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THE INFLUENCE OF DOSE, DOSE RATE AND RADIATION QUALITY ON RADIATION CARCINOGENESIS AND LIFE SHORTENING IN RFM AND BALB/C MICE[1]

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Abstract

THE INFLUENCE OF DOSE, DOSE RATE AND RADIATION QUALITY ON RADIATION CARCINOGENESIS AND LIFE SHORTENING IN RFM AND BALB/C MICE

Over the past several years we have conducted large scale experiments in mice on the late biological effects as a function of dose, dose rate and radiation quality. Specifically, we have studied the effects produced by ^{137}Cs gamma rays delivered at a high (45 rads/min) or intermediate (8.2 rads/day) dose rate and the effect of fission neutrons at a high (25 rads/min) and low (1 rad/day) rate in a population of nearly 30,000 RFM and 11,000 BALB/c mice. Gamma ray doses ranged from 10 to 400 rads with the RFM's and from 50-400 rads with the BALB/c's, while neutron doses ranged from 5 to 200 rads with both strains. Data from these studies are now available both for life shortening and for the induction of a variety of neoplastic diseases. The present paper will present an overview of these data and the general findings while subsequent publications will present a detailed analyses of each aspect. A variety of neoplasms were sensitive to induction after radiation exposure, including tumors of both reticular tissue origin (leukemia, lymphoma, etc.) and solid tumors. For the RFM, thymic lymphomas were the dominant reticular tissue neoplasm while the majority of solid

tumors were either lung adenomas or fit into the broad category of endocrine related tumors, including ovarian, pituitary, harderian, and uterine tumors. The BALB/c was much less sensitive to induction of reticular tissue neoplasms. The tumors that were most sensitive to induction included malignant lung carcinomas, mammary adenocarcinomas and ovarian tumors.

In general for both life shortening and tumor induction after gamma ray exposures, when the low to intermediate dose range was sufficiently defined, linearity could be rejected and a dose squared or linear-dose squared relationship adequately fit the data. For neutron exposures, on the other hand, linear relationships were the general finding. The RBE for neutrons varied with tumor type and total dose level. For gamma ray irradiation, the intermediate dose rate resulted in a decreased effectiveness in all cases, while for neutron exposures the dose rate relationships were more complex.

INTRODUCTION

Although a large amount of research has been directed toward the study of radiation induced life shortening and carcinogenesis, many problems remain. For life shortening it can be generally concluded that low LET radiation (X or γ rays) are more effective when delivered at high dose rates than at low dose rates, while high LET radiations show less dose rate dependency and are more effective on a dose for dose basis than are low LET radiations (1,2,3). However, information on the forms of the dose response relationships for high and low LET radiation and quantitative information on the influence of dose rate and radiation quality are still lacking. For carcinogenesis the problems are even greater. At the present time there are few tumors for which the influence of dose, dose rate and radiation quality have been analyzed systematically. Therefore generalizations from the data presently available are difficult.

Over the past several years experiments have been conducted in this laboratory on the influence of dose, dose rate and radiation quality on radiation induced life shortening and carcinogenesis. Specifically we have studied the effects produced by ^{137}Cs γ rays delivered at high and intermediate dose rates and the effects of fission energy neutrons at a high and at a low dose rate. The present paper will present an overview of these data and the general findings while subsequent publications will present a detailed analysis of each aspect.

MATERIALS AND METHODS

Experimental Protocol

The experimental groups and the number of animals in each are shown in Tables I, II and III. As shown in Table I, experiment I contained both male and female RFM mice. Although the difference in response between the RFM male and female mice are of importance, the main purpose of this paper is to present data on dose response relationship for life shortening and carcinogens and the influence of dose rate and radiation quality on the relationship. Since only female mice were used in the studies on dose rate and radiation quality I have chosen to limit our discussion of experiment 1 in this paper, to the effects seen in the females. In Table III it can be seen that the acute portion of the neutron experiment actually consisted of two separate experiments. For the RFM these were not run simultaneously and differences in control incidences of thymic lymphoma were seen between these two experiments. Therefore during analysis we have treated these two portions of the RFM experiment as separate experimental groups. For the BALB/c experiment these two experiments were performed simultaneously. Since no differences were seen in these two groups they were treated as a single experimental series. The animals used in these experiments were germ-free-derived, specific-pathogen-free, 12-week-old female RFMf/Un and BALB/c/AnNBd mice housed in the Biology Divison barrier facility.

Details of the maintenance of these animals and their environment have been reported previously (4,5). Cages were checked twice daily (5 days/week) for dead or moribund animals; these were removed and autopsied, and tissues were taken for histologic examination.

Irradiation Factors and Procedures

Mice receiving γ irradiation at high dose rates were exposed in rotating individual plastic tubes to a 2000-Ci ^{137}Cs source at a distance of 45 cm and a dose rate of 45 rad/min. For low dose rate exposures, a 10-Ci ^{137}Cs source was used. Mice were exposed at a dose rate of 8.3 rad/day for a 20 hr day with the dose calculated as the dose to the midline of the cages housing the mice.

