eliminated through the kidneys and in very small proportion via the intestine, in the bile.

In chelate therapy the inherent factors of the contamination, route of penetration, types of compounds, time elapsed, and efficiency factors of the chelate must be considered in stability, toxicity, and therapeutic doses; of these last factors the toxicity is minimal in the doses used, but the stability of the complexes with Pu is decisive for purpose of elimination. In this respect, we refer to the stability tests *in vivo* on rats (Lafuma,

*
 EDTA: ethylene-diamino-tetracetic acid
 BAETA: 2,2-bis(dicarbonylmethylamino)diethyl ether
 TTHA: triethyl tetraminohexacetic acid
 DTPA: diethyl triaminopentacetic acid

1968) using complexes of Pu with EDTA, BAETA, TTHA, and DTPA with positive results for the last two and less toxicity for DTPA. These results confirm the major therapeutic index of DTPA observed in experimentation and justifies the fact that in the last decade it has been the chelate chosen.

Routes and procedures of application of these preparations vary in each case. Therefore, in respiratory contaminations, most frequent in industrial workers, and for cases of inhalation of transportable Pu compounds, chelates have been used I.V. and in aerosols, and in the case of nontransportable compounds I.V. and pulmonary washings are used.

In Tables 5 and 6 cases of human accidents and chronic exposures have been selected, showing the treatment used as a function of the routes of penetration and the contaminating compounds.

The time elapsed after contamination until the beginning of treatment influences the choice of procedure to be used and even the dose. Nevertheless, in man, delay in beginning treatment does not seem to influence the possible tumor-causing dose for bone, although it influences the mobilization of the Pu retained in the bone marrow and other soft tissues (James et al., 1971).

Keeping in mind what was expressed earlier, it can be understood that the administration of these substances for therapeutic purposes in cases of Pu contamination must be carried out under the direct supervision of a physician, even for cases of applications to wounds.

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Register of Plutonium

Since 1967 (Bruner, 1967), there has been a register of transuranides in the USA whose objective is to "centralize, accumulate, evaluate, and dispense data about incorporation, distribution, retention, and effects of the transuranides in professionally exposed persons" (Newton et al., 1971).

Due to the fact that among the transuranides the production of isotopes of Pu has been greater, the number of persons

potentially exposed is also greater, and for the time being the register is devoted to Pu.

The programs of the register require, on one hand, international cooperation from installations and organizations involved with the risk of internal exposure to Pu, and on the other hand, the voluntary cooperation of exposed persons or of their families for the purpose of autopsy or availability of organs for anatomical and pathological studies.

In Europe there is currently a project for a similar register, sponsored by the O.M.S.

These projects can represent a great help in the field of radiotoxicology, relating real deposits to previous evaluations of internal contamination (direct and indirect) of persons exposed to Pu.

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Finally, the current director of the USA project (Norcross, 1972) hopes, with exchange of data among the different registers, to obtain a statistical basis which will constitute a great advance for preventive medicine on an international scale.

From the beginning of the Pu register in the USA, the J.E.N. has maintained direct contact with it, receiving and sending pertinent information.

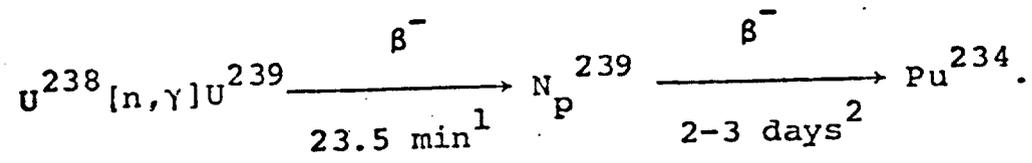
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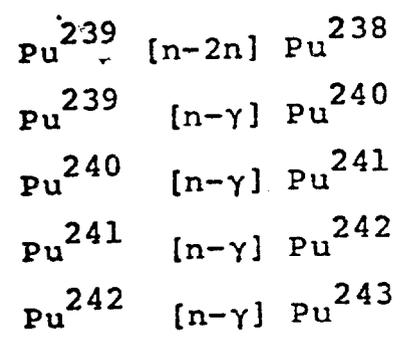
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Schema 1



Schema 2



Lister (1964)

