=== **GENERAL RADIOBIOLOGY** ===

Some Aspects Related to Transmission of Radiation-Induced Alterations due to the Bystander Effect

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Abstract—This paper presents the first results of research and observations within the framework of the Integrated Project for the assessment of radiation-induced nontargeted effects. The remote bystander effect, related to nontargeted effects, is one of the least studied phenomena in terms of manifestations and mechanisms. The international laboratory practice with respect to this phenomenon commenced with demonstration of the bystander effect in fish and other aquacultures. Our studies have revealed changes similar to radiation-induced pathologies in nonirradiated mice kept for three months in contact with the irradiated species (exposed to a 3 Gy γ-ray dose). Changes in behavioral responses, a statistically significant trend for decreasing spleen weight ($r = -0.416$; $p = 0.048$), an expanding area of alopecia ($r = -0.631$; $p = 0.001$), and other anomalies are noted. Discussions on possible mechanisms of the phenomena refer to both A.M. Kuzin's theory of radiotoxins (1966) and the interpretation of the hypotheses investigated by C. Mothersill (2010−2019). An assumption is made on the important role of derivatives of lipid peroxides in the formation of this effect. The results of these studies indicate the need for further investigation of the radiation-induced bystander effect by using the molecular and cellular methodological approaches.

Keywords: radiation-induced nontargeted effects, outbred female mice, remote bystander effect, radiotoxins, biophotons

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INTRODUCTION

The purpose of this work is to study new aspects of the phenomena known in radiobiology as nontargeted effects, which consist in the capacity to transmit changes from the irradiated (i.e., from radiation targeted) cells to nonirradiated. In recent years, one of the discoveries related to nontargeted effects has revealed remotely induced bystander effects called in the foreign research "radiation-induced bystander effects at the interorganism level." It was shown that radiation-induced alterations and damage might be transmitted not only from cell to cell, but also from the entire irradiated organism to a non-irradiated one, including higher organisms and, presumably, humans [1].

A systematic study related to nontargeted effects is currently being carried out abroad. A great contribution to the development of these investigations belongs to W.F. Morgan [2] and D.B. Little [3]. Regular experimental studies on the bystander effect in vitro and in vivo are carried out at McMaster University of Canada [1], and the first successes in studying the remotely-induced radiation bystander effects transmitted between organisms are referred to the research group of C. Mothersill (from McMaster University). After a series of studies performed by C. Mothersill

(2010−2019) in fish (rainbow trout and *Danio rerio* (Zebrafish)), the results of which finally confirmed the hypothesis on the transmission of radiation-induced changes from an irradiated organism to a nonirradiated one, it was proven that the remote bystander effects should be taken into consideration when estimating damage and risks from exposure to a low-dose radiation [4, 5]. These phenomena that were initially revealed in unicellular organisms were further found in different invertebrates and vertebrates [4−8].

In recent years, studies on nontargeted effects have been carried out in different countries world-wide, including Canada, the United States, the United Kingdom, Germany, China, Japan, France, Finland, India, South Korea, and Iran. The increased interest in different manifestations of nontargeted effects is associated with the need to assess the risks and consequences of technological disasters in the areas of prolonged exposure of biological objects to low-dose radiation. After the accident at the Fukushima nuclear power plant, Japan and, quite recently, South Korea have actively joined in this research [9, 10]. In recent years, there has been a practice of international expeditions to collect and process materials for the investigation of nontargeted effects in the regions exposed to

radiation contamination, including the Chernobyl zone [11].

When speaking of the Russian researchers that have closely approached the investigation of remote radiation-induced nontargeted effects transmitted between organisms, it is primarily necessary to mention the hypothesis on radiotoxicity made by A.M. Kuzin, a Corresponding Member of the USSR Academy of Sciences [12, 13]. This hypothesis significantly amplified N.V. Timofeev-Resovskii's classical understanding of radiation effects on biological objects: the target theory and hit principle [14]. The ideas of Kuzin had no further broad-scale development in our country, and his works are practically unknown abroad.