The details of the dosimetry and exposure conditions for both the high dose rate and low dose rate neutron irradiations have been described previously (6,7). Briefly, for high dose rate exposures, mice were exposed at the Health Physics Research Reactor (HPRR) in rotating nylon tubes. The low dose rate exposures were made with a 1.1 mg ^{252}Cf source surrounded by a depleted ^{238}U sphere to reduce the γ ray component and to degrade the neutron spectrum to make it similar to the HPRR spectrum. Animals were exposed at a dose rate of 0.96 rad/day for a 20 hr day with doses calculated at the midline of the cages housing the mice.

Statistical Procedures

To correct for animals lost to follow-up due to accidental death or removal, mean survival times and their standard errors were calculated by a modification of the method described by Hoel and Walburg and by a method based on Bayesian statistics (7,8). All regression equations were fitted to the data on mean survival times. Life shortening was calculated by subtracting the mean survival time in each experimental group from the mean survival time of the appropriate control group. The standard errors of "days of life shortening" were obtained as the square root of the summed, squared standard errors of the two groups.

The distribution of ages at death differed considerably among the various treatment groups. Because of this, the values for observed incidence of the various neoplasms do not accurately reflect the tumorigenic effectiveness of the radiation exposures. To reflect this effectiveness more accurately, we elected to use the direct age-adjustment procedure. This procedure is a common tool of epidemologist which adjusts the incidence values to those that presumably would have been observed had all the groups shown the same distribution of ages at death as a common reference population. The procedures differ somewhat for diseases that are rapidly lethal and those that are slowly progressive and often seen as an incidental finding when an animal dies from some other cause. Both procedures have been presented in detail elsewhere (6,9).

Because there were differences in control incidences of thymic lymphoma between the gamma ray and neutron irradiated groups and between neutron irradiated groups, it was necessary when making comparisons in these cases to correct for the control tumor incidence using Abbott's formula (6). These corrected incidences have only been used for drawing dose response curves which would best show the relationship between neutron and gamma ray exposure groups and have not been used for analysis of the shapes of the dose response curves.

Linear, square root of the dose, dose squared or linear-dose squared regression equations were fitted to the data. In all cases, the experimental values were weighted by the inverse of their calculated variance. Goodness of fit was tested using standard χ^2 tables.

RESULTS AND DISCUSSION

Dose Response Relationships after Acute Gamma Ray Exposures

Sufficient data to examine in detail the form of the dose response relationships for life shortening and carcinogenesis after acute gamma ray irradiation are only available for the RFM strain. For life shortening (Fig. 1) no simple model adequately described the entire dose range. Rather at least two distinct components were seen. Over the dose range of 0-50 rad a dose squared model adequately described the relationship ($P>0.80$) and linearity could be rejected. Above 50 rad, although a general linear trend was observed, linearity over the 100-400 rad range could be rejected because of inflections in the curve.

A number of neoplasms were sensitive to induction after radiation exposure, including neoplasms of reticular tissue origin and solid tumors. For the RFM female, thymic lymphoma and reticulum cell sarcoma were the dominant reticular tissue neoplasms. As has been reported previously, a decrease in reticulum cell sarcoma was observed after both gamma ray and neutron exposures (6,10). The dose response relationship for thymic lymphoma after acute γ ray exposures is shown in Figure 2. As with life shortening, no simple relationship adequately described the form of the entire dose response curve. Over the limited range of 0-25 rad linearity could be rejected ($P<0.01$) and a dose squared model adequately described the relationship. Over the 50-300 rad range the observed increase in incidence with dose was more nearly linear. The mechanistic basis for this apparent two component curve is not known.

The majority of solid tumors in the RFM female fit into the broad category of endocrine related tumors, including ovarian, pituitary, harderian and uterine. A number of lung adenomas were seen in all groups, but no

significant increases in incidence over control values were detected at any dose except at 300 rad. Two types of solid tumors, ovarian and harderian gland, shown in Figures 3 and 4 respectively, generally serve to illustrate the dose responses observed for the induction of tumors in the female RFM. Ovarian tumors were quite sensitive to induction. Over the dose range of 0-50 rad a linear quadratic relationship adequately described the relationship and both linear and dose squared models could be rejected ($P<0.01$). Following the rapid increase in incidence between 0 and 50 rad, a more gradual linear increase was observed. Most other tumors were not as sensitive to induction after acute γ ray exposures as thymic lymphoma and ovarian tumors. Rather the dose response relationship for uterine, pituitary and harderian gland tumors were all quite similar and could be illustrated by the dose response relationships for harderian gland tumor inductions shown in Figure 4. For this tumor, a linear quadratic model adequately describes the relationship between dose and tumor induction over the dose range of 0-200 rad. Over this same range a linear model could be rejected ($P<0.05$).

Dose Response Relationships after Intermediate Dose Rate Gamma Ray Exposure

Because RFM mice are known to be sensitive to the induction of reticular tissue neoplasms, in the studies on dose rate and radiation quality the BALB/c strain was used in addition to the RFM in order to obtain more information on the induction of solid tumors. A comparison of the extent of life shortening in the RFM after high dose rate and intermediate dose rate gamma ray exposures is shown in Figure 1. After intermediate dose rate gamma rays a linear relationship passing through the intercept adequately described the data. The large difference in effectiveness of the radiation at the two rates seemed to be due primarily to an upward displacement of the

regression line at the high dose rate which seem to take place over the 0-50 rad dose range after high dose rate exposures.

