Experimental studies of the biological effectiveness of accelerated charged particles at relativistic energies

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The publications and experimental studies on the relative biological effectiveness of accelerated helium and carbon ions of energy 4 GeV/nucleon, carbon ions of energy 320 MeV/nucleon, and protons of energy 9 GeV are reviewed. The studies were carried out using the synchrophasotron at the JINR High Energy Laboratory. Small laboratory animals and lymphocytes of peripheral human blood *in vitro* were used in the experiments. The mortality of the experimental animals, the cytological, cytomorphological, and cytogenetic perturbations in the mammalian cells, and the cataractogenic and carcinogenic effects of the radiation were studied. It was found that the relative biological effectiveness of accelerated charged particles is highest according to most of the criteria used. The coefficients describing the relative biological effectiveness varied in a wide range as a function of various physical and biological factors.

INTRODUCTION

The radiation risk in outer space arises from three main sources: galactic cosmic rays, the radiation belts of the Earth, and solar flares. In addition, nuclear energy installations on board spaceships can present a certain risk. Galactic cosmic rays contain heavy nuclei, in fact, nuclei from the entire periodic table, but they are mainly composed of high-energy protons ($\sim 80\%$), α particles ($\sim 13\%$), and light and intermediate nuclei. When galactic cosmic rays pass through the spaceship shielding and fall on the body of an astronaut, secondary radiation with large linear energy transfer (LET) arises, and can make up 50–100% of the dose. The inner radiation belt of the Earth consists primarily of high-energy protons, whose spectrum can be represented as a power function with exponent in the range from 1.4 to 1.8, depending on the segment of the proton energy spectrum in question. The outer radiation belt is made up of electrons and low-energy protons. There also exists an artificial radiation belt of the Earth arising as a result of high-altitude nuclear explosions. It consists of electrons with energy up to 7 MeV (Ref. 1). The particle radiation of solar flares also is mainly composed of protons and α particles. The energy content of the particles and the intensity of the radiation of the solar flares are different in each case. Therefore, taking into account these radiation sources, during an interplanetary expedition an astronaut's health will be at risk owing to low levels of radiation during flight in the near region of outer space, high-intensity radiation when crossing the Earth's radiation belts, radiation when flying in highly oblique orbits and when exiting from the spaceship to go into free space, and also a constant level of radiation of relatively low intensity when inside the spaceship and radiation from nuclear installations on board. It should be noted that in the space flights which have been made up to now the cosmic radiation has not presented any real threat to the astronauts' health, owing to the relatively low flux [~ 2.5 particles/$(\text{cm}^2 \cdot \text{sec})$]. Nevertheless, during long flights astronauts can be exposed to radiation from intense solar flares.

For a flight lasting about a year the galactic cosmic-ray dose can reach 100 rem (Ref. 1), while in solar flares the radiation dose inside the spaceship can prove fatal to living organisms.[2] Such radiation levels are a serious problem for future interplanetary flights. Several variants of physical shielding have been proposed to prevent possible injury. In flights lasting up to 3 years the mass of the shielding for the living quarters of an interplanetary spaceship reaches values making flight impossible. It is therefore of practical importance not only to study the biological action of cosmic radiation, but also to look for effective pharmacological means of preventing and treating radiation injuries due to various types of radiation.

Estimating the radiation risk in outer space is a complicated problem. It is difficult to solve not only because of the specific conditions of outer space, but also because of material and technological limitations. The complex content of cosmic radiation, the broad energy spectrum of the particles in it, and the possible modifying role of other factors in space flight (such as weightlessness, overwork, and so on) make it difficult to adequately assess the danger presented by cosmic radiation. These complications can to some degree be avoided by carrying out experiments at charged-particle accelerators, bombarding biological objects with heavy charged particles (HCPs) which are the analogs of specific components of cosmic radiation. It should be noted that experiments on the biological effectiveness of HCPs have been carried out at the Institute of Biomedical Problems of the USSR Ministry of Health for about 30 years. Detailed information about various aspects of the problem has been obtained. The basic data have been communicated in several monographs and dissertations. The data are noteworthy because of the originality of the approaches, the diversity of investigation methods, and the wide range of charged-particle energies and LETs. They have made it possible to formulate fundamental regulari-

ties of the biological action of densely ionizing radiation, and have served as the basis for criteria for estimating the radiation risk of cosmic radiation. Analysis of the results of the experiments using biological objects of various levels of organization and evolutionary development, including large laboratory animals, indicates that the perturbations caused by high-energy protons and the standard radiation (180 keV gamma or x rays) are identical, and that the relative biological effectiveness (RBE) coefficients of protons with energy from 50 to 645 MeV are equal to unity or differ from it only insignificantly. In contrast to proton radiation, in the case of heavy ions the RBE coefficients reach their maximum values in the range of LETs from 100 to 200 keV/μm, and decrease for higher LETs. Other features of the biological effects of HCPs which more or less influence the value of the RBE coefficients have been revealed, in particular, the suppression of radiation-perturbation repair processes, diminishment of the oxygen effect, the weak modifying properties of most of the known chemical radiation protectors, and so on. In recent years studies have been carried out of the biological effect of accelerated charged particles of relativistic energies: 9-GeV protons, helium and carbon ions of energy 4 GeV/nucleon, and also carbon ions of energy 320 MeV/nucleon. The main results of these studies are given in this review. They broaden our picture of the radiation biology of HCPs, and are of practical and theoretical value for understanding the mechanisms of the biological action of accelerated charged particles, for estimating the radiation risk of cosmic radiation, for solving problems of the normalization of the radiation effects, and for developing measures of medical and biological nature.

1. FEATURES OF THE BIOLOGICAL ACTION OF ACCELERATED CHARGED PARTICLES IN THE ACUTE PERIOD OF RADIATION INJURY

Sources of ionizing radiation

In order to carry out radiobiological experiments using the principal direction of the slow-extraction system at the JINR synchrophasotron, special conditions were created for irradiating biological objects.[3,4] Quadrupole-lens doublets of area up to 30 cm^2 were used to shape the radiation field such that the nonuniformity over a dose was $\pm 10\%$. The uniformity of the dose field at the location of the radiobiological experiments was determined by means of a remote setup with cylindrical ionization chambers. Here the contribution of the accompanying radiation to a dose was less than 0.5%, and less than 5.0% over a dose. It was controlled by means of a semiconductor detector. The dosimetry was carried out using condenser ionization chambers with a spherical volume of 0.1 cm^3. The efficiency of ion collection in this chamber was at least 95% at the maximum dose intensities. The charge leakage was no more than 5.0% per day. The proton energy was 9 GeV (LET equal to 0.23 keV/μm), and the helium ion energy was 4 GeV/nucleon (LET equal to 0.82 keV/μm). The maximum intensity of the extracted helium ion beam was 10^{10} particles/cycle. Cycles of duration 450 msec were spaced 8 sec apart. The particle beam extracted from the accelerator chamber had geometric dimensions of about 10×20 mm. The wider beam needed to irradiate small laboratory animals was obtained by shaping the initial beam using quadrupole-lens doublets. The widened beam had dimensions of 55×55 mm. The beam location and profile were recorded by multiwire proportional chambers. The uniformity of the radiation field was determined by means of a coordinate device and gap ionization chambers. The irradiation process was monitored by a transmitting, plane-parallel two-section chamber with a working-volume diameter of 190 mm, equal to the diameter of the ion beam pipe.

Radiobiological experiments were also carried out in beams of carbon nuclei of energy 4 GeV/nucleon (LET equal to 7.6 keV/μm) with intensity of up to 10^8 particles/cycle, and with a lower energy of 320 MeV/nucleon (LET equal to 12.0 keV/μm) and intensity of up to 10^7 particles/cycle. The cycle duration was 9 sec for a pulse duration of up to 50 msec. For experiments using small laboratory animals (rats and mice) the beam was shaped by defocusing using quadrupole-lens doublets, with the beam dimensions again equal to 55×55 mm and nonuniformity over a dose equal to $\pm 10\%$. The contribution of the accompanying radiation was less than 1% of the integrated flux, and less than 5% over a dose. The absorbed dose was determined and monitored with an error of $\pm 10\%$. The characteristics of the dose fields included information on the composition and energy distribution of the secondary charged particles needed to estimate their contribution to the absorbed dose.[5]

Study of the relative biological effectiveness of radiation requires parallel study of the radiobiological effects of standard radiation, for which the International Commission on Radiological Protection (ICRP) recommends x rays. However, in practice the γ radiation of ^{60}Co or ^{137}Cs is used just as often. In our experiments the biological objects were irradiated with γ rays from ^{60}Co at the setup RKh-γ-30 or from ^{137}Cs at the setup "Svet."

