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RESEARCH GROUP

Report

STUDIES OF THE TOXICOLOGY OF PLUTONIUM

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Harwell, Berkshire.

1959

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by

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I Historical Survey

The first self-sustaining chain-reacting pile became divergent on 2nd December, 1942 in Chicago. Having demonstrated the feasibility of a nuclear reactor, plans were made for plutonium production and extraction and for a "pilot" plant for production of plutonium to be built at Clinton in Tennessee. This pile started operating on 4th November, 1943. (Smyth, 1945).

"Since both the scale and the variety of the radiation hazards in this enterprise were unprecedented, all reasonable precautions were taken; but no sure means were at hand for determining the adequacy of the precautions. It was essential to supplement previous knowledge as completely as possible. For this purpose, an extensive programme of animal experimentation was carried out ..... Under the general direction of Dr. Stone these experiments were carried out at Chicago, Clinton and the University of California principally by Dr. Cole and Dr. Hamilton". (Smyth, 1945).

"The advent of plutonium into the world brought a new problem. Of course, at the beginning of the Project, plutonium existed only in micro quantities and, therefore, was no hazard. As the cyclotron production rose to hundreds of micrograms, and later the Clinton pile production rose to grams, the possible hazard of this material became a more serious problem. It was found that from the point of view of acute effects it was just as hazardous microgram for microgram as radium. Since it has no radioactive gaseous daughter, like radon, the problem of protection became one of protecting against dusts and vapours". (Stone, 1946).

II 1. Organisation of Research

The Health Division of the Plutonium Project was called into existence in 1942. The duties of the Biological Research Section "were to make a co-ordinated study of the effects of alpha, beta, gamma, and neutron rays on the body, whether they came from external sources or followed the ingestion, inhalation, or transcutaneous assimilation of fission products, plutonium, and uranium". (Stone, 1946).

Stone cites the leaders of the Biological Section as, Cole, Prosser, Brues, Bloom and Barron at the University of Chicago; Curtis, Zirkle and Henshaw at Clinton Laboratories; Hamilton at the University of California Radiation Laboratory; Lorenz at the National Cancer Institute; Tannenbaum at Michael Reese Hospital in Chicago.

2. Research Progress

The progress of the work was recorded in reports from the various centres. The results of the work on plutonium were briefly summarised by Stone (1946). "Plutonium was not available in the early days of the project, but on the basis of its alpha activity and long half-life it was estimated that it would be about one-fiftieth as dangerous as radium. For acute effects this has been shown to be wrong, and the fact was determined that one microgram of plutonium was about as dangerous as one microgram of radium. The reason for this discrepancy apparently lies in the different distribution of the plutonium

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within the bone. The radioautographic technique which has been developed on the project, but was not new to the project, has been very successful in the demonstration of these organ distributions. It has also been found that plutonium locates in the liver and may cause severe liver damage. Over long periods of time plutonium has been shown to cause atrophy of the bone and bone sarcomas. The tolerance amount, or maximum permissible dose, in the human has been estimated to be one microgram. Since once the material is located in the body it remains there, this low tolerance amount becomes extremely important". (Stone, 1946).

III Absorption

1. Effect of valency on absorption

Plutonium was found to have four valence states - +2, +3, +4 and +6. The valence state of the plutonium greatly affected the amount of plutonium absorbed by the body from the site of administration, excluding intravenous injection. (Kisielski and Woodruff, 1948). Results obtained by Hamilton indicated that a solution of PuO_2^{+2} was most readily absorbed, with Pu^{+3} and Pu^{+4} following in that order: the order of absorption was more or less independent of the method of administration. The rate of absorption was related to the solubility of the plutonium compound formed by hydrolysis at the pH of the tissue fluids or absorbing surfaces. However, regardless of the valence state of plutonium Pu^{+3}, Pu^{+4} and PuO_2^{+2}, and regardless of the route of administration (subcutaneous, intramuscular, intrapulmonary, intravenous injection), body deposition was essentially the same when correction was made for the amount of material remaining unabsorbed at the site of administration. The only exception was the retention of plutonium by the liver following intravenous and intramuscular injection. Hamilton found 38 per cent, 73 per cent and 29 per cent retention of plutonium in the liver four days after intravenous injection of Pu^{+3}, Pu^{+4} and PuO_2^{+2} respectively; 5.5 per cent, 3.5 per cent and 14 per cent after intramuscular administration.

There was no apparent significant difference in the excretion of plutonium in the three valence states.

2. Concentration of plutonium in plasma

In recent work (Stover, Atherton and Keller 1959) the metabolism of Pu^{239} in adult beagle dogs after a single intravenous injection of Pu. IV in citrate buffer of pH 3.5, has been studied over a period of four years. The concentration in plasma was measured from one minute to 4.5 years after injection. Between one minute and ten hours, the concentration fell to about one half of the initial value. From then until 3 weeks later, the decrease in concentration was by a factor of 200. The decrease was then slower, and at four years the value was one-fourth of that at three weeks.

Early work reported the binding of plutonium by the blood proteins and this was confirmed. In sera dialysis studies, the plutonium citrate complex was found to be stronger than the plutonium protein complex (or complexes). "The slow removal of plutonium from blood during the first day undoubtedly results from the protein binding of the plutonium. The success of citrate in competing with the blood proteins was anticipated from in vivo studies in

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which citrate increased early plutonium excretion". (Stover, Atherton and Keller, 1959).

