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HUMAN EXPERIENCES WITH PLUTONIUM

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Plutonium was discovered approximately 17 years ago by Seaborg, Wahl, and Kennedy. Beginning in 1954, it has been processed routinely in ever increasing amounts, and considerable information has been accumulated regarding its physiology and toxicology in man. Some of this information was gained by planned experiments and some by accidental exposures resulting from its production and use in the fabrication of weapon components. Canada and Great Britain also have had some experience with accidental exposures. The purpose of this short letter-type report is to summarize briefly human experience with this potentially dangerous material.

Experimental Cases

Early in 1943, it was realized that plutonium, because of its relatively high specific activity and alpha particle emission, might pose a health hazard similar to that of radium. Shortly thereafter Hamilton of the Crocker Radiation Laboratory showed that plutonium injected into rats deposited in the bone as does radium, although its pattern of deposition was qualitatively different. In the fall of 1944, Langham et al. of the Los Alamos Scientific Laboratory developed a method of analyzing human urine for small amounts of plutonium and, on the basis of rat urinary excretion data, predicted that a few Los Alamos personnel might have accumulated body burdens

approaching 1 μg (0.07 μc). Also in the fall of 1944, radiobiologists at the Metallurgical Laboratory of Chicago, the Crocker Laboratory of the University of California, and the Los Alamos Scientific Laboratory reported that small amounts of plutonium, like radium, produced osteogenic sarcoma in experimental animals. These findings made it imperative that the physiology and toxicology of plutonium in man be investigated. In the spring of 1945, the Los Alamos, California, and Chicago groups initiated studies in terminal human patients to determine whether small doses of plutonium were acutely toxic and to establish the urinary excretion rate to provide a more accurate base line from which to determine the body burden of exposed workers. The plutonium was administered intravenously. In all, 15 cases were studied, the majority of them through arrangements with the Los Alamos group.

Life expectancy of the individual was considered as the basis of selection of subjects for study. As a rule, those chosen were past 45 years of age and suffering from chronic disorders (other than of the kidneys) such that survival for 10 years was highly improbable. By adhering to these criteria, the possibility of late radiation effects developing would be negligible. Furthermore, the possibility of obtaining post mortem material within a few months,

or at most a few years, would be much greater. Table 1 gives pertinent information on all 15 subjects, including age, sex, date and amount of plutonium injected, time to death, and clinical information where applicable.

As expected, no acute toxic effects were observed from the doses of plutonium administered even though one subject (HP-13) received Pu^{238} (T/2 ≃ ~~50~~ 89.6 years) in a dose equivalent in activity to about 120 μg of Pu^{239}.

Within 5 years, 11 of the 15 patients were dead as a result of their diagnosed illnesses. Two patients (HP-3 and HP-8) are still alive and were seen 10 years after plutonium administration. Although still suffering from recurrences of their original complaints, they showed no symptoms attributable to plutonium. HP-12 is believed still to be alive, though he was last heard of 8 years after injection through a State Public Health agency where he was under treatment for syphilis. He had no symptoms attributable to plutonium. HP-13 is reportedly still alive after gastric surgery for his original complaint. He has shown no symptoms attributable to plutonium. Admittedly, these observations present no evidence that chronic effects may not occur eventually, but they do indicate that a single intravenous injection of 10 to 250 times the maximum permissible dose of plutonium was without acute subjective or

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TABLE 1. SUMMARIZED INFORMATION ON INDIVIDUALS GIVEN PLUTONIUM INTRAVENOUSLY FOR ACUTE TOXICOLOGICAL, ORGAN UPTAKE, AND EXCRETION STUDIES

Case Code	Age	Sex	Amount Plutonium Given IV (μg)	Date Plutonium Administered	Time to Death after Injection		Clinical Remarks
HP-1	67	M	4.6	October 1945	< 5 years	?	Death unrelated to Pu exposure as far as is known.
HP-2	49	M	5.1	October 1945	< 5 years	?	Death unrelated to Pu exposure as far as is known.
HP-3	49	F	4.9	November 1945	Living	>	Individual in good health at time of last examination.
HP-4	18	F	4.9	November 1945	5 months (150 days)	>	Died in uremia; no pathological findings related to Pu.
HP-5	56	M	5.1	November 1945	151 days	>	Died with bronchopneumonia; no pathological findings related to Pu.
HP-6	45	M	5.3	February 1946	< 5 years	?	Died with Addison's disease; unrelated to Pu exposure.
HP-7	59	F	6.3	February 1946	8 months	>	Died with lobar pneumonia; unrelated to Pu exposure.
HP-8	41	F	6.5	March 1946	Living	>	Individual in good health at time of last examination.
HP-9	66	M	6.3	April 1946	456 days	>	Died with heart disease; no pathological findings related to Pu.
HP-10	52	M	6.1	July 1946	< 5 years		Died with heart disease; unrelated to Pu exposure.
HP-11	68	M	6.5	February 1946	5 days		Moribund at time of Pu administration; death from portal thrombosis.
HP-12	53	M	4.7	April 1945	Living (?)	>	Individual in good health 8 years after administration insofar as can be determined.
HP-13	<45	M	120*	April 1945	Living	>	Individual in good health insofar as can be determined.
HP-14	68	M	6.5	April 1945	155 days	>	Died from metastatic carcinoma diagnosed prior to Pu administration.
HP-15	55	F	94.9	December 1945	16 days		Died from metastatic carcinoma diagnosed prior to Pu administration.

