The effect of high-energy accelerated particles on the crystalline lens of laboratory animals

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The results from experiments carried out by the authors and data from the literature are reviewed for the problem of radiation-induced cataractogenesis after exposure to various types of radiation. Laboratory animals were exposed at the accelerators of the Joint Institute for Nuclear Research, Dubna to protons of various energies and helium and carbon ions of energy 4 GeV/nucleon and 300 MeV/nucleon for a wide range of doses. It is shown that the relative biological effectiveness (RBE) of 50-MeV and 645-MeV protons is the same as that of standard radiation, and that the RBE of charged particles accelerated to high and relativistic energies is higher. The dependences of the RBE coefficients of the various types of radiation on both the LET and the dose level are obtained. Other topics discussed are the biological action of low doses and the effect of the dose rate and dose fractionation of ionizing radiation on cataractogenesis processes in laboratory animals and humans in connection with the risk of development of opacities in the crystalline lens due to exposure to cosmic rays. © *1995 American Institute of Physics.*

INTRODUCTION

As is well known, the primary sources of radiation risk in outer space are galactic cosmic rays, solar flares, and the radiation belts of the Earth. A slight increase in the amount of ionizing radiation can come from nuclear power installations on board spacecraft. Galactic cosmic rays contain nearly all the nuclei of the periodic table, but high-energy protons ($\sim 85\%$) and alpha particles ($\sim 13\%$) dominate.[1,2] Owing to the high penetrating power of galactic cosmic rays, the distribution of the dose absorbed in the body of an astronaut is uniform, and the problem of shielding is very serious. When galactic cosmic rays pass through the shielding of the spacecraft and fall on the body of an astronaut, secondary radiation arises with large linear energy transfers (LETs), the contribution of which to the total dose may reach 50–100%. Taking into account this secondary radiation, the dose rate of galactic cosmic rays in interplanetary space reaches 200–250 mrem per day.[3] The total dose from all sources of radiation can reach 100 rem or more for a flight lasting a year, and a reaction from the human bone marrow can occur already for a dose of 50 rem. The crystalline lens of the mammal eye also is particularly sensitive to radiation. According to calculations carried out on the basis of observations of the frequency of ophthalmological disturbances in survivors of the atomic bombing of Japan, the threshold for effects from radiation with low LET is around 0.6–1.5 Gy (Ref. 4). For long-term exposure to low-ionizing radiation the radiation dose which can lead to the development of opacities in the crystalline lens with disturbance of vision should be above 8 Gy (Ref. 5). However, the situation is considerably different in the case of charged particles with high LETs. During a three-year flight to Mars in a spaceship with shielding of aluminum 4 g/cm^2 thick, the total dose of galactic cosmic-ray components like carbon and iron nuclei absorbed by the crystalline lens is 0.1 Gy (Ref. 6). The RBE coefficients of carbon and iron ions at low doses reach 50 (Ref. 4). Therefore, owing to the high biological effectiveness of the heavy nuclei of galactic cosmic rays, the risk of the appearance of lenticular opacities for an astronaut is rather high. This suggests that the proposed methods of physical shielding cannot reliably shield astronauts from the effect of cosmic rays during long interplanetary flights.

This review is devoted to the analysis of the results of our own investigations and the data available in the literature on estimating the radiation risk for the crystalline lens exposed to heavy charged particles with various LETs. The LETs can be viewed as the analogs of the individual components of cosmic rays. The main goal of this research was to determine the RBE coefficients of accelerated charged particles with various physical characteristics. Such information is needed for estimating the dependence of developing effects on the quality of the radiation in order to ensure the radiation safety of long space flights. On the other hand, the normalization of radiation effects for humans is to a large degree based on the study of late-radiation pathology, which includes post-radiation clouding of the crystalline lens. Of course, other tissues of the eye can also be damaged by ionizing radiation. However, they are considerably more resistant to radiation than the crystalline lens and fall outside our discussion.

THE MATERIAL AND METHODS

The cataractogenic activity of accelerated charged particles and standard radiation was studied using 3090 mice of the line $F_1(CBA \times C_{57}BL_6)$ of both sexes and mass 14–16 g. The animals were subjected to a general or localized (at the head) single exposure to protons of energy 50 MeV, 645 MeV, and 9 GeV, helium ions of energy 4 GeV/nucleon, and carbon ions of energy 4 GeV/nucleon and 300 MeV/nucleon (Table I). The doses of the single exposure in various experiments varied from 0.25 to 6.0 Gy. The doses in the exposure of the mice to carbon ions were 0.03–0.5 Gy. In addition, the

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TABLE I. Conditions of exposure of the animals.

Radiation type and energy	Dose level, Gy	Dose rate, cGy/sec	LET, keV/μm	Number of mice	Exposure method
Protons, 50 MeV	1.0−6.0	0.4	1.25	350	Localized, single or fractionated
Protons, 645 MeV	1.0−6.0 1.0+1.0 2.0+2.0 3.0+3.0	6.3	0.25	600	General, single or fractionated
Protons, 645 MeV	4.0	0.3 3.0 30.0	0.25	100	General, single
Protons, 9 GeV	0.25−5.0	2.0	0.23	200	General, single
Helium ions, 4 GeV/nucleon	0.5−4.0	1.5	0.82	200	General, single
Carbon ions, 300 MeV/nucleon	0.03−1.0	0.004	12.0	200	Localized, single
^{60}Co gamma rays	0.5−6.0	6.0	0.25	560	General, single
^{137}Cs gamma rays	0.1−1.0	0.06	0.25	100	General, single
X rays, 180 keV	1.0−6.0 3.0+3.0	1.0	0.25	350	General, single or fractionated
Unexposed animals	-	-	-	240	-

animals were fractionally exposed to 50-MeV protons for a total dose of 6.0 Gy and 645-MeV protons for total doses of 2, 4, and 6 Gy. The number of fractions was two, and the time interval between them was 7 days. The doses of the first and second exposures were the same. The exposure to 50-MeV protons, x rays, and carbon ions was localized (at the head).

The use of mice of the line F_1 in these experiments has a number of important advantages. First, they are distinguished by a relatively high sensitivity to radiation. Second, practically all healthy mice of this line have an absolutely transparent crystalline lens. Third, the relatively short lifetime of these animals (about 2 years) makes it possible to obtain the necessary information on the dynamics of changes occurring in the lens fairly quickly.

The animals were exposed to 50-MeV and 645-MeV protons at the synchrocyclotron of the Laboratory of Physical Problems of the Joint Institute for Nuclear Research (before its reconstruction). The cyclotron provides a source of protons of energy 680 MeV with a proton flux density of about 10^7 particles$\cdot$cm$^2\cdot$sec^{-1}. The cross-sectional area of the proton beam leaving the accelerator window was 1−2 cm^2. A lead filter 1 cm thick was used to obtain a dose field of 645-MeV protons. The proton beam broadened as a result of multiple scattering in the filter, which ensured $\pm 5\%$ uniformity of the dose field over the collimator of diameter 10 cm. The monoenergetic nature of the proton beam at this energy was not spoiled at the exit from the collimator.[7,8]

To create a dose field of 50-MeV protons, as the proton moderator we used a polyethylene filter of thickness of about 170 g$\cdot$cm^2. To improve the monoenergetic nature of the proton beam and reduce the contribution from secondary radiation, the beam leaving the filter was passed through a magnetic field which deflected only charged particles of a given energy in the desired direction. After the deceleration and cleansing from secondary radiation, the proton beam was directed to one of the collimators, at the exit of which laboratory animals were placed. The energy of the extracted beam was estimated from the attenuation curve in plastic.[7] The maximum intensity of the 50-MeV proton beam determined by means of activation detectors was 1.5×10^6 particles$\cdot$cm^2/sec, which corresponds to a dose rate of 0.003 Gy/sec. The drop of the dose at the edges of the radiation field of diameter 10 cm was $\pm 7\%$. A specially designed device incorporated in the control circuit of the synchrocyclotron controlled the value of the proton dose and automatically switched off the accelerator.

Physical conditions were also specially designed for exposing biological objects to accelerated charged particles (protons, helium ions, and carbon) at the proton synchrotron of the JINR High Energy Laboratory.[9,10] Quadrupole lens doublets of area up to 30 cm^2 were used to form a radiation field whose nonuniformity in dose is $\pm 10\%$. The uniformity of the dose field at the spot where the biological object was exposed was determined by means of a remote device with cylindrical ionization chambers. Here the contribution of the accompanying radiation to the dose was less than 0.5% in the flux and 5.0% in the dose. It was monitored by means of a semiconductor detector. The dosimetry was performed using condenser ionization chambers with a spherical sensitive volume of 0.1 cm^3. The ion collection efficiency in this chamber was at least 95% at the maximum dose rates. The charge leakage was less than 5% per day. The energy of the accelerated protons was 9 GeV ($dE/dx = 0.23$ keV/μm), and that of the helium ions was 4 GeV/nucleon ($dE/dx = 0.82$ keV/μm). The maximum intensity of relativistic nuclei was 10 particles per cycle. Cycles of duration 450 msec were repeated every 8 sec. The particle beam extracted from the accelerator chamber had geometrical dimensions 10×20 mm^2. A wider beam was obtained by shaping the initial beam, using quadrupole lens doublets. The widened beam had dimensions 55×55 mm^2. The location and profile of the beam were recorded by multiwire proportional counters. The uniformity of the radiation field was determined by means of a coordinate device and gap ionization chambers. The exposure process was monitored by means of a feed-through plane-parallel two-section ionization chamber with diameter of the working volume equal to 190 mm, equal to the diameter of the ion pipe.