Since the metabolism of plutonium following intramuscular injection was the same after the administration as Pu^{+3}, Pu^{+4} and Pu^{+6}, Hamilton considered that plutonium is converted by the body to one valence state regardless of the valence when administered and the evidence indicated that plutonium in the body is tetravalent. (Hamilton, 1947).

3. Absorption and retention after inhalation and ingestion

Absorption and retention from the lungs was found to vary according to particle size and solubility of the compound. Absorption from the gastro-intestinal tract is not significant: in feeding experiments using solutions of plutonium at very low concentrations (range of 10^{-5} µg./ml.) on average, the percentage absorbed of the amount fed was 0.0028 per cent (Katz, Kornberg and Parker 1955). With a single large dose of plutonium given orally to pigs, the total absorption was not significantly different from the results obtained in continuous feeding experiments with rats (Weeks et al 1956) and was, on average, 0.0022 per cent of the amount fed.

Langham (1956) has calculated retention from excretion analyses in humans after injection: this is 96.7 per cent at 22 days after injection and 90.7 per cent at 4 years.

In adult beagle dogs, Stover et al (1959) found 87.9 per cent and 71.5 per cent retention at comparable time intervals after intravenous injection. For times greater than 3 weeks after injection, the per cent retention calculated from excretion measurement was

$$R = 90.0 - 0.434t^{0.515} \text{ (t in days)}$$

Of the 16 per cent excreted between 22 days and 4 years, 6 per cent was considered to come from the liver and about 10 per cent from the skeleton.

4. Subcutaneous and intramuscular injection

There was considerable retention at the site of injection and both local and distal effects were seen. The subcutaneous injection of one microgram gave rise not only to a local fibrosarcoma but to distal bone sarcomata: death with an osteogenic sarcoma of the spine produced by plutonium deposition from subcutaneous injection was reported in a rat. (Lisco 1947).

With intramuscular injections, local epilation, ulceration, necrosis of muscle and spontaneous amputation occurred.

IV Toxicity

1. Acute effects

The earliest studies were concerned with acutely lethal doses with survival times ranging from 1 to 30 or 40 days. The effects were those of acute irradiation: haemorrhages, oral ulceration and oedema were noted. At

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a lower dosage level, the animals showed marked anaemia, haemorrhage, liver disease, ascites and emaciation. Death from hepatic disease was observed during the first six months since plutonium initially deposits in the liver. Benign tumours and cirrhosis were observed and pathological examination showed atrophy and degenerative changes in the parenchymal cells. Clinically there was ascites, anasarca and jaundice.

Other effects seen were greying of hair and bone tumours. Depression of the various formed elements of the blood persisted. It was not an uncommon finding for animals to die with aplastic anaemia.

2. Late effects. Chronic toxicity

The most striking late effects arose from irradiation of bone. The indices for estimating chronic toxicity were taken as bone tumour formation, fractures, radiological evidence of bone disease and shortening of life.

Depression of the various formed elements of the blood persisted for well over a year from plutonium injection. Aplastic anaemia was a common terminal result of plutonium administration.

Injection of plutonium into female mice decreased the number of litters produced and increased the number of stillborn in each litter.

V. Organ deposition

The distribution of plutonium in the various organs and tissues was determined by a number of experiments on rats and mice, a few on rabbits and dogs and two with human subjects.

Bone and several organs including liver, kidney, spleen and lymph nodes were the principal sites of deposition. The plutonium content of nerve, muscle and reproductive tissue was low. Bloom (1948) however, reported that mice ovaries showed extreme damage after intravenous injection of 0.03 μc. per gram of plutonium.

The distribution in the human subjects was, in general, the same as in the animal studies.

VI. Bone studies

The biological half-life in the rat skeleton was reported as 1 to 3 years (Hamilton et al 1948) (Copp, Axelrod and Hamilton 1947).

A much longer biological half-life in bone was found when quadrivalent plutonium was administered intravenously as citrate (Carritt et al, 1947); but more recent work (Kawin and Dockum, 1958) gives a biological half-time of 40 to 50 weeks.

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1. Deposition

In all the animal studies more than half of the absorbed dose was retained in bone, regardless of valence or mode of administration. In the skeleton, higher values were found in the lumbar and thoracic spine, average values in the femur, lower values in ribs, skull and jaw bone. There was a consistent significantly lower value for the radius than for the tibia. The percentage distribution was spine 62, pelvis, 15, long bones 8, jaw and ribs 7.5.

In mice and rats, bone tumours usually appeared in the axial skeleton: vertebrae, pelvis, jaw and scapulae. In dogs, tumours were in the maxilla, spine and skull.

Radioautographs showed that in rats, most of the plutonium was deposited in the periosteum, endosteum and in the region of the trabecular bone. (Hamilton 1946). In beagle dogs, concentration was highest in those bones which contain much trabecular bone - e.g. the sternum. Atherton, Mays and Stover (1958) found the concentration in the skeleton of dogs greatest near the proximal end of the humerus where most of the trabecular bone is located and lowest in the shaft which is composed of cortical bone. The deposition, as in rats, was on endosteal and periosteal surfaces and about vascular channels in bone. There was considerable variation in this surface deposition and the "hottest surface" was forty times the average dose to a cell 10 μ in diameter.