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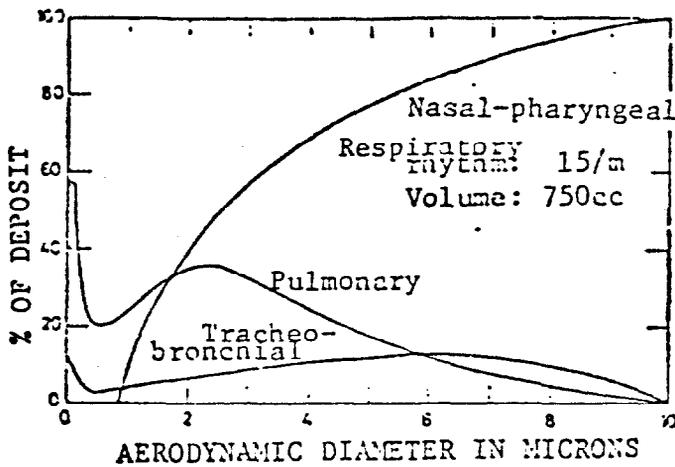


Fig. 1. Deposit in the respiratory tract in relation to the aerodynamic diameter of the particles. ICRP, 1964.

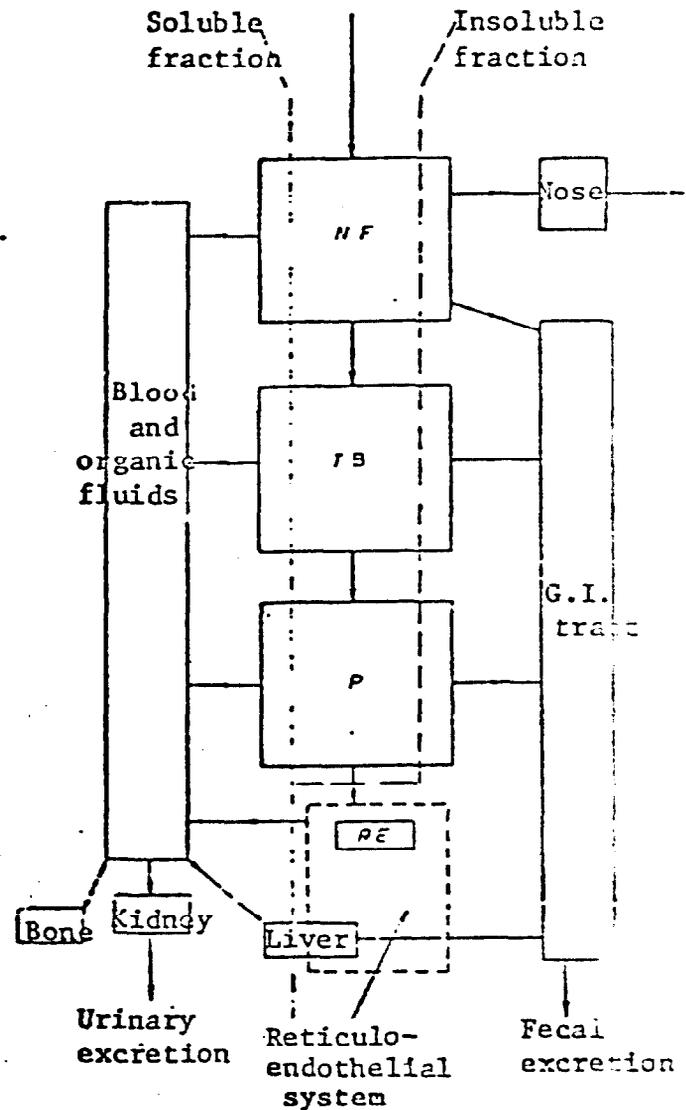


Fig. 2. Outline of the deposit of plutonium particles and subsequent movement of the soluble and insoluble fractions. ASHB(RP)R96, 1969.

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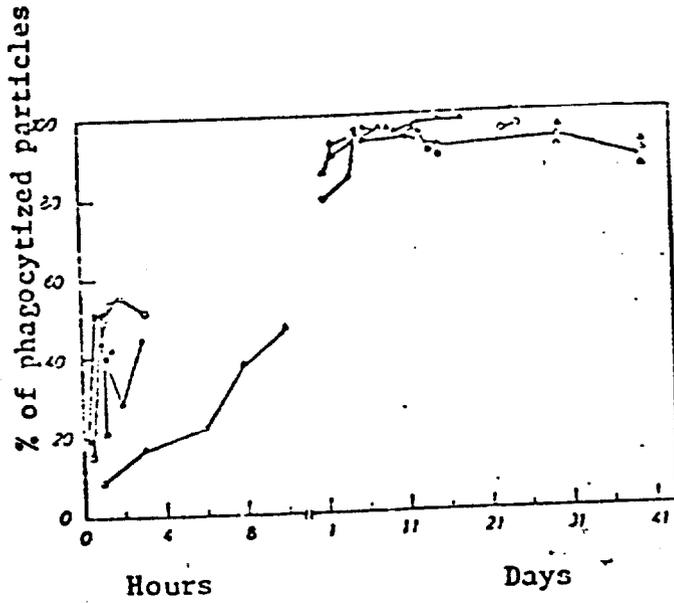


Fig. 3. Sanders, 1969a.