*Injection solution consisted of 5 μg Pu^{239} and 0.3 μg Pu^{238}, giving a total of 120 μg Pu^{239} equivalent.

objective clinical effects. They further show that no chronic effects are evident 8 to 10 years later. A complete report of plutonium excretion and deposition as determined from the above studies was prepared by Langham, Bassett, Harris, and Carter (Los Alamos Scientific Laboratory Report LA-1151, Official Use Only).

Occupational Exposures

Occupational exposures to plutonium have occurred at the Los Alamos Scientific Laboratory, Hanford Atomic Products Operation, Dow Chemical Company (Rocky Flats plant), Canadian Atomic Energy Agency, and the British Atomic Energy Authority.

Most of the Los Alamos exposures occurred from the fall of 1944 through 1945. During this period 27 workers accumulated plutonium body levels of 0.1 μg or greater, and 11 individuals accumulated body levels equal to or greater than the presently accepted MPL of 0.5 μg. The estimated body burdens, average dates of exposures, and other pertinent information for these 27 cases are given in Table 2. Most of these exposures were believed to have occurred via inhalation as evidenced by the strong correlation with frequent contamination of the nasal vestibule determined by counting special nasal swabs rotated in the nares immediately following especially hazardous operations.

TABLE 2. RESULTS OF URINE ASSAYS AND NOSE SWAB COUNTS CONDUCTED ON LOS ALAMOS PLUTONIUM OPERATORS SHOWING POSITIVE EXPOSURE

Case Code	Average Date of Exposure	Total Number High Dose Swab Counts	Estimated Body Burden from Urine Analysis (μg)	Estimated Highest Lung Contamination from Body Burden (μc)
	June 1945	24	1.3	0.9
	May 1945	37	1.2	0.8
	June 1945	55	1.2	0.8
	June 1945	32	1.0	0.7
	July 1945	22	1.0	0.7
	June 1945	28	1.0	0.7
	July 1945	24	0.8	0.6
	June 1945	60	0.7	0.5
	August 1945	14	0.7	0.5
	August 1945	9*	0.6	0.4
	Late 1944	1*	0.5-1.0	0.4-0.7
	August 1945	8	0.5	0.4
	July 1946	6	0.4	0.3
	July 1945	23	0.4	0.3
	August 1945	6	0.3	0.2
	August 1945	28	0.3	0.2
	August 1945	22	0.3	0.2
	October 1945	3	0.3	0.2
	September 1945	8	0.3	0.2
	July 1945	8	0.3	0.2
	October 1945	11	0.3	0.2
	July 1945	2	0.2	0.15
	July 1945	7*	0.2	0.15
	Late 1944	3*	0.1-0.5	0.07-0.4
	September 1945	8	0.1	0.07
	July 1945	4	0.1	0.07
	September 1945	8	0.1	0.08

*Incomplete records were available for these cases.

The amounts of air-borne activity to which some of these persons were exposed were occasionally orders of magnitude above the presently accepted maximum permissible air concentrations. As an example, the nasal swabs from 1 individual , after a particularly risky operation yielded over 1 μg of plutonium from each nare. His body burden after this and several other operations was 0.5 to 1 μg. These experiences indicate the difficulty with which plutonium gains entry into the systemic circulation.

There is no satisfactory method of diagnosing the amount of plutonium in the lungs. A rule of thumb method is to assume (if the individual has no record of a contaminated lacerating accident) that all of the body burden was accumulated via inhalation. Some data have been accumulated suggesting that about 10 per cent of the plutonium deposited in the lungs is absorbed into the systemic circulation. On this basis, the lung contamination immediately after exposure might be expected to be about 10 times the systemic burden. Table 2 shows, on this basis, the maximum lung burdens that the various individuals could have had.

A second method of estimating plutonium lung burden is from fecal to urinary excretion ratios. Since the majority of plutonium deposited in the lungs is eliminated from the bronchial tree via

ciliary action and swallowed, large fecal to urinary excretion ratios indicate a lung burden which can be estimated from the fecal and urinary excretion values. Because of the difficulty of analyzing and interpreting fecal excretion data, this method is not practical on a routine basis.