Mortality of laboratory animals

The study of the interspecific radiation sensitivity of mammals is one of the most important problems of radiobiology. Among the characteristics used to describe it are the average lethal dose $LD_{50/30}$ or $LD_{100/30}$, i.e., the radiation dose causing the death of half or all the irradiated animals in a period of 30 days or some other period. The radiation sensitivity of various species of animals depends on many biological and physical factors and varies by about a factor of 10 (Ref. 6). The reasons for such great interspecific variations in the radiation sensitivity of mammals have not been clearly determined up to now.[7] On the basis of numerous experiments with irradiation of animals by electromagnetic radiation it has been assumed that for doses of up to 10 Gy animal death occurs as a result of bone-marrow syndrome, and that the survival time of various species of mammals after irradiation is a function of the dose. This feature of the development of radiation injuries is also seen in the action of protons with energy in

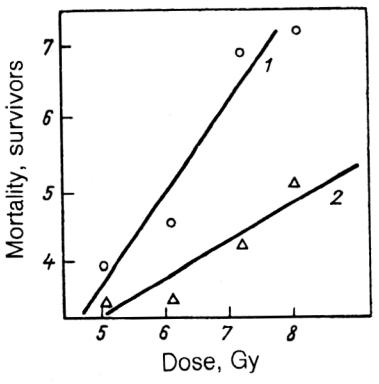

FIG. 1. Mortality of mice as the number of survivors 30 days after irradiation by (1) helium ions with energy 4 GeV/nucleon and (2) γ radiation.

the range 50–660 MeV (Ref. 8). The RBE coefficients of protons in this energy range obtained by studying the mortality of laboratory animals varied from 0.7 to 1.0. This has led to the idea that protons and α particles accelerated to higher energies will have the same or even lower biological effectiveness in relation to the standard radiation.[9] However, the results of a study of the mortality of mongrel rats irradiated by protons of energy 9 GeV and mice of the line $F_1(\text{CBA} \times \text{C}_{57}\text{BL}_6)$ irradiated with helium ions of energy 4 GeV/nucleon indicate that the RBE of these radiations is higher (Fig. 1). The approximation of the dose-effect dependence by a linear equation ($y = a + bx$) agrees with the experimental data fairly well. The values of the criterion F exceed the corresponding values for the confidence coefficient $1 - \alpha = 0.95$ and the corresponding numbers of degrees of freedom. The $\text{LD}_{50/30}$ for mice after irradiation by helium ions is 5.2 Gy, and after irradiation by γ rays it is 6.2 Gy. For rats irradiated by protons $\text{LD}_{50/30}$ is 5.3 Gr, and for irradiation by γ rays it is 6.9 Gy. According to the Student criterion, the difference between $\text{LD}_{50/30}$ for the irradiation of mice by helium ions and γ rays and also for the irradiation of rats by protons and γ rays should be considered reliable. The RBE coefficient for helium ions is 1.2, and for protons it is 1.3. The higher biological effectiveness of helium ions and protons of relativistic energies is also confirmed by another criterion. If the parameter b of the linear equation corresponding to the slope is interpreted as the mortality level per unit dose (on a logarithmic scale), then the larger the parameter b, the higher the effectiveness of the radiation regarding animal mortalities per unit dose. The RBEs for the two types of radiation can therefore be expressed as the ratio $b(\alpha)/b(\gamma)$. For helium ions this ratio compared with γ radiation is 1.2, while for protons it is 1.9 (Ref. 10). Therefore, in spite of the relatively low LETs of helium ions and protons at relativistic energies, the biological effectiveness of these particles is higher in relation to the standard radiation.

Cytological and cytogenetic perturbations in mammalian cells

In experiments using cultured mammalian cells[11–13] and also vegetable objects[14] it has been established that the RBE coefficients of nitrogen ions with energy 3.9 GeV/nucleon varied, according to various indicators, from 1.0 to 6.0 for mammalian cells and from 2.0 to 18.5 for objects of vegetable origin.

By studying the survival rate of spermatogenic cells of rats and the frequency of lenticular opacities in rabbits, RBE coefficients of 3-GeV protons equal to 1.31–1.50 and 1.0–2.0, respectively, were obtained for these two indicators.[15,16] The results of these studies revealed a significant dependence of the RBE coefficients on various biological and physical factors. However, the data obtained are not sufficient for estimating the radiation risk from radiation of energy comparable to that of cosmic-ray nuclei.

Study of the dependence of the number of karyocytes of the bone marrow of mice on the dose of 9.2-GeV protons, 4.6-GeV/nucleon helium ions, and γ rays at early times after irradiation[17] has shown that these types of radiation lead to a uniform, dose-dependent decay of nucleus-bearing cells. Cells undergoing regeneration experience strong perturbations of their genetic apparatus, which are manifested as a decrease of the reproductive activity and the formation of cells with various types of chromosomal abnormality. When animals are irradiated by accelerated particles at doses above 3 Gy, the cellular devastation of the bone marrow can reach extremes up to complete aplasia. The process of cell-structure devastation develops more intensively after the irradiation of animals by charged particles. The RBE coefficients of protons and helium ions calculated according to the criterion of 50% decrease of the number of karyocytes of mouse bone marrow 24 hours after the irradiation are 2.7 ± 0.9, and after 8 days they are 1.5 ± 0.3.

The action of the radiation leads to a significant increase in the number of cells with chromosomal perturbations. The curves for the dose-effect dependence obtained by studying the frequency and type of chromosomal abberation in bone marrow and cornea epithelium cells of mice and *in vitro* cells of Chinese hamsters and in lymphocytes of peripheral human blood irradiated by relativistic helium ions and protons have a linear segment up to doses of 2.0–2.5 Gy (Refs. 17–20). Beyond this the curve deviates from linearity in the direction of decreasing number of damaged cells, which is usually associated with the elimination of nonviable cells. These types of radiation are considerably more effective than γ radiation in the number of abnormal cells formed. In human lymphocytes irradiated by helium ions at a dose of 4.0 Gy the number of abnormal cells approached 100% (Ref. 20). The effectiveness of helium ions and protons according to the number of chromosomal perturbations in human lymphocytes *in vitro* was 1.5–2 times higher than in the case of γ rays. The higher biological effectiveness of charged particles is also indicated by calculations of the number of chromosomal abberations per abnormal cell and the number of perturbations per cell per unit dose (1 Gy). After the irradiation of lymphocytes by helium ions at doses of 0.5 and 4.0 Gy each damaged cell contained 1.73 and 4.40 abberations, respectively, and after irradiation by γ rays they contained

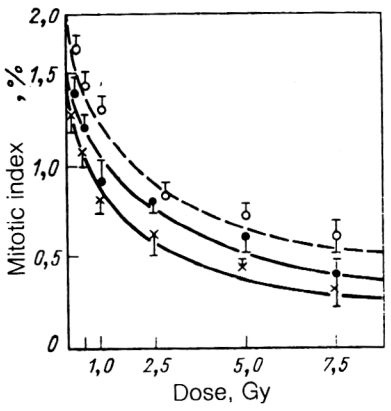

FIG. 2. Decline of the mitotic index in cells of the corneal epithelium of mice 24 hours after irradiation with γ rays (○), protons (●), and helium ions (×) (Ref. 17).

1.42 and 2.15. At the same helium-ion doses there were 0.346 and 1.045 abberations per cell per 1 Gy, while after irradiation by γ rays these values were 0.260 and 0.397.

The generation of chromosomal perturbations in mammalian cells irradiated *in vivo* and *in vitro* is accompanied by a decline in the mitotic cell activity which is stronger than for γ radiation. In particular, the mitotic index of bone marrow cells one day after irradiation by protons and helium ions at doses of 5.0–10.0 Gy did not exceed 20–30% of the control level.[17] The decline of the mitotic index of mammalian cells is also a function of the radiation dose (Fig. 2).

