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DOSE-RESPONSE CURVES AND THEIR MODIFICATION BY SPECIFIC MECHANISMS

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RUNNING HEAD: DOSE-RESPONSE CURVES & MECHANISMS

INTRODUCTION

Many of the papers presented at this symposium will demonstrate that certain biological mechanisms or processes are theoretically able to affect the yield of radiation-induced cancers *in vivo*, but undoubtedly there will be opposing views regarding their actual importance. This stems, at least in part, from the fact that no two test systems used to assess the importance of a given mechanism are exactly alike, and different results are therefore to be expected. The point we wish to make in the present report is that it is not necessary to compare different test systems in order to generate a conflict, since it is possible to obtain diametrically opposed evaluations regarding the importance of a given mechanism merely by altering the region of the dose response curve studied.

In specific terms, our proposal states that the relative importance of each biological mechanism will vary as a function of the total dose or dose rate, because these two variables affect not only the extent but also the nature of the injury induced in target and non-target cells, alike. In a sense this proposal is not new since it follows quite logically from a variety of predictions obtained in the study of dose response curves (1). What little originality exists stems from the combination of these predictions with biologically observable phenomena. If this proposal is valid, its value lies not only in resolving certain of the conflicts in the literature, but also in providing a rational means of predicting the carcinogenic hazards associated with radiation exposure conditions which cannot be simulated in the laboratory.

A priori, there are a number of cases in which support for our proposal is self-evident: low radiation doses ($\leq$100 rads), which are at best marginally immunosuppressive (2) do not compromise the hosts ability to cope with oncogenic virus or tumor cell antigens, while higher doses do (3); fractionation or protraction of a radiation dose can either increase or decrease the cancer yield, depending on the region of the dose-response curve studied (4,5); and low doses of radiation can produce "negative injury" as evidenced by prolongation of the lifespan of the exposed animals (6). We concern ourselves here, not with these aspects, but with two more subtle problems which have been the subject of debate in recent years: the dependence of recovery from radiation carcinogenic injury on dose size, and the role of immunosuppression versus target cell disturbances in radiation leukemogenesis.

RECOVERY FROM RADIATION CARCINOGENIC INJURY AS A FUNCTION OF DOSE SIZE

The dose-response curves for low linear energy transfer (LET) induction of cancers are, at least theoretically (7) composed of three regions: the low dose region in which tumor yield increases linearly with dose; the intermediate region in which tumor yield increases as a >1 power of the dose; and the high dose region in which the cell killing effects more than counterbalance the increased number of transformations and tumor yield declines progressively. The radiation doses which delimit these regions vary as a function of the tumor type in question (see below), but in most instances it is not possible to differentiate between the low and intermediate regions of the curve, i.e., the low dose region is small relative to the dose levels normally employed. We will use the terms low and linear interchangably; this also holds true for the terms intermediate and curvilinear.

In the absence of a system which would allow differentiation of the low from the intermediate dose region, few of the questions relating to the role of dose size in radiation recovery from carcinogenic injury could be addressed. A number of test systems were studied in an attempt to develop one for this analysis, and the most useful of these was the radiation induction of benign lung adenomas in the RF mouse (8). The unique features of this test system include: negligible mortality between treatment and analysis; constant tumor yields between 6 and 12 months after treatment; and the development of multiple tumors in individual animals, thereby allowing use of "mean number of tumors per mouse" as the response endpoint, as opposed to the more erratic incidence data (8).

In our pilot studies, a dose range of 750 to 3000 rads of localized thoracic 250 kVp X-rays were studied (8). Two points were established in these experiments: that the dose-response curve between 750 and 1500 rads was curvilinear, and that 1500 rads was the upper limit of the intermediate dose region. In order to determine whether the theoretically predicted linear component would be observed, we expanded these studies to include localized doses of as low as 250 rads. Figure 1 is a plot of the mean number of induced adenomas (treated mean minus control mean) per mouse observed 7 to 11 months after localized thoracic doses of 250 to 1500 rads. Between 250 and 750 rads, the slope of the log-log plot of response on dose is not significantly different from 1, indicating that the induction of benign adenomas in this dose range is a simple linear function. At the higher doses (750 to 1500 rads), the log-log slope of response on dose is significantly greater than 1 ($P < .01$) suggesting that an interaction between events is contributing to tumor yield. For comparison, we have included data on similar mice given graded doses of

urethane (ethyl carbamate) instead of localized X-rays. The shape of the overall dose-response curve for this chemical carcinogen is essentially identical to that for the localized X-rays: 125 to 500 mg of urethane per kilogram of body weight defines the linear portion of the dose-response curve, while higher doses are described by a curve which has a log-log slope of >1 ($P < .001$)(Figure 1).