The system of slow extraction of the accelerated nuclei from the chamber of the proton synchrotron also can be used to obtain beams of carbon ions with the lower energy of 300 MeV/nucleon (dE/dx=12.6 keV/μm) with a flux of up to 10^7 particles per cycle. The duration of the cycle ranged from 9 sec for a long pulse to 50 msec. The beam for radiobiological experiments using laboratory animals was shaped by defocusing using quadrupole-lens doublets, again to dimensions 55×55 mm^2 with a nonuniformity of $\pm10\%$. The contribution of the accompanying radiation was less than 1% in the integrated flux and less than 5% in the dose. The absorbed dose was determined and monitored with an accuracy of $\pm10\%$. The characterization of the dose fields included information about the content and energy distribution of the secondary charged particles needed for estimating their contribution to the absorbed dose.[11]

We used gamma rays or x rays as the standard radiation. The animals were exposed in an RKh-γ-30 setup with a ^{60}C radiation source or in a "Svet" setup with a ^{137}Cs source. X-ray beams of energy 180 keV were used in the case of localized exposure of the animals (the RUT-250-15-1 setup; current equal to 15 mA, filters of 0.5 mm Cu and 1.0 mm Al).

The frequency and time for the appearance of lenticular opacities in the initial stage were taken into account, together with the dynamics of their maturation as a function of the radiation dose, the LETs, and the duration of the post-radiation period. The frequency with which lenticular opacities appeared in the lens was defined as the percentage ratio of the number of eyes with lenticular opacities and the number of eyes inspected in each group of laboratory animals. The resulting data were compared with the results of similar observations obtained after exposure of animals to standard radiation, and also the results for a group of unexposed mice. The crystalline lens was examined by means of an electro-ophthalmoscope and a lens of ±15.0 D before each exposure and every four weeks afterwards until the animal died. The pupil was dilated using a 1% solution of hydrobromine homatropine. The exposure and examination of the animals were performed without anaesthesia. The lenticular opacities were diagnosed according to stages using the technique proposed for small laboratory animals,[12] according to which four stages of lenticular opacity are distinguished. The first stage is characterized by the appearance of tiny points under the posterior capsule of the crystalline lens, which group together and form small clusters. In the second stage the number of pointlike opacities increases and some of them merge, forming an opaque disk at the center of the crystalline lens. In the third stage the disk grows in size and radial lines diverge from it in all directions. The opacity acquires a floccular structure. The fourth stage is that of complete clouding of the crystalline lens. The use of this technique allowed us to compare the results of our experiments with the data of other authors obtained in experiments using small laboratory animals.

For estimating the values of the RBE coefficients of relativistic radiation and heavy charged particles we used the nonparametric method suggested in Ref. 13. It amounts to the following. Assume that in the exposure of biological objects to standard radiation in doses $D_{A1},D_{A2},\dots,D_{AN}$ effect levels $A_1,A_2,\dots,A_N$ are recorded, and that in exposure to the studied radiation in doses $D_{B1},D_{B2},\dots,D_{BM}$ effect levels $B_1,B_2,\dots,B_M$ are recorded. Using statistical tests, the effect level B_1 due to the dose D_{B1} of the studied radiation is compared with the effect level A_1 induced by the dose D_{A1} of standard radiation. If the difference between the effect levels A_1 and B_1 is statistically unreliable, the RBE coefficient, equal to the ratio of the doses of the standard and studied radiation, $\mathrm{RBE}_1(D_{B1})=D_{A1}/D_{B1}$, is assumed to be significant. Otherwise, the coefficient $\mathrm{RBE}_1(D_{B1})$ is treated as statistically unreliable. Next, a systematic comparison of the effect levels B_1 with the levels $A_2,\dots,A_N$ is made. As a result, we obtain the range of significant RBE coefficients $\mathrm{RBE}_{\min}(D_{B1})-\mathrm{RBE}_{\max}(D_{B1})$ corresponding to the dose of studied radiation D_{B1}. This procedure is performed for all the other effect levels $B_2,\dots,B_M$ induced by the doses $D_{B2},\dots,D_{BM}$ of the studied radiation. The dose dependence of the RBE coefficients is thereby determined. Regarding the statistical tests, the Fisher criterion or test is used in comparing effect levels of the "all or nothing" type.[13,14] In those cases where the biological effect has several gradations, the nonparametric Wilcoxon criterion is used.[13] The results are presented either in the form of a table listing the limiting values of the range of significant RBE coefficients ($\mathrm{RBE}_{\min}-\mathrm{RBE}_{\max}$) or in the form of graphs. In graphs the doses of the radiation studied are plotted along the axis of abscissas, and the values of the RBE coefficients are plotted along the axis of ordinates. The limits of the range of significant RBE coefficients are denoted by arrows. The vertical lines correspond to the regions of statistically unreliable values of the RBE coefficients.

In this study the RBE coefficients of the studied radiation in relation to the standard radiation have been estimated from the frequency of post-radiation lenticular opacities. Here we considered five gradations in the degree of opacity of the lens, including zero, which corresponds to the absence of opacities. Therefore, the Wilcoxon criterion was used to calculate the statistically significant RBE coefficients.

In a number of cases the RBE coefficients were calculated by the traditional method, i.e., by comparing equally effective doses of the standard and studied radiation for each observation period. In particular, this was done in processing the experimental data on the exposure of animals to 50-MeV and 645-MeV protons.

EXPERIMENTAL RESULTS

Features of the formation of lenticular opacities after exposure of animals to high-energy protons

Study of the cataractogenic activity of neutrons and x rays together with study of morphological changes in the crystalline lens developing in the earliest period after exposure did not reveal any qualitative differences in the effects of these types of radiation.[15,16] This is also true of accelerated charged particles of various energies.[17,18] The appearance of visible changes in the crystalline lens is preceded by a latency period whose duration depends on the dose level, the intensity of the radiation, and other conditions of the exposure. In particular, the first pointlike opacities of the lens

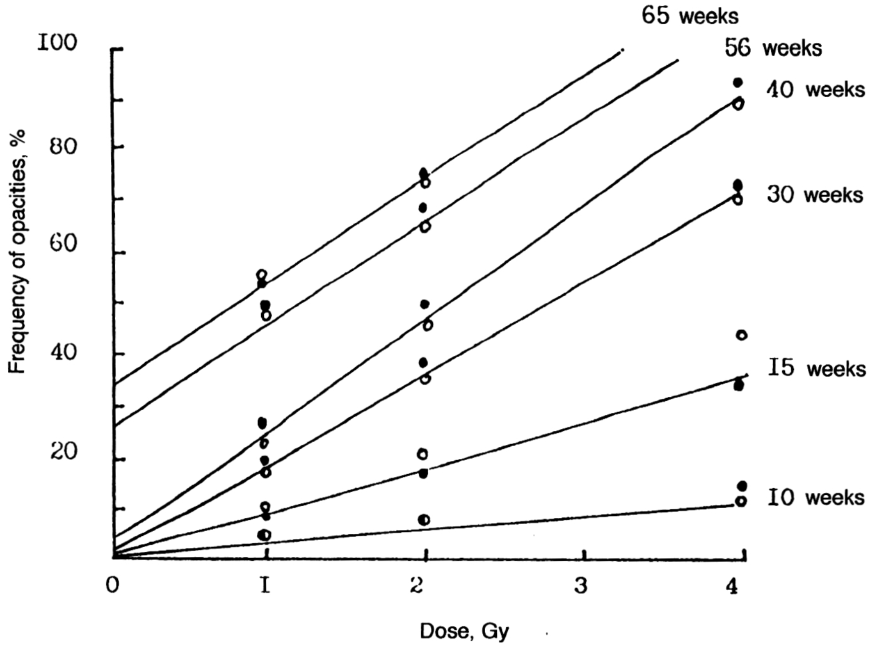

FIG. 1. Dependence of the frequency of lenticular opacities in mice on the dose of 645-MeV protons (●) and ^{60}Co gamma rays (○) at different times after exposure.

in mice appeared 8 weeks after general exposure to 645-MeV protons and gamma rays in doses of 4 and 6 Gy and 10 weeks after localized exposure to 50-MeV protons at the same doses. Exposure of animals to protons in doses of 1 and 2 Gy leads to the development of lenticular opacities, with the initial stage occurring 10 and 15 weeks after general and localized exposure, respectively. It should be noted that a significant fraction of unexposed animals developed lenticular opacities as a result of aging, and these as a rule appeared 19–20 weeks after the experiment started. They developed more slowly than those in exposed animals and rarely reached full maturity in mice of this line. Lenticular opacities in mice exposed to 50-MeV protons developed a little more slowly, which may be due to the low dose rate. Here the dose dependence of the duration of the latency period (the time interval between exposure and the appearance of the first signs of clouding) was nearly linear:

$$\lambda = \lambda_0 - \alpha D, \qquad (1)$$

where λ is the duration of the latency period, D is the dose in Gy, α is the regression coefficient in days$\cdot$Gy^{-1}, and λ_0 is the duration of the latency period of formation of lenticular opacities for unexposed animals, measured from the time of birth in days. Experiments on the exposure of mice to 645-MeV protons and gamma rays showed that the frequency of formation of lenticular opacities grows with increasing dose. Statistical analysis of the results did not reveal any reliable differences in the effects induced by these types of radiation. The data also allowed us to find the dependence of the frequency of lenticular opacities in mice on the dose of protons and gamma rays at various observation times (Fig. 1). This dependence is nearly linear:

$$\nu = \nu_0 + 100\% \cdot \beta D, \qquad (2)$$

where ν is the frequency of formation of lenticular opacities in exposed animals in %, D is the dose in Gy, ν_0 is the frequency of formation of lenticular opacities in unexposed animals in %, and β is the regression coefficient in Gy^{-1}.