There are still very few systematic and comprehensive studies on nontargeted effects in Russia. Among the recent studies, one should mention the works of the research groups of I.I. Pelevina [15–17] (Semenov Institute of Chemical Physics, Russian Academy of Sciences, Moscow) and of B.P. Surinov [18] (Tsyb Medical Radiological Research Center, Branch of the National Medical Research Radiological Center, Ministry of Health of the Russian Federation, Obninsk) We should note the differences in the conceptual apparatus used in the Western and domestic studies. Here, the definition of "remote bystander effect" includes the effects transmitted not only between organisms, but also at the level of one organism, arising in distant cells, organs, and tissues not adjacent to the irradiated ones [13, 15].

The group of I.I. Pelevina have recently created a cytogenetic model to assess this phenomenon based on studies of chromosomal aberrations in human peripheral blood cells. The scheme of the genotoxic effect of lymphocytes in patients with malignant neoplasms on the blood cells of healthy individuals in a medium (in vitro) that imitates a natural one was demonstrated, thus demonstrating the possibility of the remote transmission of such changes. This model turned out to be applicable to remote radiation-induced nontargeted effects. Later, from the example of abscopal effects (from the word "abscopal," distant from the site of irradiation), Pelevina et al. demonstrated in vivo remotely induced nontargeted effects on the level of the same organism, which occurred in lymphocytes of radiotherapy-treated patients [16, 17]. Due to the relevance of the theme of the radiation-induced bystander effect, I.I. Pelevina scheduled a series of studies in animals to investigate the phenomena of the transmission of radiation-induced changes from an irradiated organism to a nonirradiated one.

This paper presents the first results of our studies performed in small mammals, demonstrating changes that occur in nonirradiated mice that have been in contact with irradiated animals.

MATERIALS AND METHODS

The study was performed in 25 outbred female mice (3–4 months of age). All animals were obtained from the Stolbovaya nursery. Before the experiment, they were kept in groups of ten specimens per group under vivarium conditions, with access to approved feed, on a balanced food allowance, under normal water conditions and a natural light regimen (autumn–winter season). The applied bedding was from an approved hypoallergenic natural material (wood shavings). Prior to the experiment, the mice were maintained for at least two weeks in standard wire mesh cages to adapt to the laboratory vivarium conditions. Healthy animals not previously subjected to any other experimental manipulations were used in the experiment. The groups were formed by the continuous sampling method. The experimental procedures were conducted in accordance with the relevant international guidelines for working with animals [19].

Ten mice to be irradiated were labeled with dye and placed in special plastic boxes with individual sections, five specimens per box. Mice were exposed to radiation (at a dose of 3 Gy) on a γ-therapeutic device ROKUS-AM (JSC Ravenstvo, St. Petersburg, Russia, plant no. 71) with a ^{60}Co γ-ray source (γ-ray energy of 1.25 MeV; radiation yield: the exposure rate measured at a distance of 75 cm from the source in a 10×10 cm field center is 64.7 R/min (on September 24, 2018)). The irradiation was carried out from one direction (from the top downwards), while the body of each mouse was completely irradiated from the dorsal side, achieving the effect of uniformity.

A container with mice was placed on the treatment table of the γ-apparatus in such a way that the radiation field of 22×22 cm covered the entire container with a margin. At the same time, the distance from the source to the object (the mouse dorsal surface) was set to 75 cm. The dose (3 Gy) was calculated at 1 cm depth (being 98% of the dose maximum). In this case, the maximum dose (100%) was at 0.5 cm depth (3.06 Gy), and if taking the object (mouse) thickness as 2.0 cm, then the dose at the exit from the mouse body is 93.1%, i.e., 2.8 Gy.

After the irradiation, the irradiated mice ($n = 10$) were returned back to the vivarium and placed in cages to interact freely with nonirradiated specimens ($n = 10$) as follows: two standard metal cages were used, each contained five irradiated mice and five nonirradiated mice (bystanders). Both irradiated and nonirradiated mice could freely interact with each other. All other conditions of mouse maintenance were the same as before the radiation exposure. Thus, the 20 mice (outbred female mice) participating in the experiment were kept in two separate cages under equal conditions, which excluded randomness (Figs. 1, 2). The experiment lasted for three months. The mice were monitored constantly.

