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DOSE-RATE EFFECT ON LIFE SHORTENING IN MICE

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ABSTRACT

An adult population of strain RF female mice were conditioned with thirteen discrete doses of cobalt-60 gamma rays ranging from 457-3455 rad given at a dose rate of 2.76 rad/h. Median after-survival times of conditioned groups were compared with control nonconditioned groups to determine life-shortening effects of gamma rays given at a relatively low dose rate. No linear dependence of life shortening on dose was observed. The average life shortening for all conditioning doses used was 83 days (0.04 day/rad). The relatively small life-shortening effects observed were attributed to several factors, including age at exposure and dose rate, and not to dose rate alone.

1. INTRODUCTION

Radiation-induced life shortening is recognized as one of the few consistently observed effects of persistent injury from whole-body exposure to ionizing radiation, and the effect *per se* does not appear to be age-, sex-, species-, or strain-dependent. Although small but permanent decrements in body weight, ⁽¹⁾ activity, ⁽²⁾ and resistance to cold stress ⁽³⁾ have been shown to be effects of persistent radiation injury, the major concern is the damaging effects that cause premature mortality, their nature, and extent to which they may depend on dose rate.

The specific nature of the chronic or long-term lesion from exposure to ionizing radiation is not well understood. A reduction of life span in rodents given a single acute dose or several doses in discrete fractions is generally accepted as a chronic effect of whole-body exposure to ionizing radiation. This radiation-induced life shortening has been called "radiation aging." Similarities and differences between natural and radiation-induced aging have been reviewed and studied extensively. ⁽⁴⁻¹²⁾ Definitive studies on experimental animals and human populations exposed to ionizing radiation ⁽¹³⁾ have shown that radiation-induced life shortening

cannot be described as an acceleration of normal aging in that it does not hasten the onset or progression of natural aging with all of the latter's manifestations.

Radiation-induced life shortening from acute radiation insults is reported to be a function of, and generally linear with, dose. ^(4,8,10,14,15,16) The average life-shortening effect of acute x- or gamma-ray exposures in the reviewed reports was 0.34 day/rad. ^(4,5,8,10,14,16) Dose fractionation is reported to be less effective than single acute doses in reducing life span, and as the interval between fractions is increased there is a tendency toward increasing the survival time. ⁽¹⁷⁾ Dose protraction has been estimated to be less effective than acutely delivered ionizing radiation by a factor of approximately four. ⁽¹⁸⁾ Although some data are available on the possible ameliorating effects of dose protraction on the persistent radiation lesion resulting in life shortening, ^(2,17) this estimate is based primarily on continuous low-dose-rate exposure-to-death data. Investigations designed to determine the life-shortening effects of whole-body exposure at low dose rate are not evident in the literature. This investigation was performed to provide the needed information in this area.

II. METHODS

Nine hundred and forty-four virgin female RF strain mice were used. The mice averaged 317 days of age, with a standard deviation of 27 days. This age group was selected to simulate an adult population that has attained full growth⁽¹⁹⁾ and peak activity.⁽²⁰⁾ The animals were selected at random and were divided into thirteen groups. Each group was exposed to ⁶⁰Co gamma rays at 2.76 rad/h until a predetermined dose had been accumulated. The dose received by each group is shown in Table I. Earlier dose-rate investigations using RF mice suggested that 5455 rad given at 2.76 rad/h would be the maximum dose from which survival might be expected.⁽²¹⁾ Dose rates were determined with a 2.5-r high-energy range Victoreen chamber at the front, mid-point, and back of the exposure cage, and the average of the three dose measurements was used. After exposure, the mice were housed five per cage on wood shavings in box-type, 12.7 x 20.32 x 30.48-cm, stainless-steel cages. Fresh bedding and water were provided on a weekly basis, and rodent food was given *ad libitum*. The mice were observed daily to record deaths and to ensure proper animal care. Survival

TABLE I

STRAIN RF VIRGIN FEMALE MICE 317 ± DAYS OLD EXPOSED TO DISCRETE GAMMA-RAY DOSES AT 2.76 rad/h

Total Dose (rad)	Exposure Time (days) ^a	Number of Mice			
		Exposed	Completed Exposure	Survived 60 Days Post-Exposure (No.)	Survived 60 Days Post-Exposure (%)
457	7	75	74	72	96
914	14	75	74	71	95
1354	18	78	78	75	96
1788	21	75	74	69	92
2264	24	76	76	70	92
2841	28	75	73	68	91
3408	32	75	71	50	67
3914	36	75	71	49	65
4503	38	75	73	42	56
5183	43	95	94	57	60
5908	46	30	27	11	37
6455	53	30	10	0	0
0	28 ^b	110	110	106	96

^a Rounded to days and includes source down-time.

^b Mean exposure time of 11 groups used.

times for this investigation were determined from the first day of exposure.

III. RESULTS AND DISCUSSION

Conditioning doses used, exposure times, number of mice exposed, those completing exposure, and those surviving to 60 days after exposure are shown in Table I. Only mice that survived to 60 days after termination of exposure were used in the comparative survival-time calculations. Mice that died within 60 days after being removed from the exposure environment were assumed to have died from injury other than that resulting in a long-term residual lesion.