The more limited data comparing high and intermediate dose rate effects in BALB/c females were consistent with the RFM data. As shown in Figure 5 the major differences in the two curves is in the upward displacement at the high dose rate which has occurred over the 0-50 rad range. These data suggest a highly sensitive dose rate dependent injury component for life shortening in both the RFM and BALB/c which presumably saturates at high dose rates at about 50 rad. This component may be similar to the "dose independent component of radiation mortality in female mice" earlier identified by Sacher in mice given 200R or more (11).

For tumor induction in the RFM female the lower gamma ray dose rate was significantly less effective in all cases. Surprisingly, for thymic lymphoma and ovarian tumors, the relationship between tumor induction and dose shown in Figures 2 and 3 respectively, were best described by a linear quadratic model and linearity could be rejected ($P<0.001$) even at this lower dose rate. For harderian gland tumors (Fig. 4) dose response at the lower dose rate was linear ($P>0.90$).

The more limited data comparing the effects of high and intermediate dose rate gamma ray exposures on tumor induction in female BALB/c mice are shown in Table IV. The BALB/c was much less sensitive to the induction of reticular tissue neoplasms. The tumors that were most sensitive to induction included malignant lung adenocarcinomas, mammary adenocarcinomas, and ovarian tumors. As in the RFM, the lower dose rate was less effective in all cases. Also as in the RFM, the dose response relationship for the induction of ovarian tumors at the lower dose rate was adequately described by a linear quadratic and linearity could be rejected ($P<0.05$). For mammary

and lung adenocarcinomas, the dose response relationships at the lower dose rate could be adequately described by the linear relationships:

$$y=7.8+0.035X$$

and

$$y=12.5+0.043X,$$

respectively. Since the limited high dose rate data for mammary and lung tumors were also adequately described by linear relationships:

$$y=7.9+0.067X$$

and

$$y=13.4+0.12X,$$

and since the intercepts of the equations were similar, the differences in slope were a reflection of differences in effectiveness of the two dose rates. The ratio of the slope constants for mammary tumors ($\frac{0.067}{0.035}$=1.9) and lung tumors ($\frac{0.02}{0.043}$=2.8) suggest a greater dose rate effect for lung tumor induction than for the induction of mammary tumors.

Influence of Radiation Quality on Dose Response Relationships for Life Shortening and Carcinogenesis

After high dose rate neutron irradiation of both RFM and BALB/c females, the dose response for life shortening over the dose range including 0, 24, 47 and 94 rad was adequately described by regression of survival time as the square root of the dose (Figures 6 and 7). However, for the data covering the dose range of 0-47 rad shown in Table V a square root regression could be rejected ($P<0.01$) and linearity gave a good fit for both the RFM ($P>0.9$) and the BALB/c ($P>0.5$). After low dose rate neutron irradiation, the response was somewhat different. In RFM mice, the low dose rate was less effective than the high dose rate at 24 rad, but more effective at 188 rad (Fig. 6).

In the BALB/c, little dose rate dependence was observed at low doses, while at the 188 rad dose the low dose rate was more effective (Fig. 7). The greater life shortening at 188 rad with low dose rate neutron exposure is consistent with previous observations (12). The reduced effectiveness at 24 rad in the RFM mice was more surprising. Since the result was obtained at one dose and in only one of the strains, it might be argued that this was a spurious point or may reflect some effect unique to the RFM female mouse. However, recent data from the Argonne National Laboratory also suggest such a reduced effect at a dose of 20 rads when the dose was fractionated (13). Such data suggest that further studies examining the effects of low dose rate neutron irradiation below 20 rads are warranted.

Irradiation with neutrons was also more effective in inducing tumors than was irradiation with gamma rays, particularly in the low dose range. For the RFM, because of the small sample sizes used in the experiment examining the 0, 4.8, 9.6, 19, 24, and 47 rad range solid tumors could not be analyzed and information in the low range was only available for the induction of thymic lymphoma. The data from the larger experiment covering the range of 0, 24, 47, 94, and 188 rad are shown in Figure 8. For the acute neutron dose response curve over the 0-94 rad range linearity could be rejected ($P<0.001$) and a dose squared model adequately described the data. The 0-47 rad range was able to be examined more fully by using the data for thymic lymphoma from the smaller experiment. Although the control incidence in this smaller experiment was slightly different than in the larger experiment, correction with Abbott's formula indicated that the excess incidence was similar at similar doses for both experiments. Because of this we felt that the data from the smaller experiment would be applicable for defining the shape of the dose response curve. Using these data shown in Table VI a linear relationship adequately described the curve over the

0-47 rad range (P>0.75):

$$y=5.2+0.56X$$

In the chronically exposed group a linear relationship adequately described the curve over the 0-94 rad range (P>0.8):

$$y=5.3+0.39X$$

The ratio of the slope constants suggest that chronic exposure was less effective in the low dose range, but this difference was not significant. In the high dose range chronic irradiation was significantly more effective than acute neutron irradiation for the induction of thymic lymphoma.