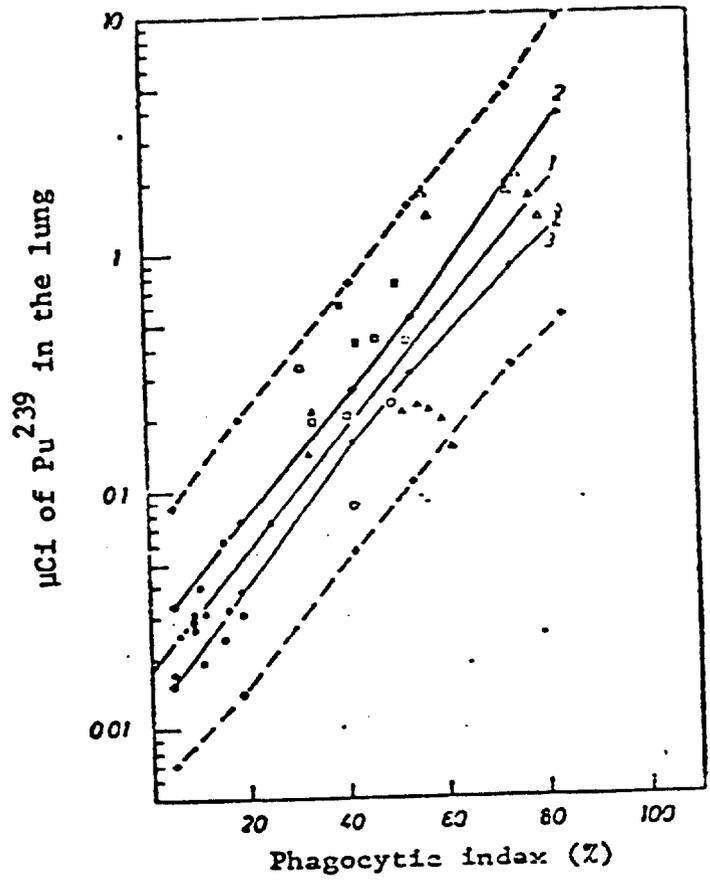


Fig. 4. Sanders, 1969a.

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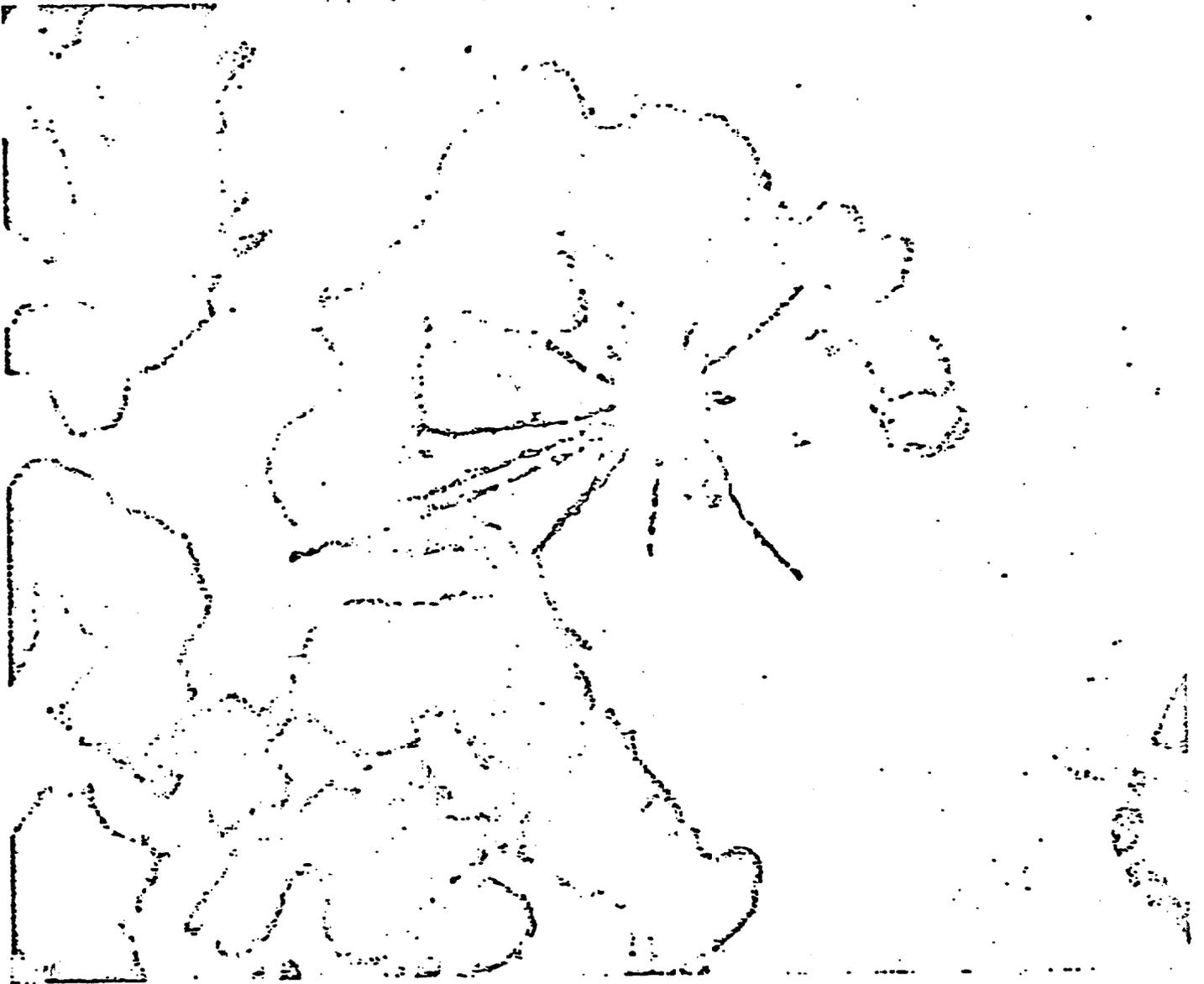