A characteristic feature of the biological action of relativistic charged particles is the higher yield of two-hit abberations. In epithelium cells of mouse cornea the bridge content was 3–6 times greater than the content of cells with fragments,[21] and in human lymphocytes the number of complex exchange abberations was 1.5–2 times greater than the number of paired acentric fragments.[20] A large number of exchange chromosomal abberations is, on the one hand, an indication of deeper injury of the genetic apparatus of mammalian cells after the action of relativistic radiation, and, on the other, it can be an indication of intensive repair of radiation perturbations of the chromosomes.

Owing to the extremely high sensitivity of the sex glands of mammals to radiation, they are convenient for studying the parameters describing radiation injuries by various types of ionizing radiation. The intense mortality of spermatogenic cells in the acute period of radiation injury leads to decrease of the testicle mass, which is fixed already 24 to 72 hours after the irradiation of animals by accelerated charged particles and the standard radiation at doses of 0.5–7.5 Gy. The decrease of the testicle mass progresses gradually, reaching a maximum by 30 days after the irradiation. The dose-effect dependence in this case has an exponential behavior. A similar dependence of the effect on the dose was established earlier in the irradiation of mice by helium ions of energy 230 MeV/nucleon, carbon and neon ions of energy 400 MeV/nucleon (Ref. 22), and also in the irradiation of rats by 3-GeV protons.[15]

Later there is gradual restoration of the gonad mass, and by 3 months after irradiation with γ rays or 6 months after irradiation with helium ions the masses reach the control values. Cytological analysis of the testicles of experimental animals in the early period after irradiation revealed a decrease in the number of spermatogenic cells at all stages of pubescence. The number of surviving spermatogonia decreases with increasing radiation dose. In all cases, spermatogonia of type B have the highest sensitivity to radiation. The LD_{50} of protons, helium ions, and γ radiation for spermatogonia of type B was 1.25 ± 0.2, 4.25 ± 0.4, and 6.3 ± 0.8, respectively. Analysis of the survivability of spermatogonia of type A and also of the intermediate type did not reveal any reliable differences after irradiation of animals by the three types of radiation. At the same time, the restoration processes in the testicles after irradiation by charged particles proceed at a slower rate. By 30 days after the irradiation of mice by helium ions at a dose of 2.0 Gy the number of spermatogonia of type B was $(67.0 \pm 8.6)\%$, while after γ irradiation their number had reached the control level by this time.[23] The radiation sensitivity of spermatogonia depends on the degree to which they are differentiated, which is closely related to the DNA synthesis activity.[24]

The radiation sensitivity of spermatogonia has a definite predictive value, since the spermatogonia ensure the continuity of the spermatogenic cycle throughout the entire reproductive life of the individual. In relation to this it is important to estimate the genetic risk of ionizing radiation, an indicator of which is the frequency of reciprocal translocations (RT). These are exchange abberations which in some cases can lead to unfavorable consequences, although in practice they do not hinder the development of the spermatogonia to maturity, when they are capable of fertilizing gametes with balanced genome. Analysis of the results of the experiments revealed a linear dose-effect dependence described by the expression $Y = (-0.104 + 1.60) \cdot 10^{-4} D$, $Y = (-0.25 + 2.25) \cdot 10^{-4} D$, $Y = (0.065 + 1.58) \cdot 10^{-4} D$, and $Y = (0.61 + 2.04) \cdot 10^{-4} D$, respectively, for γ rays, 9-GeV protons, and helium and carbon ions with energy 4 GeV/nucleon. Comparison of the regression coefficients made it possible to obtain the values of the RBE coefficients. They were 1.4 for protons, 1.0 for helium ions, and 1.5 for carbon ions.[25,26]

In Table I we give the experimental values of the RBE coefficients of helium ions and protons of relativistic energies obtained from various indicators of radiation injury. We see that the RBE coefficients of protons varied from 1.0 to 2.1, and those of helium ions varied from 1.0 to 3.8. The highest values of the RBE coefficients of helium ions were determined according to the 25% and 50% lowering of the nucleic acid concentration in peripheral blood cells of animals.[29]

Since 9-GeV protons and 4-GeV/nucleon helium ions have small LETs, the question arises of why the RBE coefficients for these types of radiation are higher. One of the main reasons for the larger damaging capability of protons

TABLE I. Experimental values of the RBE coefficients of helium ions of energy 4 GeV/nucleon and 9-GeV protons obtained by studying mutations during the acute period of radiation injury.

Biological object	Effect studied	RBE coefficients		Reference
		Protons	Helium ions	
Mice	Mortality, $LD_{50/30}$	-	1.2±0.1	[27]
Rats	the same	1.3±0.2	-	
Mice, epithelium of the cornea	Frequency of aberrant mitosis 24 hours after irradiation:			[18]
	damage at the 30% level	1.9±0.2	2.7±0.3	
	damage at the 50% level	1.8±0.2	2.6±0.3	
	72 hours after irradiation:			
	damage at the 30% level	2.1±0.1	2.2±0.2	
	damage at the 50% level	1.5±0.1	1.6±0.2	
	Lowering of the mitotic index 24 hours after irradiation	1.8±0.2	2.5±0.2	
	72 hours after irradiation	1.3±0.2	1.5±0.2	
Mice, sex cells	Survival of spermatogonia:			[23]
	type A	1.1±0.1	1.0±0.1	
	intermediate type	1.0±0.1	1.0±0.1	
	type B	2.0±0.2	1.3±0.1	
	Frequency of reciprocal translocations	1.1–1.4	0.7–1.2	[25,26]
Rats, sex cells	the same	1.7–2.0	1.3–1.8	
Lymphocytes of peripheral human blood	Frequency of aberrant cells	1.4±0.2	1.6±0.2	
	Number of paired fragments	1.3±0.2	1.4±0.2	
	Number of dicentric fragments and rings	1.4±0.2	1.8±0.2	
Erythrocytes of donated human blood	Electrophoretic mobility	-	1.0	[28]
Mice, erythrocytes of peripheral blood	Decrease of the level of nucleic acid synthesis by	-		[29]
	25%	-	3.8	
	50%	-	3.0	
	75%	-	1.5	
Rats, bone-marrow karyocytes	Total number of aberrant cells	-	1.8±0.2	[30]
	Total number of chromosomal aberrations	-	1.5±0 1	

and helium ions might be nuclear interactions, which lead to the production of secondary radiation with LET higher than that of the primary radiation. Calculations show that as the charged-particle energy increases the contribution of secondary radiation to the dose grows.[31] The contribution of secondary radiation in a beam of helium ions in our experiments varied from 6 to 13%, depending on the phantom thickness.[5] This contribution to the dose comes from secondary charged particles making up from 0.4 to 1.0% of the primary radiation.

An important factor determining the differences in the biological effectiveness of different types of ionizing radiation is the ability of cells to repair the damaged caused to them by the radiation. The increase of the radiation sensitivity of eukaryote cells with increasing LET of the radiation is thought to be related to a decrease in the repair of two-strand DNA damage relative to the repair of single-strand damage.[32,33] Analysis of the frequency and type of chromosomal abberations in mammalian cells after irradiation by relativistic protons and helium ions shows that a significant part of the resulting damage is two-hit damage.