The effects of dose and dose rate on tumor induction after neutron exposure in female BALB/c mice are shown in Table VII. Lung adenocarcinomas were quite sensitive to induction with neutrons with the incidence increasing rapidly with dose to a peak incidence of 38.7 at 10 rads. This curve could be adequately described by a linear dose response relationship (y=12+2.6X) over the 0-10 rad dose range. The dose response for the chronic neutron exposure was somewhat different and a linear relationship adequately described the curve over the entire dose range:

$$y=12.8+0.17X$$

Because of the nature of the two dose response relationships, low dose rate neutron irradiation appeared to be less effective than high dose rate irradiation at low total doses, but more effective at high total doses. The data for mammary tumor induction was quite similar to those for malignant lung tumors with a rapidly rising neutron dose response over the 0-10 rad range with a linear slope of 1.14 for acute exposures. The low dose rate appeared to be less effective at low total doses, but markedly more effective than acute exposures at 188 rads. For the low dose rate exposures

a linear dose response relationship ($y=7.3+0.18X$) adequately described the dose response over the 0-188 rad range.

Neutron irradiation at low dose rates was less effective than at high dose rates in inducing ovarian tumors at all doses tested. For acute neutron irradiation the dose response could be adequately described by a linear ($P>0.750$) ($y=4.4+0.87X$) or a linear quadratic ($P>0.975$) ($y=5.2+0.52X+0.0072X^2$) while for chronic neutron irradiation a linear model ($P>0.75$) ($y=4.8+0.13X$) adequately described the relationship.

The relative biological effectiveness (RBE) of neutron varied with endpoint and in some instances with dose level. At high dose rates of neutrons and γ rays, the RBE for life shortening in the RFM female varied with the level of effect as indicated by the dissimilar shapes of the dose response curves. Calculation of RBE was further complicated because of the apparent two component nature of the life shortening response. In the dose range below 50 rads of γ rays it was found that the RBE of neutrons varied with the inverse of the square root of the dose. Such a relationship has been predicted by the theory of dual radiation action and has previously been reported for a variety of endpoints by Kellerer and Rossi (14). At doses above 50 rad, an estimate of RBE, based on the ratio of slope of the linear regression of γ ray and neutron responses was obtained. Because of limited data, a similar procedure was used for the RBE estimates in the BALB/c. In this dose range the RBE estimates for RFM mice (RBE=2.9) and BALB/c mice (RBE=3) were remarkably similar.

Estimates of RBE values for tumor induction were also obtained. For the induction of thymic lymphoma in the RFM mouse, over the dose range of 0-50 rad the response to gamma rays varied with the square of the dose while the response to neutrons varied linearly. Thus, as with life

shortening, the RBE increased with decreasing dose in a manner proportional to the inverse of the square root of the neutron dose. The exact relationship ($RBE=20D_n^{-0.5}$) would predict an RBE of 4 at 25 rad and 20 at 1 rad. For the other tumors examined the dose response relationships were less well defined and the relationship between neutron dose and RBE could not be properly examined. For lung adenocarcinomas and mammary adenocarcinomas, because the dose response relationships for both γ rays and neutron could be described by linear relationships, a comparison of the slope constants provided an estimate of the RBE for neutrons. For lung adenocarcinomas this method gave an estimated RBE of 21.7 while the RBE estimate obtained for mammary tumors using this method was 17. For ovarian tumors, because of limited information on the gamma ray dose response relationship in the region between 0-50 rad, no RBE could be estimated. At 50 rad however, the RBE appeared to be close to one.

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TABLE I. EXPERIMENT I — RADIATION DOSES AND SAMPLE SIZES OF RFM MICE EXPOSED TO γ RAYS AT 45 RADS/MIN

Strain and sex	Dose (rads)	Number of mice exposed
RFM ♀♀	0[a]	4014
	10	2827
	25	965
	50	1143
	75	246
	100	1100
	150	1043
	200	333
	300	4133
	400	396
RFM ♂♂	0[b]	430
	10	256
	25	94
	50	247
	100	230
	150	204
	300	571

[a]Controls.

TABLE II. EXPERIMENT II — RADIATION DOSES AND SAMPLE SIZES OF RFM AND BALB/C FEMALE MICE EXPOSED TO γ RAYS AT 40 RADS/MIN OR 0.0069 RADS/MIN

Strain and sex	Dose rate (rads/min)	Dose (rads)	Number of mice exposed
RFM ♀♀		0[a]	749
	40	50	775
		200	766
	0.0069[b]	50	1468
		100	1531
		200	1526
		400	866
BALB/c ♀♀		0[a]	865
	40	50	860
		200	865
	0.0069[b]	50	1293
		100	1323
		200	1372
		400	1013

[a]Controls.

[b]At this dose rate the mice received 8.3 rads/20-hr exposure day.

