BIOLOGICAL ACTION OF PROTONS WITH AN ENERGY OF 120 MeV

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In cosmic flight the astronaut may be subjected to the action of various unfavorable factors, among them ionizing radiation. Protons are an important component of cosmic radiation. For this reason the study of the biological action of protons is of great theoretical and practical interest. During recent years an extensive series of investigations has been carried out in the USSR, to study the action of protons of different energies [1, 3]. However, many aspects of the action of protons have not yet received adequate study.

In the present investigation, the relationship between the effectiveness of action of protein and the dose and energy of the radiation was studied.

EXPERIMENTAL METHOD

In this investigation protons with an emission energy of 120 MeV were studied. Experiments were carried out on 921 Wistar rats, irradiated with a single dose of protons of between 10 and 1000 rad on the syndhrocyclotron at the Joint Nuclear Research Institute (Dubna). The controls were 311 rats. The morphological composition of the peripheral blood and the relationship between the period of survival and the dose of irradiation were studied periodically.

EXPERIMENTAL RESULTS

The doses causing death of 50% of the animals in 7-600 days are given in Table 1. It will be noted that the doses causing death of 50% of the animals after 30, 60, 120, and 240 days were practically equal. This fact indicates that after a single irradiation with protons practically no animals died at these times. The doses causing death of 50% of the animals after 7 and 15 days ($LD_{50}/_7$ and $LD_{50}/_{15}$)—864 and 725 rad respectively—were noticeably higher than the $LD_{50}/_{30}$ (660 rad). No significant differences could be found in the radiosensitivity of the rats depending on sex; only $LD_{50}/_{480}$ and $LD_{50}/_{600}$ for the females (500 and 380 rad respectively) were lower than for males (560 and 479 rad). This fact shows that in the late periods after irradiation with protons, females died more rapidly than males. This was evidently because in the later stages, the females developed neoplasms of the mammary glands and the glands of internal secretion much more frequently than the males.

The effectiveness of action of protons with energies of 120 and 500 MeV [2] was the same. $LD_{50}/_{15}$ for these energies of protons were 725±22 and 710±45 rad, and $LD_{50}/_{30-120-639}$ was 660±23 and 600±35 rad respectively. Compared with γ-rays the RBE (relative biological effectiveness) of protons with an energy of 120 MeV was 0.7 [3].

TABLE 1. LD_{50} (in rad) for Various Times after Irradiation (with confidence intervals for P = 0.05)

Day	Males and females	Males	Females
7	864±25	813±48	795±16
15	725±22	724±43	741±24
30	660±23	660±32	670±25
60	660±20	620±32	668±20
120	639±18	638±31	654±19
240	616±18	610±34	630±22
360	569±23	588±27	602±20
480	513±21	560±33	500±22
600	436±24	479±39	380±24

The length of survival is widely used in radiobiological investigation as criterion of the injurious action of radiation. However, with rare exceptions, observations on the animals are limited to 30 days. Because of this, the effect of a given dose of irradiation on the mortality rate of the animals in late stages of the experiment cannot be assessed, nor can its relationship to the dose of irradiation be determined.

Analysis of the dynamics of mortality of the animals showed that during the four months after irradiation with protons in doses of between 10 and 100 rad, the mortality of the rats in the experimental and control groups was almost identical, amounting to 1.3% in the controls and 0.95, 1.2, and 0.63% respectively in the experimental group irradiated in doses of 10, 50, and 100

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TABLE 2. Mean Life Span of Rats (with confidence intervals for P = 0.05) Dying 4 Months after Irradiation with Protons with an Energy of 120 MeV

Dose (in rad)	No. of rats taken in expt.		No. of rats dying in late periods		Mean life span of rats (in days)		
	males	females	males	females	males	females	males and females
0	145	166	143	165	537±53	560±25	556±29
10	60	45	60	44	567±51	484±53	548±39
50	30	55	29	55	657±76	578±41	596±38
100	75	85	74	85	530±37	477±35	506±26
200	32	40	29	37	574±67	549±45	560±37
400	56	46	51	43	495±47	412±29	459±27
600	30	69	26	61	466±57	443±29	447±25
700	—	89	—	21		467±49	—
800	20	80	3	10	319±14	363±53	356±40

rad. Just as in the control group, after irradiation with the doses listed above, 99% of the animals died in the late periods (after 4 months). After irradiation in higher doses (200, 400, 600, 700, 800, and 1000 rad), the mortality of the animals in the early periods (during the first four months) increased and amounted to 8.3, 7.8, 12.1, 76.5, 87, and 100% of the total number of animals used in the experiment. The mean life span of the animals dying in the later stages of the experiment correlated with the dose of irradiation (Table 2). After irradiation in doses of between 10 and 200 rad, the mean life span of the males and females dying in the later period (after 120 days) was practically the same, and indistinguishable from that in the control rats. After irradiation in higher doses (from 400 to 800 rad), a decrease in the mean life span of the rats dying in the later periods was observed, proportional to the dose of irradiation. Within this dose range the relationship between the mean life span of the rats and the dose of irradiation was well described by the equation [3]:

$$y = 560\ e^{-0{,}000665^{D}}\quad (D \geqslant 200\ \text{rad}),$$

where 560 represent the mean life span of the control rats and the rats irradiated in a dose of under 200 rad and dying in the late period; D is the dose of irradiation (in rad); y is the expected mean life span of rats dying in the late periods after a dose of irradiation of 200 rad or more.