As seen from Fig. 1 and shown by the calculations (Table II), when the observation time increases from 10 to 40 weeks the coefficients ν_0 and β increase. At later times (56 and 68 weeks) the coefficient ν_0 continues to grow, and the values of the coefficient β remain practically unchanged. This result indicates that by 40 weeks after the exposure the potential damage to the crystalline lens is already fully manifested. Apparently, its frequency increases further only owing to the increased frequency of lenticular opacities associated with aging, which appeared in some of the older unexposed animals.

To obtain a more complete characterization of the effect of 645-MeV protons on the process of formation of lenticular opacities in mice we kept track of the times needed for the development of individual stages of clouding of the crystalline lens. It was found that the time needed to form the first stage of clouding of the crystalline lens is 55–70 days, the time for the second stage to form is 175–280 days, for the

TABLE II. Values of the coefficient β in Eq. (2) calculated for various periods of studying the frequency of lenticular opacities in mice.

Observation period, weeks	Coefficient β, Gy^{-1}
10	0.03
15	0.09
30	0.17
40	0.22
56	0.21
68	0.22

third stage it is 370–450 days, and for the fourth stage it is 460–570 days. Here comparison of the data on the development of the individual stages of lenticular opacity induced by 645-MeV protons and ^{60}Co gamma rays did not reveal any reliable differences and therefore supported the view that the two types of radiation have equal biological effectiveness.

Study of the regularities in the development of lenticular opacities in mice exposed to 50-MeV protons and 180-keV x rays for localized exposure of the animal's head revealed the following. The development times for lenticular opacities due to 50-MeV protons and x rays are different. After exposure to protons at a dose of 6 Gy, the frequency of formation of lenticular opacities up to 30 weeks later was almost two times lower than after exposure to x rays. Later the effects of exposure to protons and x rays become the same, and after 50 weeks no reliable differences in the effectiveness of these types of radiation were found. The dose dependence of the frequency of formation of lenticular opacities is linear, as in the case considered above.

Study of the dynamics of the maturation of cataracts in laboratory animals has shown that the first stage of lenticular opacity in mice develops no earlier than 10 weeks after exposure and reaches its maximum frequency (21, 36, and 76%) 30 to 40 weeks after exposure to protons at doses of 1, 2, and 4 Gy, respectively. After this the frequency of lenticular opacities of the initial stages decreases as the opacities evolve to the next stage of maturity. This process also depends on the size of the radiation dose. After exposure of the mice to protons at a dose of 4 Gy, the frequency of opacities of the second stage reached its maximum (83%) by 44 weeks, while for doses of 1 and 2 Gy it took 68 weeks to reach it. At later times the frequency of lenticular opacities decreased for all dose levels owing to further maturation of the cataract, but opacities of the third stage were seen only in mice which had been exposed to protons and gamma rays in doses of at least 2 Gy. They had formed by 65 weeks, and by 81 weeks after exposure their frequency had reached 40%. Mature cataracts (3%) appeared after 65 weeks, and after 81 weeks their frequency reached 27%. By this time most of the exposed animals had died, so that it was impossible to follow the dynamics of the maturation of lenticular opacities at later times.

The dynamics of the maturation of lenticular opacities in animals exposed to 50-MeV protons and x rays displayed several features. The development of the individual stages of opacity occurred more slowly in this case. Lenticular opacities of the first and second stages were predominantly formed in the animals. Cataracts of the third stage developed only in 1–2% of the animals, and no earlier than 30–35 weeks after exposure. The development of lenticular opacities was more intense after exposure to x rays. Animals exposed to 50-MeV protons usually did not survive long enough for a mature cataract to appear, while after exposure to x rays the frequency of mature cataracts (fourth stage) had reached 30% by 80 weeks after exposure. These differences arose from the differing dose rates of the protons and x rays, as was confirmed by the results of specially performed experiments.[19]

Experimental studies of the cataractogenic activity of protons in large laboratory animals are very interesting. Observations for more than 20 years of monkeys exposed from age 2 to protons of energy ranging from 32 to 2300 MeV for a wide range of doses have revealed a progressive increase in the frequency of lenticular opacities starting 18 to 20 years after exposure.[20,21] The RBE coefficient of 55-MeV protons in this case was also close to 1. Therefore, comparison of the doses of protons and standard radiation equally effective in cataractogenic activity indicates that the RBE coefficients of protons for energies in the range from 50 to 645 MeV are equal to 1. The equal biological effectiveness of 60-MeV protons and standard radiation is also indicated by the results of the experiments of Ref. 22, in which the cataractogenic activity of radiation was judged from the ratio of the volumes of the changed and unchanged parts of the crystalline lenses of laboratory animals. In addition, it should be realized that not only the decreased proton energy, but also interspecific variations of laboratory animals and other biological and physical factors can change this ratio. In particular, studies of the state of the crystalline lens in rabbits for fractionated exposure to x rays and protons showed that the RBE coefficient of 100-MeV protons reached about 2, while for 20-MeV protons it was 3 (Ref. 23).

Lenticular opacities in mice exposed to radiation of relativistic energies

The regularities in the development of lenticular opacities observed in laboratory animals exposed to 9-GeV protons and helium ions with energy 4 GeV/nucleon were rather different from those in the case of cataract formation induced by protons of lower energy and standard radiation.[17,24] The differences were mainly quantitative and were primarily in the times for the first visible lenticular opacities to appear. After exposure to relativistic helium ions and protons in doses of 4–5 Gy the first pointlike lenticular opacities were observed after 4 weeks, while for doses of 0.5–2.0 Gy they were observed 8 weeks after exposure. Analogous effects appeared 8 to 10 weeks after exposure to gamma rays. In other words, after exposure to protons and helium ions the times for lenticular opacities to appear are significantly shortened, depending on the dose (Fig. 2).

Analysis of the results showed that for the selected observation times the dose dependence of the frequency of lenticular opacities is linear in the dose range 0.5–2.0 Gy (Fig. 3). When the dose of helium ions of energy 4 GeV/nucleon is increased from 2.0 to 4.0 Gy, the frequency of lenticular opacities grows nonlinearly and reaches roughly the same level (95–100%) for all three selected observation times.

The dependence of the frequency of lenticular opacities on the dose of 9-GeV protons is similar for the observation time farthest from the time of exposure (Fig. 4). In the dose range 0.5–1.0 Gy it is linear, and then it reaches a constant value (95%). For earlier observation times this dependence is linear over the entire dose range studied, 0.5–5.0 Gy.

Regarding the dependence of the frequency of lenticular opacities for gamma rays, for the selected observation times it is linear over the entire dose range studied (Figs. 3 and 4).

It is important to note that the results shown in Figs. 3 and 4 indicate a higher rate of formation of lenticular opaci-

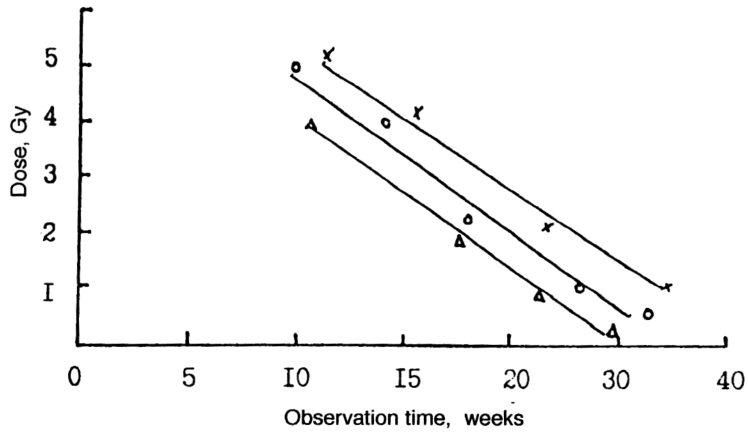

FIG. 2. Dependence of the duration of the latency period for 30% clouding of the crystalline lens on the dose of helium ions of energy 4 GeV/nucleon (△), 9-GeV protons (○), and ^{60}Co gamma rays (×).

ties in animals exposed to relativistic helium ions and protons than for animals exposed to gamma rays.