The number of 60-day survivors of each dose group is expressed as % of the total number exposed in Table I and in Fig. 1. Most of the mice exposed to 1841 rad or less survived through the 60-day post-exposure period and were included in the median after-survival (MAS) calculations. As conditioning doses were increased above 1841 rad, the % of 60-day survival decreased. In Figs. 2 and 3, the cumulative distribution of survival time (from the beginning of exposure) is shown for the control group, the group with the lowest conditioning dose (457 rad), and the group with the highest conditioning dose (3008 rad). For comparative purposes, a normal distribution with mean ($\bar{x}$) and standard

Fig. 1. (A) Survivors (at 60 days) of thirteen conditioning doses, expressed as % of the number of mice exposed. (B) Reduction in survival time vs conditioning dose of 60-day survivors of thirteen conditioning doses. The life-shortening effects of doses between 0-457 rad and between 3000-3500 rad (from which there were no survivors) were not studied. These points are connected with dashed lines.

Fig. 2. Survival time distributions of nonconditioned mice and mice conditioned with 457 rad of gamma rays.

Fig. 3. Survival time distributions of nonconditioned mice and mice conditioned with 3008 rad of gamma rays.

deviation (s) is plotted for each set of data as a solid line. While the control group appears to be normally distributed, the treated groups have a skewed distribution. As a consequence, the median seems to be more meaningful than the mean as an expression of the most typical survival time.

Table II gives, for each conditioning dose, the reduction in survival time (i.e., the difference between the expected survival time and the observed median survival time). The expected survival time is the median survival time of the control group

TABLE II
REDUCTION IN SURVIVAL TIME^a OF MICE GIVEN GRADED
DOSES OF GAMMA RAYS AT 2.76 rad/h

Accumulated Dose (rad)	Expected ^b Median Survival Time	Observed Median Survival Time	Reduction in Survival Time (days)
0	---	315	---
457	315	236	79
914	315	239	76
1154	278	215	63
1388	315	194	121
1564	285	219	66
1841	315	217	98
2078	293	201	92
2314	315	217	98
2503	301	238	63
2783	308	207	101
3008	308	258	50
3455 ^c	---	---	---

^aSurvival time was calculated from the first day of exposure.

^bThe expected median survival time varies because the first day of exposure was not the same for all groups.

^cThere were no 60-day post-exposure survivors in this group.

(because of normality, the median for the control group is quite close to the mean). Both observed and expected survival times are reckoned from the beginning of exposure, and both quantities are given in Table II. The lowest conditioning dose given (457 rad) caused a reduction in survival time of 79 days, whereas the largest conditioning dose with 60-day survivors (3008 rad) caused a reduction in survival time of 50 days. As conditioning doses were increased, there was no accompanying increase in life shortening. This relationship between life shortening and conditioning dose is also apparent in data reported by Upton *et al.* (16)

Figure 1 shows the reduction in survival time vs conditioning dose. The slope of the regression line (not shown) is not significantly different from zero; therefore, there is no linear dependence on dose, as has generally been reported in the literature. (5-8,10,11,13,14,18) We conclude that

any dose between 457 and 3008 rad has about the same effect on survival time (i.e., there is an average life shortening of approximately 83 days for any dose in this range). This would indicate that, if one were to assume a linear relationship with dose between 0-457 rad, the effect on life shortening would be on the order of $83/457 = 0.18$ day/rad, about half the 0.34 day/rad reported in earlier investigations. (2,7,8,14,15,18,19) It may be that the saturation point of injury that hastens the onset of killing diseases is reached earlier than this dose, but the question which also raises itself at this point is the following: Is the effect of radiation dependent on the age at which it is received? If so, is the effect linear with age? The answer to the last question seems to be in the negative. Radiation-induced life shortening, as reported by several researchers, is plotted as a function of age at exposure in Fig. 4, with 600 days as the mean life span for the mouse. Most studies reported used relatively young mice. A straight line appears to be a reasonable fit on a semi-log graph. Thus, a nonlinear relationship between age at exposure and radiation-induced life shortening from the long-term lesion does appear to exist (Fig. 4). Mole⁽⁹⁾ has

Fig. 4. Life shortening (in days/rad vs age) of mice when exposed to conditioning doses: Storer (●); Lindop (Δ); Upton (□); Spalding (○); Silini (●); and estimate from current data (Δ).

reported that chronological aging and radiation are not additive and that life shortening is not a linear function of dose. Thus, the life-shortening effects of radiation exposure may be assumed to be influenced by both dose rate and age at exposure. The relatively small life shortening observed here is perhaps attributable to several factors, including age and dose rate. The cause of death of mice with different challenge doses was not determined. However, survival time distributions of nonconditioned and conditioned groups did not show a clustering effect. Survival-time distributions of the nonconditioned group are compared with those of the groups given the highest and lowest conditioning doses, as shown in Figs. 2 and 3. Although the survival curves of conditioned groups were shifted to the left of those for nonconditioned groups, the slopes of the curves were similar (i.e., the means are different, but the variances are not very different). Radiation-induced life-shortening investigations, including the dose rate and age factors required to provide definitive answers to the dose-rate and age questions such as how they may affect the incidence of neoplasms and other killing diseases, have not yet been done.

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