Fig. 5. Photograph of an autoradiograph of traces produced by alpha particles of Pu, engulfed in an alveolar macrophage (Sanders, 1970).

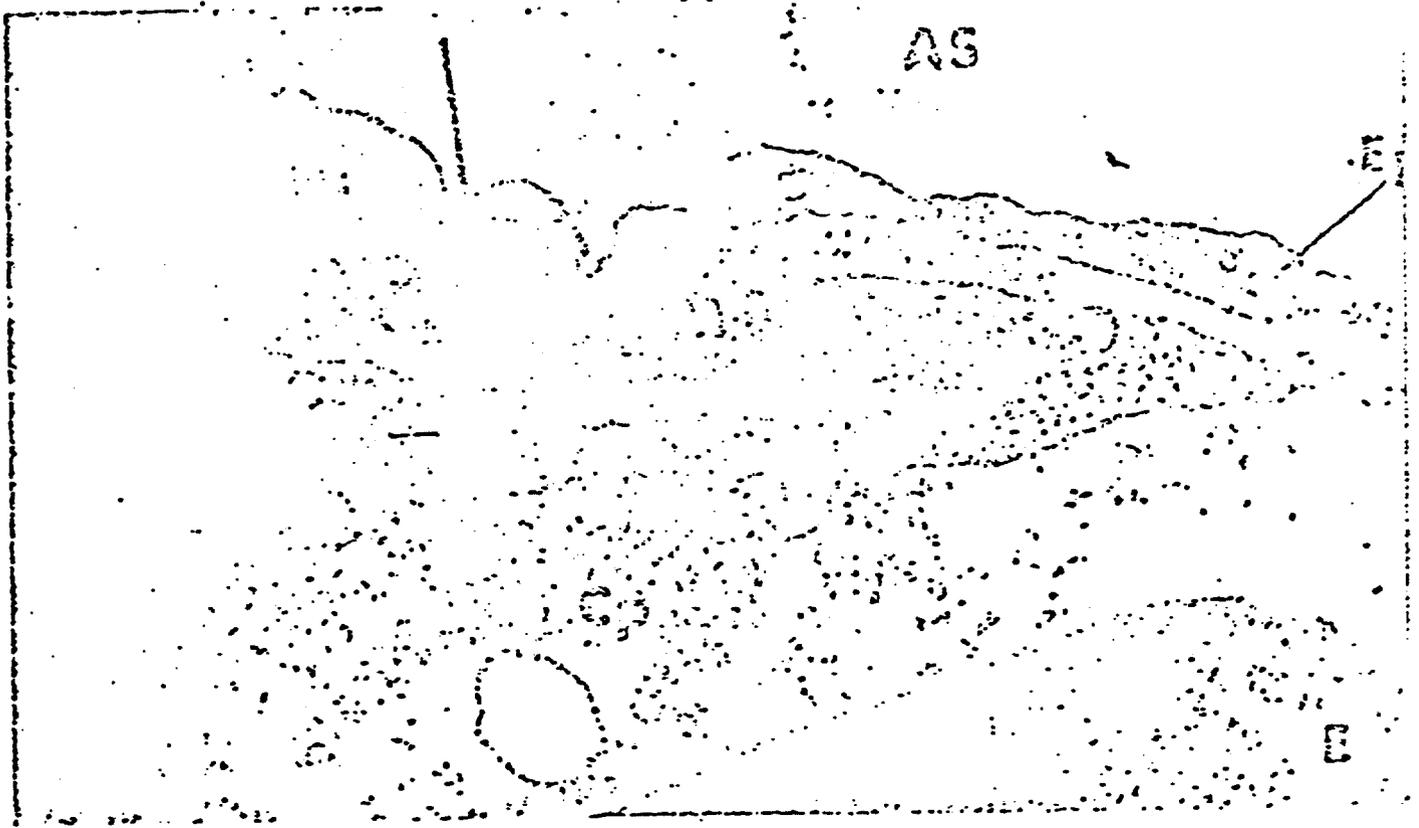


Fig. 6. Particle of Pu located in the