The experimental results indicate that the frequency of lenticular opacities is a linear function of the time after exposure to helium ions of energy 4 GeV/nucleon in doses of 1–4 Gy (Fig. 5):

$$\nu = \nu_0 + 100\% \cdot \delta t, \tag{3}$$

where ν is the frequency of lenticular opacities for the exposed animals in %, t is the time since exposure in weeks, ν_0 is the frequency of lenticular opacities in animals before exposure in %, and δ is the regression coefficient in inverse weeks. The values of the coefficient δ calculated for helium ions and protons and also the ratio of these coefficients for the studied radiation and standard radiation also indicate a higher intensity of formation of lenticular opacities after exposure to accelerated charged particles (Table III).

The results of these studies made it possible to determine the value of the RBE coefficients of protons and helium ions of relativistic energies. In Fig. 6 we show the dose dependence of the RBE coefficients of protons (a) and helium ions (b) at different times after exposure to radiation. We see that there is a characteristic drop in the values of the RBE coefficients as the dose increases. For observation at 25 weeks the RBE coefficients of protons decreased from 2–4 at a dose of 0.25 Gy to 1–2 at a dose of 5.0 Gy, and 67 weeks after exposure the RBE coefficients had decreased from 4–8 for a dose of 0.25 Gy to 1.0 for a dose of 4.0 Gy.

Similar values of the RBE coefficients were found for 3-GeV protons.[25]

Thus, study of the RBE of protons and helium ions of relativistic energies and also high-energy accelerated charged particles with various LETs has shown that these types of radiation are more effective at cataractogenesis than protons of energies in the range 50–645 MeV and standard radiation. The frequency of formation of lenticular opacities is a function of the dose and the time since exposure.

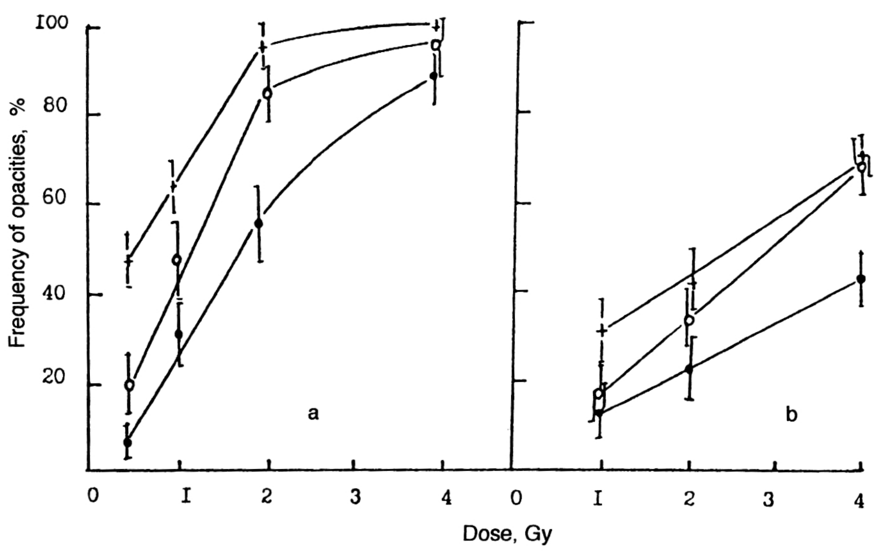

FIG. 3. Dependence of the frequency of lenticular opacities on the dose of helium ions with energy 4 GeV/nucleon (a) and gamma rays (b) 20 (●), 30 (○), and 40 (+) weeks after exposure.

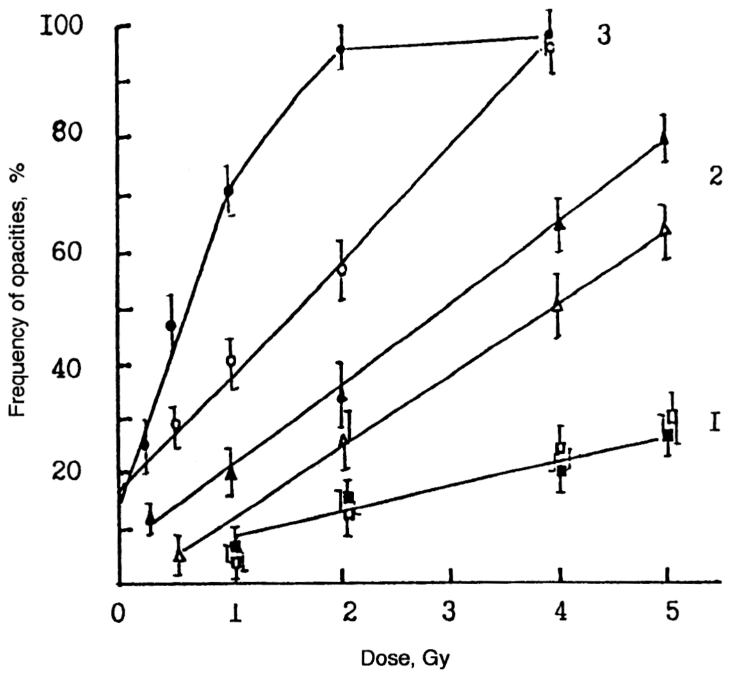

FIG. 4. Dependence of the frequency of lenticular opacities in mice on the dose of 9-GeV protons (solid points) and ^{60}Co gamma rays (open points) 13 (1), 20 (2), and 40 (3) weeks after exposure.

The effect of low doses of accelerated charged particles on the frequency of lenticular opacities

The study of the biological effects induced by low doses of ionizing radiation is one of the most important practical problems in cosmic radiobiology. The analysis of the radiation environment of the route between Earth and Mars carried out by American specialists indicates that the risk of astronauts developing lenticular opacities is fairly high.[6] The dose received by the crystalline lens due to exposure to only carbon and iron nuclei can reach 0.1 Gy over the three-year period of a flight to Mars.

In experiments on animals exposed a single time to carbon ions of energy 300 MeV/nucleon, the first tiny, pointlike lenticular opacities in the form of individual lacunae were discovered already 6 weeks after exposure at doses of 0.1–0.5 Gy (Ref. 26). Lower doses of carbon ions (0.03 and 0.05 Gy) led to the appearance of the first signs of disturbance of the transparency of the crystalline lens 14 weeks after exposure to radiation. After exposure to gamma rays at doses of 4.0–6.0 Gy, analogous changes in the lens were observed only after 8–10 weeks, and for doses of 0.5–2.0 Gy they were observed after 15 weeks. The clouding of the lens progressed steadily, and 17.5 weeks after exposure to carbon ions at doses of 0.03 and 0.05 Gy, and 30 weeks after exposure to gamma rays at doses of 2.0–6.0 Gy, the second stage of lenticular opacity was observed in some animals. At doses of 0.5 and 1.0 Gy the second stage of lenticular opacity ap-

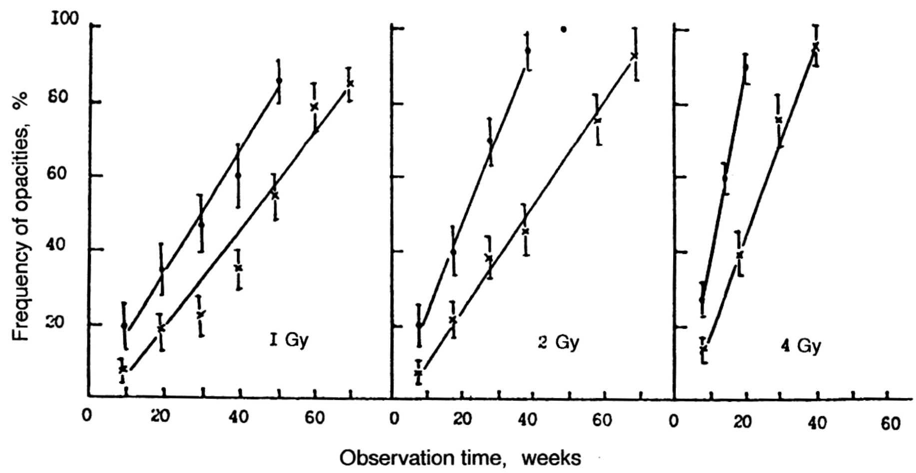

FIG. 5. Dependence of the frequency of lenticular opacities in mice on the time since exposure to helium ions of energy 4 GeV/nucleon (●) and ^{60}Co gamma rays (×) at doses of 1, 2, and 4 Gy.

TABLE III. Values of the coefficient δ calculated for various doses of charged particles accelerated to relativistic energies and standard radiation.