When estimating the radiation effects of HCPs it is necessary to take into account factors unrelated to ionization of the medium and nuclear interactions. It has been established in experiments carried out on artificial Earth satellites that single heavy nuclei can damage biological structures at distances from the track which are larger than the range of δ-electron propagation in the medium. However, effects due to heavy charged particles turn out to be larger than the effects which would have been expected from the absorbed dose.[34] A possible reason for the observed phenomena might be acoustical or shock waves arising in the abrupt heating and change of the aggregate state of the matter in the charged-particle track.[35] The role of Vavilov–Čerenkov radiation, the intensity of which grows with increasing energy of multiply charged ions, is also not yet completely clear.[36]

2. REMOTE AFTEREFFECTS OF RADIATION INJURIES

Cytomorphological mutations of the neurons of the cortex in experimental animals

The first studies of the effect of accelerated charged particles on nerve tissue were performed to see whether such particles could be used to treat brain tumors.[37] Experimental studies using rats irradiated by a 10-GeV proton beam at a dose of 50 Gy revealed the development of hemorrhages, foci of necrosis and gliosis, and tissue destruction in the form of a channel along the proton beam path appearing 10 weeks after the irradiation. The low penetration power of protons of this energy was responsible for the brain damage being at the surface. Similar but more pronounced mutations of the brain and spinal tissue appeared in rabbits and goats irradiated by 185-MeV protons at doses of up to 400 Gy (Refs. 38–40). Proton doses of order 200 Gy on the spinal cord led to the development of progressive conductor disorders, and on the second day

after the irradition of rabbits at a dose of 400 Gy paralysis of the rear extremities and perturbation of the functions of the pelvic organs developed. Extensive necroses of the brain tissue with perifocal destruction and perivascular hemorrhages appeared in the rabbits and goats in the acute period after local irradiation by protons at doses of 200–400 Gy (Ref. 41). In these studies it was shown that the structural changes of the nervous-system tissue which develop depend on the absorbed proton dose, and that morphological changes develop earlier when the dosage is increased. In experiments on monkeys irradiated by a proton beam, a dose of 50 Gy was deemed to be tolerated by the nerve tissue, while a dosage of 100 Gy led to necrosis of the irradiated parts of the brain 1.5 to 2 months after the irradiation.[42] It should be noted that at the present time beams of high-energy protons are successfully used in our country for treating tumors of the hypophysis and in other locations. One third of the 6000 patients in the world have received proton radiation at the medical beams of the accelerators at Moscow, Dubna, and Leningrad.[43]

The first studies of the biological effects of protons in our country had a somewhat different focus. Along with radiological research, the main goal of these studies was to understand the effectiveness of new forms of radiation in order to understand the risk presented by cosmic rays. The single-stage and fractionated irradiation of dogs by 510-MeV protons at doses of 2.5–7.0 Gy led to the development of severe dystrophic mutations in various sectors of the brain.[44] The perturbations which developed were very similar to those arising after irradiation with x rays or γ rays. In addition, the dogs developed subarachnoidal hemorrhages and focal necroses of the brain matter which were usually not seen after irradiation by the standard radiation. It is significant that the mutations of the central nervous system (CNS) developing after repeated proton irradiations were more pronounced than in the case of a single irradiation of the same dose. The authors of Ref. 45 also saw more expressed signs of hemorrhagic diathesis in the acute period of radiation injury by protons of energy 126 and 510 MeV in the single and multiple irradiation of dogs (doses of 2.5–6.7 Gy), while other authors conclude that the dystrophic changes of the nerve and glial cells are identical in the acute stage of radiation sickness for animals irradiated by protons of energy 126 and 660 MeV (Ref. 46). Identical damage to the gray and white brain matter in the irradiated zone has been demonstrated clinically.[47]

Attempts were also made to estimate the number of nerve cells killed as a result of irradiation by heavy charged particles. In studies of the structural damage to neurons of the cortex, cells of the retina of the eye, and other tissues of pocket mice irradiated with neon ions (^{20}Ne) of energy 400 MeV/nucleon in doses of 0.1, 1.0, and 10.0 Gy, 2 to 3 weeks later necrotic mutations of the neurons were observed, with their number reaching a maximum 4 to 5 weeks after the irradiation and respectively amounting to 0.0005, 0.03, and 0.04% of the total number of cells for these three radiation doses.[48] For a neon-ion dose of 10 Gy structural changes of the retina of the eye, a peripheral analyzer of the CNS, were seen after 28 to 42 days. Taking into account the mutations in various organs and tissues of the experimental animals, the authors conclude that the dose of cosmic rays with similar characteristics which can lead to harmful consequences is greater than 0.1 Gy. However, this depends on the interspecific and individual radiation sensitivity of the animals. In experiments on amphibians with irradiation of the head by neon ions, structural mutations of the retina were observed also at doses below this level, while such damage to the retina is not seen after irradiation with x rays or helium ions at a dose of 0.5 Gy (Ref. 49). On the basis of this it is assumed that the incidence of a single heavy particle on the retinal membrane can damage it. This is the conclusion drawn by investigators who used light and electron microscopy to study the brain damage of Drosophila melanogaster irradiated by a beam of argon ions (^{40}Ar) of energy 4.8 MeV/nucleon with an ionizing-particle intensity between 6×10^4 and 8×10^7 particles/cm^2 (Ref. 50). Extensive fragmentation of the tissue and cysts appearing where the tissue was destroyed appeared 35 days after irradiation with the higher beam intensity. At lower charged-particle beam intensities at the level of one particle per two cells and one particle per 90 cells, swelling of the neuron cytoplasm and membrane fragmentation were observed. It is assumed that a single HCP can damage one or several nerve cells.

Study of the light-sensitive elements of the retinal membrane in Macaca mulatta monkeys locally irradiated with oxygen ions of energy 250 MeV/nucleon in the region of the Bragg ionization curve corresponding to its peak revealed the development of ischemic necroses and perturbation of the transmission accompanied by congestion phenomena.[51] The RBE coefficient of oxygen ions according to the criterion of formation of ischemia foci in the retina is 10.

The study of rabbit brains over a period of 5 years after irradiation by γ rays of ^{60}Co (LET equal to 0.3 keV/μm), argon ions (LET equal to 90 keV/μm), and neon ions (LET equal to 35 keV/μm) revealed a marked dependence of the development of necroses and degenerative mutations of the nerve tissue on the dose and LET of the radiation.[52] The relative biological effectiveness of HCPs also depends on the location of the irradiated object relative to the Bragg ionization curve. In particular, whereas in a single irradiation of experimental animals by accelerated neon and carbon ions obtained from the plateau of the curve the values of the RBE coefficients were 1.46 and 1.45, respectively, for irradiation at the Bragg peak the RBE coefficients were 1.86 and 1.48. For daily irradiation lasting 4 days with carbon and neon ions obtained at the plateau of the curve, the RBE coefficients were 1.31 and 1.8, while for the same particles at the Bragg peak the RBE coefficients were 1.95 and 2.18, respectively.[53]

In order to understand the quantitative regularities of the damaging effect of high-energy charged particles on tissue and cells of the brain we carried out experiments at the JINR synchrophasotron with the irradiation of animals at relatively low doses of 4-GeV/nucleon helium ions and 9-GeV protons, and also small fluxes and low doses of accelerated 4-GeV/nucleon and 320-MeV/nucleon carbon

TABLE II. Number of dystrophically mutated neurons of the outer granular layer of the sensomotor cortex of the large cerebral hemispheres in rats at various times after irradiation (Ref. 54).

Type and energy of radiation	Dose, Gy	Number of distrophically mutated neurons, %		
		1 month	2 months	3 months
Protons, 9 GeV	0,5	9,7±1,3	14,5±0,6	27,8±1,6
	1,0	16,2±2,5	20,4±2,2	35,6±1,5
	2.0	19,9±2,2	25,1±6,7	39,3±1,3
	4,0	26,8±3,2	30,5±2,5	45,0±1,2
Helium ions, 4 GeV/nucleon	0,5	9,4±1,3	12,6±1,9	21,8±0,9
	1,0	12,3±1,3	16,9±1,6	27,5±1,0
	2,0	19,2±2,2	24,1±2,2	34,6±0,6
	4,0	22,3±2,2	29,6±1,9	40,5±0,5
γ radiation of ^{60}Co	1,0	3,5±1,6	4,2±1,3	13.0±2,2
	2,0	5,4±5,4	6,1±2,2	18,0±3.8
	4,0	10,8±2,2	11,9±1,6	26,5±4,2
	6,0	18,1±2,5	20,6±1,6	30,4±2,8
Nonirradiated animals	—	2,0±0,6	2,3±0,6	1,7±0,6

ions (Refs. 54–57). Analysis of the degree of severity of dystrophic mutations of the neurons of the cortex of mice indicates that mammals are highly sensitive to heavy-charged-particle radiation. The severity of the structural neural mutations increases markedly with increasing radiation dose and duration of the post-irradiation period (Table II). Protons and helium ions at relativistic energies have a higher damaging capability than the standard radiation. A dose of protons and helium ions of 1.0 Gy induced the development of dystrophic mutations of neurons (including irreversible ones) of practically the same number of neurocytes as a 6.0-Gy dose of γ rays. Here the development of structural mutations is more intense. Typically, the number of dystrophic mutations of cells of nonirradiated animals remains roughly constant over the entire observation period. The increase of the number of dystrophic cell mutations with time is due to a decrease of the number of neurons which did not undergo mutation. If it is assumed that the specific rate (v) of decrease of the number of nonmutated neurons is constant, their number must be given by the expression $S_{(t)} = k + (100 - k) \exp(-vt)$, where $S_{(t)}$ is the number of nonmutated cells (in %) of the irradiated animals at time t, v is the rate of decrease of the number of nonmutated neurons, and k is the number of neurons resistent to radiation damage (in %) (Ref. 81). The approximation of this equation by the least-squares method after irradiation is not described by this equation. This indicates that there are several stages in the development of CNS damage, which might be related both to the direct action of the radiation on the neurons, and to mutations of vascular nature.[59] In the pathogenesis of structural mutations of the CNS at times long after the ionizing irradiation, a significant role is also played by perturbations of autoimmune processes. This is confirmed by the great similarity between the clinical picture and the pathogenesis of radiation injuries of the CNS with demyelinizing processes of different etiology.[60]