alveolar epithelium, Type I. AS alveolar space. Ep: epithelial cell. BM: Basal membrane. En: endothelial cell. Cp: Capillary. E: erythrocyte. (Sanders, 1970).

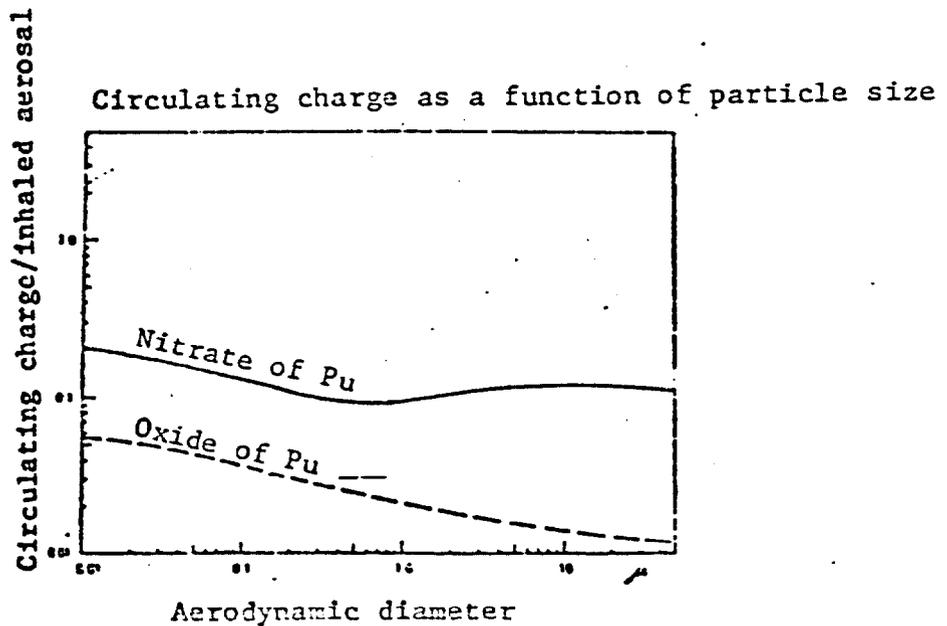


Fig. 7. Nelson, 1967.