The third group (control) consisted of five female mice (3–4 months of age) housed in a separate group of five species under vivarium conditions, on the same normal balanced food allowance, under the same water and natural light regimen, in a wire mesh (metal) cage with the approved bedding (wood shavings). The period of the control group maintenance under vivarium conditions corresponded to the dates for the main group.

Throughout the entire experiment, we monitored changes in the animal behavior. After three months, the mice were killed. In all three groups studied, we analyzed the body weight, spleen weight, and hair condition of mice, and some certain signs of changes in the internal organs and behavioral responses. The results were statistically processed using the STATISTICA-10 software package. The significance of differences between the groups was evaluated with a nonparametric Mann–Whitney U-test and Fisher's exact test. A regression analysis was also performed.

RESULTS

Changes in Behavioral Responses

After a certain period of adaptation (of about two weeks after commencement of the experiment), changes in the typical rodent behavior in outbred female mice were detected. Changes were observed in the behavior of both irradiated and nonirradiated mice (bystanders) compared to the normal behavior (control species) and to the behavior that was observed in the animals before the beginning of the experiment. The specimens of these breed characters and origin (from the Stolbovaya nursery) are characterized by a fairly stable nervous system and well-balanced and calm behavior. During the entire period of observation (of about three months), the test animals, including both the irradiated mice and the bystander mice, clearly displayed increased activity and nervousness compared to the control mice and to the species-typical behavior under ordinary conditions.

Changes in the Relative Weight of the Spleen

The results of analysis of the relative weights of the spleen in the three groups of mice are presented in Table 1 and Fig. 3. Two individual values, being far outside the 95% confidence interval, were excluded from the calculation. In the group of irradiated mice, the parameter discussed was significantly lower than that in control ($p = 0.046$ according to the Mann–Whitney test). It is quite clear that there are no significant differences in the mass index of the spleen between the irradiated mice and bystanders ($p = 0.659$), and at the same time, a clear tendency toward a decrease in this parameter in bystander mice compared to the control was observed, although no significant differences were revealed: $p = 0.182$ (Table 1). The results obtained are presented in Fig. 3. Contin-

Fig. 1. Pattern for allocating mice to cages nos. 1–2. Stage 1: five mice are irradiated at a dose of 3 Gy, five healthy mice (not exposed to radiation) from the same group are to be used as bystander mice.

Fig. 2. Pattern for allocating mice to cages nos. 1–2. Stage 2: five irradiated mice (3 Gy) are housed together in one cage with nonirradiated mice (bystander mice) for three months.

gent ranking of the results made it possible to conduct a regression analysis of the dependence of the aforesaid indicator upon exposure to radiation (nonirradiated mice, 0; bystander mice, 1; and irradiated mice, 2). The relationship considered was significantly described by a linear equation: $Y = 0.309 \pm 0.024 - 0.036 \pm 0.017x$ ($r = -0.416$; $p = 0.048$).

Changes in Hair Condition, Alopecia

One month after the experiment began, the test mice, both irradiated and nonirradiated, showed distinct signs of alopecia. This process started from the area adjacent to the nose, and gradually spread toward the top of the head. Alopecia was manifested in all-encompassing hair loss in the areas of the head affected by this process and was clearly of a pathological nature. In some species, additional foci (of almost regular geometric shape) emerged on the upper part of the head and/or on the body. In the areas of hair loss, erythema occurred. The maintenance of the mice in two separated cages (according to the pattern of mice allocation to cages: five irradiated mice and five

Table 1. Relative values of spleen weight $S/T \times 100)$* for the three groups of outbred female mice studied

