EFFECT OF CONDITIONS OF IRRADIATION ON INCIDENCE AND RATE OF DEVELOPMENT OF MAMMARY GLAND TUMORS IN RATS

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After irradiation of rats with x rays or γ rays in doses of 100 and 300 R at a single session or fractionally, it was found that fractionation of the dose does not affect the incidence or rate of development of mammary gland tumors and the composition of the circulating blood in the late stages. After fractionation of a dose of 600 R, giving rise if administered at a single session to a marked form of acute radiation sickness and causing rapid death of a high proportion of the animals in the early period, the life span of the animals is considerably prolonged.

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The incidence and rate of development of mammary gland tumors are considerably increased in female rats irradiated with x rays. The higher the dose, the sooner tumors are found and the more rapidly their maximal incidence is achieved [1-4].

The object of the present investigation was to study the effect of single and fractional irradiation on the incidence and rate of development of mammary gland tumors in female albino rats.

EXPERIMENTAL METHOD AND RESULTS

Experiments were carried out on 812 noninbred albino rats weighing 180-210 g and aged 4-5 months. The animals were irradiated with x rays at a single session or fractionally in total doses of 100, 300, and 600 R, according to the scheme in Table 1.

The composition of the circulating blood and the incidence and rate of development of mammary gland tumors (expressed as percentages of the number of animals surviving at that moment) were studied.

The incidence and rate of development of the mammary gland tumors and the dynamics of mortality among the rats are illustrated in Fig. 1, A and B.

It will be noted that, irrespective of the conditions of irradiation, the incidence and rate of development of mammary gland tumors were considerably higher in the experimental than in the control rats. For instance, when the animals were irradiated with x rays in a dose of 100 R, tumors were found after 8 months, compared with after 12 months in the control, while in animals irradiated with a dose of 300 R the corresponding figures were 8 and 13.5 months. In animals irradiated with γ rays in a dose of 600 R, neoplasms were found after 6 months, compared with after 12 months in the controls. Not only was the incidence of neoplasms of the mamary glands increased in the irradiated animals, but they also reached their largest size much sooner than in the controls (Fig. 1, A and B).

With fractional irradiation, the incidence and rate of development of mammary gland tumors showed little change within the limits of the dose range investigated. For example, after irraidation in a dose of 100 R, the incidence of mammary gland tumors was absolutely identical during the first 15 months after a single exposure and after fractional irradiation (10 R daily and 20 R on 5 occasions). In after periods, during protracted irradiation, the incidence was 10-20% lower than in animals irradiated in a single dose. However, statistical analysis by the $\chi^2(1)$ criterion showed that these differences were not significant at all times except 18 months.

The value of $\chi^2(1)$ after 16.7, 17.8, 19.7, and 20 months ranged between 0.95 and 2.35, and the value of P from 0.3 to 0.12. The differences were significant only at 18 months, when $\chi^2(1) = 4.4$ and $P = 0.035$

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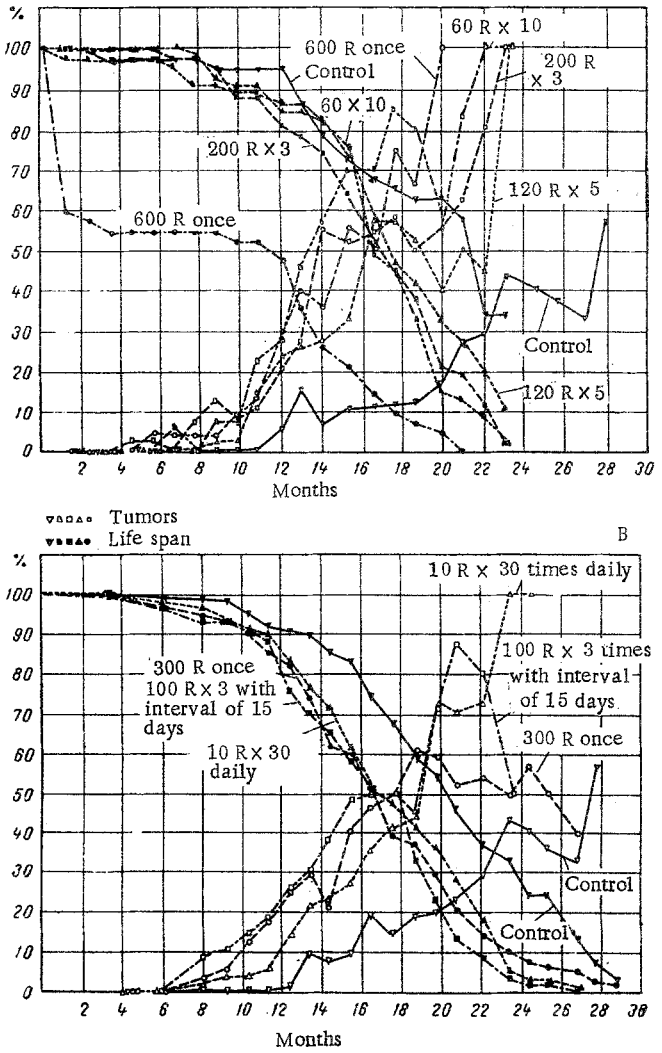