Dose, Gy	Value of the coefficient δ			Ratios	
	Helium	Protons	γ rays	δ-helium / δ-gamma	δ-proton / δ-gamma
0.5	-	1.47	1.20	-	1.22
1.0	1.83	2.30	1.46	1.25	1.74
2.0	3.25	3.75	1.55	2.09	2.37
4.0	5.20	7.0	2.12	2.45	1.48

peared in mice 42 weeks after exposure. By this time, in some of the animals exposed to gamma rays at a dose of 6.0 Gy the lenticular opacity had reached the third stage, while for mice exposed to carbon ions the development of lenticular opacities remained at the second stage for up to 70 weeks after exposure. As indicated above, the delayed maturation of radiation-induced lenticular opacities in laboratory animals can to a large degree be related to the dose rate. Similar dynamics in the development of lenticular opacities is also characteristic for exposure to protons of energy in the range 50–645 MeV at doses of 1.0–2.0 Gy.

The study of the dynamics of lenticular opacities of the initial stage for mice exposed to carbon ions has revealed an interesting phenomenon: at later observation times the frequency of lenticular opacities in certain groups of animals can turn out to be slightly lower than at earlier times. This feature in the formation of lenticular opacities is well known for both low-ionizing and densely ionizing radiation and apparently is due to variability in the individual radiation sensitivity of the crystalline lens. In addition, the tendency for the frequency of lenticular opacities to increase as the post-radiation period becomes longer was preserved, and by 49 weeks after exposure at a dose of 0.5 Gy the frequency of lenticular opacities at early stages reached 100% (Table IV).

The process of formation of the individual stages of lenticular opacities in mice exposed to carbon ions and gamma rays progressed in a similar manner, even though the doses of these types of radiation differed by an order of magnitude. The dependence of the frequency of lenticular opacities on the dose of carbon ions was nonlinear, while in the case of gamma rays it was linear (Fig. 7). As indicated above, this behavior of the dose–effect dependence is also characteristic for relativistic charged particles.[18,24]

Statistical analysis of these results showed that a carbon-ion dose of 0.05 Gy can be assumed to be the threshold for the formation of lenticular opacities in mice, because the frequency of lenticular opacities of these animals reliably exceeded the level of lenticular opacities due to aging in unexposed (intact) mice. The threshold dose for cataract formation by iron ions of energy 600 MeV/nucleon is similar,[27] while for gamma rays the threshold dose is close to 2.0 Gy (Ref. 26).

Calculations of the RBE coefficients of carbon ions based on the results of experiments repeated three times

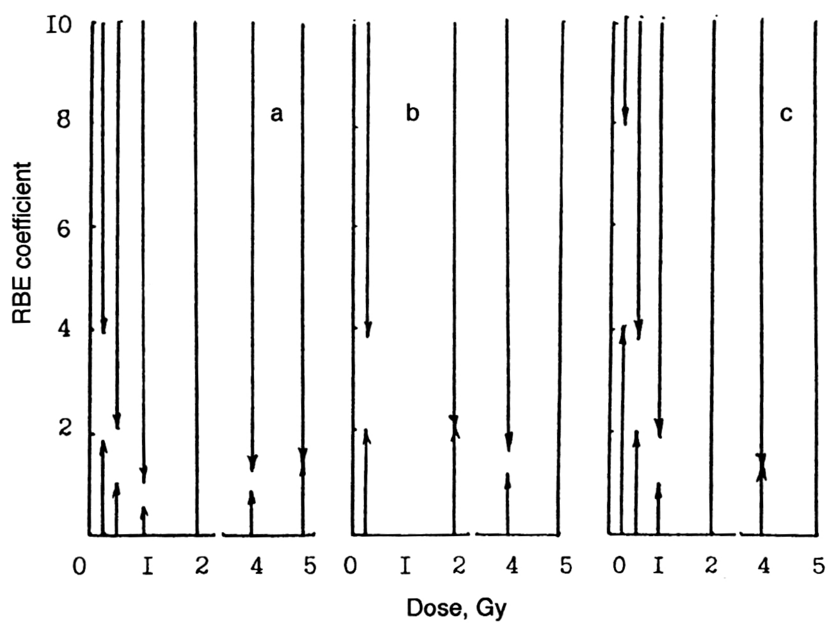

FIG. 6. Dependence of the RBE coefficients of 9 GeV protons on the dose 25 (a), 40 (b), and 67 (c) weeks after exposure. The dose in Gy is plotted along the axis of abscissas, and the value of the RBE coefficient is plotted along the axis of ordinates.

TABLE IV. Frequency of lenticular opacities in mice at different times after exposure to carbon ions of energy 300 MeV/nucleon and ^{60}Co gamma rays.

Time since exposure, weeks	Carbon ions		Gamma rays	
	dose, Gy	frequency of opacities, %	dose, Gy	frequency of opacities, %
6–10	0.03	-	1.0	6.8±3.3
	0.05	-	2.0	7.3±2.6
	0.10	4.0± 4.0	4.0	13.0±5.8
	0.25	16.7± 7.1	5.0	33.4±6.9
	0.50	15.6± 6.5	6.0	50.0±8.0
	Control	-		-
20–23	0.03	13.6± 7.3	0.5	6.5±3.4
	0.05	35.7±12.0	1.0	16.0±5.9
	0.10	32.3±12.0	2.0	27.1±4.2
	0.20	58.4±15.0	4.0	52.06±6.7
	0.25	64.2±12.8	5.0	65.0±7.0
	0.50	64.2±11.8	6.0	83.2±5.0
	Control	-		-
30	0.03	20.8± 8.3	0.5	18.0±3.8
	0.05	19.3± 7.0	1.0	28.1±5.2
	0.10	35.7±13.0	2.0	46.6±6.5
	0.20	37.5±15.0	4.0	93.0±3.8
	0.25	42.8±13.2	5.0	100.0
	0.50	50.0±18.0	6.0	100.0
	Control	12.5± 5.9		-
40–43	0.03	15.8± 8.4	0.5	22.2±4.2
	0.05	20.0±12.6	1.0	35.0±5.7
	0.10	50.0±12.0	2.0	60.1±3.1
	0.25	54.6±15.7	4.0	100.0
	0.50	77.0±11.6	5.0	100.0
	Control	15.6± 3.1	6.0	100.0

showed that the highest values of the RBE coefficients are obtained for doses in the range from 0.03 to 0.25 Gy (Table V). For example, for a dose of 0.03 Gy the significant ranges of RBE coefficients were 33.3–16.7 at 30 weeks after exposure and 66.7–16.7 at 50 weeks after exposure. At a dose of 0.1 Gy the RBE coefficient rose from 10.0 at 30 weeks to 20 at 50 weeks. After exposure of animals to carbon ions at a dose of 0.5 Gy the range of measured RBE coefficients was 1–4, i.e., the same as for 9-GeV protons. And only at early observation times (20 weeks) did it range from 8 to 12 (Ref. 26).

High cataractogenic effectiveness is characteristic for low doses of carbon ions of energy 400 MeV/nucleon (Ref. 28). In experiments on mice undergoing single and fraction-

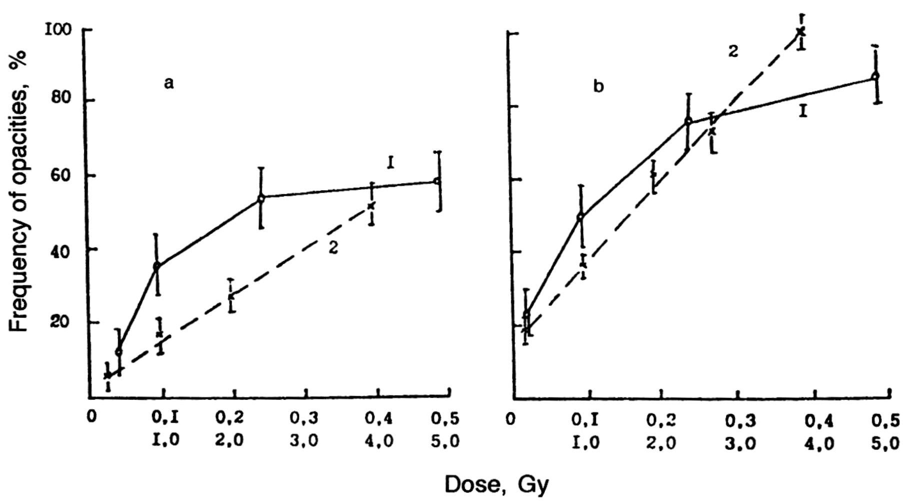

FIG. 7. Dependence of the frequency of lenticular opacities on the dose of carbon ions with energy 300 MeV/nucleon (*1*) and ^{60}Co gamma radiation (2) at 20 (a) and 40 (b) weeks after exposure. The dose in Gy is plotted along the axis of abscissas, with the upper scale for carbon ions and the lower scale for gamma rays.

TABLE V. Dose dependence of the RBE coefficients of carbon ions of energy 300 MeV/nucleon at different observation times. The ranges of statistically significant RBE coefficients are given ($RBE_{min}-RBE_{max}$).

