THE BIOLOGICAL ACTION OF HIGH ENERGY (500 Mev) PROTONS

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The biological action of radiation depends not only on the magnitude of the absorbed dose, but also on the nature of the radiation, determining the linear density of the loss of energy of the ionizing particles and the microgeometry of their distribution in the tissues. For this reason one of the most pressing problems in modern radiobiology is the study of the comparative biological action of different types of ionizing radiation and, in particular, of nuclei of heavy particles.

Very few studies of the action of high-energy protons are described in the radiobiological literature. According to some authorities [9], protons are equal to x-rays in their effect, but according to others [6, 7] they are slightly less effective than x-rays (RBE = 0.7).

Experimental studies of the biological action of protons with an energy of 660 Mev during recent years [1-3] have shown that after irradiation with protons the clinical picture of the injury in animals dying in the acute phase is essentially indistinguishable from that due to irradiation with x-rays in equivalent doses (200 kV). In contrast to x-rays, the changes in the erythrocytes, testes, and glandular epithelium of the large intestine caused by protons were more severe and, what is especially important, slower to disappear. Tumors developed more frequently than after x-ray irradiation in various tissues, including the testes and gastro-intestinal tract.

In the present paper we describe results showing the effect of high-energy protons on the life span and the state of the peripheral blood.

EXPERIMENTAL METHOD AND RESULTS

The work was carried out on 490 Wistar albino rats. The animals were irradiated once on a synchrocyclotron of the Joint Institute of Nuclear Research (Dubna) in doses of 28, 39, 114, 275, 358, 422, 760, 864, and 1008 rad.

The energy of the proton radiation was 500 Mev and the dose rate from 0.7 to 2.3 rad/sec. The mean duration of the impulses was 400 μsec (from 200 to 500 μsec), and their frequency 100/sec. The biological effectiveness of the high-energy protons was determined by the method of Miller and Tainter [8] as the size of the dose causing death of 50% of animals in 15, 30, 60, and 120 days (LD_{50}).

The doses causing death of 50% of the animals after 30, 60, and 120 days were equal, amounting to 600 ± 35 rad, and after 15 days – 710 ± 45 rad. By the criterion of the life span, the high-energy protons (500 Mev) differ only little from x-rays and γ-rays, the acute effective doses for which are practically identical [4, 5]. It was noted that the doses causing death of 50% of the animals after 60 and 120 days, like those after 30 days, differed only little from the doses causing death of the animals after 15 days. This demonstrates that after a single irradiation with protons the animals do not die between the 30th and 120th days. Analysis of the deaths of the animals during irradiation with different doses of high-energy protons confirmed that this view is correct. For instance, after irradiation in doses of 760 and 1008 rad, 86-95% of rats died before the 30th day. In the later periods up to the 120th day after irradiation in these doses, no animals died. The mean life span of the rats after doses of 760 and 1008 rad was 12 and 9 days respectively. After irradiation in smaller doses – from 28 to 422 rad – only a few animals died, at roughly the same frequency as in the control group. By the 120th day the number of animals dying in these groups ranged from 3% (at 114 rad) to 7% (at 422 rad).

The peripheral blood was investigated (erythrocyte and leukocyte counts, leukocyte formula) before and at various intervals after irradiation. The results showed that initially (within 28 days after irradiation) the white blood cells were most affected. The changes comprised neutropenia and lymphocytopenia, followed by a neutrophilic leukocytosis associated with a marked lymphocytopenia. After 6-7 months the most significant changes affected the red blood

