Title

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Abstract

Mortality at 6, 12, and 30 days was studied in male Swiss Webster white mice exposed to 730-MeV protons, 200-kVp x rays, and 100-kVp x rays at different dose rates. In the proton-irradiated mice, 6- to 8-day gastrointestinal death predominated at both 100 and 1000 rad/min, and was enhanced at the higher dose rate. In the x-ray exposures, 12- to 14-day hematopoietic death predominated and showed a similar dose-rate effect. The RBE for 30-day LD_{50} was found to be 0.8; the RBE for 6-day LD_{50} was found to be 1.2 at the same dose rate of 100 rad/min. It is suggested that the difference in injury mode may be due to differences in tissue dose distribution. The higher but variable proton RBE for 6-day gut death appears to exhibit the dose-rate effect associated with low-LET exposure. Practical consequences of the dose distribution and dose-rate factors are discussed.

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Introduction

The injury mode and relative biological effectiveness of high-energy protons in total body exposure of the mammal, in addition to their theoretical interest, have also become important in planning for future space exploration.[1]

A number of questions have already been raised in regard to this terrestrially rare but cosmically abundant radiation.[1, 2] An important one is whether different types of radiation with comparable LET--i.e., high-energy protons and x or γ radiation--will have different biological effects on man, and if so, against what type of damage should protective or therapeutic measures be directed?

Previous studies have delineated two main patterns of acute injury in the irradiated animal: First, the damage to the rapidly proliferating intestinal epithelium, occurring soon after exposure[3], and second, the more gradual onset of damage to the blood-forming tissue of bone marrow and spleen.[4] These so-called gastrointestinal and hematopoietic syndromes occur at moderate dose levels,

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lower than the supralethal doses required to produce damage to the central nervous system[5] but higher than the small doses that may ultimately result in malignant transformation or genetic mutation.[6] In x- and γ-ray exposures, the degree of damage has also been found to vary with dose rate[7] (as distinct from dose fractionation-recovery effects).

According to the relative predominance of gut or bone-marrow damage, the irradiated animal may respond to different protective measures or post-irradiation therapy. Antibiotic or electrolyte therapy may be useful in ameliorating gut damage[8]; spleen or marrow homogenate and lipid therapy may be beneficial in treating damage to the blood-forming system.[9,10] A knowledge of the injury mode of high-energy protons is therefore of obvious practical importance in planning for the protection of human beings in space exploration.

It is well known that the type and degree of biological effect from a given radiation exposure depend on a number of factors in addition to absorbed dose.[11,12] Some of these factors have been under investigation for the past year at this Laboratory. They may be grouped roughly as follows: (a) the intrinsic properties of the radiation; (b) the conditions of the exposure; and (c) the biological and environmental factors that may modify the effect.

It is now well established that RBE increases with the average LET of the radiation in many plant and animal cell populations, and may reach a maximum value in mammalian cells and organ systems beyond which further increase in LET produces a decline.[13,14] Although it is not easy to demonstrate in mammals the general principles resulting from data obtained with microbiological and cytological methods on single-cell populations, it appears reasonable to conclude that "low LET" radiation should exhibit an RBE near unity for any mammalian

end point chosen.

It also appears likely that with low-LET radiation, a "multi-event" response should be observed in the dose-effect relationship,[15] i.e., the RBE should vary both with the total dose and with the rate at which the total dose was delivered. A further condition affecting RBE is the exposure geometry or depth-dose distribution,[16] which may influence the mode of injury and thus make a particular end point or criterion of effect the significant factor in specifying an RBE value.

In these experiments we have dealt with short-term or acute effects only. In addition, the effects of dose distribution are ruled out as far as possible by producing a uniform whole-body dose with the proton beam of the 184-inch cyclotron.

In view of the difference in extent of the gastrointestinal and hematopoietic syndromes that we have observed, even in the uniformly irradiated mouse at different total doses and dose rates of proton and x-irradiation it was evident that the effect of both dose factors must be included, and the mode of injury must be specified in comparing the effectiveness of these radiations.