TABLE III. EXPERIMENT III – RADIATION DOSES AND DOSE-RATES AND SAMPLE SIZES OF RFM AND BALB/C FEMALE MICE EXPOSED TO FISSION NEUTRONS

Strain and sex	Dose rate	Dose (rads)	Number of mice exposed
RFM	--	0[a]	312
	25 rads/min	24	303
		47	324
		94	333
		94 at 25 weeks	224
		188	332
	1 rad/day	24	311
		47	311
		94	309
		188	368
	5 rads/min	4.8	112
		9.6	110
		19.2	111
		47.0	112
BALB/c	--	0[a]	296
	25 rads/min	24	324
		47	315
		94	323
		94 at 25 weeks	224
		188	328
	1 rad/day	24	311
		47	311
		94	319
		188	360
	5 rads/min	4.8	111
		9.6	112
		19.2	112
		47.0	108

[a]Controls.

TABLE IV. INFLUENCE OF DOSE RATE ON INDUCTION OF NEOPLASTIC DISEASES IN FEMALE BALB/C MICE EXPOSED TO GAMMA RAYS

Tumor	Dose (rads)	Age adjusted incidence (%±S.E.)	
		High dose rate[a]	Low dose rate[b]
Ovarian tumors	0	6.4±1.4	
	50	66.1±2.3	9.9±1.8
	100	--	21.9±2.6
	200	75.9±2.2	42.5±2.8
Mammary adeno carcinomas	0	7.6±0.9	
	50	12.1±1.4	9.0±0.9
	100	--	13.2±1.2
	200	20.5±2.5	13.9±1.3
Lung adeno carcinomas	0	12.8±2.2	
	50	21.4±3.0	14.5±1.8
	100	--	16.5±2.1
	200	36.8±5.4	21.4±2.6

[a]45 rad/min.

[b]8.3 rad/day.

TABLE V. MEAN AGES AT DEATH OF RFM AND BALB/C FEMALE MICE EXPOSED TO FISSION NEUTRONS

Strain and sex	Dose rate	Dose (rads)	Number of mice exposed	Mean age at death (days±SE)	Life shortening (days±SE)
RFM	--	0[a]	312	644.0± 8.21	--
	5 rads/min	4.8	112	620.0±15.32	24.0±17.38
		9.6	110	616.2±14.63	27.8±16.78
		19.2	111	588.0±16.97	56.0±18.85
		47.0	112	486.4±16.35	157.6±18.30
BALB/c	--	0[a]	296	794.8± 9.02	--
	5 rads/min	4.8	111	795.1±16.28	-0.3±18.61
		9.6	112	746.9±16.82	47.9±19.09
		19.2	112	686.5±16.29	108.3±18.62
		47.0	108	638.5±15.77	156.3±18.17

[a]Controls.

TABLE VI. INCIDENCE OF THYMIC LYMPHOMA IN FEMALE RFM MICE AFTER NEUTRON IRRADIATION

Type of neoplasm	Incidence (%±SE) after a dose (rad) of:				
	0 (control)	4.8	9.6	19.2	47
Thymic lymphoma	7.3±1.2	10.9±2.7	10.9±2.1	19.8±3.0	33.0±3.3

TABLE VII. INCIDENCE (%±SE) OF SOLID TUMORS IN NEUTRON-IRRADIATED BALB/C FEMALE MICE

Dose rate	Dose	Tumor type		
		Lung adenocarcinoma	Mammary tumors	Ovarian tumors
	0 (control)	12.8±3.4[a] (12.8)[b]	7.0±1.6 (7.0)	5.5±2.1 (5.5)
5 rad/min	4.8	27.1±4.8 (27.5)	6.9±2.6 (7.7)	6.7±4.1 (5.0)
	9.6	33.7±5.1 (29.2)	24.8±4.5 (20.6)	10.5±4.6 (8.3)
	19.2	19.3±5.1 (11.3)	17.8±5.0 (11.6)	19.7±4.9 (25)
	47	21.7±4.7 (13.6)	17.2±5.6 (8.[illegible])	49.2±4.0 (45.5)
25 rad/min	24	19.3±4.8 (12.2)	16.9±2.4 (9.0)	37.1±4.6 (34.6)
	47	22.7±5.1 (13.5)	18.9±3.7 (9.2)	56.8±5.4 (57.6)
	94	18.6±5.7 (8.0)	16.9±3.9 (9.3)	61.5±3.5 (47.9)
	94 at 25 weeks	20.0±5.2 (10.1)	17.2±4.9 (11.6)	43.0±5.2 (42.5)
	188	12.5±5.2 (5.0)	15.3±5.4 (5.0)	38.5±5.5 (21.3)
1 rad/day	24	12.5±4.6 (8.9)	13.5±2.9 (8.3)	6.7±2.9 (6.6)
	47	26.9±5.7 (13.1)	17.2±3.7 (8.9)	9.6±3.7 (6.9)
	94	31.6±5.5 (13.8)	19.2±3.8 (10.2)	18.6±4.2 (19.1)
	188	43.1±5.7 (15.6)	45.2±5.3 (17.0)	20.9±5.1 (6.0)

[a]Age-adjusted incidence.
[b]Observed incidence.

FIGURE LEGENDS

FIG. 1. Life shortening as a function of dose in female RFM mice after 45 rad/min (●) or 8.3 rad/day (○).

FIG. 2. Percent incidence of thymic lymphoma as a function of dose in female RFM mice after 45 rad/min (●) or 8.3 rad/day (○).