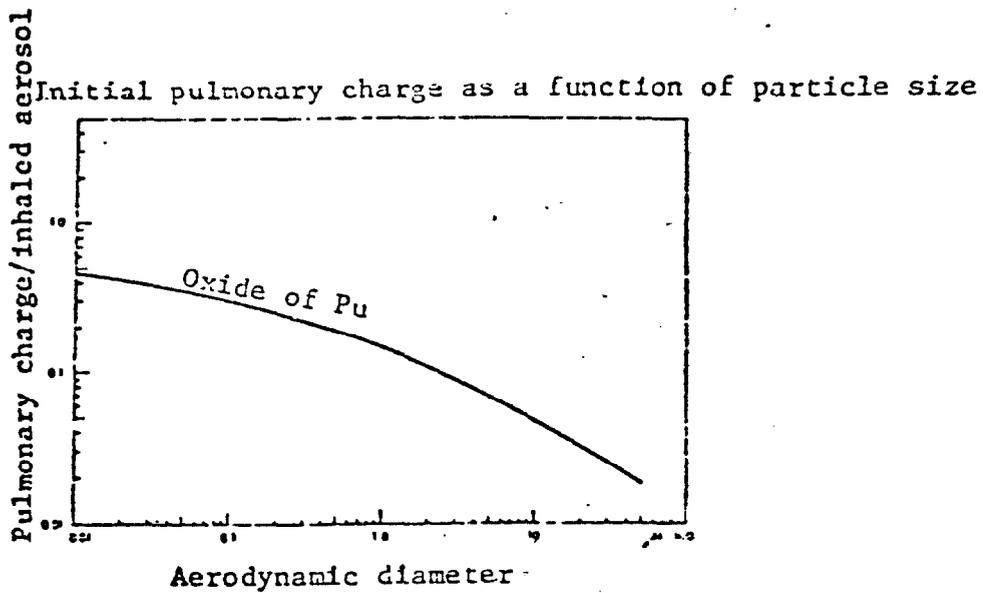


Fig. 8. Nelson, 1967.

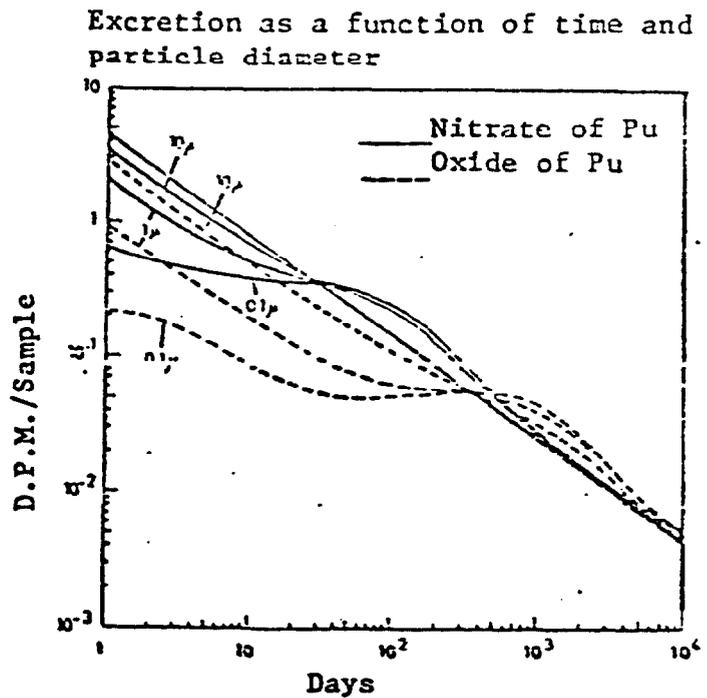


Fig. 9. Nelson, 1967.

Excretion as a function of time and particle diameter

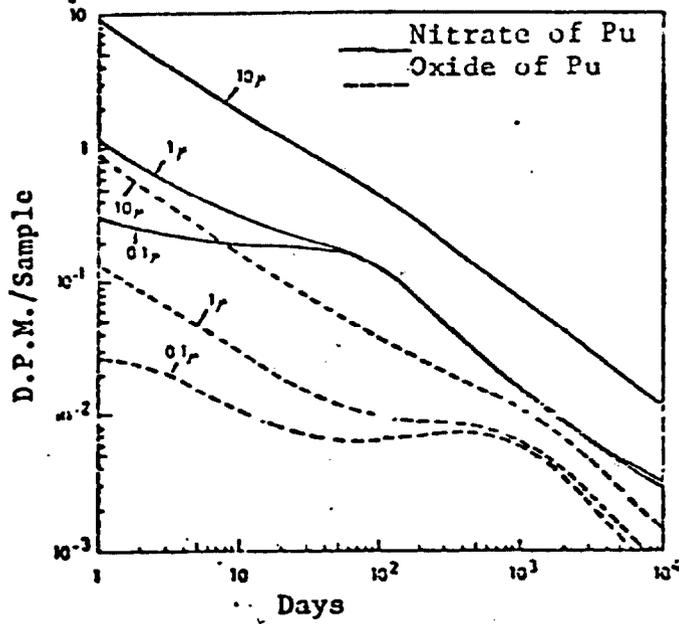


Fig. 10. Nelson, 1967.

