OBSERVATIONS ON THE BIOLOGICAL ACTION OF PLUTONIUM-239

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Plutonium-239 is one of the most biologically dangerous radioactive isotopes. It enters the human or animal body by various routes, and is deposited in the skeleton and liver [1, 4, 6, 7, 10]. In some cases, the retention of this isotope in the body leads to the formation of tumors. It has been shown that when injected intravenously into animals it may induce osteosarcomas [2, 3, 5, 8], and hyperplasia of the endocrine glands, liver, gastrointestinal tract, and hemopoietic tissue [2]. Its entry into the lungs or into the subcutaneous tissue causes tumors to develop in these parts [9, 11].

We here report observations on rats, on the relationship between the amount of plutonium-239 given and the length of life, weight, blood, and the development of osteosarcomas.

TABLE 1. Mean Survival Time of Rats and the Amount of Radioactive Substance in the Bones at the Moment of Death of Animals which had Received a Single Intraperitoneal Injection of Various Amounts of Plutonium-239

Amount of plutonium (in μCuries/g)	Males			Females		
	number of animals	length of life (in days)	dose (in kilorads)	number of animals	length of life (in days)	dose (in kilorads)
0	30	519±24	—	30	533±42	—
0,00125	29	522±21	1,5	30	489±25	1,5
0,0025	15	528±56	3,1	15	523±31	3,1
0,005	15	445±68	6,0	15	414±56	5,9
0,01	15	266±61	7,2	15	462±73	12,2
0,02	15	163±41	8,4	15	115±32	6,4
0,04	15	82±3	11,5	15	54±6	8,3
0,08	—	—	—	15	19±4	5,8

EXPERIMENTAL METHODS AND RESULTS

The experiments were carried out on 284 white rats weighing 182 ± 8.2 g. A solution of plutonium citrate at a pH of 6 was injected intraperitoneally; the amounts given were 0.00125, 0.0025, 0.005, 0.01, 0.02, and 0.08 μCuries/g. Each group, including the control groups, consisted of 15-30 rats of both sexes (Table 1).

The results of the experiment (see Table 1) show that the injection of moderate doses (0.00125-0.0025 μCuries/g) of plutonium-239 does not affect the length of life or rate of dying of the experimental group. Curves of the change of the effect with time are S-shaped.

When 0.005 μCuries/g of the isotope are injected, the rats begin to die 140 days later. The mean survival time of this group was 430 days, 18% less than in the controls. When the dose was increased from 0.01 to 0.08 μCuries/g, the survival time was reduced from 364 to 19 days. Curves of dose against survival time are linear for this dosage range. No relationship between survival time and sex was discerned.

After the injection of 0.005-0.05 μCuries/g, in 50% of the animals, at death, the amount of radioactivity in the bones was 6-12 krads.

For the range from 0.005 to 0.08 μCuries/g of the injected isotope, the mean survival time ranged from 19 to 430 days, and the ratio of survival times (22) has approximately the same value as the ratio of extreme doses (16 times). The animals die after they have accumulated approximately the same total amount of radioactive substance

in the bones. Thus, after 0.08 μCuries/g had been injected, 50% of the rats died by the 19th day, when the total amount of radioactive substance in the bones of the females was 5.8 krads. When smaller amounts of 0.02 and 0.005 μCuries/g were given, 50% of the rats died by the 115th and 414th days respectively, when the total amount of radioactivity in the bones of the female was 6.4 and 5.9 krads. This observation indicates the poor recovery, and the almost complete addition of the damage due to the action of plutonium α-irradiation. Survival time is affected only when a 'threshold' total radiation dose equal to 1.5-3.1 krads (see Table 1) has accumulated over 489-528 days.

One of the indices of the damage caused by ionizing radiation is change in weight. After the injection of 0.00125 μCuries/g of plutonium-239, there was no change in weight. With larger doses, the increase in weight in the experimental animals was less than in the controls. The difference in weight between the two groups increases with increase in the amount of isotope given, and is very well shown throughout the whole of the experiment. The difference is best shown with doses which reduce survival time. An actual fall in weight occurs only with doses as high as 0.08 μCuries/g.

The weight changes showed that this index is more sensitive than survival time. In fact, 0.0025 μCuries/g, which has no effect on survival time, will prevent gain in weight.