Quantitative analysis of the structural mutations of neurons of the CNS revealed perturbations due to impacts of carbon nuclei of energy 320 MeV/nucleon and intensity 1×10^4 particles/cm^2 (LET equal to 12.0 keV/μm). Here the number of dystrophically mutated neurons was 1.5 to 2 times greater than the number of such cells in animals that were not irradiated. Changes were also observed in the profile fields of the cytoplasm and nuclei, and also in the nucleus-cytoplasm ratio.[55] Three to six months after the irradiation of laboratory animals, the neuron mutations acquired a focal nature, and cell-devastation foci appeared. It is important to note that γ irradiation at a dose of 1.0 Gy led to the development of more weakly expressed structural mutations in neurons than for carbon ions at intensity 1×10^4 particles/cm^2. This is consistent with the results of a comparative analysis of structural mutations of neurons induced by equal doses of carbon ions of energy 4 GeV/nucleon and γ radiation, indicating that doses of the standard radiation of less than 1.0 Gy actually do not lead to the appearance of destructive mutations in neurons.[56] In these studies there was a marked growth of the degree of severity of morphological mutations of the CNS with increasing radiation dose. The structural mutations of the neurons continue to grow as the post-irradiation period increases, and the death of some of the cells leads to reorganization of the cortex. Similar mutations of the neurons in the case of γ irradiation begin to develop at a dose of 1.0 Gy and higher. The data quoted confirm the higher biological effectiveness of carbon ions. In Fig. 3 we show the dose dependence of the RBE coefficients of carbon ions calculated by a nonparametric method.[61] As tests of the

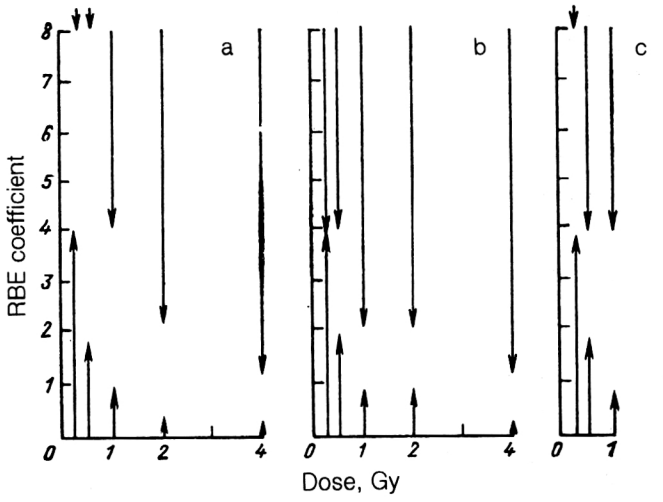

FIG. 3. Dose dependence of the RBE coefficients of carbon ions of energy 4 GeV/nucleon compared with γ rays of ^{137}Cs from the results of measuring (a) the number of undamaged cells and (b) the number of neurons with dystrophic mutations in the cortex of rats. The arrows indicate the limits of the 95% confidence interval of the RBE coefficients (RBE_{min}–RBE_{max}). The vertical lines correspond to the regions of unreliable values of the RBE (calculations carried out by O. A. Smirnova).

radiobiological damage, we used (a) the number of nonmutated neurons and (b) the number of dystrophically mutated cells of rats 1 month after irradiation. The dependences of the RBE coefficients obtained are similar to each other. As the carbon-ion dose is increased from 0.25 to 4.0 Gy the values of the RBE coefficients are decreased from 8–16 to 1.5.

Therefore, the results of these investigations of the effect of HCPs on the central nervous system of experimental animals, on the one hand, confirm the general regularities of radiation damage to the tissues of the organism, and, on the other, reveal some important features of the biological action of HCPs. In particular, the degree of severity of the structural mutations of neurons of the cortex increases not only with increasing dose and LET of the radiation, but also with the duration of the post-irradiation period. The mutations which arise progress more intensively after irradiation with accelerated charged particles, and their RBE coefficients vary within wide limits depending on the dose and duration of the post-irradiation period. In other words, the absence of pronounced morphological mutations in the brain tissue of mammals in the acute period of radiation sickness does not imply that the irradiation has no aftereffects. The manifestation of structural mutations of neurons of the CNS peaks about 4 weeks after irradiation.

The extremely high effectiveness of small fluxes of accelerated charged particles acting on brain neurons is certainly of interest. Here the number of dystrophically mutated neurons is increased by a factor of 2.5 relative to the number in nonirradiated animals. During the flights of the Apollo spaceships the astronauts' helmets were used as detectors of heavy cosmic-ray nuclei.[62] The flux of nuclei of the iron group was 0.56–1.55 particles/cm^2. Calculations based on this showed that for a space flight lasting 2 years, from 40 to 1600 cells per million neurons can die in brain tissue. It can be assumed that such a cell loss does not lead to significant perturbation of the functioning of the CNS. However, for highly specialized structural formations of the brain (the nuclei of the medulla, the hypothalamus, the optical analyzer, and so on), losses of even a relatively small number of cells can lead to certain consequences.

Features of lenticular-opacity formation in experimental animals

The formation of lenticular opacities in humans and in experimental animals as a result of contact with penetrating radiation is related to the sclerotic effect of the radiation. It is thought that radiation cataracts develop as a result of the direct effect of the radiation on the epithelium of the crystalline lens, but a mature cataract is formed only after irradiation of the entire crystalline lens or its periphery.[63] Lenticular opacity develops as a consequence of the perturbation of the physico-chemical and fermentation processes due to the action of physical or chemical factors, or to mutations of the cell metabolism that occur with aging. A senile cataract is a very common pathology of the vision organ.

Many studies have been devoted to radiation-induced opacity of the crystalline lens in humans and laboratory animals. These lead to the conclusion that the cataract-producing dose for a human after a single exposure to external, sparsely ionizing radiation lies in the range from 2.0 to 4.0 Gy (Refs. 64 and 65). Formation of lenticular opacities in laboratory animals can occur for considerably lower doses of ionizing radiation. It should be noted that the study of the effectiveness of various types of penetrating radiation in cataract generation has not revealed any qualitative features in the development of lenticular opacity in various types of animal.[66,67] The quantitative differences concern the formation dynamics and the frequency of lenticular opacities. This is equally true for relativistic charged particles. Before the studies whose results are given below were carried out, in the foreign literature there was a single publication on the problem of studying the cataract formation activity of 3-GeV protons.[16] However, information of this type is needed to develop approaches and normalization principles for radiation effects.