Groups of animals								
irradiated mice, 3 Gy ($n = 10$)			bystander mice, 0 Gy ($n = 10$)			control group, 0 Gy ($n = 5$)		
animal no.	individual values of spleen weight S	mean ($M \pm SE$)	animal no.	individual values of spleen weight S	mean ($M \pm SE$)	animal no.	individual values of spleen weight S	mean ($M \pm SE$)
Irr1	0.2667	0.243 ± 0.018	M1	0.2308	0.2594 ± 0.024	C1	0.2905	
Irr2	0.2656		M2	0.3698		C2	0.2684	
Irr3	0.1686		M3	0.3515		C3	0.3324	
Irr4	0.1881		M4	0.2852		C4	0.2842	
Irr5	0.2985		M5	0.2111		C5	0.4265	0.3204 ± 0.029
Irr6	0.2085		M6	0.1508				
Irr7	0.28		M7	0.1863				
Irr8	**2.57****		**M8**	**1.347****				
Irr9	0.1968		M9	0.2788				
Irr10	0.3125		M10	0.2701				

A statistically significant difference in the relative weight of the spleen was revealed between the groups of irradiated mice and the control ($p = 0.046$ according to the Mann–Whitney test). It is quite obvious that there are no significant differences in the mass index of the spleen between the irradiated mice and bystander mice ($p = 0.658$), and at the same time there is a clear tendency toward a decrease in this parameter in the bystander mice as compared to the control, although no significant differences were found ($p = 0.182$). Contingent ranking of the data obtained made it possible to conduct a regression analysis of the dependence of this indicator on the radiation exposure (nonirradiated mice, 0; bystander mice, 1; and irradiated mice, 2). The relationship considered was significantly described by a linear equation: $Y = 0.309 \pm 0.024 - 0.036 \pm 0.017X$ ($r = -0.416$; $p = 0.048$).

 * S/T; S, spleen weight; T, body weight.
** Abnormal values of weights, which were excluded from calculations.

bystander mice in each cage for several months) excludes random causes of this effect.

The results of the assessment of the condition of the hair in the three groups of mice are presented in Table 2 and Fig. 4. The level of alopecia in the irradiated mice was significantly higher than that in the control ($p = 0.0026$ according to the Mann–Whitney test). Significant differences in this indicator were also revealed between the irradiated animals and bystanders ($p = 0.021$), and at the same time, there was a clear tendency toward an increase in the alopecia level in the bystander mice as compared to the control, although no significant differences were found ($p = 0.178$). The results obtained are presented in Fig. 4. Contingent ranking of the data obtained allowed us to conduct a regression analysis of this indicator dependence upon te exposure to radiation (nonirradiated mice, 0; bystander mice, 1; and irradiated mice, 2). The relationship considered was significantly described by a linear equation: $Y = 1.663 \pm 7.590 + 20.914 \pm 5.367X$ ($r = -0.631$; $p = 0.001$).

Other Pathologies

Along with the decreased relative mass of the spleen and pathological alopecia in both irradiated and bystander mice in this experimental group, intestinal changes were also noted in both these categories of the studied animals. It seems to be important to mention these signs, since the intestine (along with spleen) is one of the most radiosensitive organs [12, 13]. Statistically significant differences in the indicator characterizing intestinal changes ($p = 3.3 \times 10^{-4}$ according to Fisher's exact test) were found between the irradiated and control groups of animals: plaque of complex etiology in the intestines was detected in 10 out of 10 irradiated mice (100%) and was absent in mice of the control group (Fig. 5). According to this criterion, significant differences were found between the irradiated animals and bystander mice ($p = 0.003$). Although in the bystander mice group, several species with such changes were also identified (three out of 10, or 30%), no differences from the control were found with such a sampling size ($p = 0.51$).

