QUANTITATIVE CHARACTERISTICS OF REPAIR PROCESSES IN SOME SYSTEMS OF THE BODY AFTER RADIATION INJURY

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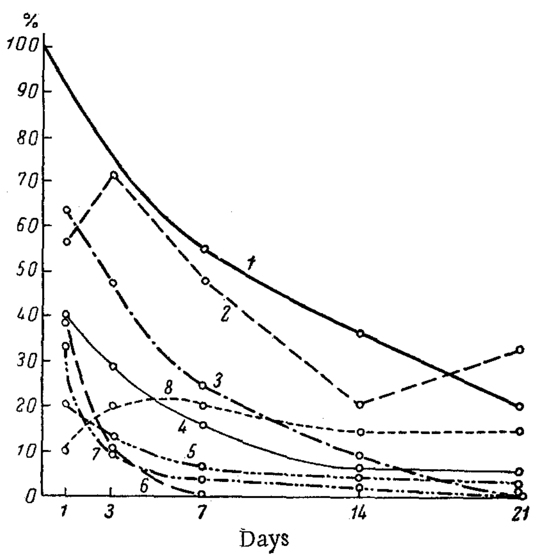
The quantitative estimation of restoration of the functions of the body makes use of the discovered effect that the resistance of animals to repeated irradiation is increased. In this case the quantitative assessment is conventional in character, because the repair processes are judged entirely on the basis of changes in radiosensitivity, without comparing the speed of repair in individual systems.

The object of the present investigation was to make a quantitative assessment of the process of recovery after irradiation, using as the test the resistance of the organism to repeated irradiation.

EXPERIMENTAL METHOD

Experiments were carried out on 640 sexually mature male albino rats weighing 180-220 g. The animals were irradiated on a cobalt apparatus at a dose rate of 192-196 R/min. Depending on the purposes of the investigation, the total number of rats was divided into four groups each containing 125-175 animals. The rats of group 1 were exposed once to whole-body γ-ray irradiation (300, 450, 500, 550, 600, 750, and 800 R). The animals of the other three groups were first irradiated in a dose of 300 R. They were reirradiated 7 days (group 2), 14 days (group 3), and 21 days (group 4) later, using different doses (300, 450, 500, 550, 600, 700 R).

By comparing the rate of survival of the animals after a single irradiation and after dividing the dose into two fractions, and using normal methods of statistical analysis, the degree of "residual" injury after the first dose of irradiation was determined on the 7th, 14th, and 21st days.



Dynamics of decline of radiation damage after γ-irradiation in a dose of 300 R. 1) "Residual" damage; 2) leukocytes; 3) bone marrow cells; 4) phagocytic number; 5) phagocytic index; 6) mitotic index; 7) aberrant mitoses; 8) erythrocytes.

The severity of the radiation injury and the characteristics of the repair processes after irradiation in a dose of 300 R were determined in 40 animals from the following indices; survival rate, peripheral blood picture, mitotic index, and aberrant mitoses in the bone marrow cells, the number of cells in the femoral marrow [9], the state of certain indices of natural immunity [2], and the pattern of changes of the body weight.

EXPERIMENTAL RESULTS

With an increase in the length of the interval between the two exposures to irradiation, a larger dose was needed to produce 50% mortality among the animals during the first 30 days ($LD_{50/30}$). This dose was equal to 600±41 R for a single exposure and 740±22, 790±12, and 840±29 R (95% confidence interval) after intervals of 7, 14, and 21 days respectively. The "residual" damage diminished during the first week by an amount corresponding to 140 R, and during the next 14 days by a further 100 R, so that the tempo of repair, which at first was quicker, gradually slowed. It was concluded from this that in these experiments the repair process was exponential in character. The theoretical curve of repair, calculated from the exponential equation $D_e = D_0 [f + (1 - f) \cdot e^{-\beta t}]$ [6], where f is the irreversible part of the lesion and β the rate of repair, coincided optimally with the experimental data when β was equal to 9.9% per day and f was 10%.