Early work in rats seemed to show that plutonium was actively laid down in the uncalcified organic osteoid matrix of bone and not in the bone salt (Copp and Hamilton 1947) but recent work (Jee et al, 1948) has failed to confirm this finding. In normal rats, plutonium localized selectively on calcified bone surfaces; whilst in rachitic rats, it penetrated the osteoid layer and deposited on the underlying calcified bone surfaces - and it was also found in osteoclasts and macrophages.

2. Bone Lesions

2.1 Tumours

Bone tumours occurred after 200 days in mice, rats, and rabbits with doses ranging from 4.5 to 0.05 micrograms/gram. The majority occurred in the spine producing hind leg paralysis and urinary retention as the first clinical symptons (Lisco, Finkel and Brues 1947).

Of five beagles given 5 μc./kg. and surviving over 590 days, all showed bone pathology and the three last survivors died with tumours of the maxilla, spine and skull at 850, 1200 and 1220 days respectively. One beagle given 0.6 μc. per kilogram died at 1510 days with a tumour of the skull.

In a series of experiments with female mice in the same laboratory, plutonium was given in a range of eleven doses: the highest 40.6 μc./kg. and the lowest at 0.04 μc./kg. All the animals that received 40.6 and 26.5 μc. per kilogram were dead before 100 days. None had tumours.

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Of 26 animals that received 15.6 µc./kg., 15 lived past 200 days, but only 2 had positively diagnosed malignant tumours.

In the 6.1 and 3.1 µc./kg. groups, a large number of tumours had occurred by 400 days.

In the 0.6 and 0.34 µc./kg. groups, one animal in each group developed a tumour as early as 250 days.

The first tumour to appear in the entire series was in an animal that had received 6.1 µc./kg. - this was at 190 days.

"The autopsy data showed that the tumours in the 6.1 µc./kg. group were of primary importance in contributing to mortality". Of the 17 animals that survived the latent period there were 11 tumour-bearing: all the last 7 animals had tumours.

There was an apparent inhibition of tumour formation at the higher dose rate of 15.6 µc./kg. Of 13 animals that survived the latent period only 2 were tumour-bearing and none of the last 4 animals had tumours.

In the Utah studies with plutonium injected beagle dogs, the lowest approximate retained dose was 0.027 µc./kg. for bone tumours to appear and with average skeletal doses of 500 to 7400 rads. (Stover, Atherton, Buster, Keller and Holt 1958). (Stover, Atherton and Keller 1959). This compares with a dosage in radium injected dogs over the range 5,600 to 15,000 rads.

2.2 Fractures

In rats, rabbits and dogs, the earliest bone fractures were seen between 120 and 160 days after injection of doses of 60, 24 and 16 µc. per kilogram and between 280 and 350 days after a dose of 8 µc. per kilogram.

In beagle dogs the earliest minimal changes were seen in the jaw (Christenson et al 1957) at average doses of about 140 rads. Fractures of spine, ribs, flat bones and loss of teeth occurred at approximate retained dose levels of 2.5 and 0.81 µc./kg. By far the largest number of spontaneous fractures occurred in the ribs. Vertebral fractures were usually in the dorsal spine of thoracic vertebrae.

3. Histopathological Studies

In rat, mouse and dog studies, a comparatively early overgrowth of bone was noted. In plutonium treated mice, the overgrowth appeared first in the primary spongiosa. Osteosclerosis of the distal end of the femur and proximal end of the tibia appeared between 100 and 200 days (Bloom 1948) with a threshold dose of 3 µc./kg. in mice and 6.-12 µc./kg in rats. In young rats, there was an initial cessation of growth, after which bone growth was resumed at a dosage of 30 µc./kg. The disturbance of bone growth was manifested as spontaneous fractures which occurred in rats, rabbits and dogs.

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In the Utah experiments on beagles, histopathological bone studies of animals reaching autopsy with a chronic retained burden of 2.5 µc. Pu/kg. bone showed an initial disturbance of normal bone growth. The continuous effect of the bone burden was seen as a disturbance in normal bone renewal or reconstruction and the late effect by the production of osteogenic sarcoma. The response of endosteal and neighbouring marrow cells was shown by acellular marrow cavities, peritrabecular fibrosis, endosteal surface fibrosis or endosteal bone growth. The disturbance in bone growth was shown by the so-called "hot line" in ribs - rib end demarcation -, "hot line" fractures or mosaic bone. In cortical bone, excessive resorption cavities were noted. Haversian systems were abnormal and there were a number of hypocalcified systems at all dosages used [approximate retained dosages of 2.5, 0.81, 0.27, 0.086, and 0.0143 µc./kg.] but most frequently in animals which had carried a plutonium burden for long times. At the higher dosage levels, there were hypercalcified Haversian systems. Another change noted was osteocytes death. Thus the continuous effect was seen in the excessive number of resorption cavities produced, in abnormal Haversian systems and eroded periosteal surfaces with fibrosis and fractures (Jee, Arnold and Cochran, 1958).