Since in mice, gut and marrow deaths occur at distinct and well-separated times after lethal total-body irradiation, these animals were chosen for the study. The characteristic times of peak death rate for each injury mode suggested that 6-day and 12-day mortality be selected as end points for comparison,[17] in addition to the more usual 30-day median lethal dose. These shorter mortality times were therefore determined for different total doses of 730-MeV protons, 250-kVp x rays, and 100-kVp x rays at constant dose rate. The effect of varying the dose rate was also studied.

Methods

A series of seven experiments was performed with 730-MeV protons and with 100-kVp and 250-kVp x radiation, and the relative lethality and time course of radiation injury were studied in more than 2000 randomly bred Swiss Webster white male mice obtained from Simonsen Laboratory.

All the animals had been inoculated against mouse pox 1 week before shipment to this Laboratory. Immediately upon arrival the animals were dipped in 1% malathion (0, 0-dimethyl dithio phosphate of diethyl mercaptosuccinate) and individually caged in pint-size Mason glass jars, according to the procedure previously found necessary to assure reproducibility of mortality data.[10] The mice were fed standard Simonsen Laboratory white diet and water ad libitum. The jars and water bottles were cleaned and sterilized at weekly intervals. During the 2-week period of pre-experimental acclimatization and isolation in the glass jars, the animals were carefully examined and weighed. Mice showing any sign of illness, abnormal growth, or loss of weight during the last 3 days of pre-irradiation isolation were discarded. Only animals that weighed 28 ± 3 g were selected for experimentation. These animals were distributed equally among the experimental groups. All animals were kept in air-conditioned rooms with continuous artificial lighting. The radiation sources were a Philips 250-kVp x ray machine and the 184-inch cyclotron. For x irradiation at 100 kVp 1.0-mm Al filters were added, and for 250 kVp, 1.0-mm Al and 0.5-mm Cu filters. The animals were irradiated in individual plastic holders on the irradiation positioning wheels, dorsoventrally in the x ray beam and anteroposteriorly in the proton beam.[18] The mouse midline air dose varied from 500 to 1100 rads per exposure.

X-ray exposure dose was measured at the centers of Lucite mouse canisters on the mouse exposure wheel, using a 250-R Victoreen thimble ionization

chamber. In the high-dose-rate exposures, the x ray beam was partially collimated by use of a modified treatment cone with Pb diaphragm so that the bulk of the intensity was received dorsoventrally by one mouse at a time. Each animal was positioned successively by modifying the rotating mechanism to allow one-step positioning. In order to achieve the high dose rate desired, the animal was placed close to the target of the x ray tube and left there for the required time, after which the next animal was moved into position. In this process, the neighboring animals also received a small fraction of the dose via scattering, so that the total exposure of each animal extended over about five wheel positions and was essentially zero at all other positions.

A series of seven 1-minute exposures was therefore made with the chamber occupying each of seven positions successively. To a first approximation the dose was equivalent to a total exposure at a dose rate of 100 rad/min. The total dose in passage through all seven positions was read on the ionization chamber and used for calculations in each experiment thereafter.

In the low-dose-rate x-ray exposures, the mouse wheel was rotated continuously and the resulting average dose rate was 20 ± 1 rad/min, midline in air.

The animals exposed to the 730-MeV proton beam were placed in a wheel-positioner which exposed one mouse at a time in a ventilated cylindrical holder. The diameter of the holder tube was about 1 inch. Dosimetry was by the parallel-plate aluminum-foil-walled ionization chambers routinely used in the medical cave.[19] These chambers are placed in the beam following its emergence from the vacuum collimating system into the air. Their effective collecting volumes are accurately known and are defined by guard rings surrounding the central foil disks mounted on Mylar film; the disks are somewhat smaller in diameter than the beam. The ion chambers are filled with nitrogen.

The emergent proton beam is nearly parallel and homogeneous and has been found to show an essentially flat intensity-distribution profile across its diameter when traversed by a miniature ionization chamber probe. By magnetically varying beam intensity, dose rates of 100 and 1000 rad/min were produced; they were measured with a relative accuracy of 2%.