Studies of cataract formation by 4-GeV/nucleon helium ions and 9-GeV protons were carried out on mice of the line $F_1(CBA \times C_{57}BL_6)$. More than 1000 animals of both sexes were used in the experiments. The results of these studies showed that for mice irradiated by helium ions and 9-GeV protons in a wide dose range, lenticular opacities appeared as in experiments with the irradiation of animals by protons of lower energies or γ rays.[68] However, the time period for visible mutations to appear in the crystalline lens was considerably shorter. In particular, after the irradiation of animals by protons and helium ions at doses of 4.0–5.0 Gy the first point-like lenticular opacities were discovered after 4 weeks, while for doses of 1.0 and 2.0 Gy they were seen 8 weeks after the irradiation. For mice irradiated by γ rays at doses of 4.0 and 6.0 Gy the first lenticular opacities were seen after 8 weeks, and for

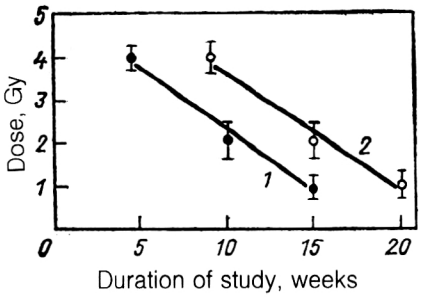

FIG. 4. Dependence of the duration of the latency period of lenticular-opacity formation (in weeks) on the dose of (1) helium ions and (2) γ rays.

doses of 1.0 and 2.0 Gy they were seen 10 weeks after the irradiation. The dependence of the duration of the latency period on the radiation dose is shown in Fig. 4. The first senile lenticular opacities in nonirradiated animals appeared 20 weeks after the start of the experiment. The frequency of lenticular opacities is a function of the time after the irradiation of the animals and of the dose. The time-effect dependence is linear and is described by the equation $N = a + bt$, where N is the frequency of lenticular opacities in %, t is the time which has passed since the irradiation in weeks, and a and b are the coefficients of the line. The coefficient a corresponds to the frequency of lenticular opacities in the control animals, and the coefficient b is the change in the lenticular-opacity frequency in 1 week for the irradiated mice. In Table III we give the values of b for helium ions and γ rays.

The values of b obtained for helium ions and γ rays, and also the ratio of these quantities indicate that the intensity of the lenticular-opacity formation after the action of helium ions is considerably greater than in the case of γ rays, and in both cases it grows as the dose increases.

The dependence of the lenticular-opacity frequency on the charged-particle dose is linear up to 2.0 Gy (Fig. 5). Then the curve describing this dependence enters a plateau. After the action of γ rays the curve enters the plateau

TABLE III. Values of the coefficient b for various doses of helium ions and γ rays.

Dose, Gy	Coefficient b		Ratio of b for helium ions and b for γ rays
	Helium ions	γ rays	
1.0	1.83	1.46	1.25
2.0	3.25	1.55	2.09
4.0	5.20	2.12	2.45

at doses above 4.0 Gy. This also indicates a higher effectiveness of accelerated charged particles than for γ rays. On the basis of these calculations the RBE coefficients obtained for protons were 1.3, 1.9, and 2.4, and for helium ions they were 1.2, 2.2, and 2.6 at 20, 30, and 40 weeks after the irradiation.[69,70] RBE coefficients of the same magnitude were obtained earlier for 3-GeV protons,[16] whereas the RBE of argon ions (^{40}Ar) of energy 570 MeV/nucleon found according to cytological mutations of the epithelium of the crystalline lens in rats is 6–10 (Ref. 71), which can be related to the higher LET of these particles.[74] In experiments on rabbits irradiated by neon ions (^{20}Ne) it has been shown that the development of cataracts during the first year after irradiation is a reaction which depends on the age of the animal.[72] The sharp increase of the RBE coefficients at low HCP doses should also be noted. On the basis of the data obtained for mice subjected to single and fractionated irradiation by carbon ions (^{12}C), the RBE coefficients were equal to 5, 3, and 1–2, respectively, for doses in the range from 0.05 to 0.9 Gy (Ref. 72), while in the case of irradiation of animals by argon ions (^{40}Ar) at a dose of 0.05 Gy the RBE coefficient reached 40 (Ref. 73). Fractionation of the HCP dose not only does not reduce the damaging effect, but also induces a dose-dependent shortening of the duration of the latency period of perturbation of the crystalline-lens transparency.

The carcinogenic effect of radiation

Experimental studies of the carcinogenic activity of ionizing radiation make it possible to obtain the most com-

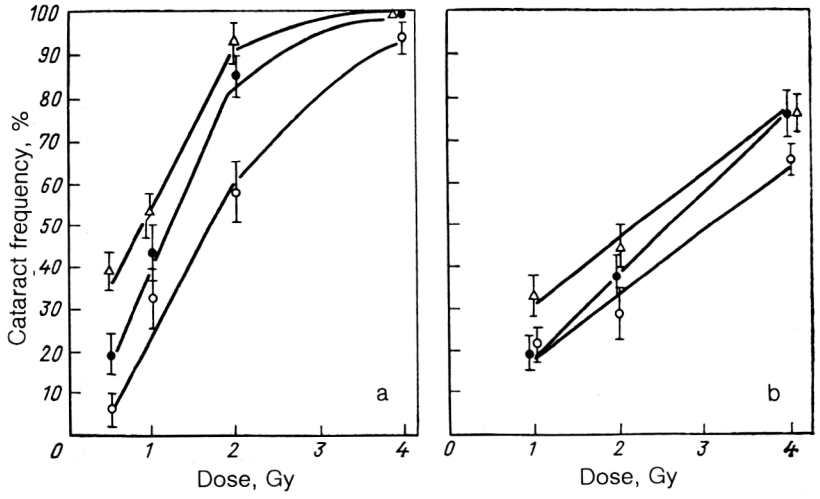

FIG. 5. Dependence of the frequency of lenticular opacities in mice on the dose of (a) helium ions and (b) γ rays 20 (○), 30 (●), and 40 (△) weeks after irradiation.

TABLE IV. Frequency of neoplasms of the mammary glands and average times for their appearance in rats irradiated by accelerated charged particles and γ rays.

Type and energy of the radiation	Dose, Gy	Effective number of rats	Overall frequency of tumors, %	Average times for tumors to appear, days
Nonirradiated animals	—	100 29*	19,0±3,9 24,1±7,9	616,0±180,0 523,3±159,0
γ rays from ^{60}Co	1,0 2,0 4,0	54 46 71	24,1±5,8 39,1±7,2 42,3±5,9	565,6±183,7 576,7±112,8 472,8±121,3
Helium ions, 4 GeV/nucleon	0,25 0,50 1,0 2,0 4,0	22 33 31 32 32	31,8±9,9 33,3±8,1 38,7±8,7 46,9±8,8 50,0±8,8	572,1±61,0 559,1±141,6 560,4±152,7 511,8±82,8 472,1±164,9
Protons,* 9 GeV	0,5 1,0 2,0 4,0	52 51 50 46	36,5±6,7 52,9±7,0 68,0±6,6 58,7±7,3	492,3±134,7 460,5±153,7 454,5±121,1 373,2±75,1

*Here and below the rats are of the Wistar line, and in the other experiments they are white mongrel she-rats.

plete idea about the dependence of tumor effects on various endo- and exogenic factors. This problem has extremely important practical and general biological significance. On the one hand, all living organisms, including humans, living in terrestrial conditions are damaged by the constant action of low levels of radiation from the natural background, and also from artificial sources of radiation. On the other hand, information on radiation carcinogenesis is of fundamental importance for normalization of radiation effects and for estimating the radiation risk to which humans are exposed in working conditions or in extreme situations.

It is assumed that the background radiation and the action of ionizing radiation as a result of medical procedures are responsible for the 1% natural human mortality from malignant neoplasms of all localizations,[75] while the mortality rates from leucoses and lung and brain tumors are 2.8, 3.0, and 3.7%, respectively.[76] In addition, there is now no doubt about the etiological role of radiation in the development of tumorous illnesses in man and animals. The increased frequency of neoplasms and the shorter time for their development are, in the opinion of many investigators, the main reason for the shorter lifetime of mammals after exposure to nonlethal doses of ionizing radiation.

A great amount of epidemiological and experimental data on the problem of radiation carcinogenesis has been published by now. However, many of the questions of radiation carcinogenesis can be studied only in experiments involving laboratory animals. The available data indicate that tumors in man and in animals are caused by precisely the same types of ionizing radiation and can arise in practically all organs and tissues. In connection with this, it is very important to understand the quantitative regularities of carcinogenesis associated with the effect of various types of penetrating radiation.

Our comparative studies of the carcinogenic effectiveness of 9-GeV protons, 4-GeV/nucleon helium ions, and γ radiation of ^{60}Co confirmed that these types of radiation tend to induce the formation of blastomas. One or several tumors developed during the lifetime of each of the animals. In Table IV we give the frequency of neoplasms of the mammary glands of mice and rats and the times at which they were found. Analysis of the results revealed a radiation-dose dependent acceleration of the tumor transformation process. In particular, neoplasms of the mammary glands after irradiation developed 100 to 150 days earlier than spontaneous tumors of these glands. The same is true of neoplasms of other localizations and leucoses. Typically, the rate of neoplasms of various localizations in nonirradiated animals peaked during the last quarter of the lifetime, while in the irradiated rats it peaked in the middle. A significant number of the animals with malignant tumors, leucoses, adenomas of the hypophysis, and so on, had their average lifetime shortened as a result of this shift. The question of whether this shift occurs because of the premature aging of the irradiated organism or whether the development of malignant tumors leads to shortening of the lifetime remains unresolved.