The early tumour was characterised as a focal lesion with active bone resorption with their spaces filled with highly cellular cells. (Jee, Arnold et al. 1958). Lisco, 1956, considered that, in rats receiving small doses of plutonium, it was likely that the bone tumour arose from cells of old peritrabecular fibrosis tissue. Jee, Arnold and Cochran (1957) supported this suggestion from their work with beagles given alpha-emitting bone-seeking nuclides.

4. Comparative toxicity of plutonium to radium for bone tumour formation

Brues found the best available ratios of plutonium to radium in terms of injected µc./kg. for bone tumour formation in rats and mice was 15 and in rabbits 8. For bone fractures in rats and rabbits the ratio was 10.

In comparative studies of toxicity with plutonium, radium, radiothorium and mesothorium in beagle dogs; Jee, Arnold and co-workers (1958) found comparable carcinogenic doses to be 0.27 µc./kg. plutonium, 0.81 µc./kg. radium, 0.086 µc./kg. radiothorium and 0.27 µc./kg. mesothorium with 0.0307 µc./kg. radiothorium.

5. Correlation of pathological bone changes with dosage

Attempts to correlate histological and pathological changes in bone with dosage are fraught with difficulty. The most recent attempt has been made using results from the extensive dog studies conducted in Utah. These metabolic studies in dogs have covered a period of 4 years from the time of injection. The dogs were given a single intravenous injection of tetravalent plutonium in a citrate buffer solution of 2 - 2½ µc./dog.

Careful measurements of the distribution in bone have been made. Differences in retention in whole skeleton, individual bones and in localized areas in bone have been found. The variation in values for the same bone from dog to dog was far greater for plutonium than for radium. The average standard deviation for variation of individual values for all bones was 35 per cent for plutonium and 14 per cent for radium. The endosteal surface

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concentrated more plutonium than the periosteal; there was greater deposition in the metaphyseal than in the epiphyseal trabeculae and apparent individual differences in plutonium retention in long bones such as femur. The periosteal surface of the mandible contained about twice the activity of other periosteal surfaces. The endosteal surfaces of other bones contained from two to four times more activity than the vertebral periosteal surface. The surface with the greatest concentration was associated with the odontoblastic layer in the pulp cavity of the teeth and had about five times more than the endosteal surfaces or ten times more than the periosteal surfaces.

In animals which survived a long time after injection, there was a diffuse distribution in parts of the skeleton as well as the initial surface deposition.

Microscopic examinations of autoradiographs of bone show that there is a great difference in concentration between adjacent areas of any one bone and bone changes, it is suggested, may be related to the local concentration (Twente, Arnold et al, 1958).

The retained dose level of 2.5 µc./kg. was very effective in the production of bone lesions and tumours: 0.81 µc./kg. was less effective in producing bone lesions, but the production of endosteal bone growth and mosaic bone in trabecular bone had an equal or greater effect at this level as compared with 2.5 µc. level.

At the 0.27 µc./kg. level, the fibroses were restricted to a few localized areas - a few trabeculae in the ribs, the metaphyses of long bones and the mandible showed peritrabecular fibrosis, eroded endosteal surfaces with fibrosis and mosaic bone.

One dog at the 0.0143 µc./kg. level surviving 1539 days after injection had a normal skeleton except for an increased number of resorption cavities in cortical bone and loss of nine teeth (Jee, Arnold, Mical, Bird, Frendenberger and Lowe, 1958). The earliest minimal changes were seen in the jaw in the beagle dogs at average doses of about 140 rads (Stover 1959).

Hypercalcification of Haversian systems was generally restricted to higher dose levels. Hypocalcified Haversian systems were widespread at all dosages and most frequently observed in animals which carried a burden for long times.

VII. Retention and Pathological effects in other organs

1. Liver

In the early work in the wartime Plutonium project, the Chicago group used higher dosages and laid more strees on the toxic effects than did the Berkeley group. It was probably as a result of this that some differences, such as the relative importance of liver effects, appeared.

Finkel (1958) has noted that there is no simple explanation for the observed differences in survival and life-shortening effect in internally deposited radioisotopes in laboratory animals and considers that the marked toxicity of Pu^{239} is probably due to liver damage. In plotting the lethal

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response after the administration of several radioisotopes relative to the response after the administration of radium, the effectiveness of plutonium in decreasing life span "probably reflects both liver damage and a more rapidly increasing integrated dose with time after injection because of greater retention".

1.1 Deposition in liver

Animal experimentation has shown the large proportion of injected plutonium collected initially in the liver - when given intravenously, as plutonic (+4) nitrate as much as 70 per cent was deposited, but from intramuscular and intrapulmonary administration only small amounts of 14 per cent or less were accumulated in the liver. However, in the +3 and +6 valency states, only about 30 to 40 per cent was deposited after intravenous injection.

In rats, 2 per cent to 5 per cent of the injected dose was found in the liver at 10 days; at 7 days the specific activity was 0.2 μg./g. in liver as compared with 0.5 μg./g. in bone (Kisielski and Woodruff 1948).

Schubert (1952) gave liver deposition in rats as percentage of injected dose as 33 per cent at 1 day, 17.5 per cent at 3 days and 15 per cent at 10 days. Other reports quoted 20 to 40 per cent as the initial liver deposit.