Changes in the circulating blood occur very soon after the plutonium injection. There is a leucopenia, whose severity depends upon the size of the dose (Fig. 1). A large dose not only causes more severe symptoms, but also accelerates the leucopenia. Fourteen days after injecting 0.00125, 0.0025, 0.005, 0.01, 0.02, 0.04, and 0.08 μCuries/g of plutonium, there was a reduction in the number of leucocytes to 11.2, 8.6, 8.2, 5.5, 3.1, 2.1 and 2.3 thousands per mm^3, and by the 30th day the values were 11.3, 7.4, 7.2, 6.3, 5.6, 2.4, and 1.9 respectively; the values in the controls ranged from 12.0 to 16.0 thousands. It was only with the smallest dose used (0.00125μ Curies/g) that the

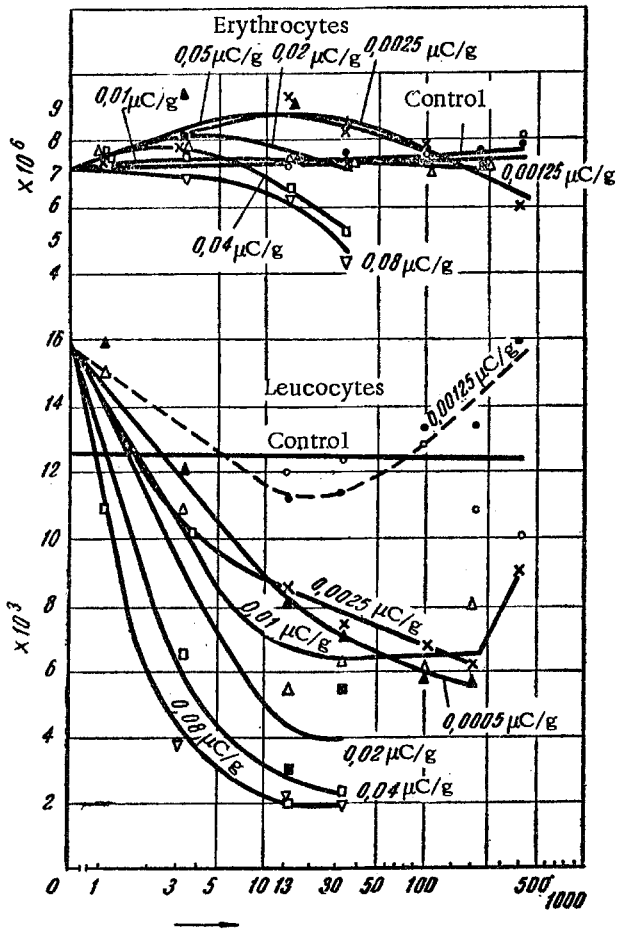

Fig. 1. Change in the number of leucocytes and erythrocytes after the injection of different amounts of plutonium-239.

TABLE 2. Incidence of Osteosarcomas in Rats after Intraperitoneal Injection of Plutonium-239

Amount of plutonium (in μCuries/g)	Males	Females	Males + + Females
0	0/20	0/21	0.42
0.00125	1/18	0/14	1.32
0.0025	1/5	2/6	3.11
0.005	0/7	1/3	1.10
0.01	0/2	0/4	0.6
0.02	0/3	0/1	0.4
0.04	0/8	0/0	0.8

number of leucocytes did not fall outside the normal range of variation. The reduction in the number of white cells was chiefly due to loss of lymphocytes and neutrophils. In the early stages, there was a relatively greater reduction in the number of granulocytes.

The stability of the leucopenia was striking. Even quite long after the experiment, the number of white cells in the blood was considerably less than in the controls. The slow rate of excretion of plutonium from the body, and the deposition of large amounts in the bones and parenchymatous organs results in a prolonged action of the ionizing radiation on the hemopoietic organs, and prevents restoration of the blood to normal.

Curves showing the relationship of the dose to the number of leucocytes in rat blood at different stages are given in Fig. 2. They show that for leucocytes, the graph

is S-shaped; the relationship is best shown between the 14th and 30th days.

Marked changes in the number of red cells are also related to the amount of plutonium injected(see Fig. 1; Fig. 3). After an injection of 0.0025-0.005 μ Curies/g of plutonium, the red cells increased from 6.7-7.2 to 9.2-9.4 millions per mm^3, while for higher doses, either there was no change, or the blood count fell. As a rule, there was no change in the color index. After an injection of 0.04-0.08 μ Curies/g of plutonium, by the 7th-14th day, there was a reduction both in the number of erythrocytes and in the amount of hemoglobin-the erythrocytes had fallen from 7.1 million to 5.2-4.4 million per mm^3, and the hemoglobin from 80.6 to 63.2-42.6%.

The initial increase in the number of erythrocytes in the blood stream, caused by the injection of 0.0025-0.005 μ Curies/g of plutonium was apparently due to an excess production of erythrocytes and their liberation into the blood stream from the bone marrow, and was caused by the radioactive substance.

Curves showing the change in the number of erythrocytes at different times and their relationship to the amount of the isotope are shown in Fig. 3. They show that the relationship is complex. It should be noted that amounts of plutonium which initially caused an increase in the red cell count later did not affect it. In this respect, the change in the red cells was very different from that of the white, where the numerical changes due to small doses are maintained at later dates.