The important point for the present discussion is not the specific doses which define the transition from a linear response to a curvilinear one, but rather the implications these two areas of the curve have for the process of recovery. For the case of the localized X-rays, at least, the linear relationship between dose and response (Figure 1; 250 to 750 rads) indicates that a single ionizing event is responsible for tumor induction in this dose range. In the higher dose region, where the log-log slope is significantly greater than 1 (Figure 1; 750 to 1500 rads) an additional mechanism appears to be contributing to the yield of tumors, namely, the interaction of ionizations, each of which alone was unable to produce a tumor. A carcinogenic process which requires only a single ionization should be independent of the rate of carcinogen administration, whereas, if more than one ionization is required, a slow rate of administration might allow recovery of the initial injury before additional ionizations occur. In other words, there should be no recovery from total doses which fall on the linear portion of the dose response curve, but there should be significant recovery from total doses which fall on the curvilinear portion of the curve, when the doses are given over a prolonged period of time as opposed to acute administration.

In order to test this prediction of the dose-response curve (Figure 1), we chose the highest total X-ray doses which fell on the linear portion of

the dose response curve (750 rads) and on the curvilinear portion of the same (1500 rads) and administered them either as a single dose or as two equal fractions separated by 24 hours. If no recovery occured during the 24 hour fractionation interval, then the tumor yield should be the same in the single and split dose groups. If recovery from the first dose equalled 100%, then the tumor yield in the split dose group should equal that of mice given only one of the two fractions (i.e., half of the total dose). The theoretical predictions of the dose-response curves were confirmed quite clearly, in that highly significant recovery was observed in the group given two fractions which totalled a dose which fell on the curvilinear portion of the dose response curve, 1500 rads (Table 1), while no recovery was apparent when a dose which fell on the linear portion of the curve (750 rads) was fractionated (Table 1).

Similar fractionation experiments were performed with urethane, since it showed a single dose-response curve similar to that of localized X-rays (Figure 1). Table 2 summarizes the results of an experiment in which we fractionated urethane doses which fell either on the linear (500 mg/kg) or curvilinear (1000 mg/kg) portions of the dose response curve. Again, the same pattern was observed (Table 2): significant recovery was observed when a total dose within the curvilinear range was fractionated ($P<0.02$), bu no recovery was apparent when a single dose on the linear portion of the curve was fractionated. Extension of the recovery interval from 24 to 96 hours (Table 2) failed to allow the demonstration of recovery in the low total dose group, and, in fact, apparent "negative recovery" was observed. It should be noted that urethane data similar to that presented above (Figure 1 and Table 2) has been published elsewhere (9,10) and extension of our analysis to it leads to essentially the same conclusions.

For the localized X-rays, we propose that the single events which are

contributing to tumor yield in the linear range, and the single and multiple events which are contributing to tumor yield in the curvilinear range are ionizations within the target cells of the irradiated lung. In brief, we propose that our results are compatible with the predictions of the dual action theory of radiation injury (7). The urethane data, although showing similar kinetics, need not be the product of identical or even similar processes. Urethane was administered systemically, and it is possible that the event interaction in the curvilinear portion of the dose-response curve (Figure 1) reflects the development of significant immunosuppression (11) or prolonged retention time of the carcinogen (12) which does not occur in the low dose region[1]. Immunosuppression would appear to be an unlikely candidate for this additional event, since the adenomas are very weakly immunogenic, and mice treated with 1000 mg/kg of urethane are no more or less resistant to transplants of this tumor (13). Although unlikely, due to the time factors involved, a prolonged carcinogen retention time remains a possible interpretation.