Fig. 1. Life span and incidence and time of origin of mammary gland tumors in rats irradiated with x rays and γ rays in a single dose and fractionally in doses of 600 R (A) and 300 R (B).

for the group of animals irradiated in a dose of 20 R weekly. Differences were almost significant ($\chi^2(1) = 3.68$; $P = 0.035$) for the group of animals irradiated with 10 R daily. The incidence of mammary gland tumors during the 20 months after irradiation in a dose of 300 R was practically the same if irradiation was given in a single dose or fractionally. It can thus be concluded from the results of the experiments with irradiation of rats in a dose of 300 R that fractionation of a dose which is allowable at a single session has little effect on the incidence and rate of development of mammary gland tumors. The most that can be said is that development of the neoplasms was slightly slower if the animals were irradiated in a dose of 10 R daily for 30 days. It is interesting to note in this connection also that the dynamics of mortality of rats irradiated in a dose of 300 R was the same regardless of whether the rats were irradiated once or fractionally. Compared with the control (20.4 months), the mean life span of the irradiated rats was much shorter (16.7 months).

A noteworthy fact concerning animals irradiated in a dose of 600 R was the considerable shortening of their life span after irradiation in a single dose. About 40% of the rats died during the first months. Half the rats in this group died before 11.3 months, compared with 16.5-17.4 months for those fractionally irradiated, and 21.3 months for the controls.

TABLE 1. Mean Life Span (in months) After Single and Fractional Irradiation of Rats in Accordance with the Selected Scheme

Agent used	Total dose (in R)	Conditions of irradiation	Dose rate (in R/min)	Number of rats	Length of survival (in months)
X rays	100	Single dose	5	75	16.2
" "	100	10 R daily	5	75	18.0
" "	100	20 R weekly	5	75	18.6
—	0	—	—	75	19.0
X rays	300	Single dose	5	90	16.7
" "	300	10 R daily*	5	60	16.7
" "	300	100 R once every two weeks	5	60	16.7
—	0	—	—	90	20.4
γ rays	600	Single dose	172	42	11.2
" "	600	60 R daily	172	45	16.5
" "	600	120 R weekly	172	45	17.4
" "	600	200 R monthly	172	42	16.8
" "	0	—	—	38	21.3

* Except holidays

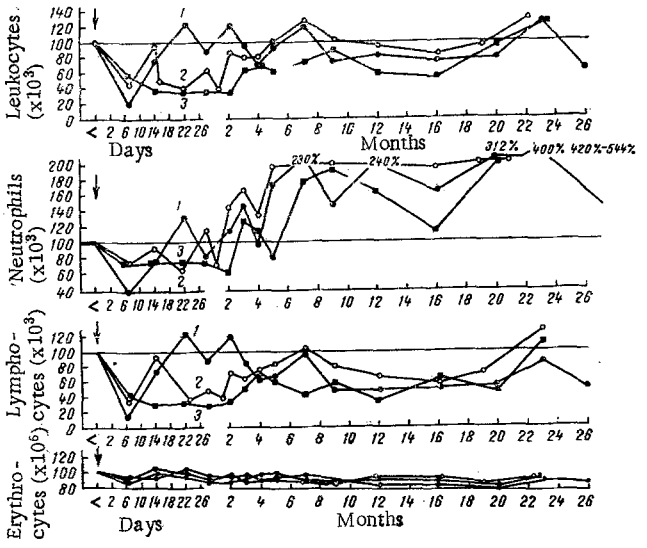

Fig. 2. Changes in blood composition of rats irradiated with x rays in dose of 300 R. 1) Single dose of 300 R; 2) 3 doses of 100 R; 3) 30 doses of 10 R.

Hematological investigations showed that irradiation in a single dose caused a more severe leukopenia than irradiation in fractional doses, the total dose being the same (Fig. 2), and recovery after leukopenia resulting from a single irradiation took place sooner than after fraction irradiation. Leukopenia after fractional irradiation persisted throughout the period of irradiation, while that developing after a single exposure took place within 14-21 days.

It can be concluded from the results of these investigations that after irradiation with x rays in total doses of 100, 300, and 600 R the incidence of mammary gland tumors is practically the same whether the irradiation be given as a single dose or fractionally. The fact must also be noted that in the case of effective doses by subacute or chronic administration (100 and 300 R), protraction and fractionation of the dose had no effect on the survival period of the rats or on the composition of their blood in the late stages. It should be remembered that injury to the ovaries, which are highly sensitive to the action of ionizing radiation, plays an extremely important role in the genesis of mammary gland tumors. A dose of 25 R gives rise to irreversible changes in the ovaries of some rats and mice, and the extent of these changes varies only slightly with an increase in the dose. It can therefore be postulated that it is not simply a matter of inadequate regeneration of irradiated cells and tissues, but also that the reaction investigated possesses a threshold. These facts are evidence of the virtually complete summation of radiation damage. By contrast, with the use of doses effective under acute conditions (600 R), causing death of a high proportion of animals in the acute stage of radiation damage, fractionation or protraction of the exposure considerably increases the life span of the animals. This observation indicates yet again the need for a differential approach to the analysis of reactions of the body to irradiation depending on the dose.

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