DISCUSSION

We, thus, have demonstrated the existence of the bystander effect induced in a nonirradiated organism due to its contact with an irradiated organism. The results obtained raise several questions, the answer to which will bring us closer to understanding the mechanisms of radiation-induced bystander effects revealed in the experiment. "Are there any possible conditions that permit the manifestation of radiation-induced changes in an organism without the exposure of this organism to radiation?" "What are the "transport"
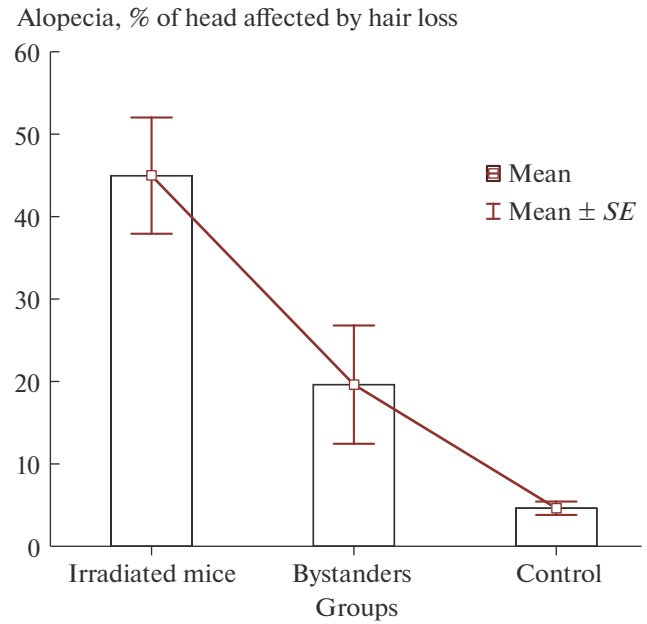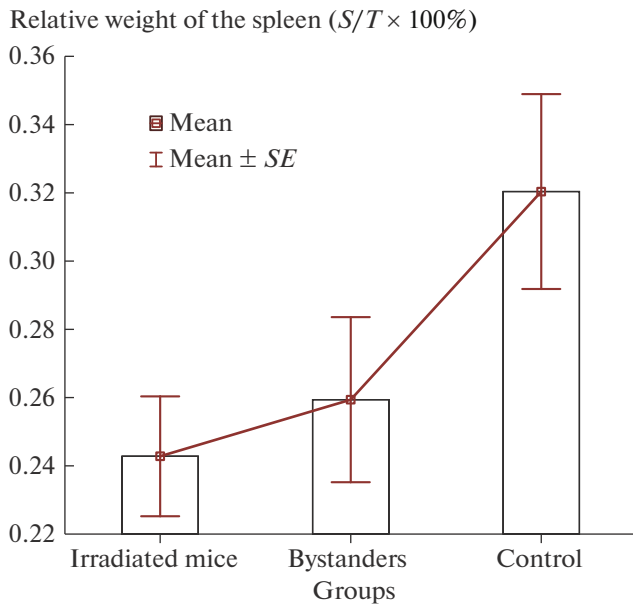
Relative weight of the spleen ($S/T \times 100\%$)

Fig. 3. Relative weights of the spleen for the three groups of mice studied. ($S/T \times 100\%$; S, spleen weight; T, body weight). Means ($M \pm SE$): irradiated mice, 0.243 ± 0.018; bystander mice, 0.2594 ± 0.024; control group, 0.3204 ± 0.029.

Alopecia, % of head affected by hair loss

Fig. 4. Alopecia scale for the three groups of animals studied: irradiated mice (3 Gy), bystander mice (0 Gy), and control group (0 Gy). Means ($M \pm SE$): irradiated mice, 44.970 ± 7.051; bystander mice, 19.620 ± 7.176; control group, 4.620 ± 0.808.

mechanisms of the radiation-induced alteration transmission from irradiated to nonirradiated organisms?" To explain the radiation-induced bystander effect, three mechanisms have recently been proposed: (1) transmission of damaging factors *via* direct contact; (2) generation of toxic compounds that can cause long-distance effects, similar to those induced in irradiated cells; and (3) the action of biophotons [1].

Table 2. Alopecia in the three groups of mice: irradiated (3 Gy), bystander (0 Gy), and control (0 Gy), % of head affected by hair loss.