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Coefficients of Correlation between the Extent of the "Residual" Damage and the Degree of Change in the Investigated Systems

Index of investigated system	Coefficient of correlation	90% confidence interval
Leukocytes	0.76	− 0.265 − + 0.968
Erythrocytes	−0.297	− 0.882 − + 0.717
Bone marrow cells	0.98	+ 0.766 − + 0.997
Mitotic index	0.832	− 0.072 − + 0.978
Aberrant mitoses	0.861	+ 0.027 − + 0.982
Phagocytic activity	0.992	+ 0.912 − + 0.999
Body weight	− 0.897	− 0.182 −− 0.987

The half-repair period, calculated for these values of the rate of repair and of irreversible damage, was 7 days. However, the experimental results showed that for any value of f from 0 to 10%, and of β from 7.7 to 12.3%, the theoretical curve of repair lay within the limits of the confidence intervals of the biologically effective dose. It was concluded from an analysis of data in the literature [8, 10], and from the fact that optimal coincidence between the theoretically calculated values and the mean experimental results that the most accurate value of the irreversible damage was 10% and of the rate of repair 9.9% per day.

The dynamics of the injury and repair after irradiation in a dose of 300 R are illustrated in the figure. The radiation sickness in the rats followed the typical course for exposure to γ rays in minimal lethal doses. The number of leukocytes in the peripheral blood fell to a minimum of 28% of the initial level at the end of the 3rd day, and then rose slowly to 66% of normal after 21 days. Statistical analysis of the experimental results showed that the differences in the numbers of erythrocytes throughout the period of observation were not significant. In the irradiated rats, considerable changes were observed in the number and quality of the dividing bone marrow cells.

These results show that maximal suppression of mitotic activity and damage to the bone marrow took place immediately after irradiation. The rate of recovery of mitotic activity in the bone marrow cells was relatively high. By the 7th day the mitotic index was identical with the control value. The curve of increase in the number of bone marrow cells, estimated for the whole femur of the rat, followed an exponential course.

Chromosomal aberrations (fragmentation and rupture of chromosomes, chromosome bridges) in the ana- and telophase were regarded as signs of pathological cells in mitoses. A rapid fall in the number of pathological ana- and telophases was observed during the first 3 days, but a relatively small number of cells with chromosomal aberrations remained for a long time.

The curves showing the phagocytic activity of the neutrophils revealed a decrease in the protective power of the blood after irradiation. The depression of phagocytosis was shown by a decrease in the phagocytic index toward the end of the first day by 20% and a decrease in the phagocytic number by 40%, so that a reduction was observed both in the ingestive power of the leukocytes and in the percentage of neutrophils undertaking phagocytosis. Comparison of the severity of the damage and the extent of repair of the bone marrow with the functional capacity of the neutrophils reveal fluctuations in these two indices, although the severity of the damage to the bone marrow was greater immediately after irradiation.

As mentioned above, the object of the investigation was to reveal the relationship between recovery of resistance to repeated irradiation, assessed quantitatively by Blair's [6] method and recovery of the individual functional systems of the body. There are two possible approaches to this problem, depending on the experimental biological method used. The use of the classical method of multivariate correlation is beset by insuperable difficulties in the present case, such as the nonhomogeneity of the biological material, and the impossibility of determining the biological parameters at different times after irradiation and the time of death in the same animal. The method used in the present investigation [7] enabled the correlation to be made from the mean values of the "residual" damage and the changes in the physiological system aggregated for the various groups of animals. For this reason, for each of the comparisons correlation between two values only was used (the "residual" damage and the leukocytes, the "residual" damage and the bone marrow cells, and so on). The coefficients of correlation (see the table) and the 90% confidence intervals for the coefficients of correlation were calculated. Since the number of observations was small [5], Fisher's method [7] was used for constructing the confidence intervals.

The mechanisms and causes of the rapid increase in resistance of animals to repeated irradiation are not yet clear. The recovery of resistance to radiation is explained by an increase in the intensity of processes of regeneration in the body [5], the formation of artificial immunity to the ordinary microflora of the organism and to products of tissue destruction [3], or to a complex group of adaptive reactions of the organisms to radiation injury [4]. The hypothesis has been put forward [1] that the rapid recovery of radioresistance is connected with changes at the subcellular level and is independent of the physiological state of the organism. According to these results, radioresistance is determined by the physiological state of the organism (peripheral blood, thyroid function) only when 5 months have elapsed after irradiation. The suggestion that the role of physiological processes in the recovery of radioresistance is manifested only in the late stages seems unlikely. The results of the present experiment showed that the recovery of radioresistance is associated with the state of certain physiological parameters of the organism immediately after irradiation. The high positive correlation between the state of the bone marrow and phagocytic activity, on the one hand, and the level of "residual" damage on the other hand, demonstrates the important role of these systems in producing the recovery effect.

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