In a small number (3) of miniature pigs (Clarke et al 1958) given 30 microcuries Pu intratracheally, the average organ burden per gram, expressed as per cent of administered dose, gave liver as the major organ of concentration - followed by flat bone and kidney - in two pigs, sacrificed on the 25th day. Pig number 1 sacrificed at 12 days post injection showed the highest concentration in bone followed by liver.

In the Utah studies Stover, Atherton and Keller (1959) using beagle dogs showed that the most significant difference found between the metabolism in the rat and in the dog was in the liver deposition. Although the initial deposition was similar, the rate of removal was slower in the dog studies and the liver deposition persisted over long periods of time. Most of the liver values fell between 30 and 15 per cent of the injected dose. The dogs in one category were injected for special studies and sacrificed at times ranging from one day to 2.5 ye rs after injection. The other category was of dogs kept for lifetime studies. The liver results showed incomplete deposition at one day, a slight decrease with time and considerable scatter.

1.2 Dosage to liver

Equations to describe the decrease in both amount and concentration were

$$L = 28.4\ t^{-0.0691}$$

$$l = 0.0919\ t^{-0.0678}$$

where L is % dose/liver, l is % dose/g., and t is days.

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The average dose rate to liver for a dog injected with A microcuries was calculated:-

$$\frac{d}{dt} DL = 0.25\ t^{-0.68}\ A \text{ rads/day.}$$

as compared with a dose rate to bone:-

$$\frac{d}{dt} DB = 0.21\ t^{-0.04}\ A \text{ rads/day.}$$

The cumulative doses for times greater than 100 days were plotted, and the doses to liver and to bone of plutonium injected dogs were esentially the same. However, skeletal damage was the more marked effect. The authors consider that "this finding indicates that the assumption of uniform distribution is more valid for liver than for bone, which is in agreement with radioautographic findings".

One dog with an injected dose of 3 µc./kg. died at 499 days of chronic hepatitis and erythropenia - another with an injected dose of 0.05 µc./kg. died of hepatitis at 468 days. There was no tumour formation in these cases. The authors noted that from Langham's tissue measurements for humans he estimated that 65 per cent of the injected dose deposited in the skeleton, and 23 per cent in the liver - a similar distribution to that measured by Stover and co-workers in beagles. "In addition, the liver deposition was like that of the beagles in that it persisted over long periods of time (in contrast with the observations on rats)". (Stover et al. 1959).

1.3 Mechanism of liver deposition

In the early work with plutonium there was a hypothesis that the liver deposition was due to a filtration mechanism by the macrophage system and the varying times of removal of plutonium from the liver could be due to the deposition of different compounds formed in the blood. Blood studies of plutonium injected rabbits showed the Pu to be associated with the plasma rather than with the cells. Preliminary experiments on dialysis and electrophoretic studies were discontinued apparently on account of difficulty in finding an acceptable buffer.

The mechanism involved does not appear to be a simple precipitation since plutonium absorbed after intramuscular, intraperitoneal and intratracheal administration follows the same course so that the collection of plutonium by the liver is not a finding confined only to intravenous administration. The data presents a range with widely varied initial depositions, conversion points and removal time. The size of the dose does not have an overriding effect. Moreover, the deposition in the spleen and removal from it is not similar to that in liver. It appears that there are unknown variables which influence the mechanism.

Radioautographic studies have shown that the plutonium deposits both in the reticulo-endothelial system and in the parenchymal cells of the liver (Jee cited by Stover et al 1959).

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2. Lungs

2.1 Retention

Lung retention was found to be variable: physical properties such as particle size, solubility of the administered compound in water, and valence states altered the degree of uptake. In rats, citrate ion was found to increase absorption of Pu^{4} and PuO_2 from the lung (Langham 1947). Scott and co-workers (1949) found that the inhalation of plutonium in the form of finely suspended particles of its water soluble salts resulted in considerable and prolonged pulmonary deposition and retention - greatest for Pu^{+4} then Pu^{+3} and least for Pu^{+6}. Following intrapulmonary administration, plutonium was deposited in the alveoli and alveolar ducts: in these particular circumstances, there was no significant deposition in blood vessels, bronchial tree or lymph nodes. Hamilton (1944) noted that the plutonium was widely scattered through the alveolar structure in myriads of areas of diameter less than fifty microns. There were significant differences according to valency: for Pu^{+4} 95 per cent was retained by lungs up to the 16th day, for Pu^{+3} and Pu^{+6} the percentiles were 50 and 32 respectively. Abrams and co-workers (1946) found retentions for Pu^{+4} nitrate, Pu^{+4} citrate, Pu^{+6} nitrate and Pu^{+6} citrate of 42, 13.6, 33 and 12.8 per cent respectively at 15 days with corresponding pulmonary half-lives of 12, 0.7, 1.8 and 0.7 days respectively. With an insoluble PuO_2 smoke, the pulmonary half-life was about 30 days. The particle size was not given but was probably in the range of 0.1 to 0.5 micron by analogy with other similar work in California.

Scott and Hamilton (1949) stressed the importance of particle size in the retention of plutonium aerosols in the lungs - particulates of one micron in size or less penetrated to the alveoli.

From alveolar deposition, part was eliminated by the blood with later skeletal deposition.