Whether or not the event interaction involved in the two carcinogenic mechanisms is the same, it is interesting to note that recovery is dose dependent in both cases. However, at equally carcinogenic doses (e.g., a mean of 1 induced adenoma per mouse) one is well into the X-ray dose range in which recovery would occur (Figure 1), but is still well within the "no recovery" dose range for urethane. Therefore, protraction of this X-ray dose would produce significantly fewer tumors, while protraction of the

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1 - The author acknowledges these suggestions by Profs. N. Haran-Ghera and J. Neyman, respectively.

urethane dose would produce as many tumors as the same total dose given acutely. We suggest that information such as this may prove to be more valuable to those estimating comparative hazards than simple estimates of carcinogenic efficiency.

As a last point, it must be emphasized that the radiation doses which define the break between the linear, "no recovery" portion of the dose-response curve and the curvilinear portion are heavily dependent on the tumor being studied. As an example, in the ovarian tumor system, recovery is constant between doses of 49 and 392 rads (14). In this highly radiosensitive system, we have been unable, as yet, to detect the linear portion of the dose-response curve. We concur,therefore, with the reccomendations of the Aspen report (15), which suggested that the definition of the low dose range is dependent on the test system employed, and that for each it is that region in which the effect is linearly proportional to dose.

ACUTE AND CHRONIC RADIATION EFFECTS ON RESISTANCE TO ONCOGENIC VIRUSES

For a number of years, it has been known that administration of 600 to 700 rads as four equal weekly fractions was far more leukemogenic than the administration of the same total dose acutely (16), at least in the C57BL mouse. This repeatedly observed phenomenon stands in contrast to what might be expected if significant recovery from immunosuppression occured or if recovery from carcinogenic injury occured in the fractionally exposed group. It has been suggested,therefore, that fractionation proves to be more leukemogenic because these exposures disturb the normal target cell kinetics thereby placing more of them in a sensitive state (17). The exact nature of

this disturbance is not clear, but recent evidence provided by Tennant (18) has demonstrated that actively dividing cells are more susceptible to radiation activation of endogenous leukemia viruses, and that chronic irradiation is more effective in this regard than is acute irradiation, even after cell survival is taken into account.

At the risk of over-generalizing, we propose that radiation can increase the leukemia incidence either by inducing such a heavy viral burden that immune responsiveness is irrelevant, or by suppressing immune responsiveness such that even small viral burdens can prove to be significant. In addition to being a means of reconciling the opposing views in this argument, this proposal is consistent with established patterns: those exposure regimens, such as fractionated or chronic exposures, which are highly leukemogenic in spite of their weak immunosuppressive capabilities, are highly efficient in activating endogenous leukemia viruses (18); and, conversely, those exposure regimens, such as acute exposures, which are moderately leukemogenic in spite of their weak virus activation capabilities (18,19), are strongly immunosuppressive (3). Consistency alone cannot prove or disprove a proposal, so we have initiated a series of experiments designed to test this proposal, and present below the results of these initial investigations.

For the host in these studies we have used adult (4-month-old) BALB/c females, which are essentially insensitive to the induction of leukemia by either acute or chronic gamma rays over a wide range of doses and dose rates (13,14). Groups of these mice (N=16) were exposed to 392 rads of ^{137}Cs gamma rays at dose rates of 41 rads/min (ACUTE) or 28 rads per day (CHRONIC). Following exposure, these mice, along with unirradiated controls, were allowed to recover through the age of 6-months, at which time all mice were given

an intramuscular injection of 0.1 ml of the Moloney strain of the murine leukemia/sarcoma virus complex, henceforth referred to as MSV/MLV. Since our intent in these studies was to study the development of leukemia, we passaged our original low-leukemia line of this virus (20) through two in vivo passages, and thereby increased its leukemogenic potency (see below).

This experiment is still in progress but the data obtained to date are more than sufficient to answer the question posed by these studies. It should be noted that unirradiated and irradiated (ACUTE or CHRONIC) mice demonstrated less than 7% mortality within the first 8 months of the experiment in the absence of MSV/MLV injection.

