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The Plutonium Project

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Carcinogenic Properties of Radioactive Fission Products and of Plutonium¹

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A SERIES OF STUDIES dealing with the late effects of internal and external irradiation upon experimental animals were undertaken by the Biology Division of the Clinton Laboratories at Oak Ridge and by the Biology Division of the Metallurgical Laboratory, University of Chicago. The results of the studies concerned with external gamma and beta rays and neutrons have been discussed by Dr. P. S. Henshaw and Dr. J. R. Raper. In the experiments at Chicago a number of representative radioactive isotopes were chosen for study, isotopes which are released in the fission of uranium. One of the end products of the fission process is plutonium (Pu^{239}), and particular attention was paid to this substance. At the time these chronic experiments were undertaken, a limited amount of information was available concerning acutely toxic levels and distribution of plutonium.

An intelligent appreciation and evaluation of health hazards, whether by ingestion or inhalation or by way of wound contamination with minimal amounts of radioactive substances while working in potentially contaminated laboratories, is, of course, difficult without experimentation. It was with this in mind that the following experiments were undertaken, even though it was realized that it is notoriously difficult to design animal experiments which precisely duplicate the human hazards.

The late effects of various modes of treatment with Sr^{90} , ^{90}Y , Ce^{144} , Ra, and Pu^{239} were studied in mice, rats, and rabbits. Sr^{90} , ^{90}Y , and Ce^{144} are pure beta emitters with energies of 1.5, 1.5, and 0.35

Mev., respectively, and half lives of 55, 57, and 275 days, respectively. Plutonium is an alpha emitter with a half life of about 25,000 years.

Radiostrontium, like radium, was largely concentrated in bone, and the average total retention at fourteen days was 45 per cent for the mouse, 50 per cent for the rat, and 21 per cent for the rabbit; these figures are corrected for decay. Almost all of the retained Sr^{90} was found in the skeleton, and consequently bone tumors were readily produced. The incidence of bone tumors was approximately proportional to the dose administered, and the latent period—in no case less than about 200 days—increased gradually with decreasing dose. In the animal species studied, single and multiple bone tumors were observed, and in many individuals widespread metastases occurred, especially in rats and rabbits. Bone tumors were produced in considerable numbers by doses ranging from 5.0 to 0.05 microcuries per gram, both with single and with monthly repeated injections. Osteogenic sarcoma induced by Sr^{90} involved the long bones in preference to the spine, a fact which will be discussed briefly later.

It is not clear as yet whether Sr^{90} had any effect on the incidence of spontaneous lymphoma in mice.

Radio-yttrium and cerium, after either intravenous or subcutaneous administration, also produced sarcomas in the skeletal system. These tumors localized primarily in the long bones.

When plutonium and yttrium (YPO_3) were given subcutaneously or intramuscularly to mice, various manifestations of radiation damage were observed locally.

¹ The work reported herein was done in the Metallurgical Laboratory of the University of Chicago and the Biology Division of the Argonne National Laboratory, Chicago, under the Manhattan Project. This paper is a brief version of material to be published in the Plutonium Project Record of the Manhattan Project Technical Series. Presented at the Thirty-Second Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 1-6, 1946.

These included graying of hair, epilation, ulceration of the skin, and destruction and atrophy of muscles, often followed by spontaneous amputation of the injected leg. Of particular interest has been the occurrence locally of malignant fibrosarcomas in a very high percentage of animals at doses ranging from 0.5 to 0.05 μgm per gram of Pu^{239} and at doses of 1.5 to 0.05 μc per gm of YPO_4 . In other words, a total of 1 μgm of plutonium or 1 μc of YPO_4 injected locally under the skin induced fibrosarcomas even though a certain portion of the injected dose was removed from the site of injection and was distributed throughout the body and partially excreted.

Bone tumors were seen frequently in mice, rats, and rabbits injected with plutonium at levels ranging from 4.5 to 0.05 μgm per gram. The minimal latent period again was about 200 days. The majority of the plutonium-induced tumors occurred in the spine, often producing hind leg paralysis and urinary retention as the first clinical symptoms. An explanation for this difference in localization probably lies in the fact that plutonium has a greater affinity for collagenous tissue than for bone proper. This fact has been clearly demonstrated by radioautographs.

The distribution of bone tumors in the skeleton of rats and mice with various radioactive isotopes is summarized in Table I.

TABLE I: DISTRIBUTION OF BONE TUMORS (PER CENT)

Agent	Spine	Long Bones	Pelvic Bone	Jaw	Ribs
Pu	62	8	15	7.5	7.5
Sr	22	61	6	10	1
Y	14	86	0	0	0
Ce	16	74	5	0	5

Both plutonium and cerium showed a consistently high concentration in the liver. Hence, liver damage was frequently noted in animals at the higher dose levels, but no true liver tumors have been seen to date. Small adenomata have, however, occurred in the liver in the process of regeneration

and repair. The liver damage produced was unique, as it probably represented direct radiation damage of this organ, which is not very vulnerable to high doses of external irradiation. A third compound which also produced liver damage upon intravenous injection was the insoluble salt, yttrium phosphate. An interesting corollary to these experimental studies is the fact that "thorotrast" (a colloidal suspension of thorium dioxide) is frequently used in human diagnostic work. It behaves not unlike the aforementioned substances in its distribution in the human and animal body. Therefore, it may be well to keep this in mind, particularly in diagnosis of those patients who do not suffer from an incurable disease.

Another example of the carcinogenic properties of internal irradiation was the occurrence of carcinoma of the colon in rats which had been fed Y^{90} . This substance was practically not absorbed from the intestine and, when fed by stomach tube, remained longest in the colon. One group of rats received a single feeding of from 1.0 to 6.0 millicuries. Of a total of 33 animals, 4 died with adenocarcinoma of the colon. The earliest tumor was seen 135 and the last 506 days after feeding. A second group of animals was given repeated feedings of 0.46, 0.20, or 0.06 millicuries of Y^{90} per feeding over a period of three months, so that the total accumulated doses were 31.20, 15.60, and 4.68 millicuries, respectively. Clinically all animals appeared well during the feeding period and growth was not impaired. Six of the 8 animals at the two higher dose levels died with carcinoma of the colon between 304 and 548 days after the first feeding. No malignant lesions were observed at the lowest level.

It would not have been possible to carry out these experiments without the help of many people, too numerous to mention here. Their enthusiastic cooperation in these studies is gratefully acknowledged.

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