2.2 Metabolism

The metabolism of plutonium oxide after lung exposure in dogs has recently been investigated (Bair 1958). Preliminary results during the period 2 to 46 days after intratracheal administration have been given, "of the small per cent of administered plutonium appearing after 10 days in tissues other than the lung, the pulmonary lymph nodes, ovaries and bones showed relatively high concentrations. No relationship between the lung burden and the blood and urine content could be derived from the data". The distribution in the tissues of two dogs was evaluated 10 days after pulmonary administration.

2.3 Excretion

The excretion was mainly in the faeces - in 10 days in three out of four dogs - this varied from 40 to 75 per cent. In the fourth dog, there was a markedly different excretion pattern and one µg./day (315 µg. $Pu^{239}O$ administered) was excreted in the faeces for 120 days after exposure. The excretion in the urine was low. In faeces the excretion

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was given by the equations $y = 6.3\ t^{-2.2}$, $5\ t^{-2.1}$, $24\ t^{-2.9}$ and $0.17\ t^{-0.1}$ respectively, whilst in urine, these were $y = 2.2\ t^{-2.9}$, $1.2\ t^{-2.6}$, $1.8\ t^{-2.8}$, $0.19\ t^{-1.9}$ respectively where y = per cent of administered dose and t = time in days after administration, followed from 2 days to 46 days.

In studies with mice, the translocation and tissue distribution following intratrachael administration of PuO_2 and $Pu(OH)_4$ has been studied (Bair et al. 1958).

$\mu c. \times 10^{-3}/g.$ tissue (wet wt.)/$\mu c.$ of original dose

Tissue	After six months		After one year	
	PuO_2	$Pu(OH)_4$	PuO_2	$Pu(OH)_4$
Lung	46	93	85	57
Bone	31	50	50	63
Adrenals	18	10	19	7
Muscle	15	10	8	8
Ovaries	14	-	28	-
Spleen	10	4	45	5
Liver	3	28	24	60
Lymph	3	8	17	14
Kidney	1	2	3	1

Autoradiograms of lung and adjacent lymph node at 100 days showed the accumulation of plutonium in the lymphoid tissue and in spleen and liver tissue: the appearance of stars showed the accumulation at discrete sites within the tissue.

2.4 Histopathological Studies

The histopathology of the lungs in rats, mice and rabbits (Bloom) showed an inflammatory process which did not lead to sufficient repair of the lung for full normal functioning. In a specimen from a rat sacrificed one month after inhalation of plutonium the proliferation of epithelial cells appeared suggestively neoplastic. Lung abscesses which appeared differed from those in untreated rats by a proliferation of epithelium - possible neoplastic.

In studies in mice (Temple et al 1958) two squamous cell carcinomata were seen in the lungs about 400 days after the intratracheal injection of 0.06 $\mu c.$ $Pu^{239}O_2$ of average particle size 0.5 microns. After the

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intratracheal injection of 0.003 μc. $Pu^{239}O_2$, a well differentiated fibrosarcoma was found in the mediastinum of a mouse - the lung tissue was essentially normal and no other pathology was seen in other organs. In autoradiograms, tracks were not visible in this neoplasm, but could be seen in the alveoli of the apparently normal lung tissue.

The retained amount, after about a year in the lung was about one-twentieth of the dose administered. This dosage resulted in bronchial metaplasia, cellular infiltrations and fibrosis after a few months.

The Report of the National Academy of Sciences on Pathological Effects of Atomic Radiation 1956 concluded that "Little information is available on the potential hazard to the respiratory system and other organs following chronic exposure to small amounts of long-lived radio-isotopes such as $Strontium^{90}$ and $Plutonium^{239}$. The occurrence of epidermoid carcinoma in the lungs of mice after exposure to plutonium particles suggests that accumulations of such materials may present a similar hazard to man".

The recent preliminary results of inhalation studies on two dogs only (Bair 1958) notes "An appreciable concentration of plutonium was observed in the pulmonary lymph nodes."

Studies of the rate of transfer of insoluble plutonium deposited in the lungs of humans indicated movement with half-times of the order of two years. (Healy 1957).

3. <u>Spleen</u>

In the early work on the toxicity of plutonium, in animals given plutonium, abnormalities in spleen and very high concentrations of plutonium were observed. It is evident that the findings for liver, spleen and other organs were somewhat overshadowed by the finding of the affinity of bone to capture and hold the material, and there was no extensive study of this data. The deposition in spleen did not, however, follow the same trend as for plutonium deposited in liver. The concentration of plutonium in spleen was also found to rise for a time following intravenous injection.

Following intramuscular injection in rats of the +6 citrate salt, Kisielski and Woodruff noted that the spleen contained very dense deposits of plutonium. This became more evident when the content of plutonium per unit weight of tissue rather than content in entire organ was taken as the basis of comparison.

One account cited specific activity as about one fifth to one tenth that of bone. Occasionally, however, "very dense deposits of plutonium, exceeding even bone in its concentration" appeared in the spleens of rats and "similar higher spleen concentrations in other animals following intravenous administration of plutonyl nitrate".

In the Utah studies on beagle dogs the amount in the spleen was small and variable and decreased at about the same rate as the liver. This did not confirm the earlier findings in rats and mice.

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The equation given by these workers for the percentage dose/spleen was $S = 0.391\ t^{-0.119}$ where S is percentage dose and t is days after injection. No special pathological findings have been noted in the spleens of these dogs.