Figure 2 is a plot of the percent mortality versus time for the virus injected control and irradiated mice. Control mice began to die between 90 and 100 days after virus injection, but this wave of deaths completed by the 160th day after injection, with negligible further mortality through the 230th day. Radiation exposure of the mice prior to the virus injection altered the mortality pattern, but the direction of its alteration depended on the manner in which the 392 rads was applied (Figure 2). Mice given 392 rads at 28 rads per day (Figure 2; CHRONIC) began to die between days 70 and 80 of the experiment, and all had died by the 160th day post-virus-injection. Conversely, mice given 392 rads in a matter of minutes (Figure 2; ACUTE) did not start to die until the 110-120 day interval, and then only gradually, but significant mortality was observed between days 160 and 230 of the experiment. The apparent explanation for these anomalous patterns can be seen in the analysis of the causes of death in these mice. Typical MSV/MLV induced leukemias occured exclusively within the first 160 days after virus

injection while none of the sarcomas which developed occured before the 140th day after injection. This latter observation confirms our earlier estimates on the rate of development of sarcomas under similar conditions (21). Table 3 summarizes the probabilities of dying of leukemia during the early period (through day 160) and of dying of a sarcoma during the later period (day 140 through 230) for each of the experimental groups. Relative to unirradiated mice, chronic irradiation increased the probability of developing leukemia, and acute irradiation suppressed it, and both of these alterations are statistically significant (Table 2). No valid estimate of the probability of dying with a sarcoma is available for the chronically irradiated group, but acute irradiation induced an increase in the risk of sarcoma relative to unirradiated mice. At the time of writing (day 230 of the experiment) the difference in risk of dying with sarcoma between the control and acutely irradiated group was not statistically significant ($P < 0.10$). It should be remembered, however, that almost all of these mice will eventually develop an injection site sarcoma (21), with the acutely irradiated group demonstrating a much faster rate of development (see above and 21). In support of our prediction regarding the eventual fate of the control and acutely irradiated mice still alive at day 230 of the experiment stands the observation that none of the control mice possessed palpable injection site tumors on day 230 (0/6), while almost all of the acutely irradiated mice did (7/9). We conclude,therefore, that exposure of mice to chronic gamma rays prior to a large virus challenge sensitizes them to the development of leukemia, while acute pre-exposure makes them resistant to leukemia but sensitive to sarcoma induction.

Our proposal was that immunosuppression would only be important in the development of radiation induced leukemia if the viral burden were low, but that disturbances in the target cell kinetics could more than counterbalance any lack of immunosuppression either by providing a source of sensitive cells

in which the virus can accomplish transformation or by placing the target cells in a sensitive stage for activation of endogenous viruses (18). The data presented above have provided only a partial test of this proposal, in that we have standardized for the amount of virus present (by adding it exogenously) and determined the role of chronic versus acute exposure in altering sensitivity to the virus. Quite clearly, one cannot argue that immunosuppression is responsible for the radiation induced alterations in sensitivity to the exogenous virus. What appears more likely is that chronic irradiation enhances the sensitivity of the target population either quantitatively (more cells at risk) or qualitatively (more rapid cycle times), while acute irradiation depletes or at least reduces the size of the target population. We are at present testing these points directly. Preliminary results suggest that the chronic radiation induced sensitization to leukemia declines as the time between completion of exposure and virus injection increases. Conversely, the acute irradiation effect does not alter appreciably as the interval between the two is increased. These observations are consistent with our proposal.

An interesting point observed in these studies is that although acute irradiation elevates resistance to the leukemogenic effect of MSV/MLV, it apparently sensitizes to the sarcomagenic effects of the same (Table 3). Undoubtedly, this is related to the fact that the target and effector cells in virus induced leukemia are one in the same, while in sarcomagenesis, they are quite distinct. Therefore, in the development of sarcomas, depletion of the lymphoid tissue can only serve to reduce the hosts resistance to the development of tumors from muscle cells.