Dose, cGy	Observation period, weeks 31	43	50	64
3.0	16.7–33.3	-	16.7–66.7	-
5.0	10.0–20.0	10.0–20.0	10.0	-
10.0	10.0	-	5.0–20.0	10.0–20.0
15.0	13.3	13.3–40.0	3.3–26.7	6.7–13.3
20.0	2.5–10.0	-	2.5–10.0	5.0–10.0
25.0	8.0	2.0–4.0	2.0–8.0	4.0–8.0
50.0	2.0–4.0	4.0	1.0–4.0	2.0–4.0

ated exposure to carbon ions at doses from 0.05 to 0.9 Gy, the RBE coefficients varied from 5 to 1–2, depending on the dose.

The same regularities in the development of lenticular opacities were found for rats subjected to localized (at the head) exposure to accelerated argon ions of energy 570 MeV/nucleon and 185-keV x rays at various doses.[29] The earliest disturbances of the transparency of the crystalline lens after exposure to argon ions at a dose of 1 Gy were found in the central and posterior subcapsular regions of the crystalline lens, while in animals exposed at a dose of 3.5 Gy they were found in the central anterior subcapsular region. Their rate of development also manifested a marked dependence on the radiation dose. The RBE coefficients for argon ions increased with decreasing dose and ranged from 6 to 10 after exposure at a dose of 10 Gy (Ref. 30) and were about 40 for a dose of 0.05 Gy (Ref. 29).

Very high values of the RBE coefficients were found when the nonparametric method was used to process the results of experiments on the cataractogenic action of low doses (0.01–0.25 Gy) of argon ions of energy 570 MeV/nucleon for the crystalline lens of 28-day-old rats of the Columbia–Sherman line. For observation 62 weeks after exposure, the RBE coefficients of argon ions were between 50 and 100 for a dose of 0.01 Gy, between 10 and 50 for a dose of 0.05 Gy, and between 4 and 8 for a dose of 0.25 Gy (Ref. 6). It is also possible that for earlier observation times the RBE coefficients can be even higher.

Thus, analysis of the results indicates that there is a large risk from small doses of heavy charged particles in the sense that the risk of developing lenticular opacities grows at long times after exposure to radiation.

Formation of lenticular opacities for various dose rates of ionizing radiation

The effect of the dose rate of ionizing radiation on the frequency and time for development of lenticular opacities has hardly been studied up to now. However, this question is important in the problem of normalizing the effects of radiation.

In order to understand the possible effects of the dose rate on the frequency and time of formation of lenticular opacities, mice were exposed to 645-MeV protons at a dose of 4 Gy for dose rates of 0.18, 1.8, and 18.0 Gy/min. In Fig. 8 we show the dependence of the frequency of formation of lenticular opacities on the time since exposure of the animals to protons for these three dose rates. Calculations showed that in mice of the first group (0.18 Gy/min) lenticular opacities appeared at a rate of $1.1\pm0.2\%$ per week, in mice of the second group (1.8 Gy/min) they appeared at a rate of $1.6\pm0.2\%$ per week, and in mice of the third group exposed to protons at a dose rate of 18.0 Gy/min the rate at which lenticular opacities appeared was $1.9\pm0.2\%$ per week.

A similar regularity was found in the analysis of the results of an experiment in which mice were exposed to 645-MeV protons at doses of 0.5, 1.0, and 2.0 Gy with dose rates of 0.7 and 7.0 cGy/min (Table VI). Analysis of the dose dependences of the frequency of lenticular opacities in mice exposed to 645-MeV protons revealed the following. For all observation times the change in this characteristic calculated per unit dose is more significant, the greater the dose rate N of the radiation effect. In particular, for observation times of 8, 25, and 40 weeks the increase of the frequency of lenticular opacities as the dose is increased to 1 cGy is 0.06, 0.22, and 0.34% if $N=0.7$ cGy/min and 0.15, 0.41 and 0.65% if $N=7.0$ cGy/min.

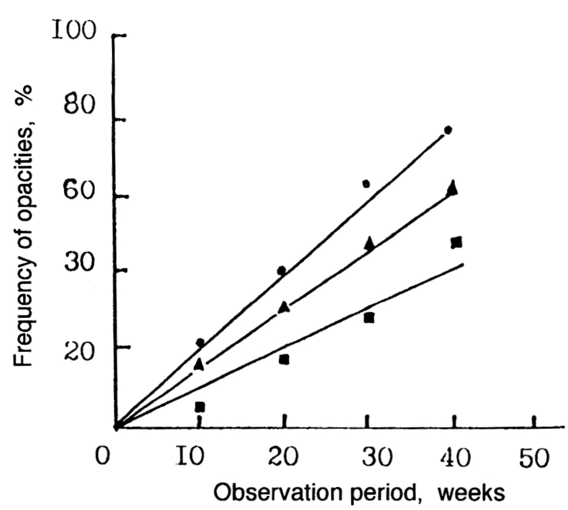

FIG. 8. Dependence of the frequency of lenticular opacities in mice on the time since exposure to 645-MeV protons at a dose of 4 Gy for dose rates of 0.18 (■), 1.8 (▲), and 18.0 (●) Gy/min.

TABLE VI. Rate of appearance (v) of lenticular opacities in mice exposed to 645 MeV protons at various doses and dose rates.

Dose power, cGy/min	Dose, Gy	ν, % per week
	0.5	0.40
0.7	1.0	0.55
	2.0	2.35
	0.5	0.85
7.0	1.0	1.55
	2.0	3.10

Thus, the dose and dynamical characteristics of the development of lenticular opacities in animals exposed to 645-MeV protons depend directly on the radiation dose rate.

Comparison of the biological effects of short- and long-term exposures of guinea pigs to gamma rays at different dose rates showed that disturbances in the animal organism develop earlier in the case of long-term exposure than for short-term exposure. One reason for the difference between the effects of long- and short-term exposure to radiation is the difference between the cell lifetime and the duration of the exposure. It is thought that differences in the "stability" to long-term exposure of different cells might be related to the point in the cell cycle at which the dose is received. On the other hand, weakening of prolonged exposures may be determined by the role played by recovery processes occurring during the exposure to radiation. As the duration of the exposure is increased, the fraction of radiation damage repaired during the exposure must grow.[31,32]

Structures of the eye in the fetal stage are extremely sensitive to radiation and depend on the dose rate. Experiments on rats exposed to radiation on the 11th day of pregnancy showed that there is a high frequency of anomalous eyes of various types among the descendents when the x-ray dose is above 50 rad. For exposure at a dose of 100 rad with dose rates of 0.1, 2.0, 3.3, 5.0, 10.0, 25.0, and 47.0 rad/min, the authors found a rapid increase in the frequency of damaged eyes in animals exposed to radiation in the prenatal stage at dose rates of 3.3 and 10.0 rad/min. Further increase of the dose rate to 47.0 rad/min did not lead to any significant increase of the effect.[33]

Frequency of formation of lenticular opacities after fractionated exposure

To study processes of post-radiation recovery in the crystalline lenses of laboratory animals, we performed experiments in which mice were exposed to protons of energy 50 and 645 MeV. Here we used the technique of comparing the magnitudes of effects observed after one and two exposures for the same total dose. We also studied the effect of the time interval between the two fractions on the dynamics of the formation of lenticular opacities in mice exposed to ^{60}Co gamma rays.

The results of studies of the cataractogenic activity of 645-MeV protons[19] showed that 35 weeks after a single exposure to protons at a dose of 6 Gy the frequency of lenticular opacities reached 100%. The data obtained in fractionated exposure to gamma rays showed that during a 30-week period after exposure the frequency of lenticular opacities for

TABLE VII. Frequency of lenticular opacities in mice at various times after single and fractionated exposure to 50-MeV and 645-MeV protons and x rays with 7 days between equal fractions.

	654-MeV protons		50-MeV protons		X rays	
Observation time, weeks	Dose, Gy	Frequency of opacities, %	Dose, Gy	Frequency of opacities, %	Dose, Gy	Frequency of opacities, %
20	2.0	29.3±5.9				
	1.0+1.0	16.1±3.8*				
	4.0	57.5±5.1				
	2.0+2.0	37.8±5.6*				
	6.0	77.9±4.4	6.0	11.3±4.0	6.0	12.4±3.8
	3.0+3.0	91.4±4.7	3.0+3.0	10.0±3.1	3.0+3.0	7.7±2.8
30	2.0	43.3±6.5				
	1.0+1.0	27.5±4.7*				
	4.0	85.9±4.1				
	2.0+2.0	69.0±5.3*				
	6.0	94.6±2.6	6.0	68.4±7.5	6.0	100.0
	3.0+3.0	94.1±3.9	3.0+3.0	83.3±4.4	3.0+3.0	97.2±1.9
40	2.0	92.0±3.5				
	1.0+1.0	34.8±5.1*				
	4.0	100.0				
	2.0+2.0	96.1±2.3				
	6.0	100.0	6.0	100.0	6.0	100.0
	3.0+3.0	92.0±3.0	3.0+3.0	83.9±3.3	3.0+3.0	100.0
50	2.0	81.7±5.2				
	1.0+1.0	72.8±4.9				
	4.0	100.0				
	2.0+2.0	96.1±2.2				
	6.0	100.0	6.0	100.0	6.0	100.0
	3.0+3.0	89.5±7.0	3.0+3.0	96.0±2.3	3.0+3.0	100.0

*The differences in the effects of single and fractionated exposure are statistically reliable.

all the time intervals (3, 7, 14, and 30 days) used between exposures by equal fractions (3 Gy, 2 times) was lower than after a single exposure. In other words, fractionation of the gamma-ray dose increases the latency period for the formation of lenticular opacities. However, this effect is gradually smoothed out 40 weeks after exposure to gamma rays. The duration of the time interval between the separate fractions of radiation has no significant effect on the frequency of lenticular opacities in laboratory animals. A time interval of 7 days between exposures is quite sufficient for repair processes for post-radiation damage to appear in the epithelium of the crystalline lens, if they do indeed take place. Experiments with exposure of mice to 645-MeV protons in two different fractions for total doses of 2, 4, and 6 Gy and also to 50-MeV protons for a total dose of 6 Gy confirmed the conclusion that fractionation of the dose retards the formation of lenticular opacities up to a certain time after the exposure. In particular, for fractionated exposure to 645-MeV protons the frequency of lenticular opacities 30–45 weeks after exposure was 1.5–2 times lower than in the case of single exposure at the same dose levels (Table VII).