The results in Table 2 also demonstrate clearly that the degree of reduction of the mean life span of the rats per rad of accumulated dose depended on the dose of irradiation and was 0.167, 0.195, 0.222, and 0.225 days after irradiation in doses of 400, 600, 700, and 800 rad respectively. After irradiation in these high doses the mean life span of the rats dying in later periods than the adequate control (560 days) was shortened by 12, 21, 28, and 32% respectively.

Differential analysis of the dynamics of mortality of the animals dying in the early period shows that the mean life span of the rats dying in a particular time interval (1-4, 5-15, 16-30, 31-60, and 61-120 days) was only slightly dependent on the dose of irradiation.

However, the number of rats dying within a particular period increased with an increase in the dose (Table 3). For instance, the mean life span of the rats dying in the time interval from 16 to 30 days after irradiation in doses of 400, 600, 700, and 800 rad was 23, 22, 22 and 23 days respectively, whereas, the percentage of animals dying during this time was 2, 2.1, 42.8, and 32.4 respectively. After irradiation in the doses indicated above in the time interval from 61 to 120 days, 1, 3.7, 8.7, and 26.3% of the rats died and the mean life span of the animals was 81, 81, 74, and 79 days respectively. The absence of significant differences between the mean life spans of the rats dying in the corresponding time interval showed that the mechanisms of death of the animals in these periods were the same. The significant differences in the percentage of dying animals depending on the dose of irradiation show yet again the important role of physiological factors in the reaction of the living organism to radiation.

Dynamic observations on the state of the peripheral blood of the experimental rats showed that in the early periods after irradiation the most substantial changes affected the composition of the white blood. These changes took the form of neutropenia and lymphocytopenia, followed by neutrophilic leukocytosis. The total number of leukocytes fell by the greatest degree in the first week after irradiation. Later the number of leukocytes in the blood gradually recovered, and after two months it regained its initial values. In the period of recovery of the initial

TABLE 3. Mean Life Span (MLS) of Rats Dying in the Early Periods after Irradiation, Depending on Dose and Time of Observation

Dose of irradiation (in rad)	Original No. of rats	Time interval (in days) during which the mortality rate (in %) and the mean life span (MLS) of the dying rats are assessed									
		1—4		5—15		16—30		31—60		61—120	
		%	MLS	%	MLS	%	MLS	%	MLS	%	MLS
400	102	0	—	2,9	8,3	2,0	23	1,0	39	1,0	81
600	99	0	—	3,0	12,3	2,1	22	3,2	39	3,7	81
700	89	1,1	4	43,7	10,0	42,8	22	17,8	43	8,7	74
800	100	48	3,7	34,6	10,6	32,4	23	17,3	36	26,3	79
1 000	22	36	4	100	7,4	—	—	—	—	—	—

Note. The mortality of the rats in the corresponding time interval was calculated as a percentage of the number of rats surviving to the beginning of the corresponding time interval.

number of leukocytes, and later throughout the life of the animals, distinct changes were found in the leukocyte formula. The number of lymphocytes was reduced by 20-40% and the number of neutrophils increased by 80-100% compared with the original values. In the control rats throughout life the total number of leukocytes fluctuated within the limits of ±10-30% of the initial value. As the rats grew older (2 years and more) these fluctuations became larger on account of the increased number of neutrophils.

In contrast to the irradiated rats, in the control animals the ratio between the numbers of neutrophils and lymphocytes remained normal, i.e., the lymphocyte profile of the blood was maintained in the rats.

The number of erythrocytes in the control rats throughout the period of observation varied within limits of ±10-18% of the initial values. In the experimental animals the greatest decrease in the number of erythrocytes was observed after irradiation in doses of 700,800, and 1000 rad. In rats irradiated with protons in a dose of 1000 rad, the number of erythrocytes fell after 7 days to 45%. After irradiation in doses of 700-800 rad, the number of erythrocytes was reduced in the period 7-21 days by 20-40%. In the surviving rats (irradiated in doses of 700-800 rad), the number of erythrocytes was restored and remained within the limit of the initial values until death (9-13 months). In rats irradiated with protons in doses of 10-25 rad, fluctuations in the number of erythrocytes were observed between the limits of ±10-15%, coinciding with the fluctuations in the control animals.

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