Groups of animals								
irradiated mice, 3 Gy ($n = 10$)			bystander mice, 0 Gy ($n = 10$)			control group, 0 Gy ($n = 5$)		
animal no.	% of head affected by hair loss	mean ($M \pm SE$)	animal no.	% of head affected by hair loss	mean ($M \pm SE$)	animal no.	% of head affected by hair loss	mean ($M \pm SE$)
Irr1	33.3	44.970 ± 7.051	M1	33.3	19.620 ± 7.176	C1	3.3	4.620 ± 0.808
Irr2	33.3		M2	16.6		C2	6.6	
Irr3	83.3		M3	16.6		C3	6.6	
Irr4	33.3		M4	16.6		C4	3.3	
Irr5	50		M5	16.6		C5	3.3	
Irr6	16.6		M6	50				
Irr7	33.3		M7	66.6				
Irr8	83.3		M8	33.3				
Irr9	33.3		M9	16.6				
Irr10	50		M10	6. 6				

A statistically significant difference in the alopecia level was revealed between the groups of irradiated mice and the control ($p = 0.002$ according to the Mann–Whitney test). Significant differences in this indicator were also identified between the irradiated mice and bystanders ($p = 0.021$), while there was a clear tendency toward an increase in this indicator in bystander mice compared to the control, although no significant differences were found ($p = 0.178$).
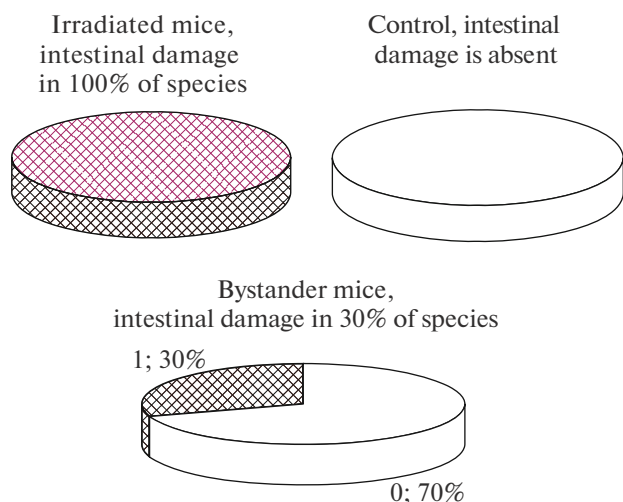
Irradiated mice,
intestinal damage
in 100% of species

Control, intestinal
damage is absent

Bystander mice,
intestinal damage in 30% of species

1; 30%

0; 70%

Fig. 5. The presence (absence) of signs of intestinal damage (plaque of complex etiology) in the groups of mice studied: irradiated mice (3 Gy), bystander mice (0 Gy), and control (0 Gy).

Today, there are several publications devoted to the issues of nontargeted effects. The term "nontargeted effects" itself appeared rather late, at the turn of the 20th to 21st centuries, resulting from the All-European Project Radinstab. By that time, according to C. Mothersill et al., the radiation-induced bystander effect was periodically discovered repeatedly, but "the theme appeared at certain periods only to disappear again" [6]. The fact, almost unknown abroad, is that key mechanisms of modern nontargeted effects from the point of view of cellular and biochemical processes were shown in the experiments conducted by A.M. Kuzin in the 1960s and were presented in his publications related to the action of radiotoxins (RTs).

When characterizing stages of the development of typical radiation sickness in human (which occurs at a total dose of 1–10 Gy), A.M. Kuzin paid attention to the generation of free radicals of water and organic compounds in all tissues of the exposed organism, which occurs already at the moment of irradiation. In the presence of oxygen, they produce toxic substances such as hydrogen peroxide, hydroperoxides and peroxides of unsaturated fatty acids, semiquinoid and quinoid forms of polyphenols, toxic histidine-hydrogen peroxide adducts, and other primary RTs [13, pp. 122–124].

The action of radiotoxins is related to secondary changes induced by irradiation of cells. Numerous experiments have shown the ability of primary radiotoxins to slow down cell division and cause cell death, as well (and this is important for discussing the results of our experiment) as to imitate radiation injury in animals [12, p. 88]. Radiotoxins generated in irradiated plants are easily extracted. Upon the introduction of such isolated extracts to nonirradiated animals, the

decrease in the animal body weight (followed by inhibition of growth), a sharp decrease in the number of leukocytes in the first hours after injection, and changes in the weight of some internal organs are observed [12, p. 88].