4. Kidney

Following intravenous injection of the quadrivalent citrate complex in rats, the "plutonium deposited in liver and kidney was relatively labile as compared with that deposited in spleen, lung and ovary, where no turnover was evident". (Kawin and Dockum 1958).

The distribution was followed by autoradiography and in the kidney there was early widespread diffuse distribution of plutonium followed by localization in the region of the glomeruli. The retention in the kidney was kinetically similar to that in the liver.

5. Ovary

Following administration of 0.03 µc./gram of plutonium to mice, there was extreme damage to ovaries at 7 months (Bloom). The localization of plutonium in the ovaries of rats has been followed by autoradiographic studies (Vogt and Kawin 1958). When sacrificed 30 minutes after intravenous injection of 0.015 µc. Pu/gram body weight, alpha tracks were evenly distributed over most of the ovarian tissue. Considerable movement and alteration in localization with time were observed. The connective tissue was the ultimate area of localization. There was a decrease in the number of developing follicles and a decreased volume of the ovary. This work is in a preliminary stage, and limited in extent. A group of 60 rats was used and the animals were killed at intervals ranging from 30 minutes to 43 weeks.

Kisielski and Woodruff (1948) had previously noted that in rats, the concentration in gonads did not decrease with time as with other soft tissues, but "a reverse trend was observed".

In a preliminary report on dog inhalation studies using only two animals, Bair noted that there was a relatively high concentration in the ovaries of the females. This was reported "because of the current interest in dosage to gonads".

VIII. Maximum permissible body burden

As stated in the Smyth Report (1945) the purpose of this very extensive animal experimentation has been to ensure that all reasonable precautions are taken when working with plutonium.

There has been considerable discussion on the amounts of plutonium to be allowed under varying conditions of possible intake based on the assumption of a tolerance value or maximum permissible body burden of plutonium. This follows the concept first developed for radium where it was possible to make an assessment of the total body burden of radium by the sum of the results of exhaled radon and body gamma emission. Thus the degree of pathological damage observed clinically could be compared with the retention of radium in the body. This was linked with the lower limits of radium retention which gave

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rise to symptons and signs of radium poisoning. To this lower limit of radium retention, below which no abnormal signs were detected, the phrase "tolerance value" was given. This phrase was changed some years later to "maximum permissible value" - though the use of the word "tolerance" in regard to derived values for air and drinking water is still sometimes used, but to be deprecated.

1. Estimation of body burden Historical survey

The "tolerance" value of radium in the United States was linked with the method of estimation. For early diagnosis of cases of radium poisoning attempts were made to establish the presence of radium in the body. Since one of the radium daughter products is a gas, it was found possible to detect the presence of absorbed radium by the detection of radon in exhaled breath. Robley Evans developed instruments for making this measurement. A fraction of the radon produced by the total radium content of the body is exhaled: the remainder decays and radium C - which is a gamma emitter - can be detected as gamma radiation outside the body. The total radium content of the body is given by the sum of the results of exhaled radon and body gamma emission. It is thus possible to assess the total body burden of radium. In this way the degree of pathological damage observed clinically can be compared with the retention of radium in the body. This is linked with the lower limits of radium retention which gave rise to symptons and signs of radium poisoning.

In 1941 a committee was called together by the National Bureau of Standards of the U.S.A. to consider the lower limit of radium retention below which there was no evidence of radium poisoning. This committee tentatively established 0.1 μgms. of radium fixed in the body as the "tolerance" value for humans.

However, the ultimate sensitivity of gamma-ray measurement for radium as radium C was at that time about 0.2 μgms. of radium. Since it was considered that approximately 50% of the radon produced was exhaled, this figure corresponded to about 0.4 μgms. of total radium burden within the body, or four times the then accepted tolerance level. Thus individuals carrying a body burden of radium could not be detected by routine gamma-ray measurements.

Radon in exhaled air could be detected at a much lower level and the method was capable of detecting the presence of as little as 10% of the "tolerance" amount of radium in the body. At this level the gamma radiation was "much too feeble to be detected and, consequently, the body radium determination must be based on exhaled breath radon alone. For this reason the National Bureau of Standards and the Departments of Labour and Industries of several of the States have wisely set their standards of the tolerance value of body radium content in terms of the radon content of the exhaled breath. Thus an individual whose exhaled breath contains 1 μμc. of radon/litre is said to contain 100% of the tolerance value of radium". (Evans, 1943). Since that time, the increase in sensitivity of instrumentation enables estimations to be made at much lower levels.

1.2 Method for plutonium

The extension of the concept of a tolerance value for plutonium brought with it the necessity of measurement and the methods for radium could not be used. "It was essential to devise a means of detecting and

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measuring in an individual quantities of plutonium less than the tolerance limit. It appeared that this might be feasible through the analysis of excreta."..... "In order to estimate the plutonium content of the body by analysis of excreta, it was first necessary to determine the rate of excretion of plutonium". It was found, however, that animal experiments showed considerable species differences in excretion rates and the excretion rate varied by a factor of 5. "This made it necessary to establish the plutonium excretion rate for man by direct experiments with human beings". On this account plutonium was administered to terminal cases. The urinary plutonium excretion rate was determined and the actual plutonium content was calculated on the basis of an excretion rate of 0.01% per day and it was stated that this rate had been fairly well determined through a number of human experiments. (Nickson, 1951)

1.3 Excretion rate

From a study of individuals occupationally exposed to plutonium, the excretion rate of plutonium was shown to change continuously over a period of five years. This rate was expressed as a power function of the type

$$Y = at^{-c}$$

where Y is the excretion rate (fraction of the injected dose excreted per day)

t is the time after exposure (days)

a and c are constants.

