DYNAMICS OF REGENERATION OF BONE MARROW AFTER LOCAL IRRADIATION IN MICE AND RATS

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Comparison of regeneration of hematopoiesis in areas of bone marrow locally irradiated in various doses showed that these processes take place much more rapidly and completely in mice than in rats. The observed difference in repopulation is attributed to a relatively high lability of the stem cells in mice. With large doses of radiation, in late stages after local irradiation in mice and rats, a secondary decrease in the cell population of the bone marrow is found, coinciding with the onset of sclerosis.

The presence of a certain quantity of undamaged hematopoietic tissue in an irradiated animal gives a definite therapeutic effect [9]. The beneficial effect of screening is characterized by a marked increase in the survival rate and in the indices of regeneration of the circulating blood and bone marrow. It is most marked after the administration of doses causing death of most animals 7-20 days after irradiation from a bone marrow syndrome. The chief mechanism of repair processes is considered to be the liberation of intact polypotent hematopoietic cells from the screened areas, their survival, and their proliferation in the irradiated organism.

According to some results, the ability of stem cells to migrate spontaneously in the irradiated organism differs from one species of animal to another. Screening the leg of an irradiated mouse for 5 h is sufficient to obtain the maximum effect of an increase in survival [6], whereas in rats, to obtain this result the screened area of bone marrow must be present in the irradiated organism for a much longer time [13]. Screening of the forearm bones (2×10^6 nucleated bone marrow cells) gives high protection in mice irradiated in a lethal dose; in rats, to obtain the same result, both femora must be protected (250×10^6 nucleated marrow cells) [3]. In this connection, autografting of bone marrow, like stimulation of hematopoiesis (bleeding for 10 days before subtotal irradiation in a lethal dose) [7], remains effective in rats if a relatively greater volume of bone marrow is screened than in mice. It can be postulated on the basis of these results that in mice, polypotent stem cells possess a higher degree of mobility and greater powers of migration, colonization, and survival in irradiated areas than in rats. It is interesting to note that in monkeys, protection of an area of bone marrow (leg) is relatively less effective than in mice; subsequent transfusion of intact bone marrow from the screened area therefore increases their survival rate to a much greater degree [1].

To clarify the mechanisms lying at the basis of these differences, it was decided to compare the repopulation of bone marrow tissue in rats and mice following local irradiation of the bone marrow under conditions when most of the hemopoietic tissue remains intact, and the possibility of its recovery on account of bone marrow cells preserved in the irradiated area seems improbable because of the use of high doses of radiation. Such a comparison is particularly interesting in connection with existing data showing that repopulation on account of spontaneous migration of cells from unirradiated areas is not observed in man in areas irradiated in doses causing aplasia of the bone marrow [11, 12].

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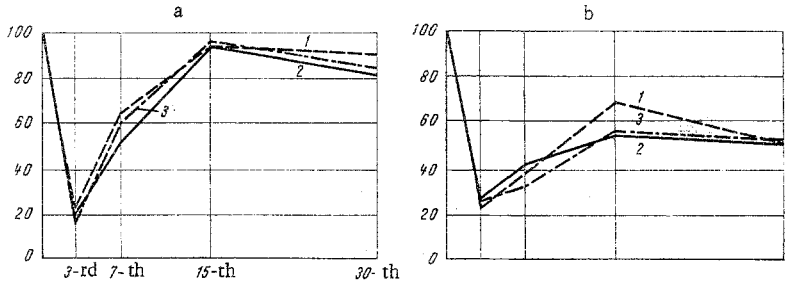

Fig. 1. Changes in number of karyocytes in bone marrow of tibia after local irradiation in mice (a) and rats (b). Ordinate, number of karyocytes in irradiated tibia (in % of control); abscissa, days after irradiation. 1) Local irradiation in dose of 1500 R; 2) local irradiation in dose of 2000 R; 3) local irradiation in dose of 3000 R.

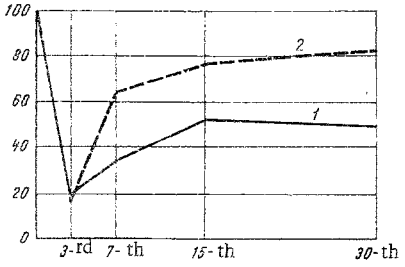

Fig. 2. Effect of autografting of bone marrow on dynamics of changes in number of karyocytes in tibial bone marrow following local irradiation in rats and subsequent autografting of bone marrow. Ordinate, number of karyocytes in irradiated tibia (in % of control); abscissa, days after irradiation. 1) Local irradiation in dose of 2000 R; 2) local irradiation in dose of 2000 R followed by autografting of bone marrow.

