EFFECT OF SINGLE AND FRACTIONAL IRRADIATION ON NORMAL AND TUMOR TISSUES WITH SIMILAR MITOTIC ACTIVITY

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Single and fractional irradiation of normal (corneal epithelium) and tumor (ascites and solid forms of Ehrlich's carcinoma) tissues of mice possessing approximately equal mitotic activity produces different effects. Unlike in normal tissue, radiation damage in tumor tissue persists for a long time, and in the case of fractional irradiation summation of the damage takes place.

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Tissue systems differing in their rate of proliferation suffer different degrees of injury during irradiation over a period of time, and repair of damage produced by single irradiation also differs in its completeness [2]. No investigations have yet been carried out to determine whether the proliferative activity of a tumor has the same significance as for normal tissues in determining its response to single and protracted irradiation.

In this investigation the reaction of normal and tumor tissues with approximately the same proliferative activity to single and fractional irradiation was studied.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino mice weighing 20-22 g. The effect of single and fractional irradiation was studied on a normal tissue (corneal epithelium) and tumor tissue (ascites and solid forms of Ehrlich's carcinoma), on the basis of the results of a preliminary investigation which showed that these tissues are closely similar in their proliferative activity. The mean mitotic index for the 24-h period in the corneal epithelium is $18.7 \pm 1.7^0/_{00}$, and in ascites and solid forms of the tumor (on the 6th-12th day after transplantation) 16.4 ± 1 and $15.4 \pm 1.2^0/_{00}$, respectively. The duration of mitosis in both tissues, determined by the method of counting the rate of their disappearance after irradiation [1, 3], is also very similar.

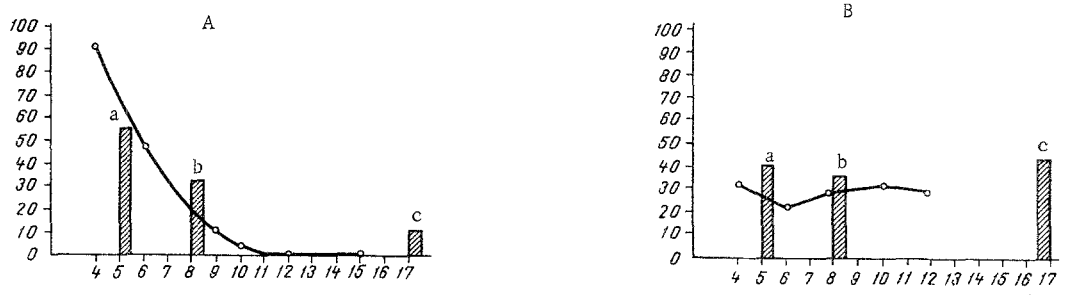

Fig. 1. Percentage of aberrant forms of mitoses in the corneal epithelium (A) and in the solid form of Ehrlich's carcinoma (B) after single and fractional irradiation in a dose of 1000 R. Continuous line 1000 R × 1; a) 250 R × 4; b) 147 R × 7; c) 62.5 R × 16. Ordinate, percentage of pathological mitoses; abscissa, time after irradiation (in days).

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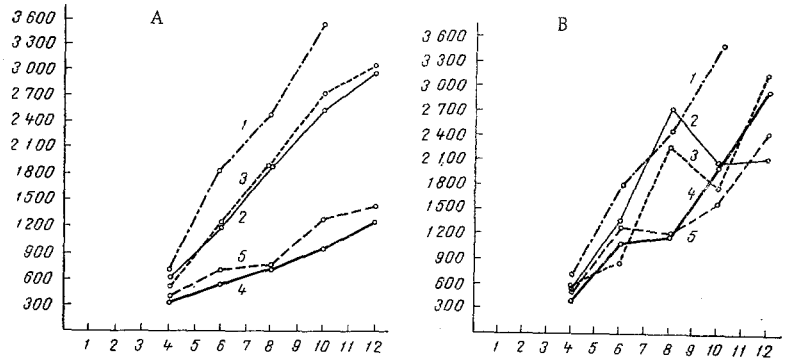

Fig. 2. Growth of tumor after single and fractional irradiation. A: 1) control; 2) 1000 R × 1; 3) 1000 R (250 R × 4); 4) 2000 R × 1; 5) 2000 R (500 R × 4). B: 1) control; 2) 1000 R × 1; 3) 1000 R (143 R × 7); 4) 2000 R × 1; 5) 2000 R (286 R × 7). Ordinate, weight of tumor (in mg); abscissa, time after transplantation (in days).

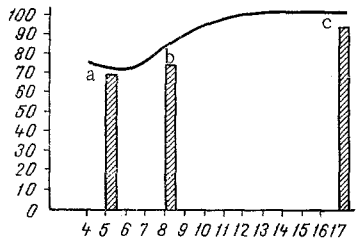

Fig. 3. Number of cells in stratum basale of corneal epithelium after single and fractional irradiation in a dose of 1000 R. Continuous line 1000 R × 1; a) 250 R × 4; b) 147 R × 7; c) 62.5 R × 16. Ordinate, number of cells in stratum basale of epithelium (in percent of control); abscissa, time after irradiation (in days).