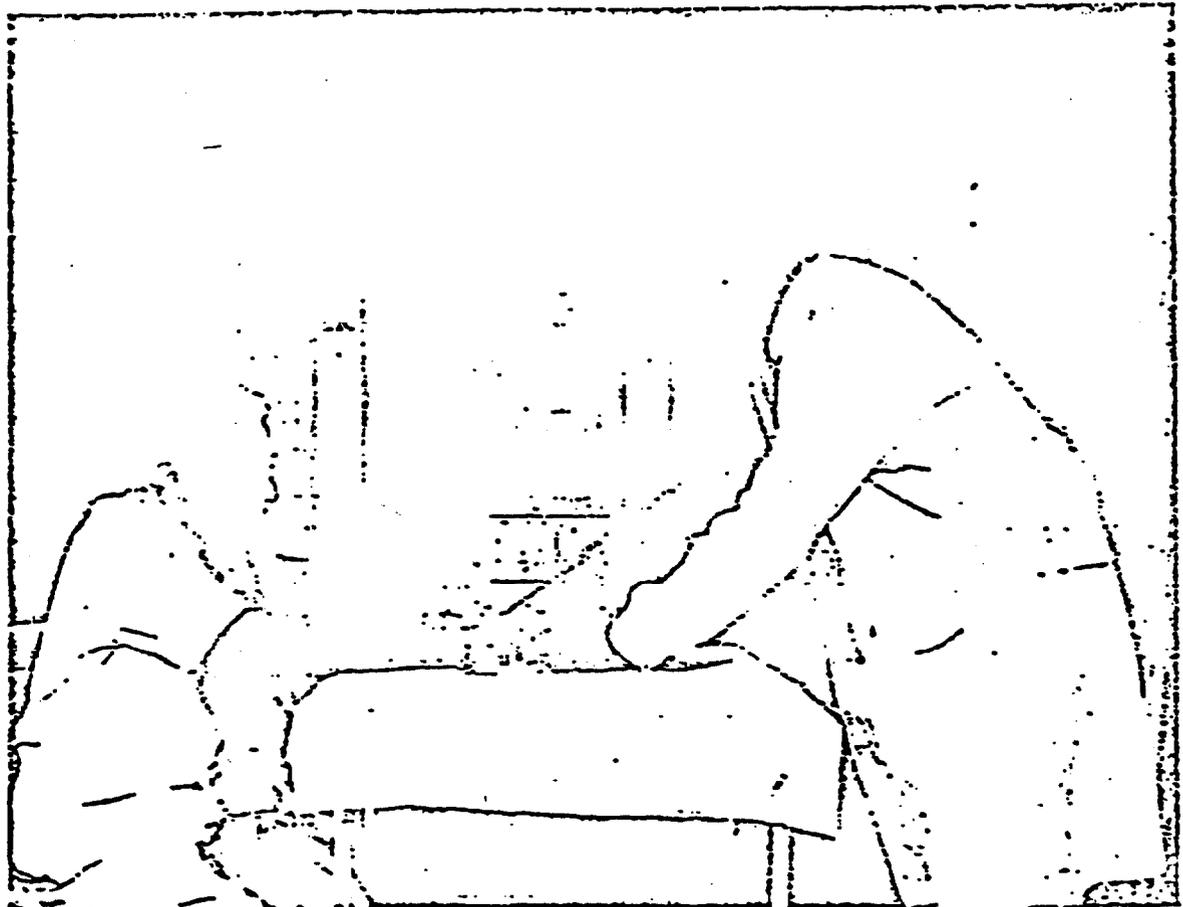


Fig. 11

Table 1
Maximum permitted organic charges of Pu isotopes

Isotope	Transportable compounds of Pu	Critical organ	Non-transportable compounds of Pu	Critical organ
Pu ²³⁸	4 × 10 ⁻⁴ Ci	Bone	1.5 × 10 ⁻⁴ Ci	Lung
Pu ²³⁹	4 × 10 ⁻⁴ Ci	Bone	1.5 × 10 ⁻⁴ Ci	Lung
Pu ²⁴⁰	4 × 10 ⁻⁴ Ci	Bone	1.5 × 10 ⁻⁴ Ci	Lung
Pu ²⁴²	5 × 10 ⁻⁴ Ci	Bone	1.5 × 10 ⁻⁴ Ci	Lung

Data from I.C.R.P. (1959).