The creation of secondary particles (neutrons, mesons, recoil nuclei) in the body of the animal by passage anteroposteriorly of the proton beam was not believed to be significant in such a small body as that of the mouse. Ionization in the mouse body probably remained uniform within 5 to 10%, according to measurements made in a mouse-sized water phantom with a small ionization chamber.

After irradiation the animals were returned to their respective cages for the duration of the experiment.

Results

Figure 1 shows the time course of mortality after various doses of proton radiation at 1000 and 100 rad/min. In the proton-irradiated mice, peak mortality occurred at 4 to 6 days postirradiation in the 30-day lethal range. Previous work at this and other laboratories has repeatedly demonstrated that death during this period in the mouse is due predominantly to gastrointestinal injury.[20] Since in the mouse this injury syndrome is well separated in time from the bone-marrow syndrome, it was considered reasonable to assume that all mortality up to 7 or 8 days be taken as gut death.

In Fig. 2, cumulative mortality is plotted in probit units vs time after 730-MeV proton irradiation. For each dose rate, total mortality data are combined for 700, 800, and 900 rads air dose. The use of cumulative mortality data plotted on a probability scale linear in standard deviation units clearly illustrates the marked increase in incidence and abruptness of 4-to-6-day gut deaths in animals

receiving a proton dose at 1000 rad/min compared with those irradiated at 100 rad/min. Thus at 5 days, 30% mortality was observed in the 100-rad/min animals, while 60% mortality had already been reached in the 1000-rad/min groups, although for a given total dose the 30-day mortality was the same in both groups.

In mice irradiated with 30-day lethal doses of 100-kVp x rays, peak mortality occurred at 12 to 14 days postirradiation. Figure 3 shows the time course of mortality after various doses of x radiation at 100 and 20 rad/min. Death in the mouse during this period has been shown to be due mainly to loss of hematopoietic function,[21] and it was assumed in these experiments that all mortality after about 10 or 11 days postirradiation could be considered as bone marrow death.

In Fig. 4, cumulative mortality for 850, 1000, and 1150 rads is plotted on the probability scale vs time after 100-kVp x irradiation. In animals irradiated with 30-day lethal doses, a fivefold increase in dose rate from 20 to 100 rad/min still produced few deaths from the gut syndrome, but the higher dose rate did effect an enhancement of the marrow syndrome similar to that observed for the gut syndrome with protons. When a total x ray dose high enough to produce 100% lethality in 12 days was given, however, 6-day gut death and the dose rate effect on it were again observed; when the data are combined for higher doses as shown in the figure, this effect is evident. Thus, 10% 6-day deaths were observed at 20 rad/min, while 30% 6-day deaths were seen at 100 rad/min. Since a dose rate higher than 100 rad/min was unobtainable with 100-kVp x rays, the effect of 1000 rad/min could not be investigated.

The 6-, 12-, and 30-day mortality values presented here for Swiss Webster male mice exposed to 100- and 250-kVp x rays and 730-MeV protons are based on a preliminary analysis of our mortality data. For accurate comparison of the different experimental parameters, each LD_{50} value was calculated from the regression of mortality by graphical probit analysis.

For 730-MeV protons, the total-body 30-day LD_{50} was found to be 650 rad air dose. It was found that this value was not significantly different at dose rates of 1000 and 100 rad per minute. The 12-day LD_{50} values, however, were 680 rad at 1000 rad/min and 700 rad at 100 rad/min, and the 6-day LD_{50} was 730 rad at 1000 rad/min and 810 rad at 100 rad/min.

It was found that for 250-kVp x radiation filtered with 0.5 mm Cu + 1.0 mm Al, the 30-day total-body LD_{50} was 520 rad air dose for both 100 and 20 rad/min dose rates. The 12-day LD_{50} was 610 and 630 rad respectively. The 6-day LD_{50} was approximately 1000 rad at 100 rad/min; the 6-day LD_{50} at 20 rad/min is being investigated.

For 100-kVp x radiation filtered with 1.0 mm Al, the 30-day total-body LD_{50} was 750 rad, midline air dose, for both 100 rad/min and 20 rad/min dose rate experiments. The 12-day LD_{50} was 850 and 900 rad respectively; the 6-day LD_{50} levels were not reached at the total doses given so far but can be estimated to be approximately 1100 rad at 100 rad/min and greater than 1300 rad at 20 rad/min.