Irradiation was carried out on the RUM-3 x-ray apparatus under the following conditions: 180 kV, 20 mA, filter 0.5 mm Cu + 1 mm Al, distance from source 30 cm, dose rate 78-87 R/min (ΔCu = 0.8). The effect of x rays was studied in doses of 2000 and 1000 R given at a single session, or after irradiation in equal fractions every 24 h in the course of 4, 7, and 16 sessions. The criterion of radiation damage to the corneal epithelium was the number of aberrant mitoses and the decrease in the number of cells in the stratum basale. Damage to both types of tumor was assessed from the number of pathological mitoses and from disturbance of the rate of growth after irradiation.

EXPERIMENTAL RESULTS

In the corneal epithelium during the first 24 h after single irradiation about 90% of all mitoses were pathological (Fig. 1A). Very quickly, however, their number fell sharply and when the dose used was 1000 R, aberrant mitoses in the epithelium were practically absent on the 10th-11th day after irradiation. With fractional irradiation, distribution of the total dose over 4 days resulted in a distinct weakening of the radiation effect. This weakening was still more marked when the total dose was divided into 7 and 16 fractions, for after its end, the number of pathological mitoses in the epithelium was 33 and 12%, respectively. With single irradiation this percentage of aberrant mitoses occurred only by the 7th-9th day for the same dose (Fig. 1A).

In contrast to the results obtained for the corneal epithelium, atypical mitoses persisted for a long time in the tumors: the percentage of aberrant mitoses was about the same on the 4th-12th day after a single irradiation, and in the case of fractional irradiation there was no decrease in the damage to the tumor (Fig. 1B). With a dose of 1000 R, for instance, the number of aberrant mitoses remained at about 30% after the end of irradiation split up into 4, 7, and even 16 fractions (daily dose 62.5 R).*

It can be concluded from the results of counting aberrant mitoses that repair of radiation damage in the cornea takes place more rapidly than in the tumor, despite the fact that the original level of mitotic activity in the compared tissues was the same. This conclusion is in agreement with the results obtained using another criterion of radiation damage to the tumor, namely disturbance of its growth determined from its weight, giving indirect evidence of changes in the number of cells in the tumor after irradiation. Changes in the number of cells in the cornea were determined by counting their number in the stratum germinativum of the epithelium.

* The number of pathological mitoses in the unirradiated tumor was about 8%.

The results of experiments in which the weight of the solid tumor was used as criterion of the action of single and fractional (4 and 7 fractions) irradiation on the ascites form of the tumor are given in Fig. 2. It is clear that under these experimental conditions, when fractional irradiation was used, approximately the same number of cells in the ascites tumor was damaged as after a single irradiation in the same dose. A similar result was obtained by irradiation of the solid tumor. Meanwhile, counting the number of cells in the stratum basale of the cornea after fractional irradiation revealed regeneration (Fig. 3).

Comparison of the injurious action of x rays on the corneal epithelium and on tumor tissue (Ehrlich's carcinoma), which observations showed to have closely similar mitotic activity, thus revealed essential differences. In contrast to what took place in the corneal epithelium, when repair was rapidly completed after single irradiation, and when the effect of fractional radiation was much weaker, in the tumor tissues radiation damage persisted for a long time, and in the case of fractional irradiation, even when the course stretched over 16 days, summation of the damage took place. It can be concluded from these results that repair after irradiation in normal tissue takes place more rapidly than in tumor tissue. It is difficult to explain the differences in the effect of irradiation on these two tissues. It is not yet known how the same percentage of aberrant cells in the tumor remains at a constant level over a very long period of time (17 days) despite its growth (4-5 periods of doubling the cell population). One possible explanation of the phenomenon could be to assume that a certain fraction of the damaged cells in the tumor remain capable of dividing and of yielding aberrant daughter cells. This hypothesis, which is supported by evidence in the literature showing that cells damaged by radiation are capable of dividing not once, but several times, is at present being verified. On the whole it seems to be established beyond doubt that differences in the capacity of normal and tumor tissues to undergo repair are dependent on differences in the degree of integration of these systems [4, 5]. Some particularly demonstrative evidence has been obtained in this respect from the study of postradiation changes in the number of cells in the corneal epithelium and tumor tissue. Whereas in the first case the number of cells in the stratum basale becomes normal as a result of processes of substitution by the 12th day after irradiation, in the tumor tissue no such compensation occurs. Depending on the size of the dose, a certain proportion of cells capable of growth remains in the tumor, for which, if comparatively small doses are given, the tumor develops at about the same rate as before irradiation (Fig. 2). Substitution processes taking place in the tumor after irradiation are thus less important than in normal tissue systems, and this may perhaps explain the difference obtained when changes in the number of cells in these tissues are studied after irradiation.

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