At later times (50 weeks or more) after exposure the differences in the effects of fractionated and single exposure were statistically unreliable. In addition, no differences were found between the effects after fractionated and single exposure at a dose of 6 Gy. However, the development of a mature cataract after fractionated exposure to protons was delayed by 14 weeks. A similar effect has been observed after fractionated exposure to x rays, but the delay in the development of a mature cataract in this case was not as long (5 weeks). The final effects of fractionated and single exposures were in practice the same ($P \geq 0.05$).

Fractionated exposure of mice to 50-MeV protons at a total dose of 6 Gy led to a delay in the development of lenticular opacities in the early stages. For these animals, at 70 weeks after exposure to radiation only the first and second stages of development of lenticular opacities were observed, while for animals subjected to a single exposure at the same dose, development of the third stage of a cataract was observed after 65 weeks in 7% of the cases.

Thus, after fractionated exposure of mice to 50-MeV and 645-MeV protons and also to x rays, it is probable that post-radiation recovery processes occur whose rate and completeness depend on the dose and on the dose rate. Variation of the proton energy in the range 50–645 MeV does not significantly affect the rate and completeness of the repair processes in the crystalline lens. Fractionation of the proton dose tends to retard the formation process and reduce the frequency of lenticular opacities in mice by a factor of 1.5–2 in relation to single exposure at the same doses, as occurs in exposure to standard radiation. However, later in the life of the animal (actually, near the end), the differences in the frequency of lenticular opacities disappear.

The effect of reduction of the frequency of formation of lenticular opacities has also been observed in fractionated exposure of mice to x rays[34] and rats to x rays or 20-MeV and 100-MeV protons.[35] As the LET of the radiation grows, the effect of reduction of the frequency of formation of lenticular opacities disappears. For example, in experiments using mice of the line CB_6F_1 exposed to 225-MeV carbon ions with high LET at doses of 0.4, 0.8, and 1.2 Gy, it was shown that fractionation of the dose has no effect on the cataractogenesis.[36] In the case of exposure of rats to argon ions of energy 570 MeV, fractionation of the dose not only did not lower the cataractogenic activity of heavy charged particles, but it induced a dose-dependent cancellation of the latency period of formation of lenticular opacities.[37] Research on the cataractogenic activity of accelerated iron ions is of great interest. In experiments with exposure of animals to iron ions of energy 600 MeV, it has been found that fractionation of the dose in this case leads to an increase in the frequency of formation of lenticular opacities.[38]

The LETs and cataractogenic action of various types of radiation

It is well known that most radiobiological effects arising from highly ionizing radiation reveal a marked dependence on the LET. However, at the level of late post-radiation pathology this dependence is not always very obvious. In experiments with exposure of laboratory animals (mice, rabbits, monkeys) to accelerated neon, carbon, argon, and iron ions of various energies, a clear dependence of the cataractogenic activity of charged particles on their LET has been found (Table VIII). We see that the RBE coefficients are functions of the LETs of the types of radiation studied. The highest values of the RBE coefficients were obtained for argon and iron ions. The maximum values of the RBE coefficients are usually reached at a low dose level.[27] The RBE coefficients of argon ions calculated according to the criterion of cataractogenic effectiveness were 3–5, while for carbon and neon ions they were only slightly greater than 1 (Ref. 39). The effectiveness of 0.6–0.9 Gy doses of argon ions is close to that of a 3.0-Gy dose of x rays, and a 0.3-Gy dose of argon ions is comparable to a 1.5-Gy dose of x rays.

As seen from Table VIII, in spite of the low values of the LETs, the RBE coefficients of 3-GeV and 9-GeV protons and also of helium ions of energy 4 GeV/nucleon are fairly large. One of the main reasons for the high effectiveness of such radiation is nuclear interactions, which lead to the formation of secondary radiation with higher LETs than the primary radiation. Calculations show that as the energy of the charged particles increases, the contribution to the dose from secondary radiation increases.[44] The contribution of secondary radiation in a beam of helium ions of energy 4 GeV/nucleon varies from 6 to 13%, depending on the phantom thickness. It is created by a flux of secondary charged particles making up from 0.4 to 10% of the flux of the primary radiation.[11]

It is important to note that for higher values of the LETs of charged particles, the lenticular opacities mature more intensively.[39] In addition, increase of the dose and the LET of the radiation tends to shorten the latency period for lenticular opacities to develop.

TABLE VIII. Dependence of the RBE coefficients on the LETs of heavy charged particles.

Radiation type and energy	LET, keV/μm	Dose, Gy	Biological object	RBE coefficient	Ref.
p, 50 MeV	1.25	1.0–6.0	mice	1.0	40
p, 160 MeV		15–100	monkeys	0.94–1.19	41
p, 645 MeV	0.25	1.0–6.0	mice	1.0	17
p, 3 GeV		0.85–57.0	rabbits	0.55–2.0	25
p, 9 GeV	0.23	0.25–5.0	mice	1.3–2.4	24
^{4}He, 4 GeV/nucleon	0.88	0.5–4.0	mice	1.2–2.6	18
^{20}Ne, 365 MeV/nucleon	35.0	0.05–5.0	rabbits	2.0	42
^{40}Ar, 530 MeV/nucleon	90.0	0.05–5.0	rabbits	3.5	
^{56}Fe, 460 MeV/nucleon	223.0	0.05–5.0	rabbits	4.5–5.0	
^{20}Ne, 365 MeV/nucleon	35.0	1.4–12.8	rabbits	2.07–2.22	43
^{40}Ar, 530 MeV/nucleon	90.0	0.7–8.1	rabbits	3.28–3.61	
^{56}Fe, 600 MeV/nucleon		0.05–1.6	mice	40.0	27
^{12}C, 400 MeV/nucleon	10	0.05–9.0	mice	1.0	39
^{20}Ne, 425 MeV/nucleon	30	0.05–9.0	mice	1.0	
^{40}Ar, 570 MeV/nucleon	100	0.05–9.0	mice	3–5	
^{12}C, 300 MeV/nucleon	12.65	0.03–0.5	mice	1–66.7	26

The effect of age on the frequency of post-radiation lenticular opacities

The sensitivity of the crystalline lens to radiation to a large extent depends on the age of the laboratory animal or human. Independently of the type of radiation, the highest frequency of lenticular opacities is seen for the youngest animals. In experiments on mice exposed to x rays at a dose of 300 rad, the crystalline lens of animals of age 1–3 days was the most sensitive to exposure.[45] By the time they were 5 days old the resistance of the mice was maximal, and then high sensitivity increased up to 5–7 weeks, after which it again decreased. The reasons for this wave-like sensitivity of the crystalline lens to radiation are not yet understood. Analysis of the dynamics of the development of the capsule of the crystalline lens has not made it possible to explain the mechanisms of differences in the sensitivity of the crystalline lens of mice of different ages to radiation.

Large laboratory animals of a young age are also highly subject to the development of clouding of the crystalline lens.[28] It was found that the number of early cataracts was higher for rabbits subjected to localized exposure to neon ions at a dose of 9 Gy (LET=425 MeV/nucleon) at an age of 8 weeks, but the development of late cataracts and loss of vision occurred earlier than for rabbits exposed during the second half of their life.[46]

Morphological studies of the cells of the epithelium of the crystalline lens in rabbits, frogs, and mice of various ages after localized exposure of the eyes to x rays at doses of 20–50 Gy have shown that among rats, 4-week-old animals were the most sensitive to the development of fragmentation of the cell nuclei in the equatorial epithelium of the crystalline lens. The appearance of the same amount of damage in older animals required considerably larger doses of x rays.[47] Meanwhile, in spite of the fact that for young animals the damage to the crystalline lens developed earlier, the lenticular opacities matured more slowly in later years.[46,48] Deep destructive damage of not only the crystalline lens but also other structures in the eye developed in the descendents when pregnant female dogs were exposed to ^{60}Co gamma rays at doses of 125 and 435 rad at various times after fertilization; they also developed in the newborn puppies. It is reported that the eyes of dogs are most sensitive to radiation on the 28th and 55th days in embryo and on the second day after birth.[49]

Here we should make note of the high frequency of initial clouding of the crystalline lens (24.5%) in children of ages 4–6 who live in the countryside in areas exposed to radioactive contamination as a result of the accident at the Chernobyl nuclear power plant.[50] It is not yet known whether this clouding will develop further and lead to deterioration of vision.