FIG. 3. Age adjusted percent incidence of ovarian tumors as a function of dose in female RFM mice after 45 rad/min (●) or 8.3 rad/day (○).

FIG. 4. Age adjusted percent incidence of harderian gland tumors as a function of dose in female RFM mice after 45 rad/min (●) or 8.3 rad/day (○).

FIG. 5. Life shortening as a function of dose in female BALB/c mice after 45 rad/min (●) or 8.3 rad/day (○).

FIG. 6. Life shortening as a function of dose in female RFM mice after irradiation with neutrons at a high (●) or low (○) dose rate.

FIG. 7. Life shortening as a function of dose in female BALB/c mice after irradiation with neutrons at a high (●) or low (○) dose rate.

FIG. 8. Percent incidence of thymic lymphoma after acute gamma-ray (△), acute neutron (●), or chronic neutron (○) irradiation.

34360

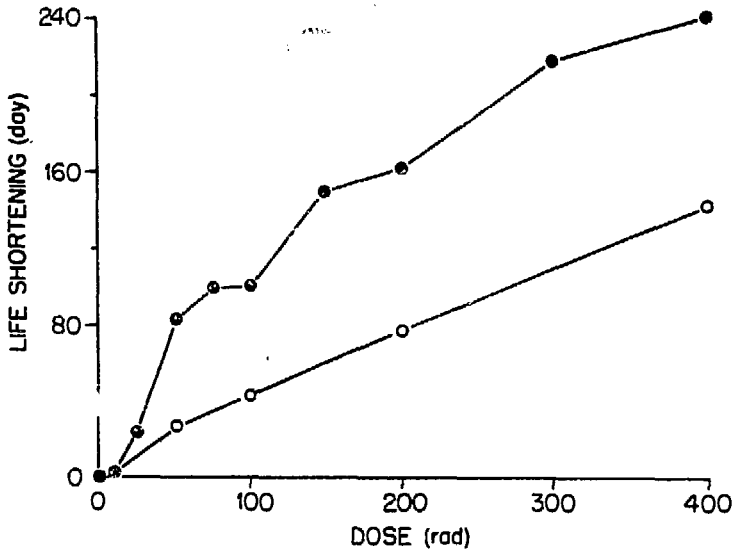

Fig 1

34326

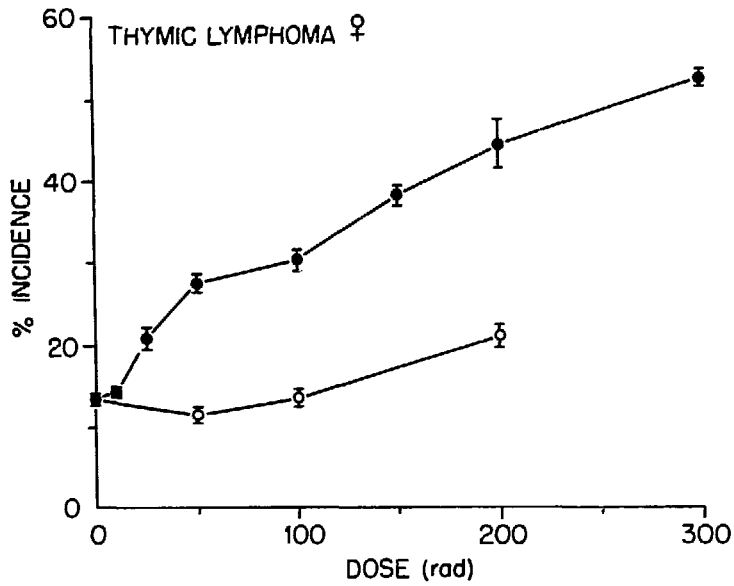

Fig 2

34334

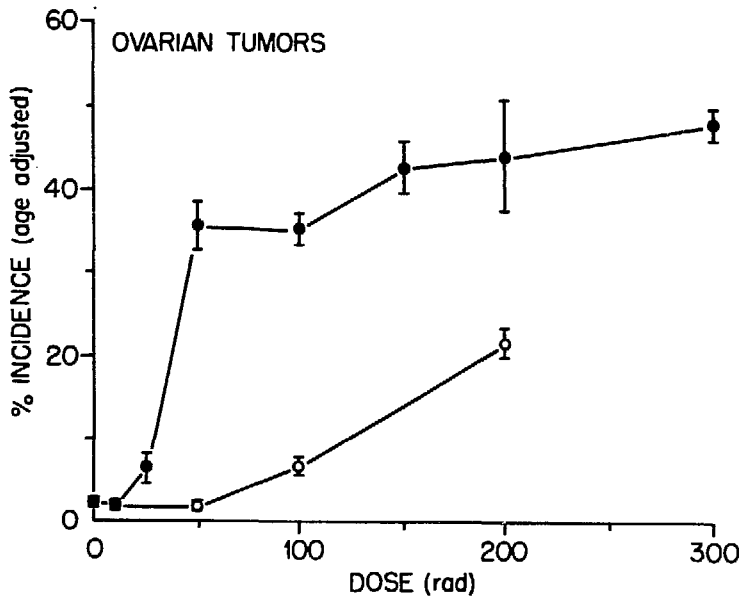
OVARIAN TUMORS
% INCIDENCE (age adjusted)
60
40
20
0
0
100
200
300
DOSE (rad)