Leucoses developed in some of the animals. The dependence of their frequency on the radiation dose differs for different types of leucosis. In rats the leucoses were predominantly of the lymphoblast type. In nonirradiated mongrel she-rats observed until the end of their life the leucosis frequency reached (10.1±3.0)%. Dose dependence of the frequency of leucosis generation appeared to a high degree in animals irradiated by helium ions (Fig. 6), and varied from 9.1% at a dose of 0.25 Gy to 30.0% after

TABLE V. Estimate of the risk of development of neoplasms of the mammary glands in irradiated rats.

Type and energy of the radiation	Dose, Gy	Relative frequency of tumor development per unit dose, %/Gy	Average number of tumors per animal in the group	Average number of tumors per animal in the group with tumors	Tumor frequency excess, %
γ rays of ^{60}Co	1,0	8,9	0,28	1,15	8,9
	2,0	13,5	0,46	1,17	26,5
	4,0	7,7	0,59	1,40	30,7
Protons, 9 GeV	0,5	24,6	0,40	1,10	12,3
	1,0	34,9	0,67	1,26	34,9
	2,0	27,9	1,26	1,85	55,8
	4,0	10,8	0,80	1,37	43,0
Helium ions, 4 GeV/ nucleon	0,25	84,4	0,40	1,12	21,1
	0,50	27,0	0,36	1,20	13,5
	1,0	20,0	0,42	1,18	20,0
	2,0	15,2	0,62	1,43	30,3
	4,0	9,5	0,59	1,19	38,0
Nonirradiated animals	—	—	0,17	1,05	—
			0,55	1,12	—

irradiation at a dose of 4.0 Gy. Here for helium-ion doses of 1.0, 2.0, and 4.0 Gy the leucosis frequency actually stayed the same (28.6, 32.3, and 30.0%). A helium-ion dose of 0.25 Gy did not lead to an increase in the frequency of blood illnesses, whereas for a dose of 0.5 Gy the leucosis frequency increased by a factor of 2. Doses at the same level cause the leucosis frequency in humans to double. These estimates assume that the dose-effect dependence is linear for leucoses and that there is no threshold dose.[77] Typically, in nonirradiated rats of the Wistar line the number of leucoses was 2 times smaller than in mongrel animals of the same sex and age, and for rats of this line irradiated by protons the leucosis frequency remained constant (21.6–25.6%) for all radiation doses.

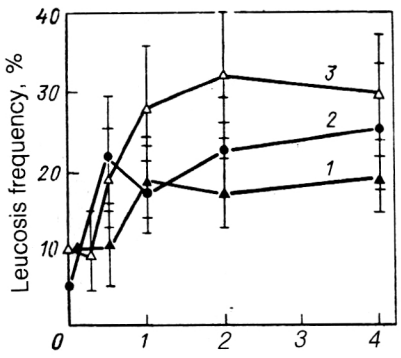

FIG. 6. Frequency of blood illnesses in rats irradiated by (1) γ rays, (2) 9-GeV protons, and (3) helium ions.

Irradiation leads to an increase in the frequency of formation of adenomas of the hypophysis. A test for this tendency[78] confirms the increase of blastoma generation in the hypophysis with increasing radiation dose to a high degree of accuracy. The highest rate of formation of adenomas of the hypophysis $(60.4 \pm 8.9)\%$ is reached after irradiation by helium ions at a dose of 0.5 Gy [in nonirradiated mongrel animals it was $(20.2 \pm 4.4)\%$].

Among neoplasms of other localizations we should note the high frequency of tumor formation in other internal secretion glands: the thyroid and parathyroid glands, the adrenal glands, the ovaries, and also in the uterus and other organs, soft tissues, and integuments, which occur rarely or practically never in nonirradiated animals. This indicates a broadening of the spectrum of neoplasms induced by ionizing radiation.

In radiobiological practice the carcinogenic risk is estimated by calculations of the relative frequency of tumor development per unit radiation dose, per animal, and so on. The experimental data indicate that as the radiation dose increases the relative frequency of neoplasms of the mammary gland per unit dose decreases, the mean number of neoplasms per animal increases, and the frequency of tumor formation is increased over the control level (Table V). Similar regularities are typical for tumors of different localizations. However, the description of the dose-effect dependence by a linear function is an extreme simplification which can tend to overestimate the actual level of carcinogenic risk from sparsely ionizing radiation in small doses, while for radiation with large LET the risk can be underestimated.[79] In order to avoid such fluctuations in

TABLE VI. Estimate of the risk of development of neoplasms of the mammary glands in rats irradiated by relativistic protons and helium ions according to the lognormal dose-effect dependence.

Type and energy of the radiation	Risk dose, rel. units			
	R^2	10^{-4}	10^{-5}	10^{-6}
γ rays of ^{60}Co	0.99	0.25	0.19	0.15
Helium ions, 4 GeV/nucleon	0.81	0.014	0.007	0.004
Protons, 9 GeV	0.41	0.017	0.010	0.006

estimates of the tumor-formation risk from radiation, we attempted to approximate the dose-effect dependence in the case of tumors of the mammary gland by a nonlinear lognormal dependence (Table VI). Since for such a dependence there cannot be a single coefficient, as the criterion we used the unit of "risk dose," i.e., the dose responsible for a certain risk of tumor formation.

The risk of death from cancer induced by radiation is commonly expressed as the number of deaths per number of human cancers, i.e., 1×10^{-4} human cancers or 1 case per 10 000 humans, each irradiated with a dose of 0.01 Gy. In particular, the risk of death from cancer of the lung, stomach, breast, and other localizations in the period from 1975 to 1978 in Nagasaki and Hiroshima was 4.4×10^{-4} human cancers for men and 3.0×10^{-4} human cancers for women.[80]

Calculations carried out on the basis of our experiments showed that the risk of formation of breast tumors from a single dose of γ radiation in animals is 10^{-4} during the entire lifetime for a dose of 0.25 Gy and 2×10^{-5} and 10^{-6} for doses of 0.19 and 0.15 Gy, respectively. The levels of risk are the same for protons and helium ions at considerably lower doses. If we take the acceptable carcinogenic risk to be 10^{-4} for the entire lifetime, the allowed dose of accelerated helium ions of energy 4 GeV/nucleon is 0.014 Gy, that of 9-GeV protons is 0.017 Gy, and that of γ rays of ^{60}Co is 0.25 Gy (the ICRP takes the risk coefficient for human breast tumors to be $660 \times 10^{-6} \cdot 1$ Gy/yr).

The risk estimates obtained therefore indicate that the biological effectiveness of helium ions and protons at relativistic energies estimated from their ability to induce neoplasms in experimental animals is higher.

As is well known, the basis for the tumor-inducing action of radiation is changes of the DNA molecules and cell repair systems. The curve for the dose-effect dependence obtained on the basis of the experimental model of radiation-induced cell transformation has the typical form with a clearly expressed maximum and emergence onto a plateau for doses in the range 1.0–3.0 Gy. As the LET of the radiation increases the transforming activity of the radiation increases like the growth of the frequency of chromosomal abberations or cell death.[81] This behavior of the dependence of the effect on the charged-particle dose is demonstrated in our studies. However, in experiments on laboratory animals it is not always possible to reproduce a clear dose-effect dependence. This is apparently related to the impossibility of accumulating a sufficient number of tumors of a single type. Therefore, three basic models are used to describe the behavior of the dose-effect dependence: the linear model, the linear–quadratic model, and the quadratic model.[82] The complicated shape of the dose-effect curves here is a result of two independent phenomena related to the dose: the probability of tumorous transformation of cells, which grows with the dose, and the survival probability of the transformed cells, which decreases as a function of the dose. The risk of development of remote aftereffects is higher for radiation with high LET than for electromagnetic radiation. For many tumor systems there is no clearly expressed relation between the maximum value of the dose-effect curve and the nature of the radiation. The effectiveness of radiation with high LET is to a large degree manifested in lower doses and depends little on the strength of the dose.[77]

It should be noted that questions of the carcinogenesis of accelerated charged particles of various energies have been studied far too little. On the whole, studies of the carcinogenic effectiveness of high-energy protons have not revealed any special features of the transformation effect in relation to the standard radiation.[83–87] In addition, the more than 20-year-long observation of monkeys irradiated by protons in a wide range of doses and energies and also by x rays and electrons has led to the conclusion that the neoplasm frequency depends on the dose and the LET and on the radiation.[88] It has been established that the dose of 55-MeV protons which doubles the tumor frequency is 2.45 Gy. However, the radiosensitivity of the tissues of the organism varies within wide limits, which means that the doses doubling the number of tumors in various tissues and organs must be different. In particular, the dose of 120-MeV protons which doubles the leucosis frequency in rats is 0.5 Gy (Ref. 84), while for other systems this rule is not followed. Another feature of the study of Ref. 89 is the significant number of brain tumors in the experimental animals, which are rarely encountered for other sources of radiation and in nonirradiated animals.