Thus, age is of primary importance in the development of radiation-induced clouding of the crystalline lens.

Radiation-induced cataractogenesis in humans

The crystalline lens of a human, as in other mammals, is one of the structures most sensitive to radiation. At the same time, its sensitivity to radiation is no higher than that of laboratory animals. The minimum cataractogenic dose of low-ionizing radiation for humans varies from 2.0 Gy, according to the data of Refs. 34 and 51, to 4.0 Gy according to other data (Refs. 52–54). Most of the information on radiation-induced cataracts in humans has been obtained by studying the survivors of the atomic bombing of Hiroshima and Nagasaki.[55] According to calculations based on these observations, the threshold for effects from low-LET radiation lies in the range 0.6–1.5 Gy (Ref. 4). Further investigation and analysis of the data on the relation between the action of ionizing radiation and the development of cataracts in people who survived the atomic bombing showed that the contribution of neutrons to the total radiation dose at Hiroshima was 4.2 times higher than at Nagasaki. Taking into account the 1986 revision of the estimated individual radiation doses, the risk of cataract development became 1.6 times higher than when the doses calculated in 1965 were used.[56] In occupational exposure to ionizing radiation (small doses extending over very long time periods), the dose of low-ionizing radiation which can lead to the development of lenticular opacities with damage to vision must be about 8 Gy

(Ref. 5). The authors of Ref. 57 report that radiation-induced cataracts are unavoidably formed for a total dose of more than 40 Gy, received during treatment of tumors of the eyeball by x-ray therapy and implantation of radioactive radon and gold. Of 38 patients, 18 developed a radiation-induced cataract 3–11 years after treatment.

Analysis of the results of a 30-year study of the health of victims of the atomic bombing in Japan reveals differences in the degree of expression and frequency of development of cataracts, depending on the radiation dose and on the age of the victim. Among the people exposed to a dose of ~5 Gy in Hiroshima, a radiation-induced cataract has been diagnosed in 70–98% of the cases. As the dose decreases the frequency of lenticular opacities strongly decreases, and for doses of order 0.2–0.025 Gy cataracts did not develop. Radiation-induced cataracts are encountered in 55.6% of the cases among the inhabitants of Hiroshima exposed in early childhood to a dose of more than 4.5 Gy.

Information has recently become available on the development of radiation-induced lenticular opacities in people exposed to radioactive contamination as a result of the accident at the Chernobyl nuclear power plant, especially children.[50] Also among adults, a significant fraction of eye pathologies are cataracts.[59] The total dose of gamma rays in the areas which have been studied did not exceed 7 rem according to the official data. There is also other information about various aspects of the development of radiation-induced cataracts in humans.[60,61] However, these data cannot be used directly to estimate the risk of cosmic rays. They only supplement the information obtained from experiments on animals exposed to heavy ions at accelerators. It is well known that in interplanetary space flights, astronauts can be subjected to short exposures with relatively high dose levels of high-energy radiation from solar flares, and also small doses over a long time period of heavy nuclei with various LETs from galactic cosmic radiation.[62]

On the basis of the results of experiments involving large laboratory animals, in particular, rabbits exposed to standard radiation, it is reasonable to suggest a linear dose–effect dependence for doses in the range 0.5–10 Gy (Ref. 35). The same dependence is characteristic in the case of small laboratory animals exposed to electromagnetic radiation. There are some differences in the quantitative aspects of the cataractogenic effect. However, accelerated charged particles induce considerably more severe damage at the molecular, cellular, and tissue levels than low-ionizing radiation (Refs. 62–66). Obviously, there is also a corresponding increase in the risk of developing lenticular opacities at late times after exposure to heavy charged particles. Under these conditions, the best method of estimating the risk of development of radiation-induced cataracts in humans is to obtain the required information for model biological systems and extrapolate it to humans. Here the unavoidable question is, just how well justified is this extrapolation? This question is so important that it requires special consideration and lies outside the scope of this review. Here it is appropriate to note again that experiments on animals are the only way of obtaining the objective information needed to understand the mechanisms of the effect and to estimate the radiation risk of heavy charged particles to humans. Moreover, the crystalline lenses of rats, rabbits, dogs, monkeys, and humans have comparable sensitivity to low-ionizing radiation in forming lenticular opacities,[43] while the crystalline lenses of mice are more sensitive to x rays than those of humans.[67] Nevertheless, on the basis of the results which have been obtained, it can be stated that charged particles with high LETs will pose a considerably higher risk of damage to the crystalline lens for humans than does standard radiation.

CONCLUSION

The exploration of outer space has not only intensified the development of new approaches in the radiobiology of forms of ionizing radiation which were not well known before, but has also presented the problem of developing scientifically justified approaches to estimating the radiation risk of cosmic rays for spacecraft crews and life-support systems. In addition, the types of ionizing radiation obtained using accelerators are finding more and more applications in medicine and other fields of human activity.

The presence of charged particles in cosmic rays can seriously hinder space flights outside the Earth's magnetosphere. It has been established that heavy particles interacting with biological tissues possess certain special properties: by creating a high ionization density in a limited region of the tissue, where the dose can reach several tens of grays, they cause a cell to die. Observation of solar bursts by astronauts[68,69] and experimental and clinical studies on subjects[70] show that the possibility of heavy charged particles of cosmic rays acting on the structures of the human eye during space flights is very real. Radiobiological studies have shown that the risk of developing lenticular opacities, a late consequence of radiation, is very high. The late-radiation pathology of the crystalline lens can be judged on the basis of observations of the victims of the atomic bombing in Japan, the victims of the Chernobyl accident, and also cases of exposure to ionizing radiation in occupational situations. Although tumor-forming processes are more dangerous in terms of risk to human health at long times after exposure to ionizing radiation, late degenerative processes unrelated to tumors, including cataract formation, also present a serious problem. While not presenting a direct threat to human life, they certainly lower the quality of life. Moreover, in spite of the great practical importance of existing experimental–clinical observations, their results have little application to the problem of estimating the radiobiological risk of cosmic rays and developing measures to ensure radiation safety in space flights. The main source of information about the effect of heavy charged particles on the cells and tissues of mammals is research at charged-particle accelerators. The studies which have been carried out have shown that heavy charged particles are distinguished by higher biological effectiveness in their action on the crystalline lenses of laboratory animals than low-ionizing radiation. This is manifested as an increase in the frequency of developing lenticular opacities and a decrease of the duration of the latency period before they appear. The developing disturbances are functions of the dose and the time since the exposure to accelerated charged particles. In exposure to low-LET radiation the dose–effect dependence is nearly linear. In the exposure of small laboratory animals to heavy charged particles the dose–effect curve emerges onto a plateau for doses of about 2 Gy.

The latency period of forming lenticular opacities in humans and large laboratory animals after exposure to relatively low doses of ionizing radiation can last for many years, while in experiments on small laboratory animals it lasts for weeks. In general, it can be assumed that the duration of the latency period for lenticular opacities to develop is inversely proportional to the size of the radiation dose. Low doses of densely ionizing radiation are especially effective. This is suggested by the significant increase of the RBE coefficients of accelerated charged particles as the size of the dose decreases. The mechanisms on which this phenomenon is based require careful explanation. An important factor in the development of clouding of the crystalline lens in mammals is the age at the time of exposure to ionizing radiation: the younger the animal, the earlier and more serious the damage to the crystalline lenses of its eyes.

Special studies indicate that the dose rate and manner in which the dose is received play an important role in recovery from disturbances of the transparency of the crystalline lens after exposure to rarely ionizing radiation. A decrease of the dose rate of ionizing radiation leads to an increase of the duration of the latency period for lenticular opacities to develop, and retards and inhibits their maturing. A characteristic feature of the effect of such charged particles on the crystalline lens of the eye of higher animals is the absence of any effect of fractionation of the dose.

It should be noted that clouding of the crystalline lens causes significant damage to the health of a human when it reaches the stage where it makes vision poor. It is known that the insignificant radiation-induced clouding of the crystalline lens seen only in highly skilled research does not lead to damage of sight, does not progress with time, and can disappear. This is true for exposure to both rarely and densely ionizing radiation.

In cosmic biology and medicine the chronic effect of small doses of charged particles is quite interesting, but so far the study of this subject remains problematic.

The development of lenticular opacities induced by radiation of various types does not manifest any clinicomorphological features. The differences are all quantitative.

Heavy charged particles are distinguished by higher cataractogenic activity than standard radiation. The values of the RBE coefficients depend on the size of the radiation dose and on the time since exposure.

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