Fig. 3

34333

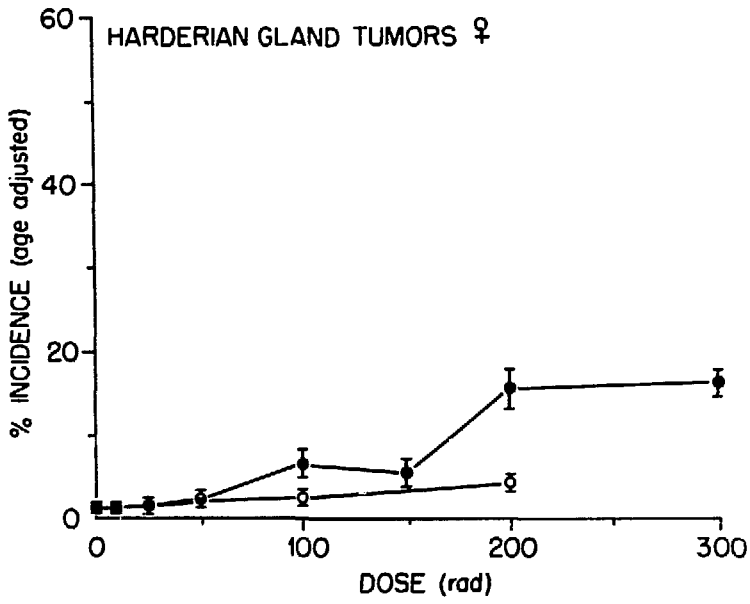
HARDERIAN GLAND TUMORS ♀
% INCIDENCE (age adjusted)
60
40
20
0
0
100
200
300
DOSE (rad)