We are currently testing the second aspect of our proposal, i.e., that immunosuppression can prove to be important in radiation leukemogenesis when the viral burden is low. The results are too preliminary to warrant discussion, but they are not inconsistent with the argument that the immune system is able to cope with only limited tumor burdens (or viral burdens), and that their importance is restricted to a very limited range of experimental conditions (22).

SUMMARY

In the data presented above, we have demonstrated that at least three types of mechanisms can contribute to the yield of radiation induced cancers, but that the relative contribution of each depends heavily on the exposure conditions, and on the tumor type in question. A continued consideration of the mechanisms involved relative to the dose response curves observed would appear to be the most fruitful approach to the study of the biology of radiati carcinogenesis.

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Table 1. Recovery from radiation carcinogenic injury to the mouse lung as a function of dose size. The exposures were given either as a single dose or as two equal fractions separated by 24 hours.

Exposure Method	Total Radiation Dose (rads)	Number of Mice	Induced Lung[a] Adenomas (mean ± s.e.)	Recovery[b] (%)
Single Dose	1500	27	1.56 ± 0.21	-
Single Dose	750	29	0.38 ± 0.09	-
Two Fractions[c]	1500	24	0.96 ± 0.19	51
Single Dose	750	29	0.38 ± 0.09	-
Single Dose	375	21	0.09 ± 0.04	-
Two Fractions[c]	750	28	0.49 ± 0.06	-38

a - mean observed in the irradiated group minus the control mean of 0.39 adenomas per mouse.

b - 100% recovery equals a mean number of induced adenomas identical with that observed in mice given only half of the total radiation dose, i.e., 750 rads and 375 rads, respectively.

c - two equal fractions given at a 24 hour interval.

Table 2. Recovery from urethane-induced carcinogenic injury to the mouse lung as a function of dose size. The injections were given either as a single dose or as two equal fractions separated by 24 to 96 hours.

Injection Method	Total Urethane Dose (mg/kg)	Time Between Fractions (hrs)	Number of Mice	Induced Lung[a] Adenomas (mean ± s.e.)	Recovery[b] (%)
Single Dose	1000	-	31	16.64 ± 0.89	-
Single Dose	500	-	36	4.12 ± 0.39	-
Two Fractions[c]	1000	24	32	8.73 ± 0.91	63
Single Dose	500	-	36	4.12 ± 0.39	-
Single Dose	250	-	35	2.13 ± 0.26	-
Two Fractions[c]	500	24	31	3.97 ± 0.39	7
Two Fractions[c]	500	48	31	4.56 ± 0.35	-22
Two Fractions[c]	500	96	30	5.52 ± 0.39	-70

a - mean observed in the treated group minus the control mean of 0.43 adenomas per mouse.

b - 100% recovery equals a mean number of induced adenomas identical with that observed in mice given only half the total urethane dose, i.e., 500 mg/kg and 250 mg/kg, respectively.

c - two equal fractions given at the specified intervals.

Table 3. Deaths attributable to leukemia and sarcoma in control and pre-irradiated mice given MSV/MLV[a], through the first 230 days of the experiment.

Pre-irradiation	Leukemia Deaths[d]	Sarcoma Deaths[e]
Controls	9/16	1/7[f]
Chronically Exposed[b]	16/16[h]	-
Acutely Exposed[c]	2/16[i]	5/14[g]

a - MSV/MLV given intramuscularly at the age of 6-months; this equals day 0 of the experiment.

b - given 392 rads at 28 rads per day starting at 4-months.

c - given 392 rads at 41 rads/min at the age of 4-months.

d - cause of death disseminated leukemia; no sarcomas detected, except in one on the two Acutely exposed mice.

e - deaths due to local and metastatic sarcoma deposits.

f - none of the 6 mice surviving to 230 days possessed palpable sarcomas

g - 7 of the 9 mice surviving to 230 days had palpable sarcomas.