Despite the fact that much factual material concerning the radiation response of locally irradiated bone marrow has now been obtained, indicating that repopulation of damaged tissue can take place on account of migrating cells [2, 4, 5, 8], no special comparative investigations on different species of animals have been carried out. In addition, in most studies the response of the bone marrow tissue has been investigated only at different times after irradiation.

In the present investigation repopulation of locally irradiated bone marrow was compared in mice and rats.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 180-220 g and on noninbred male albino mice weighing 18-22 g. Local irradiation of the right leg was given from a type RUM-3 x-ray apparatus in single doses of 1500, 2000, and 3000 R, at a dose rate of 92 R/min. During irradiation,the animals were kept in a lead box with walls 1 cm thick, providing almost 100% protection as confirmed by dosimetry. The animals were sacrificed 3, 7, 15, and 30 days and 2, 4, and 6 months after irradiation, 5-10 animals at each time. The dynamics of changes taking place in the locally irradiated bone marrow was judged from the total number of nucleated bone marrow cells in the leg. The bone marrow from the leg of intact animals and the screened legs of irradiated animals served as the control.

EXPERIMENTAL RESULTS

By the 3rd day after irradiation of the leg, a sharp decrease in the total level of nucleated bone marrow cells was observed. On the average 20% of the cells remained. This was followed by a rapid and considerable increase in the number of cells reaching the control level by the 15th day (Fig. 1a).

In experiments on rats (Fig. 1b), the level of nucleated cells in the bone marrow in the tibia on the 3rd day after its irradiation was, just as in mice, 20% of the initial value. By the 7th day the total number of karyocytes in the irradiated tibia showed a slight increase, and by the 30th day it reached its maximum – about 50% of the control level.

Both in mice and in rats, the dynamics of the changes within the limits of the radiation doses of 1500, 2000, and 3000 R used was not substantially altered.

The results indicate that considerable specific differences exist in the rate and degree of regeneration of locally irradiated bone marrow in mice and rats. After an identical decrease in the number of karyocytes in the irradiated tibia, by the 15th day the normal level of bone marrow cells was restored in mice, whereas in rats the process of regeneration was much slower and repopulation to the normal level did not take place.

TABLE 1. Dynamics of Changes in Total Number of Karyocytes in Tibial Bone Marrow of Mice and Rats following Local Irradiation in Dose of 2000 R (in % of control)

Animals	Days				
	15th	30th	60th	120th	180th
Rats	54	51	36	31	43
Mice	94	82	93	70	41

The fact that the dynamics of the changes is only slightly dependent on the dose suggests that the observed specific difference between rats and mice are not the result of differences in radioresistance of the bone marrow tissue of the animals compared, but rather that they are attributable to differences in the ability of their stem cells to repopulate the damaged areas. Confirmation of this hypothesis is given by experiments in which, after local irradiation of the leg in a dose of 2000 R, rats were treated by autografting of bone marrow from a screened area. If irradiation in rats prevented repopulation by directly injuring the irradiated area of bone marrow and by creating conditions under which intact cells cannot be implanted in it and develop, autografting of unirradiated bone marrow could neither lead to repopulation nor intensify it. However (Fig. 2), autografting immediately after irradiation considerably accelerated recovery and significantly increased the number of karyocytes in the irradiated tibia. These results suggest that in rats, the stem cells are less mobile than in mice, and this may account for differences in the course of recovery processes in the animals compared.

In late periods after irradiation, in animals locally irradiated in a dose of 2000 R, a considerable secondary decrease in the number of bone marrow cells was found in the irradiated tibia (Table 1). This secondary decrease is evidently connected with the sclerotic changes developing at this time in the bone marrow stroma.

According to Knospe [10], autografting of bone marrow cells in the period of marked aplasia of bone marrow tissue in rats in the late stages after irradiation does not cause an increase in the number of karyocytes in the irradiated areas. This observation is in full agreement with the observed secondary depopulation of an irradiated area of bone marrow in the late stages after irradiation in large doses.

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