Table 2
Disintegration characteristics

Isotope	Half-life	Specific activity Ci/g	Emission energy MeV						
	Years		α	β	%	γ	neutrons	LX	β _{max}
Pu ²³⁸	25.4	17.4 α	5.45-5.49		100	0.044-0.15	4.7 × 10 ⁻²	0.017	10
Pu ²³⁹	2.44 × 10 ⁴	6.2 × 10 ⁻² α	5.10-5.15		100	0.033-0.33	1.4 × 10 ⁻²	0.014-0.02	33
Pu ²⁴⁰	6.6 × 10 ⁴	0.23 α	5.11-5.16		100	0.045	4.0 × 10 ⁻²	0.017	10
Pu ²⁴¹	13.2	1.13 × 10 ² β	4.84-4.89		3 × 10 ⁻³	0.10-0.14	1.2 × 10 ⁻¹		
				0.02	99.997				
Pu ²⁴²	3.8 × 10 ⁵	4.0 × 10 ⁻³ α	4.85-4.89		100	0.045	~ 10 ⁻²	0.017	10
Pu ²⁴³	5	2.57 × 10 ² β		0.49-0.53	100				

Data from Vaane (1969).

Data from Lister (1964).

Table 3

Lethal and tumor-causing doses

Species	Compound	Route	Activity μCi	Time		Median accumulated dose Rads	Effects	Reference
				Days	Years			
Dog		I.v.	19/kg	30			DL ₅₀ (*)	Langham (1959)
Dog		Inhal.	0.9/g lung	55		4,000	DL ₅₀	Park (1952)
Dog		Inhal.	0.1/g lung	412		14,000	DL ₅₀	Park (1952)
Dog	CitratePu ²³⁹	I.v.	0.015/kg			86	Osteo-sarcomas	Dougherty (1970)
Dog	CitratePu ²³⁹	I.v.	0.015-2.9/kg				Bile duct tumors	Taylor (1959)
Dog	Oxide Pu ²³⁹	Inhal.	0.1 $\mu\text{Ci/g}$		1	2.5×10^4	Neoplasm	Bair (1970)
Dog	Oxide Pu ²³⁹	Inhal.	0.05/g lung		10	2.5×10^4	Neoplasm	Howard (1970)
Rabbit	—	I.v.	14/kg				Acute toxicity	Finkel (1952)
Mouse	OxidePu ²³⁹	Inhal.	10^{-4} - 10^{-7} /lung				Shortening of life	Bair (1952)

* DL = lethal dose.

Table 4

Possible estimates of Pu as a function of existing data

Characteristics		Compounds of Pu	Time since inhalation		Possible estimates	
Known	Unknown		Days	Years	C.C.	C.P.I.
Chemical	Granulometry	Nitrate	30	—	C.C.	C.P.I.
Chemical		Oxide	—	1	C.C.	C.P.I.
Chemical	{ ϕ 0.1 ϕ 1.0 ϕ 10.0	Oxide	1 to 6	—		
Granulometry		Oxide	30	—		C.P.I.
Analytic		Oxide	—	1		
Chemical	{ ϕ 0.1 ϕ 1.0 ϕ 10.0	Nitrate		~2		
Granulometry		Nitrate		~2		C.P.I.
Analytic		Nitrate		~3		

Table 5

Human cases

Route of penetration	Compounds of Pu	Treatment		Reference
		Technique	Compounds utilized	
Wound	Nitrate of Pu ²³⁸	Tourniquet Washing & excision I.V. injection I.V. injection Aerosol	Water, detergent & oxidant DTPA in glucose solution DTPA in saline solution DTPA	Jolly (1972)
Wound	Nitrate of Pu ²³⁹	Excision I.V. injection	DTPA	Jech (1972)
Wound	Isotopic mixture of Pu ²³⁹ , Pu ²⁴⁰ and Am ²⁴¹	Excision-washings I.V. injection	DTPA DTPA	Testa (1971)
Wound	Nitrate & oxide of Pu and Am	Excision I.V. injection	DTPA	Hesp (1970)
Wound	Oxide of Pu ²³⁹	Washings Intermittent I.V. injections	DTPA DTPA	Norwood (1959)

Table 6

Human cases

Route of penetration	Pu Compounds	Treatment		Reference
		Technique	Compounds used	
Inhalation	Isotopic mixture of Pu ²³⁸ " Pu ²³⁹ " Pu ²⁴⁰ " Pu ²⁴¹ " Pu ²⁴²	Aerosol I.V. injection	DTPA DTPA	Alderhout (1971)
Inhalation	Nitrate of Pu ²³⁹	I.V. injection	DTPA in saline sol after 16 days & after 183 days.	Alderhout (1970)
Inhalation	Oxide	I.V. injection Pulmonary washing	DTPA DTPA	McClellan (1972)
Inhalation	Oxide	Inhalation	DTPA	Jech (1968)