Post-mortem investigations of animals which died after a considerable time showed various pathological processes, including osteosarcomas (Table 2). The incidence of osteosarcomas in our experiment was 3.1-27.2%, and was about the same in males and in females.

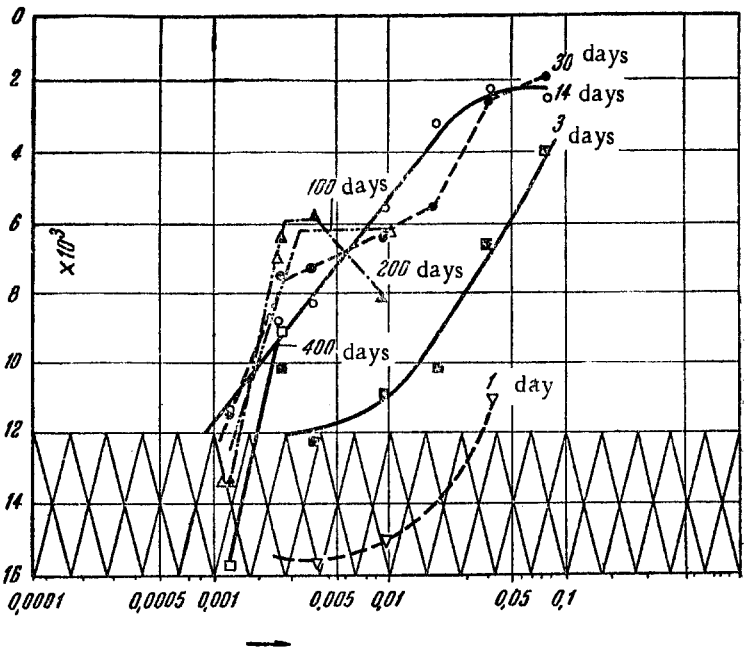

Fig. 2. Curves showing the number of leucocytes at different dates after injecting plutonium-239.

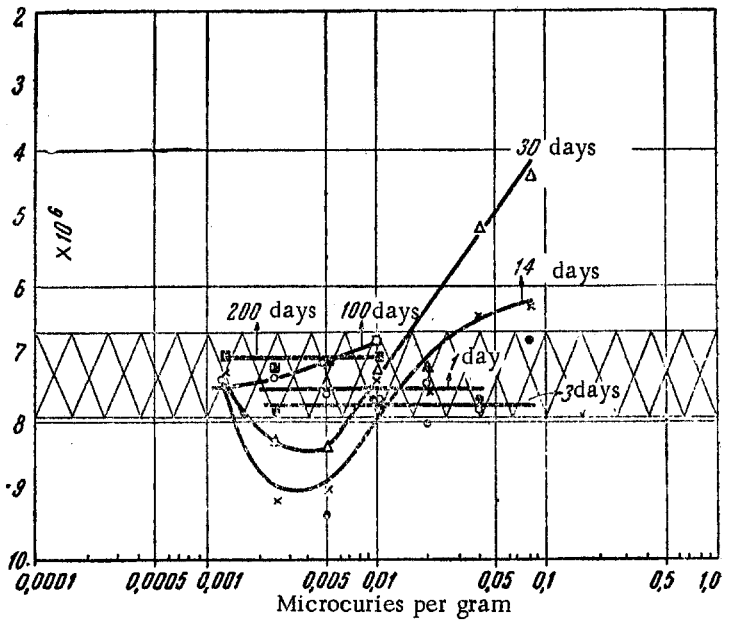

Fig. 3. Effect of dosage on the number of erythrocytes at different times after the injection of plutonium-239.

SUMMARY

Experiments were staged on 284 albino rats. The effect of various amounts of plutonium-239 on the life span weight and peripheral blood as well as on the development of bone tumors was investigated. Time-effect and dose-effect curves were traced and their relationship with the life span, body weight, erythrocyte and leucocyte count was established. As shown, according to the life span criterion, the action of plutonium-239 was of a threshold character. The maximal noneffective dose of plutonium-239 was equal to 0.0025 microcurie per gm. With the administration of plutonium-239 in a dose of 0.0025-0.005 microcurie/gm a brief erythrocytosis is revealed, subsequently followed by stabilization of the number of erythrocytes at the initial level. When plutonium is given in higher doses an anemia leading to the death of the animal develops by the 14th-30th day of the experiment. Leucopenia occurring as a result of plutonium-239 administration is irreversible. At remote periods of plutonium intoxication in rats there occur tumors of the bone tissue, the incidence of which is about the same both in male and female animals.

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