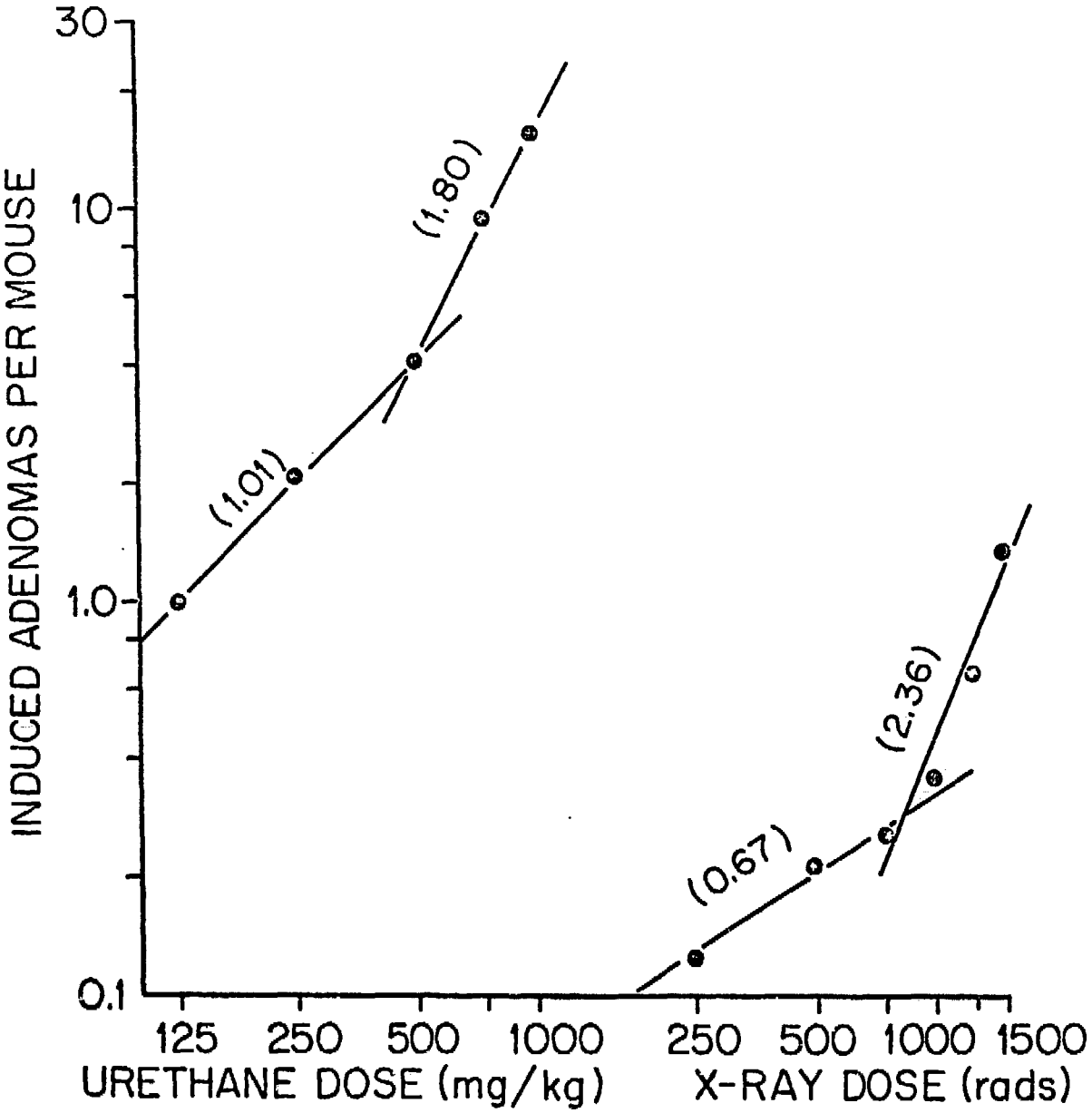
h - significantly greater than respective value in controls ($P < .005$) and in acutely exposed ($P < .0005$)