Based on these data, tentative estimates of proton RBE may be made for gut death as well as for 30-day LD_{50}. If 30-day LD_{50} is used as end point, a value of 0.8 is found for 730-MeV protons, which agrees well with previous results obtained at this Laboratory and elsewhere.[22] On the other hand, if gut death is used as end point, a higher RBE results and dose rate is found to influence it. The 6-day RBE

for protons at 1000 rad/min relative to 250-kVp x rays at 100 rad/min is the highest value observed, a value of 1.4 being found. For protons at 100 rad/min, however, the 6-day RBE was 1.2 if the 250-kVp x irradiation was at the same dose rate.

The higher but variable RBE at 6-day LD_{50} level appears to be due to two factors. The first is the difference in tissue dose distribution between the two radiations, which favors the production of gut death by high-energy proton exposure. The second is the dose-rate dependency of the syndrome.

The 100-kVp x radiation is particularly efficient in producing marrow death, but causes gut death only at high air doses. Thus, a midline air dose more than 1.3 times that for 730-MeV protons was required to produce 50% gut death at 6 days, although 1.2 times the proton air dose produced a 30 day LD_{50} at 100 rad/min. To derive a true ratio of marrow doses, however, the average value of dose in the microscopic marrow cavities for 100-kVp x ray would have to be obtained. This dose has been shown to be several times as high in the smallest cavities as in the soft tissue surrounding the bone,[23] but no average value can be assigned to the marrow as a whole at this time.

If the cumulative mortality at 8 days, for example, were subtracted from the cumulative mortality at 30 days, a rough measure of bone marrow mortality might result for each radiation, since most gut deaths have occurred by this time and marrow injury has not yet manifested itself to any extent. If this is done for the proton exposures, very little mortality remains at later times, in contrast to the x ray exposures, and much higher marrow RBE values would result for the remaining mortality. The poor statistics resulting from the present data make this procedure of doubtful significance.

Discussion

Since the LET spectrum for 100-kVp x rays does not differ greatly from that of high-energy protons,[24] the marked difference observed in mode of death in these experiments appears to be due to the difference in tissue-dose distribution in gut and bone marrow between the two radiations, rather than to a change in sensitivity of the mouse intestine with change in LET.[25] In the high-energy-proton exposure, dose is "uniform" and thus comparable in both organs, and has a constant relation to air dose. Calculation has shown that, in exposure to soft x rays local dose in the marrow cavities may reach several times the average air dose[26], whereas the decrease in tissue dose with depth in turn lowers the gut dose relative to air dose.

It thus becomes difficult to observe a bone-marrow death with high-energy protons, because the rapidly occurring gut syndrome supervenes first if a uniform dose high enough to produce either mode of death is given. With soft x rays, on the other hand, either the high ratio of bone marrow dose to gut dose or a greater radiosensitivity of the marrow causes the marrow death to appear first.

Each syndrome in turn is subject to the dose-rate effect characteristic of low-LET radiation;[7] this has been found to appear in the gut syndrome with protons, and can be made to appear in either syndrome with x rays. If the total air dose in the latter case is not high enough to produce gut death, either a high local marrow dose or a high marrow radiosensitivity may produce marrow death, which also exhibits dose-rate dependency.

By protecting the proton-irradiated animal against gut death, it should be possible to produce the marrow syndrome and to demonstrate its dose-rate depend with protons. It should then also be possible to determine what proton dose to the

bone marrow is required to produce the syndrome, and thus to investigate the relative radiosensitivity of the bone marrow.

It is apparent from the results of these experiments that RBE values can differ between radiations of similar LET even under uniform exposure geometry, when there are differences in dose-rate dependence and injury mode. It is therefore clearly necessary to specify the effect to which a proton exposure RBE applies. In addition, a dose-rate factor must be introduced for exposures to low-LET radiations, of which the exposure to high-energy protons may be an important practical case in future space operations.