Fig. 4

33490

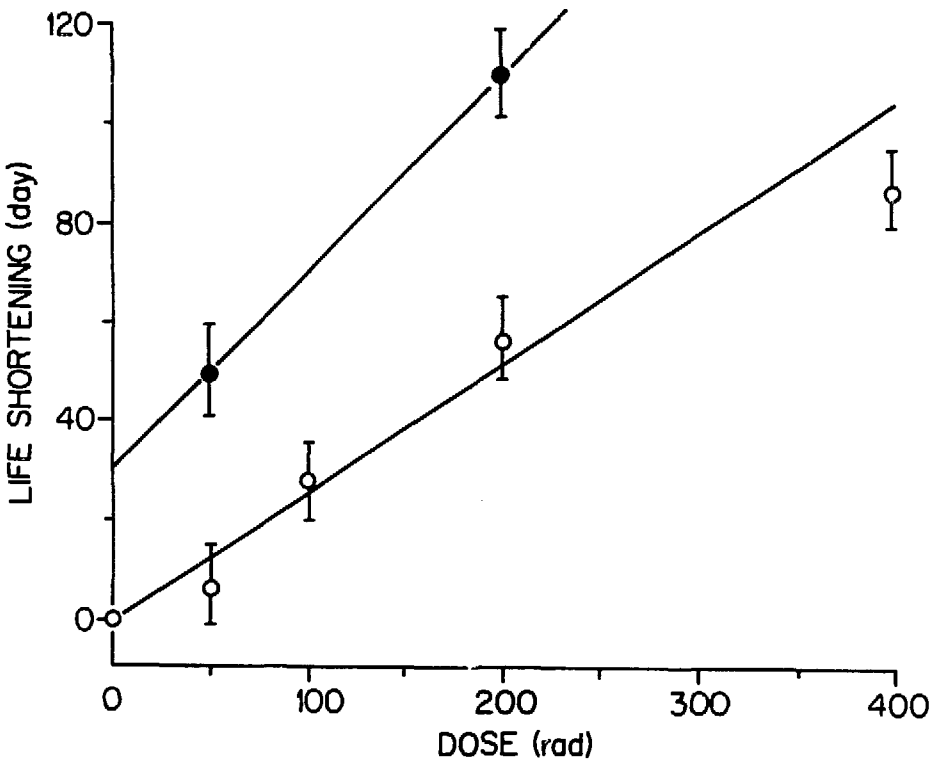

Fig. 5

33494

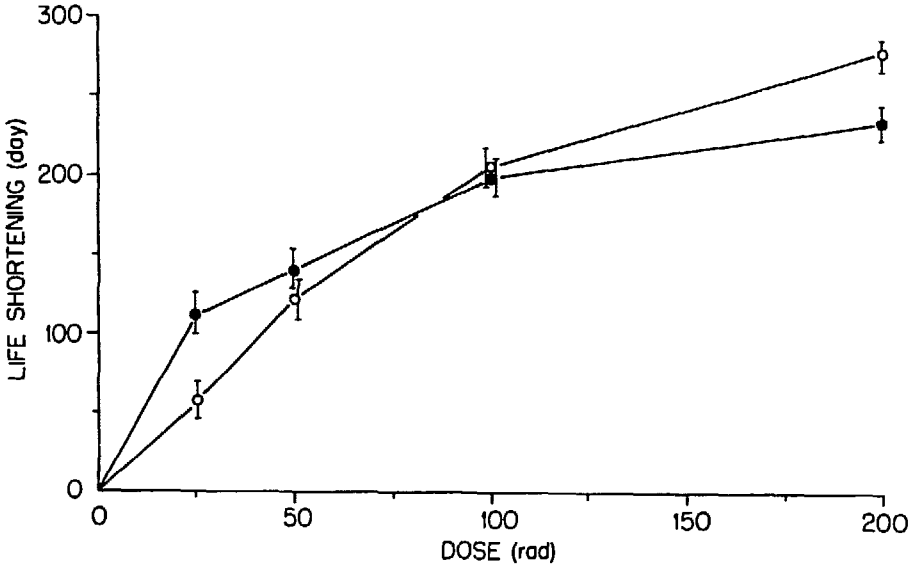

Fig. 6

33899

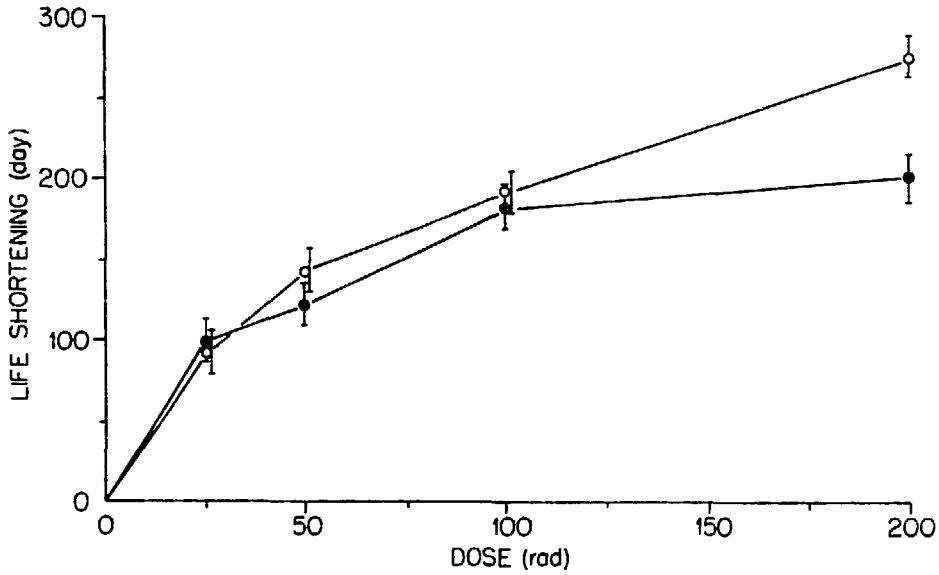

fig 7

31539-1

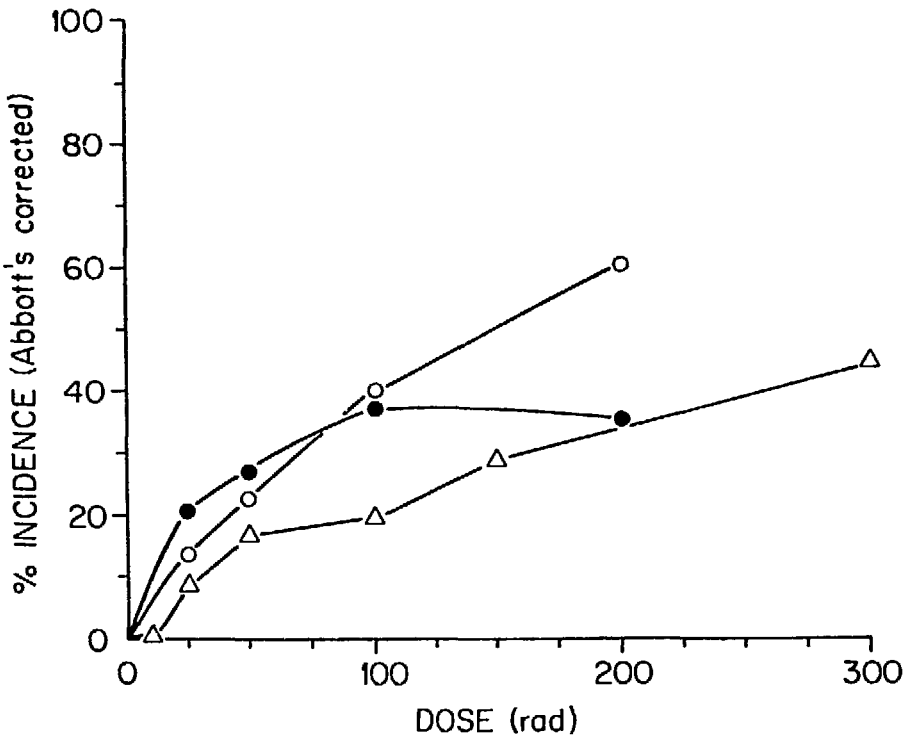
100
80
60
40
20
0
% INCIDENCE (Abbott's corrected)
0
100
200
300
DOSE (rad)

Fig. 8