Lung burdens of 5 Los Alamos subjects, calculated from fecal to urinary excretion ratios, are shown in Table 3. These subjects showed lung burdens of from 1 to 60 times the presently accepted maximum permissible level. Because of the rapid rate of lung clearance, the radiation dose to the lungs soon dropped below maximum permissible levels. No subjective or objective effects of lung exposure were observed in any of these individuals. Twenty-four of the 27 Los Alamos workers who received 0.1 μg body burden or greater are being followed routinely at 3-year intervals for the purpose of chronic observations. In 1958, they will receive their fourth follow-up examination and will have had their plutonium body burdens for a period of 12 years. Complete general physical examinations, including laboratory tests, hematological studies, and X rays are conducted. Roentgenograms include pelvis, chest, skull, knee, elbow, hand, and jaw. The roentgenograms are studied by competent radiologists for signs attributable to plutonium. At the 9-year period, all examinations, tests, and roentgenograms were

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TABLE 3. PLUTONIUM LUNG BURDEN IN LOS ALAMOS WORKERS WHEN DERIVED FROM URINARY TO FECAL EXCRETION RATIOS

Subjects	Lung Burden	
	Systemic Burden X10 (μc)	From Urinary to Fecal Ratios (μc)
	1.1	1.2
	0.043	0.027
	0.35	0.28
	0.86	0.72
	0.94	1.1

negative. No changes were observed that could not be attributed to change in age. The subjects have already been contacted in preparation for the 12-year follow-up examination, and they all report a continued state of normal health. Although the critical period for the appearance of chronic effects has not passed, the complete negative character of the data is encouraging. Plans are to follow all subjects for a minimum of 20 years.

At Los Alamos, two significant plutonium exposures through contaminated cuts have occurred. One individual received a body burden of approximately 0.3 μg plutonium in 1945 through a deep laceration of the end of the thumb. He had also had some additional exposure via inhalation. The second case occurred in 1954, when a technician) broke a beaker containing a concentrated solution of plutonium nitrate and received a serious laceration of the hand. As a result of the accident, she accumulated a plutonium burden of approximately 0.15 μg. This individual was treated with calcium ethylenediamine tetraacetate (Ca EDTA) as a means of hastening plutonium elimination. Treatment resulted in about a 25 per cent decrease in her body burden.

In the history of the Laboratory, some 90 potentially contaminated wounds have been treated by surgical debridement of the lacerated area. In most instances, analysis of the excised tissues

showed the amount of contamination they contained was essentially negligible.

In 1957, the Dow Chemical Company (Rocky Flats plant) had an explosion involving several hundred grams of plutonium. Two persons were exposed through contaminated cuts from flying glass. One individual received a body burden of 2.2 μg and the other 0.9 μg. Neither showed any appreciable lung burden. Both were treated with calcium ethylenediamine tetraacetate (Ca EDTA) to hasten excretion. Treatment decreased their body burdens by about 10 per cent.

The Hanford Atomic Products Operation at Richland, Washington, has had considerable experience with plutonium exposure. They developed a method of urine analysis capable of detecting body burdens at least a factor of 20 below tolerance. By means of this refined technique, they reported that over 100 individuals, in 10 years of operation, have accumulated small internal body burdens far below the tolerance range. No signs or symptoms of radiation damage have been associated with these low levels of plutonium contamination.

The Canadian Atomic Energy Agency at Chalk River had one accident in 1950 in which 2 individuals received plutonium exposure. One individual received a body burden of 0.15 μg and the other 0.10 μg. They also reported that 10 per cent of the individuals working with plutonium showed small but positive body burdens.

No signs or symptoms of radiation damage have been reported.

The Atomic Energy Authority at Harwell, England, had one contaminated accident in 1952, in which a waste disposal worker received a body burden of approximately 5 μg. The mode of exposure was not known, but it was probably via inhalation. The individual has shown no objective or subjective symptoms attributable to his plutonium body burden. He was treated, however, with zirconium malate, which apparently did little to hasten the rate of excretion of plutonium but resulted in disturbance of the vestibular nerve from malic acid toxicity.

In summary, it may be said that considerable experience with the physiology and toxicology of plutonium in man is accumulating. These data definitely indicate no acute toxicity from plutonium over the range of from far below the maximum permissible level to as much as 250 times above. No chronic effects have been observed 10 to 12 years after exposure to doses at or above the tolerance limits. The critical period for chronic effects probably lies in the range of from 10 to 17 years after exposure. Although present human experience does not preclude the possibility that chronic effects may yet appear, they are at least encouraging. These observations and human data collected from cases of radium contamination support the feeling that the presently accepted maximum permissible level of 0.5 μg for plutonium includes an appreciable safety factor.