Most of the available information on RBE of external radiation for somatic effects on mammals refer to early rather than late effects, and to high rather than low dose rates.[27] Direct RBE measurements for late effects at low dose and dose rate present difficulties, and in no experiment thus far has the effectiveness of any radiation been adequately determined over a wide range of doses and dose rates for a given biological end point. In addition, other uncertainties are involved in the extrapolation to man of data from shorter-lived species with different response patterns, or of data obtained from tissue cultures or from single-celled organisms. These limitations apply to extension of these data to human exposure.

It is clear, however, that decreasing the dose rate of a high-energy proton irradiation reduces its effectiveness. Low-LET particulate radiation thus appears to behave similarly to low-LET electromagnetic radiation in this respect.[28] The explanation usually proposed for this effect is that the single cell may recover from unexpressed damage from the first of several events leading to a multi-event effect unless the first damage is followed by further damage within a given time by one or more later events. The practical implication of the phenomenon is that RBE values obtained with high dose rates may underestimate the RBE at low dose

rates or low levels of effect.

Previous work has led to the conclusion that mice exposed to "high-LET" radiations (mainly fast neutrons) show more bowel damage and die earlier than when exposed to "low-LET" radiations. The RBE for intestinal death in mice and in dogs irradiated with fast neutrons has been shown to be higher than for bone marrow death, a value of about 2 for gut death and 1 for marrow death having been observed.[21] In this study, however, greater bowel damage is apparently produced and earlier death has been observed with protons than with x rays. Both the dose-rate dependence of the effect and the calculated LET spectrum of high-energy protons suggest that this is not a high-LET phenomenon. A further point is that the 6-day gut death RBE of 1.4 for high-energy protons is not much greater than unity, although it is almost twice the proton RBE of 0.8 for 30-day mortality.

It appears that the above differences in effect may be ascribed to a difference in distribution of tissue dose, even under conditions of "uniform" dose, between the proton and x ray exposures, the latter favoring the bone marrow damage due to higher local dose, the former irradiating gut and bone marrow more equally. Differential radiosensitivity of the two tissues to each radiation may also be involved, but it cannot be inferred from the present results without additional information as to microdistribution of tissue dose. The dose-distribution factor and the dose-rate factor appear in any case to be comparable in importance to the LET in assessing the relative hazard of a proton exposure, and further investigation of each will be required to characterize it fully.

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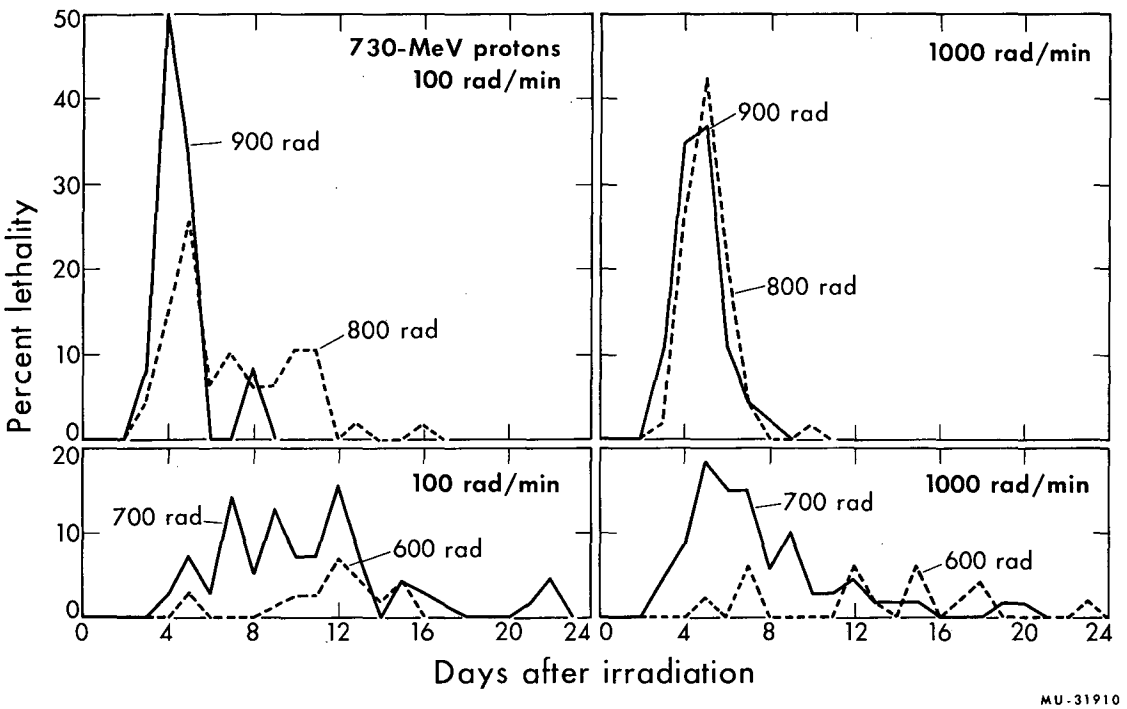
730-MeV protons
100 rad/min
900 rad
800 rad
1000 rad/min
900 rad
800 rad
100 rad/min
700 rad
600 rad
1000 rad/min
700 rad
600 rad
Percent lethality
Days after irradiation
MU-31910