The shielding from radiation in outer space is based on the fact that the main source of radiation is high-energy protons, the RBE of which is equal to or nearly unity. The results of studying the carcinogenic activity of ^{4}Ne, ^{12}C, ^{20}Ne, ^{26}Fe, and ^{40}Ar ions with LETs of 1, 80, 150, 180, and 650 keV/μm, respectively, on the basis of formation of tumors of the gland in mice indicate a general tendency for the carcinogenic effect to grow with increasing LET of the radiation. The highest frequency and multiplicity of tumors was seen after irradiation of animals by iron ions.[90] It is thought that the RBE coefficient of iron ions can reach 20 according to the tumor formation indicator.[91]

The results of experiments on the irradiation of animals by 9-GeV protons, 4-GeV/nucleon helium ions, and γ rays of ^{60}Co show that they all lead to an increase of the frequency of oncological illnesses of various localizations, decrease of the time for their development, widening of the histological spectrum of neoplasms, and decreased average lifetime of the animals. However, comparison of the data with the results of studying the carcinogenic activity of γ rays indicates that relativistic charged particles have higher effectiveness. It has been shown that there is some variation

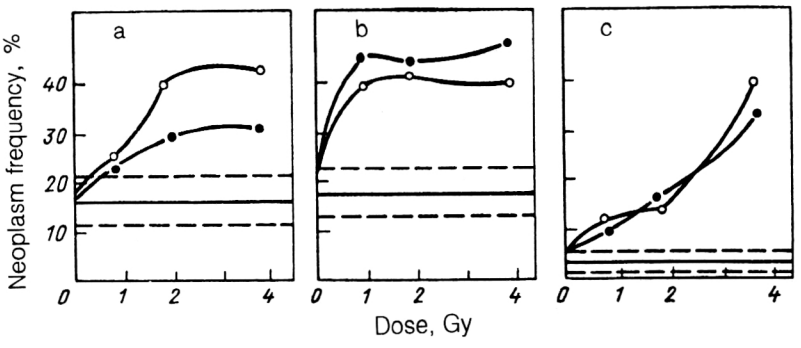

FIG. 7. Dependence of the frequency of neoplasms of (a) mammary glands, (b) the thyroid, and (c) the ovaries on the dose of 645-MeV protons (●), γ rays of ^{60}Co (○), and also for nonirradiated animals (–).

in the shapes of the curves describing the dependence of the frequency of neoplasms of various localizations on the radiation dose (Fig. 7). Breast tumors and adenomas of the hypophysis are characterized by an asymmetric S-shaped curve which can be approximated by a lognormal distribution. For doses above 2 Gy this curve enters a plateau, on which the neoplasm frequency reaches 30–40%.

For tumors of the adrenal glands and the thyroid the neoplasm frequency in the range of doses used actually stays at the same level. This leads us to assume that for tumors of these localizations the dose-effect curve has already reached the plateau, and its rising segment is located in the range of doses below 1 Gy. Finally, ovarian tumors are characterized by a dose-effect dependence in which the tumor frequency grows with constant slope. In this case the plateau, if it exists, must be reached at doses above 4 Gy. However, this is valid only for protons and γ rays, while for helium ions the emergence of the dose-effect dependence onto the plateau for ovarian tumors is seen at a dose of 2 Gy.

Analyzing these curves, we conclude that they all represent different segments of a single S-shaped curve, which more or less reflects the features of the dose-effect dependence for tumors of every localization.

In Fig. 8 we show the dose dependences of the RBE coefficients obtained from the criterion of the carcinogenic effectiveness of helium ions relative to γ rays calculated by a nonparametric method according to the criterion for the formation of tumors of various localizations during a certain observation period.[63] It can be seen that for all observation periods the RBE coefficients of helium ions decrease with increasing radiation dose. For example, for $T = 540$ days, $\mathrm{RBE}_{\max} = 8$ (for $D_b = 0.25$ Gy) and $\mathrm{RBE}_{\max} = 1$ (for $D_b = 4$ Gy). The intervals of meaningful RBE coefficients corresponding to the same helium-ion dose and different post-irradiation observation periods differ insignificantly from each other. This might indicate that the dynamical characteristics of tumor formation in animals irradiated with helium ions and γ rays are close to each other for observation periods in the range of 500–800 days after irradiation. Similar values of the RBE coefficients are also obtained for protons.

CONCLUSION

The data from the studies that have been carried out indicate that relativistic charged particles have a higher biological effectiveness than the standard radiation. There is no doubt that the features of the interaction of relativistic nuclei with biological tissues determine the essential specific features of the damage of mammalian cells characteristic of densely ionizing radiation, in particular, the higher yield of two-strand ruptures of DNA molecules or two-hit aberrations. In the final analysis, processes occurring at the molecular level are responsible for the higher relative biological efficiency of protons and of helium and carbon ions established according to most of the indicators used. At the level of the tissues and organs the biological effects of relativistic charged particles appear as a different quantitative expression of the pathological manifestations of the radiation injury.

It should be noted that the problem of estimating the risk of cosmic rays and ensuring radiation safety in space flights is not solved by these data. The further penetration of outer space, which will involve long flights and perhaps colonization of other planets, will present new problems to cosmic radiobiology. Important among them will be studies of the radiation perturbations under the conditions of outer space and the time nonuniformity of radiation effects,

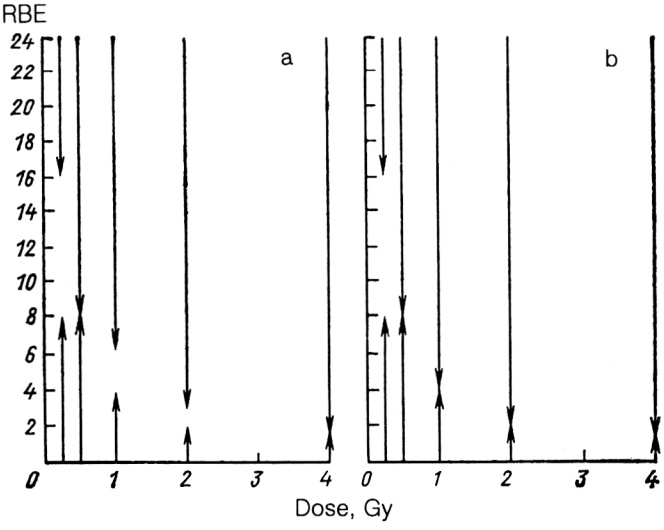

FIG. 8. Dependence of the RBE coefficients of helium ions of energy 4 GeV/nucleon on the dose, obtained according to the criterion of frequency of neoplasms of various localizations in rats (a) 540, (b) 720, and (c) more days after irradiation.

study of the biological effect of HCPs taking into account the considerably broader energy spectrum of the cosmic-ray components and also the biological mechanisms modeling the influence of space-flight factors of nonradiation nature, and so on. The results of studies performed at charged-particle accelerators must be confirmed under the conditions of outer space.

In concluding this survey of the data on the RBEs of charged particles of high and relativistic energies, I consider it my pleasant duty to express my deep gratitude to the directors of the Joint Institute for Nuclear Research and the High Energy Laboratory for making it possible to carry out these physico-biological studies with the goal of solving problems related to ensuring radiation safety in space flights, and also to everyone who directly or indirectly assisted in carrying out these experiments.

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Translated by Patricia Millard