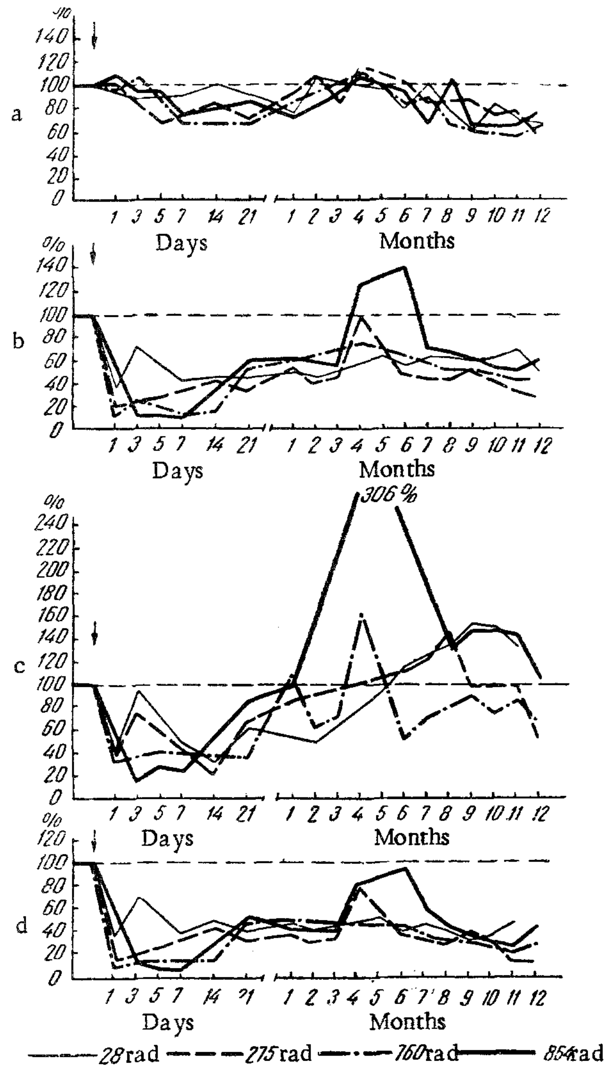

Fig. 1

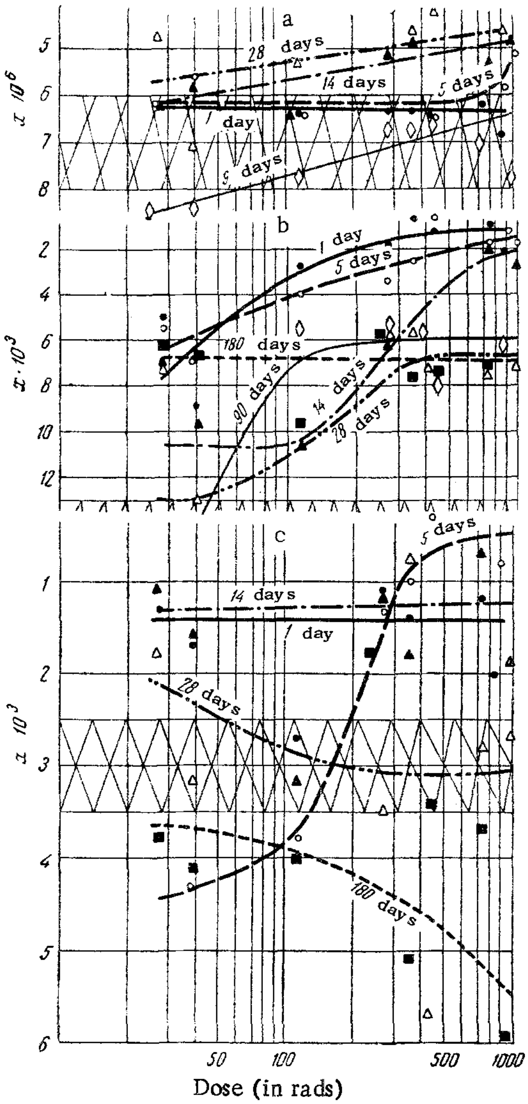

Fig. 2

Fig. 1. Changes in the numbers of erythrocytes (a), leukocytes (b), neutrophils (c), and lymphocytes (d) in the blood of rats after irradiation with protons in a dose of 28 rad.

Fig. 2. Dose – effect curves for erythrocytes (a), lymphocytes (b), and neutrophils (c) at different times after irradiation of rats with protons.

cells; erythropenia was present, with a simultaneous stimulation of erythropoiesis, revealed by anisocytosis of the erythrocytes, an increase in the number of polychromatophilic erythrocytes, and the appearance of erythroblasts in the peripheral blood.

The decrease in the number of leukocytes reached its maximum from 3 to 7 days after irradiation: with doses of 28 and 39 rad – by 30-40%, and with doses of 358 rad or more – by 75-90% (Fig. 1). The decrease in the total leukocyte count took place as a result of a fall in the number of lymphocytes (by 90-95%) and of neutrophils (by 60-80%). Restoration of the total leukocyte count began to occur after 7-14 days and affected both neutrophils and lymphocytes. However, after 21-28 days the lymphocyte count was restored by only 50%, whereas the absolute neutrophil count was higher than originally; with large doses this excess amounted to 300%.