Fig. 1.

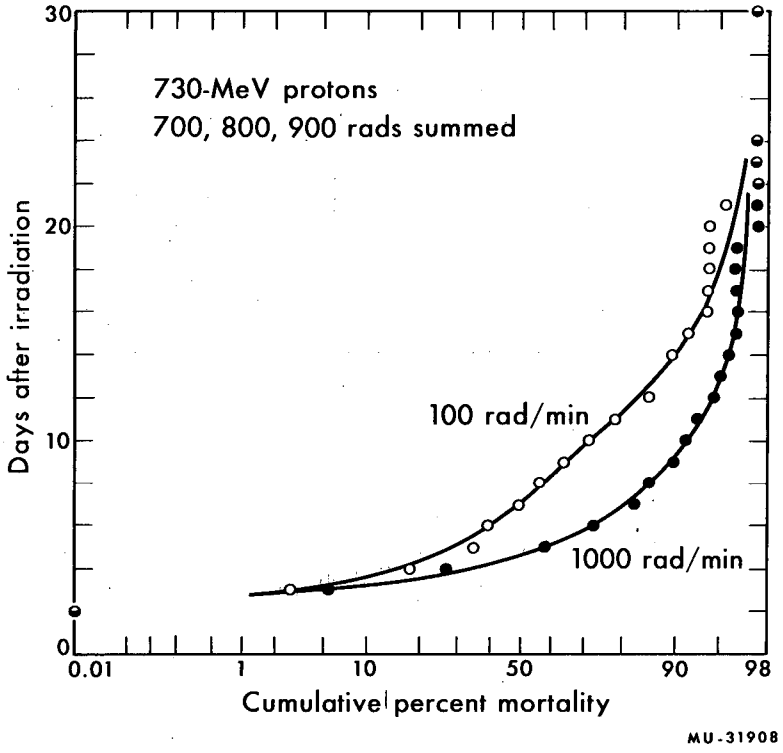
730-MeV protons
700, 800, 900 rads summed
100 rad/min
1000 rad/min
Days after irradiation
Cumulative percent mortality
0
10
20
30
0.01
1
10
50
90
98
MU-31908

Fig. 2.