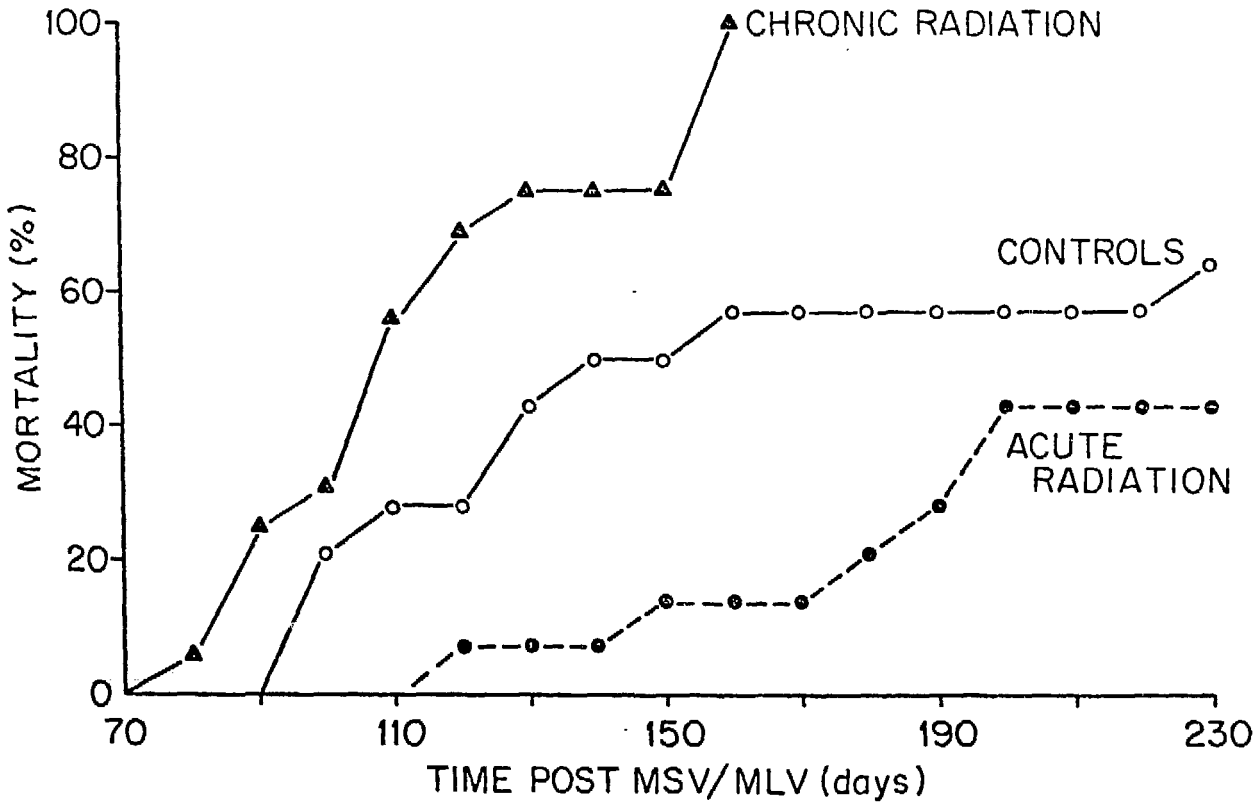
i - significantly smaller than respective value in controls ($P < .01$) and chronically exposed ($P < .0005$).

FIGURE LEGENDS

Figure 1. Mean number of papillary lung adenomas per mouse induced by graded doses of urethane or localized X-rays. Induced values corrected for spontaneous control value (0.39 to 0.43 adenomas per mouse). Numbers on each of the curves represent the maximum liklihood estimates of the log-log slope.

Figure 2. Percent mortality as a function of time in BALB/c mice given MSV/MLV at the age of 6-months. Time zero on the plot coincides with the time of virus injection. CONTROLS received no irradiated prior to the virus; the CHRONIC RADIATION group received 392 rads of gamma rays at a rate of 28 rads per day starting at the age of 4-months (exposure time = 14 days); and ACUTE RADIATION group received 392 rads of gamma rays at 41 rads per min at the age of 4-months.


30
10
1.0
0.1
INDUCED ADENOMAS PER MOUSE
(1.01)
(1.80)
(0.67)
(2.36)
125
250
500
1000
URETHANE DOSE (mg/kg)
250
500
1000
1500
X-RAY DOSE (rads)


100
80
60
40
20
0
MORTALITY (%)
CHRONIC RADIATION
CONTROLS
ACUTE
RADIATION
70
110
150
190
230
TIME POST MSV/MLV (days)