From 1 to 3 days after irradiation the erythrocyte count rose very slightly (by 3-5%), and in the period from 5 to 28 days it fell again. The larger the dose of protons, the greater the fall in the erythrocyte count. This fall was most marked with doses of 275 rad or more. Two months after irradiation the erythrocyte count was restored, and until 4-5 months it was either slightly above the initial values (by 15-20%) or within their limits. After 6 months a slow and gradual redevelopment of anemia was observed (see Fig. 1), reaching its maximum after 12 months. During the period of development of erythropenia, considerable qualitative changes were observed in the red blood cells (anisocytosis, polychromatophilia), especially when large doses were given.

The results of the observations on certain red and white blood cells may be presented in the form of dose-effect curves for different periods of observation. Due attention has not been paid to the analysis of the dose-effect relationship depending on the period of observation in the radiobiological literature. Most workers consider that the action of ionizing radiation is dependent on the dose, and that the dose-effect curve is either linear or S-shaped. However, as a result of the fact that many injuries caused by ionizing radiation possess considerable powers of recovery and compensation, and also on account of differences in the radiosensitivity and in the rate of development of the reactions of injury and recovery, the shape of the dose-effect curve may differ in respect to different physiological systems and may alter in time.

The shape of the dose-effect curve for the peripheral blood cells altered with time (Fig. 2). The number of lymphocytes in the blood after 1, 5, 14, 28, and 90 days decreased with an increase in the dose. The dose-effect curve was S-shaped. In the later periods (180 days) fewer lymphocytes were present in the blood of the experimental animals than the controls,whatever the dose used. The dose-effect curve was linear in character and the reaction was independent of the dose of irradiation.

More complex relationships were found for the cells of the neutrophil series. The number of neutrophils 1 and 14 days after irradiation was appreciably below the initial level, but no relationship between dose and effect could be detected, and the dose-effect curve was linear in character (see Fig. 2). On the 5th day this curve became S-shaped. However, with small doses (39-114 rad) the neutrophil count was above the initial level and above the number of the cells of this series in the control population; with moderate doses it was the same as in the controls, and with large doses it was significantly below the control level. At later periods (28-90 days) the number of cells of the neutrophil series lay within normal limits, and showed no regular change with an increase in the dose. After 180 days, with all doses the number of neutrophils in the peripheral blood did not decrease, but rose in proportion to the increase in the dose. With an increase in the dose the dose-effect curve moved closer to the axis of abscissas. The neutrophilia was evidently due to stimulation of myeloid hemopoiesis by the accompanying secondary infection. It is easy to see that the reactions of the lymphoid and myeloid branches of hemopoiesis differed essentially and depended on the dose of irradiation and on the period of observation. The lymphocytes were more highly radiosensitive. With an increase in the dose of radiation the number of these cells always fell, while the number of neutrophils sometimes rose, as was especially apparent in the later observations.

The dose-effect curves revealed changes in the erythrocyte count more slowly than changes in the leukocytes (see Fig. 2). Consequently, after 1-5 days no changes in the erythrocytes were observed, and the dose-effect curve was linear in character. At later periods (after 14 and 28 days) the number of erythrocytes in the blood fell in proportion to the dose and the dose-effect relationship remained as before. After 90 days, with small doses (28-39 rad), the number of erythrocytes was higher in the experimental animals than in the controls, while with larger doses it was the same as in the controls. For the range of doses investigated the dose-effect relationship was well represented by a straight line.

The results show that the shape of the dose-effect curve is essentially dependent not only on the physiological properties of the system tested, but also on the period of observation. When further investigations are made, this factor must receive particular attention. An increase in the effect cannot be expected to occur in all cases when the dose is increased.

SUMMARY

A study was made of the biological activity of protons with an energy of 500 Mev, the range being from 28 to 1008 rad – a total of 10 doses. LD_{50} was established for various periods: it proved to be 710 ± 45 rad for 15 days and 610 ± 30 for 30-120 days. A study was made of the relationship between the peripheral blood composition and the irradiation dose. The shape of the dose-effect curve for the peripheral blood cells depended on the follow-up periods and the properties of the blood cells themselves.

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