The data could also be expressed as a multiple-exponential rate function; the choice of expression depending on the specific application of the data (Langham 1956).

Individuals received tetravalent plutonium in 0.014M citrate buffer, by intravenous injection (Langham et al. 1950). The excretion rate was measured through 5 years and the data described by a single power function $Y = 0.79\ t^{-0.94}$.

In excretion studies on beagle dogs, an average of 12.1 per cent of the injected dose was excreted during the first 22 days after injection (Stover, Atherton and Keller, 1959). The equations for daily total and urinary excretion were, respectively,

$$X_1 = 6.98\ t^{-1.59} \quad (t \leqslant 22 \text{ days})$$

$$U_1 = 1.44\ t^{-1.52}$$

with X_1 and U_1 expressed in per cent dose per day and t in days.

For the successive period up to 4 years, the equations were:-

$$X_2 = 0.223\ t^{-0.485} \quad (t \leqslant 22 \text{ days})$$

$$U_2 = 0.0605\ t^{-0.409}$$

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The relative amounts excreted in the urine and faeces varied during the first 20 to 30 days: the cumulative faecal excretion was about twice the urinary excretion.

Whilst there was individual variation, about 16 per cent was excreted between three weeks and four years after injection: of this, 6 per cent and 10 per cent came from the liver and skeleton respectively.

The overall retention or excretion pattern is, very commonly, a composite of several exponential functions of time rather than one single exponential rate.

Difficulty may arise in estimates of plutonium body burden based solely on excretion measurements after inhalation of insoluble plutonium dusts. Measurements of radium in the excreta of one individual after inhalation of insoluble radium sulphate (Marinelli et al 1953) did not follow an inverse power function with time. There was early elimination of radium swallowed and a relatively high elimination at later times. The case was followed for 250 days. The urinary excretion represented 2 to 8 per cent of the total. The authors concluded that "estimates of Ra body burden based solely either on radon or excretion measurements are likely to be seriously in error if applied to cases of recent exposure to insoluble dusts."

After accidental exposure to insoluble plutonium dusts, the total excretion via both the gastrointestinal tract and the kidney will require to be studied and a number of determinations need to be made on excreta in order to arrive at an estimate of retention. Healy (1957) considered the theoretical basis for lung transfer to blood stream.

1.4 Critical organ

A further extension of the concept of maximal retention in the body, has been that of "critical organ" by the International Commission on Radiological Protection. This is taken to be the organ which bears the brunt of the damage and is chiefly responsible for the illness and possible death of the individual. For plutonium, it is considered that bone damage may be expected to dominate in most cases.

In Marinelli's study of six persons who had a single accidental exposure to radium sulphate dust, the gamma ray scanning pattern showed the sharp localization in the lungs. By analogy, this state of affairs is likely to pertain after inhalation of insoluble plutonium dusts. The lungs can, therefore, be considered as the "critical organ" in such a case.

The estimate of body burden in the case of plutonium presents a more difficult problem than in the case of radium and gamma emitters since it is not possible to make a direct physical measurement. Excretion patterns may show differences according to the method of intake and chemical properties. Since plutonium^{239} decays by emission of an alpha particle and emits also only some soft quantized radiation of energy 17 kev, it is not possible to make a direct estimate of the amount retained in the body as in the case of radium and gamma emitters. Nor is

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it possible, as for example, in the case of radioactive iodine retained in the thyroid gland as critical organ, to measure the retention in the critical organ.

Langham's calculated retention for humans after injection intravenously is 96.7 per cent and 90.7 per cent 22 days and 4 years respectively after injection.

IX. Maximum permissible values in air and water

The concept of maximal bodily retention has proved extremely valuable as a basis for extrapolation of the data to occupational exposure. Making assumptions of volume of air breathed, lung retention from aerosols and transfer to organs: proposals have been made for maximum amounts of dusts and gases in the atmospheric environment. This enables the planning engineers and health physicists to exercise adequate control. Similar considerations have led to estimates of the amount allowed in drinking water.

The Smyth Report (1945) stated "The major objective of the health group was in a sense a negative one, to insure that no one suffered serious injury from the peculiar hazards of the enterprise..... The success of the health Division in meeting these problems was remarkable..... Factors of safety used in plant design and operation are so great that the hazards of the home and the family car are far greater for the personnel than any dangers arising from the plant". This has remained true in the years that have followed, and knowledge of the toxicology of plutonium has not been extended by any human cases. It is a remarkable record and reflects great credit not only on the designers, but also on the Health physicists who, by their continual vigilance and monitoring, have exerted such efficient environmental control. The difficulty is shown by the very low concentrations of plutonium which are allowed. The International Commission on Radiological Protection recommend 2×10^{-12} $\mu c/cc$ air and 6×10^{-6} $\mu c/cc$ water for continuous exposure. These recommendations are continually reviewed and there has been a trend to reduce the concentrations as further studies on the toxicology of plutonium have extended knowledge.

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