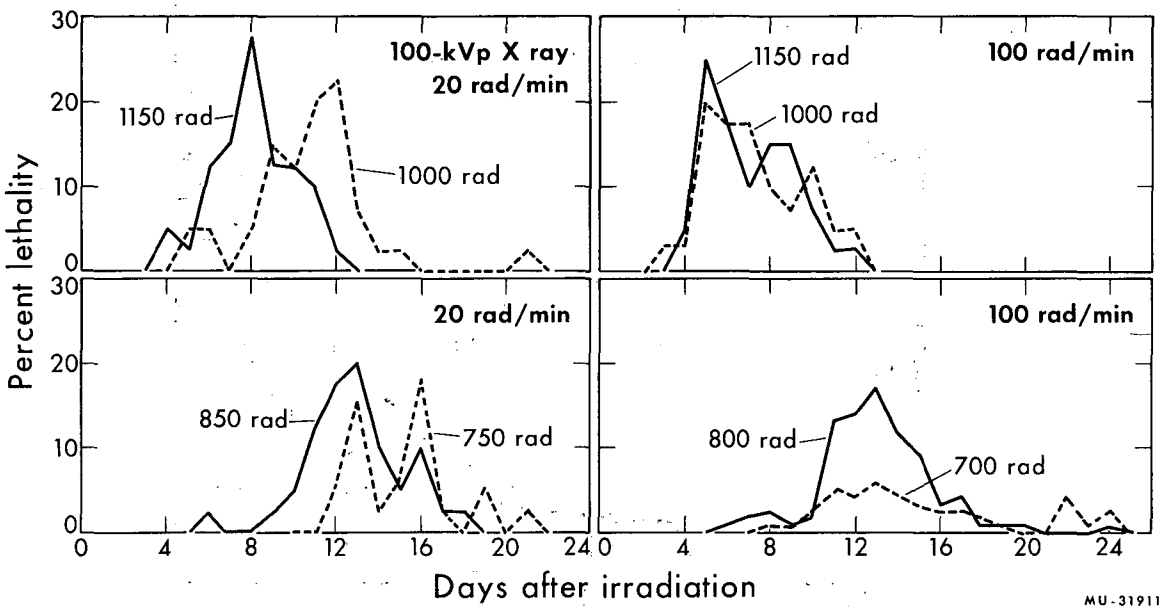
100-kVp X ray
20 rad/min
1150 rad
1000 rad
100 rad/min
1150 rad
1000 rad
20 rad/min
850 rad
750 rad
100 rad/min
800 rad
700 rad
Percent lethality
Days after irradiation
MU-31911

Fig. 3.

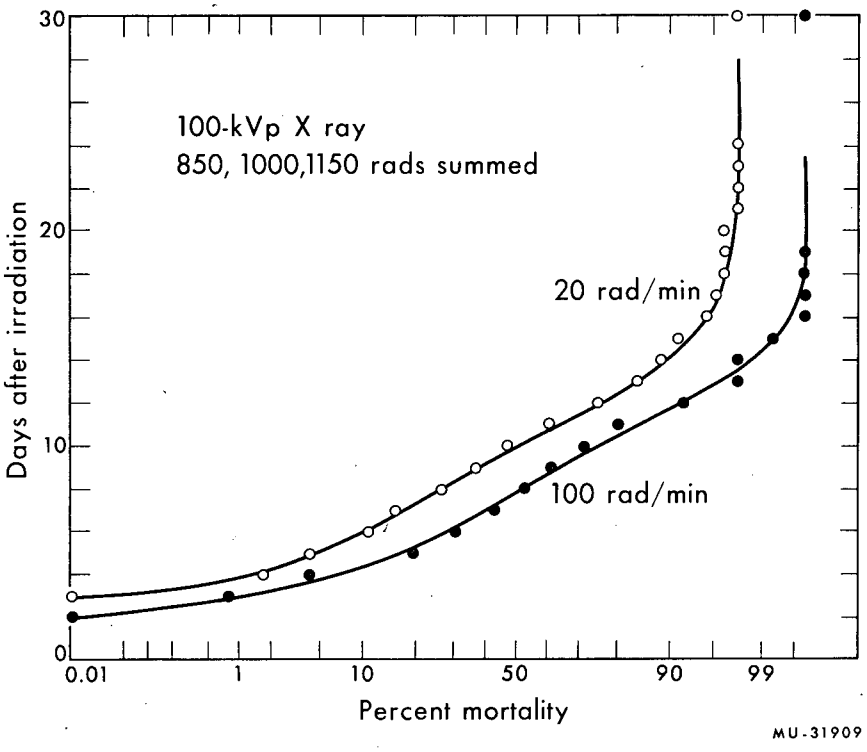
100-kVp X ray
850, 1000,1150 rads summed
20 rad/min
100 rad/min
Days after irradiation
30
20
10
0
0.01
1
10
50
90
99
Percent mortality
MU-31909

Fig. 4.