Below, we discuss the remote effects of radiation in terms of the theory of radiotoxins. As revealed by A.M. Kuzin and L.M. Kryukova, the irradiation of a leaf of the plant *Vicia faba* (with complete shielding of the rest of the plant) leads to inhibition of mitotic division at growing points. Furthermore, the removal of the irradiated leaf within the next four hours after irradiation led to elimination of this effect [12, p. 19]. It is found that along with the inhibition of mitotic division, disruption of the chromosome apparatus occurs [12, p. 19]. Thus, the question on the participation of primary radiotoxins in abscopal (distant) effects of radiation (mentioned in the introduction) has a positive answer.

As shown in the works of B.P. Surinov (in 1997–1998), the joint maintenance (in one cage) of irradiated and nonirradiated mice and rats led to manifestations of the bystander effect in nonirradiated animals, such as a decreased level of leukocytes and nuclear neutrophils in peripheral blood, as well as a decreased immune responsiveness. The same effects were caused by bedding that was transferred underneath cages with nonirradiated animals from beneath cages with irradiated rodents. It was hypothesized that the signal of the radiation-induced bystander effect (bystander signal) is transmitted between animals via sex-dependent volatile compounds (pheromones) [20–25].

The authors interpret the results of this experiment according to the theory of radiotoxins. Lipid peroxides formed by irradiation are highly toxic volatile compounds. Lipoperoxidation products and generation of volatile metabolites might lead to release of a molecular bystander signal [26, 27].

One should also mention the series of the most recent experiments conducted by a group of Canadian researchers headed by C. Mothersill (McMaster University) [28–30]. As an explanation of the mechanisms of the bystander effect, a hypothesis on the role of biophotons of the UV spectrum in the interorganism transmission of the bystander signal is being tested, and some provisions of this theory have already been confirmed. The use of the aforesaid principles of quantum biophysics is assumed to bring the discussion on the mechanism of this phenomenon to a fundamentally new level [28–30].

As was shown in the previous experiments conducted by E.A. Neifakh [31–33], the process of peroxidation in the body led to chemiluminescence, the appearance of an ultra-weak biophoton emission in the blue–green spectrum, which is caused by the interaction of radicals. One cannot exclude the role of these photons, along with the action of metabolites of lipid peroxides, in the formation and transmission of a

radiation-induced bystander signal between cells and organisms.

CONCLUSIONS

Our first results within the scope of the planned studies (as an important task of modern radiobiology) have proved the induction of the bystander effect in a nonirradiated organism, resulting from its contact with an organism exposed to radiation. It was shown that a three-month joint housing of irradiated mice (3 Gy) together with nonirradiated mice caused changes in the nonirradiated animals (in the spleen, intestines, and skin) similar to the radiation-induced ones. Pathologies detected in the irradiated mice were revealed in a less pronounced form in the nonirradiated bystander animals.

The phenomenon of nontargeted effects and its mechanisms are still poorly studied. New data on the manifestations of nontargeted effects are being published every year, and fundamentally new approaches to the investigation of this phenomenon also appear in connection with the progress in the laboratory equipment and methods. The conclusions made in the course of this study are preliminary, and it is further supposed to test various hypotheses on the transmission mechanisms of the bystander signal at the organism level. The relevance of the research on the remote radiation-induced bystander effect is associated with the wide applicability of the results. Remotely induced bystander effects, being the subject of this study, pose a population-scale risk of transmission of radiation-induced damage (including the human population), and this requires special study and attention. The results of the assessment of nontargeted effects are greatly in demand in various fields: in theoretical radiobiology as one of the fundamental areas concerned with the effects of radiation on cells and organisms, in practical medicine for radiotherapy, and in radioecology in assessing the long-term effects of technological disasters and environmental changes. In the 21st century, in connection with the development of nuclear energetics, state and society are faced with threats such as radiation risks for the population and the environment. Knowledge of the manifestations of nontargeted effects (being very important links in the chain of radiation effects on biological objects) will be helpful in developing approaches for protecting the population from negative factors associated with increased background radiation.

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